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Hyperuricemic Syndromes: Pathophysiology and Therapy

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Hyperuricemic Syndromes: Pathophysiology and Therapy

Volume Editors

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Preface

It is our pleasure to introduce the volume 'Hyperuricemic Syndromes: Pathophysiology and Therapy' as a joined editorial effort between the Department of Nephrology and that of Onco-hematology of the San Bortolo Hospital, Vicenza, Italy.

We consider the uric acid disorders as a common field between nephrological and hematological diseases and for this reason we feel that a multidisciplinary approach can probably offer new insights into these metabolic syndromes.

Gout has been recognized since antiquity, and descriptions of the disease date back to the Babylonian empire. Hippocrates described gout well as podagra (literally '*foot into a trap*'), and some of his classical aphorism withstood the test of time: '*A woman does not take the gout until her menses be stopped*' and '*A young man does not take the gout until the first sexual intercourse*'.

Gout has been the sign of distinction and was called the 'patrician malady', 'king of diseases' and the 'disease of kings'. In fact gout afflicted kings, including Alexander the Great, Charlemagne, and Henry VIII, and famous personalities like Voltaire, Isaac Newton, Charles Darwin, and Leonardo da Vinci (fig. 1: an old disease depicted in an old painting).

Anton Van Leeuwenhoek, the Dutch inventor of the microscope, observed crystals from a gouty tophus in 1679. A classic description of gouty acute attack is reported in 1683 by Thomas Sydenham, from his own gouty suffering. Sir Alfred Garrod stated the concept that gouty arthritis follows a deposition of urate from supersaturated body in 1859.

The modern history of crystal-associated disease dates from more than 50 years, when McCarthy and Hollander identified urate crystals in joint effusion from patients with gout.

Fig. 1. William Hogarth: The marriage settlement. (National Gallery, London)

The first enzymatic defect responsible for one rare subtype of hereditary gout, hypoxanthine-guanine phosphoribosyltransferase deficiency, was discovered by Seegmillere, Rosenbloom, and Kelley in 1967. Allopurinol, in 1963, opened the way to the successful clinical management of gout.

In the more recent history, the hyperuricemic syndromes affecting patients with cancer, especially in the phase of cellular destruction after chemotherapy have been identified as Tumor Lysis Syndromes. These pathological conditions, together with the improved understanding of urate handling by the kidney have spurred new interest in the pathophysiology of hyperuricemic states, their clinical consequences and their management.

The recent development of a recombinant form of urate oxidase transforming uric acid into allantoin (Rasburicase) has brought new interest into the pathophysiological mechanisms of hyperuricemia and on the potential applications of the new drug.

This volume has been made possible by Sanofi-Synthélabo thanks to an important organizational effort. We were able to put together a group of internationally recognized experts in the field and put them working together for the preparation of a book that is intended to be a compendium of the present knowledge in the field and at the same time a reference tool for professionals and students who want to expand their knowledge in this topic. The book is multidisciplinary and it takes advantage of the competence and the specific professionality of each author in the fields of biochemistry, pharmacology, rheumatology, onco-hematology, and nephrology. As we used to say for any multidisciplinary project, we cannot all play the same instrument but we can all be on the same key.

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Francesco Rodeghiero

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Purine Metabolism and Hyperuricemic States

'The Point of View of the Rheumatologist'

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Abstract

Gout is among the most common causes of acute monoarticular arthritis. It is characterized by depositions of monosodium urate crystals in a joint or in soft tissues, causing an acute inflammatory response. Gout typically occurs in middle age and more commonly in men. The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. The initial attack usually affects a single joint, although multiple joints can be affected, especially in women.

Early treatment (within 24 h) is the key to effective treatment in an episode of acute gouty arthritis. Colchicine, the traditional agent used, is more specific for gout than the NSAIDs. Treatment for hyperuricemia should be initiated in patients with frequent gout attacks, tophi or urate nephropathy.

Although hyperuricemia is a major risk factor for the development of gout, acute gouty arthritis can occur in the presence of normal serum UA levels. Patients with asymptomatic hyperuricemia do not require treatment, but efforts should be made to lower their urate levels by encouraging them to make changes in diet or lifestyle. An epidemiological link between elevated serum UA level and cardiovascular risk has been recognized. Hyperuricemia in hypertensive subjects may represent an early indicator of hypertensive cardiorenal disease.

Introduction

The term gout encompasses a heterogeneous group of diseases in which the most obvious manifestation is an increased plasma urate level. Gout is often

thought to be relatively rare and therefore of not much interest to generalists. A study of the diagnosis and treatment of gout in England revealed that less than 10% of patients diagnosed as having gout were referred to the rheumatologist [1]. Yet, it is an underdiagnosed condition that presents diagnostic and treatment challenges.

Gout is a disorder of purine metabolism or renal excretion of uric acid (UA) characterized by [2]:

(1) hyperuricemia
(2) precipitation of monosodium urate as deposits (tophi) throughout the body, with the special predilection for joints, periarticular cartilage, bone, bursae, subcutaneous tissue and kidneys
(3) recurrent attacks of acute crystal-induced arthritis
(4) nephropathy
(5) nephrolithiasis

Hyperuricemia has been defined as a serum plasma urate concentration greater than 7.0 mg/dl (0.42 mmol/l) in males and 6.0 mg/dl (0.36 mmol/l) in females.

In humans and great apes, urate oxidase (uricase) is inactive as a result of a genetic mutation, and so UA cannot be broken down to allantoin and carbon dioxide [3]. Gout develops in humans, probably because hyperuricemia spontaneously develops and serum urate level approaches the saturation point [4]. It has been postulated that humans have 'acquired' this propensity to hyperuricemia because UA confers some advantages like the ability to maintain blood pressure under low-salt dietary conditions [5] or to protect against degenerative neurological diseases by acting as an antioxidant [6].

Hyperuricemia is difficult to define because of the nonregular distribution of serum urate concentration in the population. The plasma concentration is low in both sexes at birth and until puberty. Then, the level increases in males, but does not in females.

Premenopausal women have lower serum UA levels than men or postmenopausal women, since estrogen stimulates urinary urate excretion [4]. After menopause, serum UA in women approaches those of men.

Genetic differences in the regulation of UA synthesis, renal UA excretion, or both are also likely to be important, and these factors may account for some of the racial differences in the susceptibility to gout [4].

Epidemiology

Gouty arthritis is the most common form of inflammatory joint disease in men older than 40 years [7].

The disease affects at least 1% of the men in Western countries with a male to female ratio of 7–9:1 [8], which is changing in favor of the latter.

Prevalence estimates for gout in persons aged 20 and older were 7.2 per 1,000 in men and 4.8 per 1,000 in women [9]. In other epidemiological studies prevalence reported is 6 per 1,000 population for man and 1 per 1,000 population for women [10]. Maximal prevalence rates found in persons aged 40–59 were 13 per 1,000 in men and 7 per 1,000 in women. The prevalence of self-reported gout in the USA was approximately 8.4 cases per 1,000 in 1992 [9].

The plasma urate concentration is the single most important determinant of the risk of developing gout. With prior serum urate levels of 9 mg/dl (0.53 mmol/l) or more, the annual incidence rate of gouty arthritis was 4.9%, compared with 0.5% for urate levels of 7.0–8.9 mg/dl (0.41–0.52 mmol/l) and 0.1% for urate levels below 7.0 mg/dl (0.41 mmol/l). With urate levels of 9 mg/dl or higher, cumulative incidence of gouty arthritis reached 22% after 5 years [11].

The risk of developing gout appears to be similar in males and females for a particular urate concentration: this suggests that the lower prevalence of gout in female is likely to be a reflection of their lower urate concentration.

After adjusting for confounding factors (alcohol, diuretics, body mass index) in asymptomatic hyperuricemic men, the 5-year cumulative incidence of gout was found to be 18.8% [12].

The incidence and severity of gout may be increasing in the last few years [13]; the association of alcohol consumption, obesity, and hypertension appear to be partially responsible for this [14].

Etiology

UA is a weak acid (pKa 5.8), so at normal body pH 7.4, it dissociates almost completely to form salts with various cations. In extracellular fluids in which sodium is the principal cation, approximately 98% of the UA is in the form of monosodium urate [15].

Solubility of urate and UA is critical for the development of crystals [16]. Above a concentration of about 7 mg/dl, plasma is supersaturated with urate, but this is often a stable situation because of the other constituents of plasma that reduce the tendency to form crystals.

Factors that control solubility of UA crystals are temperature, pH, plasma protein binding, and rapid mobilization of water from tissues.

There are many factors that determine the preferential precipitation of urate crystals at the base of the big toe, one of this may be the lower temperature. Solubility of urate is a direct function of temperature. At 37°C the solubility in

physiological saline is 6.8 mg/dl, but at 30°C it is only 4.5 mg/dl. The intra-articular temperature of the normal ankle is about 29°C [17].

The first MTP joint is subjected to massive forces during walking. Many attacks of gout occur early in the morning, when fluid reabsorption may occur. The diffusion of urate across the synovial membrane is much slower than the diffusion of water and the reabsorption of traumatic effusion may thus produce a transiently high intra-articular urate concentration that favors crystal precipitation [18].

During asymptomatic periods urate crystals stay indefinitely in the joint while hyperuricemia persists. There is a mild subclinical inflammation in the joint, with high cellular count. Inflammation becomes intense and symptomatic during the attacks. Cellular count decreases after treatment with prophylactic dose of colchicine. When serum UA levels are reduced to normal, the monosodium urate crystals slowly dissolve and finally disappear from the joint [19].

Factors leading to the precipitation of urate crystals are poorly understood. Necessary but not sufficient is the condition of supersaturation of serum or synovial fluid with monosodium urate. Sudden changing of urate plasma levels may provoke the loosening of crystals from tissues; this is likely to occur after allopurinol somministration. Other factors, which can precipitate acute attacks are alcohol, surgery, trauma, and dietary excess.

The physical characteristics of crystals are also known to influence their inflammatory potential. Smooth regular box-like crystals, such as cystine, are incapable of producing an inflammatory response. On the contrary, surface irregularities may allow binding with biological membranes of lysosomes through electrostatic forces [17].

The solubility of urate crystals is augmented by proteoglycans, a major component of connective tissues, whereas the proteolytic disruption of the urate-saturated polysaccharides results in precipitation of dense urate deposits in vitro: it is proposed that a similar phenomenon occurs in vivo under the influence of lysosomal enzymes [20].

The intra-articular injection of the crystals into dog and human joints results in acute synovitis that could be prevented by colchicine. Urate crystals in the synovium appear to evoke an intense foreign body-like inflammatory response [17].

Phagocytosis of monosodium urate by human leukocytes, is an essential step for the production of chemotactic factors in acute gouty arthritis. Microcrystals of monosodium urate adsorb IgG and complement and this facilitates phagocytosis by Fc and complement receptor-bearing cells, like polymorphonuclear leukocytes and macrophages, and enhance the inflammation.

Urate crystals induce arthritis, in part, because they are able to stimulate the production of neutrophil chemoattractants**,** such as interleukin-8, by the synovial cells [21].

Phagocytosed monosodium urate crystals are rapidly surrounded by a distinct phagosome membrane, then [20] degranulation of the cell ensues, followed by membrane lysis and death of 20% of the cells within 30 min [22]. Released crystals return available for phagocytosis by other leukocytes.

Interleukin-1 and TNFα released by macrophages may be responsible for the fever, neutrophil leukocytosis and for the interleukin-6-mediated stimulation of acute phase reactants, often associated with acute gouty arthritis [23].

During the resolution of inflammation, affected neutrophils are removed from the inflammation sites by a process of programmed cell death. Apoptotic cells are quickly recognized and phagocytosed by macrophages [24].

Urate crystals are capable of delaying spontaneous TNFα-induced neutrophil apoptosis. This may result in prolonged lifetimes and responses of these phagocytic cells with the potential for extended inflammation [25].

It is not known why certain hyperuricemic individuals remain asymptomatic, and how most untreated acute attacks of gout spontaneously resolve. It has been hypothesized that well-differentiated macrophages may lead to the development of a noninflammatory phenotype characterized by a lack of proinflammatory cytokine secretion. This could provide a safe-disposal mechanism for the removal of inflammatory rate crystals [26, 27].

Pathogenesis

Purine Metabolism (fig. 1)

De novo purine synthesis is a complex series of reactions that starts with the formation of phosphoribosyl pyrophosphate (PRPP) from ribose-5-phosphate and ATP. This reaction is controlled by phosphoribosyl pyrophosphate synthetase (PRPP synthetase).

The second important step is the formation of 5-phosphoribosyl-1-amine from PRPP and glutamine, the reaction being controlled by the enzyme PP-ribose-P amidotransferase. This is an irreversible reaction that is a site of feedback control. PP-ribose-P amidotransferase is a rate-limiting enzyme that exists in two forms: a larger dimeric form that is catalytically inactive, and a monomeric form that is active. The intracellular concentration of PRPP is the major regulator of the rate of de novo purine synthesis, by converting the inactive form of the enzyme into the active one.

Then phosphoribosylamine is converted in inosinic acid, the parent of purine compounds.

Inosinic acid with guanylic acid and adenylic acid serves as building blocks for DNA and RNA, as precursors of cyclic nucleotides, as a source of chemical energy and various cofactor and coenzymes.

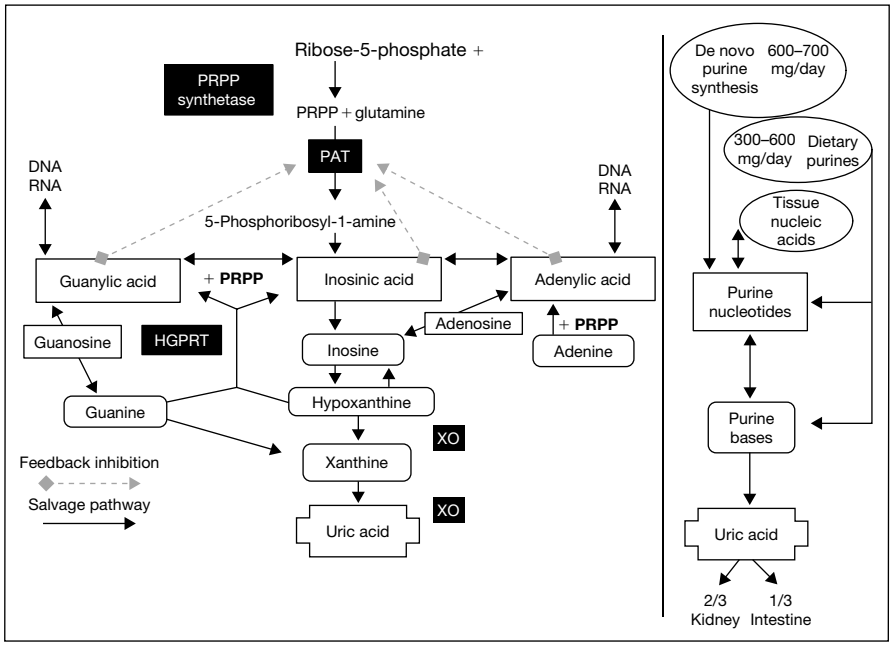

Fig. 1. Urate biosynthesis through the major pathways.

Purine bases are formed in the last phase, guanine, adenine, hypoxanthine, xanthine and finally UA. Purine bases, hypoxanthine and guanine, may be recycled (salvage pathway) into nucleotide pools by a specific enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGPRT). This reaction employs PP-ribose-P and so reduces the intracellular content of this compound, thus decreasing purine de-novo production.

In the final step, hypoxanthine is converted to xanthine and the latter to UA by the same enzyme, xanthine oxidase (XO). Guanine is converted to xanthine by guanase and then converted to UA by XO [15].

Classification of Hyperuricemia and Gout

Purines can be derived directly from the diet or synthesized from small molecular precursors (fig. 1). Purine bases derived from tissue nucleic acids may also be reutilized. This metabolic pathway is very important during hematological malignancy and cytotoxic therapy because it increases by several times.

On a purine-free diet a healthy man has an urate pool of about 1,200 mg [17]. In a normal woman this pool is half as large. In gouty patients the urate pool may be two to three times the normal and, if tophi are present, may be as high as 18,000 to 31,000 mg [17].

About half of the urate pool turnover each day, it means that on a purine-free diet a normal man synthesizes and eliminates about 650 mg of UA every 24 h. Of this amount, 450 mg is excreted in the urine and 200 mg is eliminated in the stool. The latter way to eliminate UA is enhanced several times in the presence of renal failure. Urate elimination via the alimentary tract is probably a passive process and varies with the plasma UA concentration. Negligible amounts of UA are found in the feces because colonic bacteria degrade it.

Hyperuricemia and gout are traditionally classified as primary or secondary. The former refers to patients in whom the basic metabolic defect is unknown or, if known, the main manifestation is gout. In the latter, hyperuricemia is part of a well-known acquired disorder or metabolic defect, but the main clinical aspect is not gout.

Because hyperuricemia may result from the overproduction or underexcretion of urate, a more physiological classification of hyperuricemia is based on the amount of urate excretion on a purine-free diet [17].

Overproduction

In overproduction the purine precursor may be derived from the diet or from an endogenous metabolism by an increase in the rate of purine biosynthesis de novo or by an excessive rate of cellular turnover. The former is usually caused by genetically determined defects, the latter by myeloproliferative or lymphoproliferative disorder.

HGPRT deficiency is inherited as a X-linked trait. In absence of HGPRT hypoxanthine cannot be reutilized but can only be degraded to UA. A moderate degree of deficiency results only in the overproduction of urate. On the contrary, a severe deficiency results in the Lesch-Nyhan syndrome, characterized by central nervous system abnormalities [28].

The intracellular concentration of PRPP is an extremely important determinant of the rate of purine biosynthesis de novo [17]. There are at least three genetic variants of the gene coding for PRPP synthetase that is located in the X chromosome near the HPRT locus. PRPP synthetase overactivity is associated with gout in adolescents and young adults [29].

Patients suspected with partial HGPRT deficiency or increased PRPP synthetase activity can be investigated and their enzyme activity assessed in erythrocytes by high performance liquid chromatography [30].

Recently, the early onset of gout has been associated with congenital fructose intolerance (as a result of an inherited partial deficiency of aldolase). Hyperuricemia may occur because excessive degradation of adenine nucleotides. 31P magnetic resonance spectroscopy studies of children with hereditary fructose intolerance revealed a readily detectable rise in the serum urate in response to very low doses of oral fructose. As the heterozygous state may be

Table 1. Acquired causes of hyperuricemia

Urate overproduction
Nutritional
Excess purine, ethanol, fructose consumption
Hematologic
Myeloproliferative and lymphoproliferative disorders, polycythemia
Drugs
Ethanol (ATP pathway)*, cytotoxic drugs, vitamin B12 (treatment of pernicious anemia)
Miscellaneous
Obesity, psoriasis, hypertriglyceridemia
Urate underexcretion
Drugs
Ethanol (lactic acid)*, cyclosporine, diuretics (thiazides, furosemide and other loop diuretics), ethambutol, pyrazinamide, aspirin (low-dose), levodopa, nicotinic acid
Renal
Hypertension, polycystic kidney disease, chronic renal failure (any etiology)
Metabolic/endocrine
Dehydration, lactic acidosis, ketosis, hypothyroidism, hyperparathyroidism
Miscellaneous
Obesity, sarcoidosis, toxemia of pregnancy, lead exposure

*see text

present in about 1/250 of the white population it could be a not so rare cause of gout [30].

Overproduction of UA may be acquired as a result of an excessive rate of cellular turnover and nucleic acid degradation. This is usually caused by myeloproliferative and lymphoproliferative disorders, hemolytic process and Paget's disease.

An important cause of overproduction of UA appears to be related to accelerated ATP metabolism and increased degradation to UA. This situation is observed in acutely ill patients, after streunous exercice and status epilepticus [15]. Myogenic hyperuricemia has been reported after ischemic exercise in glycogen storage diseases (types III, V, and VII) associated with metabolic myopathy. There is an impairment of ATP synthesis, thus, when ATP is consumed by muscle contraction, accelerated degradation of ATP to UA occurs [31].

The most important acquired causes of UA overproduction are listed on table 1.

Underexcretion

Most patients with primary hyperuricemia or gout have renal underexcretion of urate and no other demonstrable abnormality of renal function. About

70–90% of patients with primary gout excrete less than 600 mg and are defined as relative underexcretors. More than 50% of the tophaceous patients excrete less than 400 mg of UA in urine daily. At high plasma urate concentrations the proximal tubular cell of the underexcretor is unable to secrete as much UA as the overproducer. But at the plasma urate concentration of the less than 4 mg per 100 ml (induced by allopurinol), the (relative) underexcretor exhibits a secretory pattern similar to that of the overproducers and control [17].

The absence of significant sex-related differences in plasma and urinary purine concentrations suggests a similar tubular dysfunction for purine excretion in women and men with primary gout [32].

Monozygotic twins had more similar values of urate clearance and fractional excretion of urate than dizygotic twins. It is possible that genetic factors exert an important control on urate excretion, which determines some of the familiality of hyperuricemia and gout [33].

A dominantly inherited defect in renal tubular urate handling may be the most likely explanation in young patients with gout or hyperuricemia disproportionate to the renal dysfunction [34].

Renal disease of any etiology may lead to hyperuricemia because a urine flow rate of less than 1 ml/min is particularly associated with urate underexcretion. Acquired causes of underexcretion of UA are listed on table 1. The importance of some of these is due to their potential prevention or reversibility.

Pharmacological agents that alter renal tubular function also contribute to the underexcretion of urate. Diuretic therapy currently represents one of the most important causes of secondary hyperuricemia. Thiazide diuretics, and also furosemide, decreases UA secretion and enhances reabsorption by volume depletion. High doses of acetylsalicylic acid (more than 3 g/day) are uricosuric, whereas low doses (up to 1–2 g/day) cause UA retention. At the lowest dosage (75 mg/day), aspirin caused a 15% decrease in the rate of UA excretion in elderly patients. Hypoalbuminemia and concomitant treatment with diuretics enhanced these effects [35].

An accumulation of organic acids competitively inhibits UA secretion; through this mechanism, starvation, diabetic ketoacidosis and lactic acidosis contribute to hyperuricemia.

Alcohol ingestion results in hyperuricemia through the shift in balance between pyruvate and lactate, which reduces the renal excretion of urate. Alcohol ingestion is also associated with accelerated degradation of ATP and increased synthesis of UA. For those two reasons alcohol intake is strongly associated with an increased risk of gout.

Environmental toxins may cause hyperuricemia and lead is the best recognized.

The most important acquired causes of UA underexcretion are listed in table 1.

Radiology, Laboratory Features and Diagnosis

In acute gouty arthritis, the only radiographical abnormality may be soft tissue swelling around the affected joint. Definite articular abnormalities usually require multiple attacks over many years. Bone erosion seen in gout is due to tophi formed in situ and may occur within the joint or in para-articular location. The characteristic gouty erosion may have a sclerotic margin and classically show a 'punched out' appearence. In about a half of the patients with gouty erosions, an overhanging margin may be seen in either intra- or extra-articular location [36].

Leukocytosis, raised erythrocyte sedimentation rate and increased C-reactive protein concentration are all nonspecific indicators of inflammation and will be variably abnormal depending on the severity of gout. Hyperuricemia is essential for the development of gout but not always necessary for the diagnosis. Blood urate concentration cannot be relied on to confirm or exclude gout: in a small proportion of cases, it is normal during an attack but raised at other times. Inspite of the well-known and characteristic clinical pattern of a gouty arthritis and the presence of established clinical criteria [37], a definitive diagnosis requires the direct identification of monosodium urate crystals in the synovial fluid of inflammed joints [38].

Fresh synovial fluid or tissue should be examined under polarized light for the presence of urate crystals, which can usually be clearly distinguished from pyrophosphate crystals of pseudogout.

Clinical Features

The natural history of gout encompasses four stages: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout.

Asymptomatic Hyperuricemia

During this preclinical stage, serum urate level is elevated but no symptoms (arthritis, tophi, UA stones) occur. This stage ends at the moment of the first gouty attack.

Although it is well known that the risk of gout is directly proportional to serum UA level, hyperuricemia does not mean gout. Serum UA levels are commonly elevated in patients without gout and can be normal or even low in patients with gouty attack. In most instances gout comes first and usually after at least 20 years of sustained hyperuricemia [15].

Acute Gouty Arthritis

Classically, gout is thought to be a disease of middle-aged men. The first attack in 90% of the cases involves a single joint, that is, the first MTP joint in

more than 50% of patients [14]. The same joint is involved in about 90% of the patients in the course of the disease. Despite this, about 10% of patients may never experience podagra. In order of frequency of involvement, other joints are the instep, heel, ankle and knee, elbows, wrists, and fingers. Shoulders, hip and sacroiliac joints may also be rarely affected [20]. Gouty attack may involve not only joints but also periarticular structures like olecranon bursa and the Achilles tendon.

Thomas Sydenham's classic description of a gouty attack remains unequalled and as true today as it was in the 17th century:

> 'The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of dislocation … Then follows chills and shivers and a little fever. The pain, which was at first moderate, becomes more intense … So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room …' [15].

Redness overlying the affected part is a feature that sets gout apart from most other noninfective arthropathies. A mild attack resolves within one or 2 days, more severe within 10 days or several weeks. Subsequent attacks may affect the same joint or progress to involve other joints. Later in the disease the incidence of polyarticular attacks increases, sometimes with increase in systemic symptoms [16].

There are no obvious sequelae of an acute attack of gout apart from some desquamation overlyng the affected joint that may appear as the attack subsides.

Intercritical Gout

A natural course of recurrent acute gouty arthritis is, as a rule, increasing in frequency and severity. A significant majority of patients will have more than one attack. A second attack usually occurs within one year in about 60% of the patients, and in another 25% of the patients, after a year or two. In some, however, the attacks are always mild and infrequent [20].

Chronic Tophaceous Gout

As the disease progresses there is an incomplete resolution and shortening of symptom-free periods. The development of tophi is usually insidious. They are seldom observed in the first year after the initial attack of gouty artritis. Approximately 70% of patients remain nontophaceous at the end of 5 years. By 10 years, the number of nontophaceous and tophaceous cases is more or less equal. There are exceptions in some juvenile genetic forms with severe hyperuricemia [20].

Tophi, as a rule, are seen at the first MTP joint, at the olecranon, and in the articular synovium of tendon sheaths of the hand, and on the helix of the ear.

Tophi may entrap nerves, resulting in pain and paresthesias (e.g., carpal tunnel syndrome). Tophi may be associated with a destructive deforming arthritis of the hand and mimic rheumatoid arthritis. Tophi may ulcerate and exude white chalky material, so gout may be misdiagnosed as cellulitis or septic arthritis [10]. Rarely, gout and septic arthritis may coexist [39].

In other cases examination findings can be misleading and an ischemic foot, in a subacute phase, may be red and mimic gout [40].

Gout must be differentiated from pseudogout which is due to the shedding of pyrophosphate crystals from articular cartilage. In pseudogout the affected joints are more likely to be the knee, wrist, or shoulder.

Gout in the Young, in the Elderly and in Women

The young with gout pose different and difficult management problems. Onset before the age of 30 in a man and in any premenopausal woman should raise the question of a specific enzyme defect leading to marked purine overproduction or an inherited deficit in renal tubular handling [30]. Over 50% of the subjects with onset under the age of 25 have a positive family history and over 80% with age onset between 12 and 19 [41].

Gout in the elderly, because of its atypical presentation sometimes seems to be a separate entity. In elderly patients gout can present as chronic polyarticular disease, and in women multiple small joints of the hands are affected in 25% of the cases [42]. There is a predilection for tophi to form over the Heberden nodes in patients with concomitant osteoarthritis of the hands [43].

After menopause, serum UA level in women approach those of men; approximately half of the patients older than 60 years with newly diagnosed gout, will be women. Also, there is an increased female-male ratio in atypical gout [10]. A recent comparison with male patients showed that female patients were more frequently receiving diuretics and had significantly lower mean UA excretion. The clinical picture in women appears to be changing also because of the effect of renal transplantation and cyclosporine therapy [44].

Comorbidities Associated with Hyperuricemia

An epidemiological link between elevated serum UA level and cardiovascular (CV) risk has been recognized for many years. Multiple abnormalities have been associated with hyperuricemia, hypertension and increased cardiac morbidity and mortality [45], insulin resistance and obesity. Whether hyperuricemia plays a causal role or is a simple epiphenomenon is not completely understood.

Experimental studies demonstrate that UA is not inert but may have both, beneficial functions (acting as an antioxidant) as well as detrimental actions

(to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction) [46]. Paradoxically, potential benefits may be completely obscurated by detrimental effects [47].

During the xanthine oxidase activity, superoxide anion and hydrogen peroxide is generated. Hydrogen peroxide is converted to free hydrogen radicals, mediators of inflammation and tissue damage.

In humans, XO is found only in the liver and in the small intestine, but a very small amount is found in the endothelial cells, where it has been postulated to have a role in host defense against injury and microbial invasion. Uric acid's antioxidant properties, perhaps provided a survival advantage to early hominoids, but nowadays hyperuricemia may be directly injurious to the endothelium and to CV function and it is suspected to have a major role in the current cardiovascular disease epidemic [5].

In a large survey Italian study in untreated subjects with essential hypertension, UA was found to be a powerful marker for subsequent CV disease. After adjustment for confounding factors UA levels were associated with an increased risk for CV events and all-cause mortality [48].

The US National Health and Nutrition Survey (NHANES) III showed that age-adjusted rates of myocardial infarction and stroke are higher across increasing serum UA quartiles among male and female hypertensive patients [49].

In the MONICA cohort of 1,044 males, those with a more severe hyperuricemia had an adjusted risk for myocardial infarction and CV death increased significantly [50].

The Gothenburg prospective study [51] of 1,462 women aged 38–60 years also found a significant relationship between hyperuricemia and total mortality during the 12-year follow-up.

In a recent Italian population study [52], increased serum UA levels were found to be independently and significantly associated with risk of cardiovascular events in the 6-year follow-up.

Some studies have suggested that the importance of UA may be independent of confounding risk factors, some others have not.

In contrast to the findings of above, the British Regional Heart Study [53] of 7,688 men aged 40−59 years showed that the positive relationship between elevated serum UA and coronary disease disappeared after correcting for the other risk factors.

The Framingham Heart Study [54] conclusions indicate that UA does not have a causal role in CV risk and that any apparent association is probably due to the association of UA level with other risk factors.

Although there is an overwhelming evidence that elevated serum UA concentrations are strongly associated with increased CV risk and poor outcome, prospective population studies are often confounded by coexistent risk

factors. It remains unclear whether UA is an independent factor of poor CV outcome.

Hyperuricemia should alert physicians to the possibility of insulin resistance and may be added to the cluster of metabolic and hemodynamic abnormalities designated as Syndrome X [55].

In normal subjects, insulin decreases the urinary excretion of sodium, potassium, and UA. These renal effects of insulin are not altered in insulin-resistant hypertensive subjects [56]. Both hyperuricemia and hypertension may arise both as a consequence of enhanced renal insulin activity. Females seem to have a more strong association between UA level and insulin resistance than males [57].

Dietary intervention that enhanced insulin sensitivity may reduce or normalize serum UA level and reduce the frequency of gouty attack [58, 59].

A unifying hypothesis has been proposed that links hyperuricemia, low urinary UA excretion and decreased glucose utilization (insulin resistance). Hyperuricemia may represent the culmination of a multimetabolic syndrome in which insulin-mediated renal hemodynamic abnormalities lead to hypertensive renal damage. According to this hypothesis hyperuricemia in hypertensive subjects may represent an early indicator of hypertensive cardiorenal disease [49].

Management

The management of gout is appropriately divided among the treatment of acute attack and prevention of further attacks and joint damage.

Drugs effective in reducing acute gouty inflammation are, in general, of no value in controlling hyperuricemia. On the contrary, urate-lowering agents, while capable of ultimately reducing the frequency of acute attacks, have no value in the treatment of active gouty inflammation.

Treatment of Acute Attack

Early treatment (within 24 h) is the key to effective management of an acute gouty arthritis. Three options are available: nonsteroidal anti-inflammatory drugs, (NSAIDs), colchicine and corticosteroids.

NSAIDs may be the first choice for acute gouty attack and are very effective especially when used early. The use of these drugs is limited by their side effects, mainly gastrointestinal [60]. The presence of a diminished hepatic or renal function, hypertension, recent bleeding, peptic ulcer, advanced age or concomitant anticoagulant therapies are the most important contraindications.

Although indomethacin is commonly used, there is no good evidence that one NSAID is more efficacious than another.

Activation of phagocytosis is an early triggering event of gouty attack and constitutes an important source of the inducible isoform of cyclooxygenase (COX-2). For patients in whom the use of NSAIDs is contraindicated, an alternative could be the use of COX-2-selective agents. Etoricoxib, a recent COX-2-selective agent, has shown a similar efficacy to that of indomethacin in a head-to-head comparison [61, 62].

Colchicine is the oldest available treatment for gout. Acute gouty arthritis is a neutrophil-mediated inflammatory reaction. This drug has the ability to inhibit phagocytosis of urate crystals by neutrophil by interfering with the transport of phagocytosed material to lysosomes. Colchicine also inhibits crystal-induced COX-2 expression [63].

The drug is usually administered orally in a dose of 1 mg initially, followed by 0.5 mg every 2 h until abdominal discomfort or diarrhea develops [64].

Unfortunately, in patients with acute gout, the effective dose is close to that which causes gastrointestinal symptoms.

Low dosage of colchicine has recently been suggested for acute gouty arthritis, 500 mg three times a day or less frequently, especially in those with renal impairment [65].

For a monoarticular flare-up an intra-articular injection of corticosteroid is often the safest treatment [10]. An aspiration alone can sometimes greatly reduce the pain of gout [64].

Systemic corticosteroid therapy is usually administered only when NSAIDs and colchicine have failed. There are no convincing data that the use of adrenocorticotropic hormone is superior to corticosteroids [66].

Prophylaxis against Further Attacks

Prophylaxis is indicated during interval gout and at the onset of urate-lowering therapy. Acute attacks may be prevented by NSAIDs but small doses of colchicine are preferable because they clearly reduce the rate of recurrent acute attacks, whether or not the serum urate concentration is normal. The preventive effect of this drug may relate to its effect in reducing the baseline inflammation in asymptomatic joints [67]. Prophylaxis is usually continued until serum urate level has been maintained within normal range and there has been no acute attacks for a period of 3–6 months [15].

Correction of Hyperuricemia

There are three ways to undertake the prevention of gouty arthritis: the first way is to identify and correct the cause of hyperuricemia, the second way is prescribing a low-purine food diet, and the third way is represented by use of drugs that lower serum urate concentration. The major causes of and risk factors for acquired hyperuricemia and gout are shown in table 1.

Acquired hyperuricemia is most commonly related to factors that inhibit UA excretion by the kidney. In some cases this is the result of reduced glomerular filtration (renal insufficiency). Many conditions and medications lead to decreased tubular secretion of urate either directly or through the production of small anionic organic acids (ketones, lactic acid). Cyclosporine, used in organ transplantation and some autoimmune disorders, commonly leads to significant hyperuricemia and often tophaceous gout. Overproduction of urate is a less common cause of secondary gout. However, hematologic malignancies and cytolytic therapy lead to severe hyperuricemia.

Diuretic-induced gout is a multifactorial condition and occurs in patients in whom there is an additional cause of hyperuricemia, usually impaired renal function [68].

Aspirin is known to cause UA retention at low dosages. These findings call for clinician alertness to the use of mini-dose aspirin in the patient with gout [35].

A low-content purine diet is indicated in patients who habitually eat large amounts of purines, although diet does not usually contribute more than 1.0 mg/dl to lower serum urate concentration [64].

Higher levels of meat and seafood consumption are associated with an increased risk of gout, whereas a higher level of consumption of dairy products is associated with a decreased risk. Moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout [69].

Weight reduction with dietary measures, reported to be beneficial in insulin resistance, lowered the serum UA levels in gouty nondiabetic subjects [58].

Finally, the risk of gout is strongly associated with alcohol intake and varies substantially according to the type of alcoholic beverage. Beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk [70].

Reduction of serum urate levels to <6 mg/dl (<0.35 mmol/l) generally reduces the recurrence of gouty arthritis, but lower levels (<5 mg/dl, <0.29 mmol/l) may be necessary for resorption of tophi [37].

Drug treatment of hyperuricemia should be initiated in patients with frequent gout attacks, tophi or urate nephropathy [71].

The two choices of therapy for lowering UA levels are uricosuric drugs and XO inhibitors. The former increase the urinary excretion of urate, the latter block the final step in urate synthesis. There is some controversy in determining the treatment for each individual patient.

Allopurinol is the only inhibitor of XO in clinical use and is indicated principally for patients with established gout, particularly those who also have urolithiasis, because the prophylactic effect in both UA and calcium oxalate nephrolithiasis [72]. One can begin urate-lowering therapy with allopurinol

without measuring UA excretion in most patients, as this drug is effective regardless of the cause of hyperuricemia [71]. Allopurinol is effective in both overproducers and underexcretors of UA and is indicated for gout or hyperuricemia from renal insufficiency. Because institution of allopurinol may also precipitate acute gouty attacks, prophylaxis with colchicine is warranted.

If renal function is normal, the initial dose of allopurinol should be 100 mg/day, gradually increased to 300–400 mg with a maximum daily dose of 800 mg/day. Dose adjustments should be made in the setting of renal insufficiency. A dose of 300 mg/day is effective in 85% of patients. Tophi begin to dissolve 6–12 months after serum UA is decreased to 5–6 mg/dl or less. The metabolism of purine synthesis inhibitors 6-mercaptopurine or azathioprine is inhibited by allopurinol so that the dosage must be reduced to 25% of the usual dose with concomitant allopurinol therapy [73].

Adverse effects of allopurinol are seen in 20% of the patients, and half of these require discontinuation of the medication. The most common side effects are skin rash, gastro-intestinal distress, diarrhea, headache and interstitial nephritis. The most feared adverse reaction is hypersensitivity syndrome associated with fever, bone marrow suppression, hepatic toxicity, renal failure and a systemic hypersensitivity vasculitis. Fortunately, this life-threatening syndrome is rare [74].

Uricosuric drugs are a suitable approach to the patients with gout who show underexcretion of urate. The main risk associated with these drugs involves the increase in the urinary excretion of urate that occurs soon after the initiation of the therapy. This fact contributes to the formation of uric acid crystals in urine that is the cause of renal colic and deterioration of renal function.

In general the candidate for uricosuric agents is a patient younger than 60 years of age, with normal renal function and UA excretion less than 700 mg/24 h, and no history of renal calculi [15].

Probenecid and sulfinpyrazone are the commonest uricosuric drugs.

The former is actively secreted in the proximal tubule and prevents reabsorption of urate. The dose should be titrated according to serum UA level beginning with 250 mg twice a day, increasing to a maximum of 1–3 g/day in order to reduce the serum UA to <6 mg/l. The effect of probenecid is blocked by low-dose aspirin.

Sulfinpyrazone also has the property to inhibit platelet aggregation and may be helpful in patients with coronary artery disease. Initial dose should be 100 mg/day in two divided doses increasing gradually to a usual dose of 300–400 mg/day and maximum doses of 800 mg/day [73].

Most recently, the angiotensin-receptor blocker losartan has been shown to reduce serum UA [75]. The findings of the recent LIFE study [76] suggest the possibility that a treatment-induced decrease in serum UA may indeed attenuate cardiovascular risk.

The combined hypouricemic effect of losartan and fenofibrate should be another option recently offered to treat gout in patients with hypertriglyceridemia and/or hypertension [77].

Recombinant urate oxidase may be a further option for the management of hyperuricemia and gout. Although a dose-dependent fall in serum urate occurred, the feasibility of long-term use of this drug will depend upon how immunogenic it is. Further studies are needed to address this issue [78].

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Inherited Hyperuricemic Disorders

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Abstract

Inherited hyperuricemic disorders fall into two major classes, metabolic overproduction of purines and renal tubular undersecretion. The aim was to explore both. Methodology was a combination of personal experience and review of relevant literature. The overproduction of hyperuricemias result from deficiency of hypoxanthine-guanine phosphoribosyl transferase, overactivity of phosphoribosylpyrophosphate synthetase and deficiency of glucose-6-phosphatase. The undersecretion disorders are autosomal dominantly inherited and are heterogeneous. A major number of these patients result from mutations in the gene that codes for uromodulin. Treatment is with allopurinol.

Lesch-Nyhan Disease

Lesch-Nyhan disease is an X-linked disorder of purine metabolism, caused by an almost complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT) (fig. 1). First described as a syndrome in 1964 [1, 2], it is the most common of the inherited disorders of purine metabolism and the most common cause of hyperuricemia in infancy and childhood. HPRT catalyses the recycling reaction in which the free purine bases hypoxanthine and guanine are reutilized to form their respective nucleotides, inosinic and guanylic acids. This purine salvage mechanism provides an alternative and more economical pathway to de novo purine nucleotide synthesis. Uric acid is the end product of purine metabolism. In the absence of the salvage pathway, excessive amounts of uric acid are produced.

The molecular defect is the virtually complete absence of activity of HPRT enzyme [3]. The disease is usually fully recessive expressing only in males but a small number of females with the classic phenotype has been identified, predominantly reflecting nonrandom inactivation of the normal X chromosome

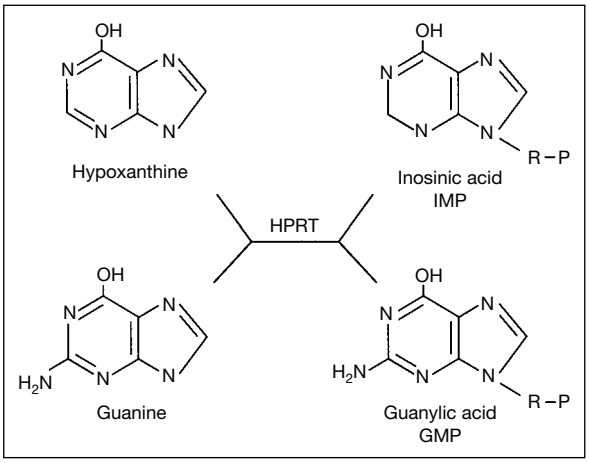

Fig. 1. The hypoxanthine-guanine phosphoribosyl transferase (HPRT) reaction. This enzyme is the molecular defect in the Lesch-Nyhan disease. GMP = Guanylic acid; IMP = inosinic acid.

[4]. The disease frequency approximates one in 380,000 births [5]. The gene was cloned in 1982 by Jolly et al. [6]. A large number of mutations has been defined [7].

Clinical Characteristics

Infants with Lesch-Nyhan disease appear normal at birth and usually develop normally for the first 6–8 months. The first manifestation is usually a consequence of hyperuricemia, the occurrence of large quantities of what appears to be orange sand in the diaper. Unaccountably, this is usually ignored until the developmental delay becomes obvious, or often much later until the onset of self-injurious behavior.

Ultimately, these patients develop dystonia, choreoathetosis, spasticity, hyperreflexia and extensor plantar reflexes. The overall motor defect is of such severity that patients can neither stand nor sit unassisted. No patient with this disease has learned to walk. Caregivers learn to secure the patient at the waist and chest, which permits wheelchair mobility and participation in the world around him (fig. 2). Most patients are cognitively impaired, but mental retardation is difficult to assess because of the behavioral disturbance and motor deficits. Many patients learn to speak, but athetoid dysarthria makes their speech difficult to understand.

Self-injurious behavior is the hallmark of the disease and occurs in 100% of patients with the classic disease. The most characteristic feature is self-destructive biting of hands, fingers, lips, and cheeks.

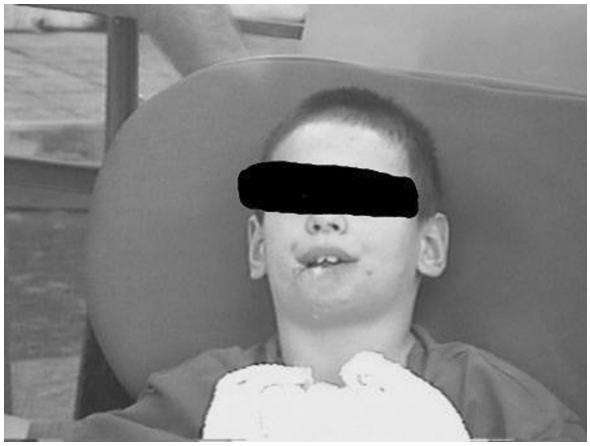

Fig. 2. A patient with the Lesch-Nyhan disease illustrating the loss of tissue about the mouth that resulted from biting.

Hyperuricemia and its Consequences

Hyperuricemia is present in almost all patients. Levels usually range from 5 to 10 mg/dl. Occasionally, a very efficient renal excretor is found in whom the level is normal. Thus, the plasma uric acid is not an appropriate way to exclude metabolic uric acid overproduction. The excretion of uric acid is 3–4 mg of uric acid per mg creatinine (1.9 ± 0.9 mmol/mol creatinine) [8]. Normal children excrete less than 1 mg uric acid/mg creatinine. The consistent finding of this elevated uric acid to creatinine ratio and its relative ease of measurement usually makes it a useful initial screening test for this and other metabolic hyperuricemic diseases [8]. Urinary data for uric acid can be spuriously low as a result of bacterial contamination and 24 h collections at room temperature are especially suspect. The clinical results of the accumulation of large amounts of uric acid in body fluids are the classical manifestations of gout.

Biochemical and Molecular Features

HPRT (EC 2.4.2.8) is a cytoplasmic enzyme expressed in every cell of the body. Highest levels are found in the basal ganglia and testis. The defect is detectable in erythrocyte hemolysates and in cultured fibroblasts. It is most readily measured in red cell lysates in which quantitative assays yield virtual zero activity [9].

The HPRT gene is located on the long gene arm of chromosome X (Xq26–37). The sequence of the gene spans more than 44 kb; the coding region consists of 654 nucleotides in 9 exons. The protein contains 218 amino acids.

Characterization of the molecular defect in the HPRT gene of a number of HPRT-deficient patients has revealed a heterogeneous pattern of mutations, with the same alteration rarely being found in unrelated pedigrees [7]. About 63% of described molecular alterations represent point mutations which yield amino acid substitution in the protein sequence or stop codons, which lead to truncated proteins. In some instances, a point mutation alters a splice site consensus sequence, activating an alternative, cryptic splice site, creating aberrant mRNA and protein products. Genotype/phenotype correlations have been elusive, but major mutations that completely disrupt HPRT enzyme function (stop codons, deletions or insertions) are usually associated with the classical Lesch-Nyhan phenotype, while variant HPRT phenotypes (v.i) are found in patients with point mutations, usually conservative amino acid substitutions.

Treatment

The excessive uric acid production in HPRT-deficient patients is effectively treated with daily administration of allopurinol. This is the unique and specific treatment available for all the patients diagnosed with HPRT deficiency, both classical Lesch-Nyhan and variants. Unfortunately, no medication has been found to be consistently effective in treating the neurological or behavioral manifestations of the disease in classical Lesch-Nyhan patients. The only successful approaches to the self-injurious behavior have been physical restraint and the removal of teeth, to prevent self-biting. Future approaches may include gene therapy; promising results have already been obtained in vitro.

HPRT Variants

Following the recognition that the defect in Lesch-Nyhan disease was in HPRT, enzyme deficiency was found in patients with gout [10] and with urinary tract calculi [11]. Initially, it was thought that this population of patients with HPRT deficiency might be quite large, but this is not the case. Most patients with HPRT deficiency have Lesch-Nyhan disease, and most patients with gout do not have HPRT deficiency. Of course, most patients with gout do not have overproduction of purines, or increased urinary excretion of uric acid, but even among those that do, HPRT deficiency is not frequently encountered. Nevertheless, a specific diagnosis is always to be desired, and in this situation it can influence not only therapy but also the genetic evaluation of the family. Any patient with gout should be studied for the possibility of increased excretion of uric acid, because the treatment of such a patient with a uricosuric agent such as probenecid can induce fatal renal shutdown. Assay for HPRT deficiency should be undertaken in any patient with overproduction hyperuricemia. The enzyme should also be assayed in any patient with uric acid calculi. In an

Table 1. Spectrum of deficiency of HPRT

	HPRT activity	Clinical features
Classic Lesch-Nyhan disease	Virtually 0 under any conditions	Lesch-Nyhan syndrome
Neurological variants	Essentially 0 in RBC assay Unstable or altered kinetics 1.5–8% activity in intact cell assay	Spasticity, choreoathetosis, good mental functions, normal behavior, hyperuricemic manifestations
Partial variants	0–50% in RBC assay >8% activity in intact cell assay	Gout or nephrologic complications, neurologically normal

infant or child with renal stones, it may be easier to obtain an assay of HPRT than of the nature of the calculus, especially since so many calculi are lost.

Some variant enzymes display some residual activity in the erythrocyte assay, often more than 5% of control, making them readily distinguishable from the classic Lesch-Nyhan pattern, a distinction that is particularly important in assessing prognosis in a newly diagnosed young infant. These patients have been referred to as partial variants (table 1). However, many patients with variant clinical phenotypes have zero activity in the erythrocyte assay, and such patients also display no activity in fibroblast lysates.

Distinctions among variants became possible with the development of methodology for the assessment of enzyme assay in intact cultured fibroblasts [12]. This assay remains the gold standard for the distinction of classic Lesch-Nyhan patients from variants. There is a rough inverse relationship between the severity of clinical manifestations and the amount of residual activity observed in the intact cell assay [12]. To carry out the assay, cultured fibroblasts are incubated with ^{14}C-hypoxanthine, the products are separated by high performance liquid chromatography, and the total number of picomoles of isotope incorporated into purine compounds is expressed per nanomole of total purine compounds. The method permits the assessment of the kinetic properties of HPRT. The K_m for hypoxanthine found in normal fibroblasts was identical to that of the purified human enzyme, and a number of kinetic variants has been reported [13]. Patients with Lesch-Nyhan have displayed activity below 1.5% of normal and the classic partial variants all had greater than 8% of control activity.

The phenotype of patients with these partial variants of enzyme consists of manifestations that can be directly related to the accumulation of uric acid in body fluids, acute attacks of gouty arthritis, tophi, and renal and urinary tract complications. The central nervous system and the behavior are normal.

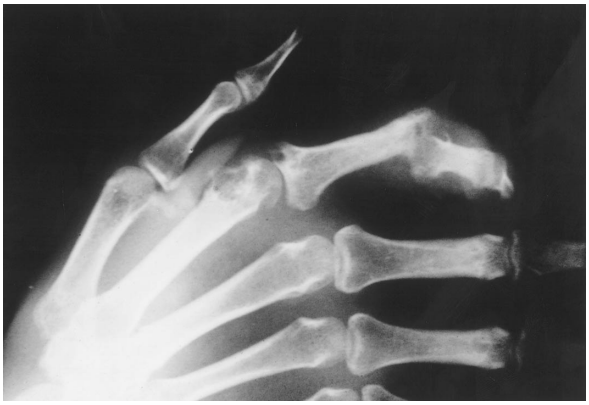

Fig. 3. Tophaceous gout in a 24-year-old with previously undiagnosed Lesch-Nyhan disease [14]. He came to clinical attention and diagnosis after developing septicemia following the breakdown of the skin over tophaceous deposits about the knee.

In addition to these two populations of HPRT deficient patients, the classic Lesch-Nyhan variants and the classic partial variants, it became evident that there was a third group, and these patients had an intermediate level of enzyme activity in the whole cell assay. We have called these intermediate patients, neurologic variants (table 1). This small but important group of patients is usually characterized by a neurological phenotype that is identical to that of the classic Lesch-Nyhan patient with spasticity dystonia and choreoathetosis. They are confined to wheelchairs and are unable to walk. However, their behavior is normal and intelligence is normal or nearly normal. Among the variants studied, one patient with a classic Lesch-Nyhan phenotype and 1.4% of control activity could be distinguished from other Lesch-Nyhan variants by the more normal behavior of his cells in selective media [14].

Another phenotype with 7.5% of residual activity in the intact cell assay and a different neurological picture was observed in a family whose HPRT variant we have called $HPRT_{Salamanca}$ [15]. Four males in 3 generations had an identical phenotype, the most prominent feature of which was spastic diplegia. They all could walk, but gait was classically spastic. Hypertonicity and brisk deep tendon reflexes were more prominent in the lower extremity. Babinski responses were positive bilaterally. There was bilateral pes cavus and exaggerated lumbar lordosis. Mental retardation was mild. Tophaceous gout appeared by 32 years in a previously untreated patient.

In variant patients, missense mutations have been the rule, and the changes have been conservative. In the original patient of Catel and Schmidt [16] and Bakay et al. [17] the mutation changed a valine to a glycine [18],

which would not be expected to make a major difference in protein structure. Others had changes such as an isoleucine to a threonine. In these patients and in the partial or hyperuricemic variants, no deletions, stop codons or major rearrangements were observed. In $HPRT_{Salamanca}$, there were two mutations: a T-to-G change at position 128 and a G-to-A at 130. These changes resulted in the substitution of two adjacent amino acids at position 43 and 44: methionine to arginine and aspartic acid to asparagine. These would not appear to be particularly nonconservative, but the phenotype was probably the mildest of the neurological variants observed. They may have reflected another observation that the milder mutations have tended to cluster at the amino terminal end of the enzyme. Point mutations in Lesch-Nyhan patients have been more likely to be sited in areas important to substrate binding and catalytic activity.

Phosphoribosylpyrophosphate (PRPP) Synthetase Overactivity

Mutant phosphoribosylpyrophosphate (PRPP) synthetase in which activity is greater than normal, leads to a syndrome of hyperuricemia and uricosuria [19]. The expected complications include hematuria, crystalluria, urinary tract calculi, nephropathy and gouty arthritis. In some kindreds there has been sensorineural deafness [20, 21].

Clinical Characteristics

In this disease hyperuricemia and uricosuria are invariant. Any of the clinical consequences of the accumulation of uric acid in body fluids may result. Gouty arthritis has been reported with onset as early as 21 years of age [19]. Renal colic has been observed, as well as the passage of calculi [22]. One boy developed hematuria at the age of 2 months and was found to have crystalluria, hyperuricemia and uricosuria [23]. In families in which clinical onset is early, females may develop symptoms prior to menopause [24].

Deafness in some families has been associated with severe neurodevelopmental retardation [21]. One of our patients [20] was thought to be mentally retarded, and his behavior was thought to be autistic, but with time it was apparent that he was deaf, and his behavior was quite appropriate.

Hyperuricemia and its Consequences

Increased amounts of uric acid in the blood and urine are the rule, and concentrations in serum may range from 8 to 12 mg/dl [19, 20]. In the initial proband [19], uric acid excretion was 2,400 mg per 24 h. Urinary excretion may range from 1.8 to 3.3 mg/mg creatinine. Overproduction of purine de novo has

been documented by measuring the in vivo conversion of ^{14}C-glycine to urinary uric acid [20].

The enzyme defect is an altered PRPP synthetase structure, which leads to superactive enzyme activity. Activity may be three times that of the normal enzyme [22–24]. The amounts of immunoreactive enzyme protein may be normal. These observations indicate the presence in normal amounts of a protein in which structural alteration leads to increased specific activity. The data are consistent with the presence of two important sites on the enzyme: a catalytic site which may be altered by mutation and a regulatory site, which may be altered by another, or altered structure may affect both catalytic and regulatory activities [25].

The altered PRPP synthetase, though hyperactive, may also be unstable. Diminished levels in old erythrocytes may be low or normal. Therefore, enzyme assay of erythrocyte lysates in this disease may be misleading [25].

Intact cultured fibroblasts in this disease incorporate purines, adenine, guanine and hypoxanthine, more rapidly into nucleotides than do controls [25], and incorporation of ^{14}C labeled formate is also accelerated. These findings indicate the presence of increased intracellular concentrations of PRPP, and this may be the most reliable method of screening for the disease.

Biochemical and Molecular Features

PRPP synthetase (EC 2.7.6.2) catalyzes the initial step in the de novo synthesis of purines in which ribose-5-P reacts with ATP to form PRPP. PRPP is the substrate for the first rate-limiting step in the 10-step reaction. Increased quantities of intracellular PRPP lead to overproduction of purine de novo which ultimately yields IMP and of uric acid. PRPP synthetase is coded for by two genes on the X chromosome at Xq22–24 and Xp22.2–22.3 [26]. The genes have been cloned and sequenced [27] and referred to as PRPS1 and S2. A small number of point mutations has been defined in PRPS1 in patients with overactivity and altered allosteric properties of the enzyme. In 6 patients with overactivity of PRPP synthetase, no mutations in the cDNA of PRPS1 or S2 were found; instead there were increased quantities of the S1 isoform whose physical and catalytic properties were normal [28].

The S1 isoform of PRPP synthetase, while coded for by a gene on the long arm of the X chromosome [28] may be fully recessive or may be expressed in the heterozygous female. This could reflect different degrees of lyonization. On the other hand, it is easier for an overactive enzyme than the more common deficient one encountered in inborn errors to function as an X-linked dominant.

Treatment

Allopurinol is the treatment of choice in any overproduction hyperuricemia including the PRPP synthetase defects. Treatment of abnormalities in

PRPP synthetase is simpler than that of HPRT deficiency because in the presence of normal HPRT activity, there is extensive reutilization of hypoxanthine accumulating behind the block in xanthine oxidase, leading to a substantial decrease in the overall excretion of oxypurines in the urine. In contrast, in HPRT deficiency, there is simple substitution of hypoxanthine or xanthine for uric acid, and the total oxypurine excretion does not change.

Hearing should be tested promptly and appropriate intervention provided.

Glycogen Storage Diseases

Hyperuricemia and typical clinical gout occur in teenagers and adults with glycogenosis type I (Von Gierke disease) due to defective activity of glucose-6-phosphatase [29]. The mechanisms responsible for the hyperuricemia include overproduction of purine de novo [29], but also diminished clearance of uric acid resulting from competition for tubular secretion by lactic acid, 3-hydroxybutyric acid and acetoacetic acid [30].

Hyperuricemia may also be encountered in type III glycogenosis in which there may be clinical myopathy, as well as in type V and type VII, but these patients do not have gout. The mechanism is abnormal metabolism of glycogen in muscle, in which carbohydrate substrates are inadequate for ATP synthesis, and its breakdown leads to purine excess and conversion to uric acid [31].

Clinical Characteristics

In classic type Ia glycogen storage disease, symptoms may be recognized at birth. Neonatal hypoglycemia is a major manifestation. Hepatomegaly is usually at birth and progresses to huge enlargement of the liver without splenomegaly.

Many infants present with vomiting or convulsions in the morning.

In addition to hypoglycemia, a variety of chemical abnormalities are classic. Lactic acidemia is a regular feature of the disease. Marked hyperlipidemia and hypercholesterolemia are also features. The hyperlipidemia leads not only to the formation of xanthomas, but also to large lipid-laden reticuloendothelial cells in the bone marrow. The plasma may be milky. Ketosis and ketonuria occur promptly with minimal degrees of fasting. This and the lactic acidosis concomitantly may lead to metabolic acidosis. Hyperuricemia is present from infancy, but clinical gout does not appear until adolescence [29]. Decreased clearance of uric acid does not occur in all patients [32]. Studies of uric acid production have indicated increased purine synthesis in this disease [29, 33, 34].

Chronic renal tubular and glomerular disease are late complications of glycogenosis I. They are independent of hyperuricemia.

Biochemical and Molecular Features

The molecular defect in glycogenosis I is defective activity of glucose-6-phosphatase. The enzyme is normally expressed only in liver, kidney and in β cells of pancreatic islets. The diagnosis is usually made by assay of biopsied liver.

The cDNA for human hepatic glucose-6-phosophatase has been cloned and a number of mutations has been identified [35]. These include an arginine-to-cysteine change at amino acid 83 (R83C) and Q347X. Assay for common mutations permits diagnosis without liver biopsy.

Treatment

Allopurinol is the treatment of choice for hyperuricemia.

Renal Hyperuricemia

Among adults with gout, the mechanism for hyperuricemia is not overproduction, but diminished renal excretion of uric acid in at least 80% of patients [36]. This may be described as excretion of less than 250–300 mg of uric acid by a hyperuricemic adult ingesting a purine-free diet. Renal clearances of uric acid are low. The mechanism appears to be diminished renal tubular secretion of uric acid [37–40]. Decreased secretion may be demonstrated by the response to the uricosuric drug benzbromarone, which inhibits reabsorption of secreted uric acid.

Uric acid is filtered freely at the glomerulus, and nearly all is reabsorbed before the distal convoluted tubule. The majority of uric acid in the urine is the result of secretion. Secretion and post secretory reabsorption are thought to occur in the proximal tubule. The minimal rate of tubular secretion of uric acid has traditionally been assessed by determining the response to pyrazinamide (PZA). Its product, pyrazinoic acid inhibits uric acid excretion [41]. In a family with dominantly inherited hyperuricemia and gout, we observed normal responses to PZA [42]. These patients had a brisk uricosuric response to probenecid, suggesting that the mechanism for decreased excretion of uric acid in these families was enhanced tubular reabsorption of uric acid. Gutman et al. [43] were also unable to identify defective tubular secretion in a series of patients with gout.

Clinical Characteristics

Patients with renal hyperuricemia have all of the clinical consequences of hyperuricemia including tophaceous gout, renal calculi and urate nephropathy [42]. Genetic transmission is autosomal dominant.

A syndrome of familial juvenile hyperuricemic nephropathy (FJHN [MIM 162000]) is an autosomal dominant disorder in which abnormal renal tubular

excretion of uric acid and gout are associated with the late development of interstitial nephritis and progressive renal failure [44–46].

Biochemical and Molecular Features

An interesting new mechanism for hyperuricemia has been recently discovered in FJHN [45, 46]. Histopathologic findings in FJHN raised similarities with autosomal dominant medullary cystic kidney disease (MCKD [MIM 174000]). MCKD was mapped to chromosome 16p12 in an Italian family [47]. This was then designated $MCKD_2$ (MIM 603860) and the MCKD linked to chromosome 1q21, $MCKD_1$. FJHN was then linked to 16p12 in a Belgian family [48], and Hart et al. [49] found the gene for FJHN and identified a number of mutations. The gene has been designated *UMOD*, because it codes for uromodulin protein, and this is the same as the Tamm-Horsfall protein, the most abundant protein in normal urine and a major component of urinary casts; it was originally characterized as an inhibitor of viral hemagglutination.

In patients with FJHN, a number of mutations has been identified in *UMOD*, most of them missense. Apparently, they code for umodulin proteins which are not found in the urine; rather they accumulate in renal tubules, which become dilated, distorted and cystic, the appearance of MCKD. A common mechanism has been discovered for hyperuricemia and for nephropathy. Mutations in *UMOD* appear to be the most common cause of FJHN [46]; it is also clear that there are other causes of FJHN, and that $MCKD_1$ is a different disease.

The gene for the urate-anion exchanger integral to the proximal tubular reabsorption of uric acid has been identified as *URAT*1. Mutations in this gene on chromosome 11p13 have been identified, and they cause uricosuria and hypouricemia [50, 51].

Treatment

Allopurinol remains the drug of choice.

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Pharmacology of Drugs for Hyperuricemia

Mechanisms, Kinetics and Interactions

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Abstract

The pharmacological profile of drugs for hyperuricemia is reviewed. These agents may reduce the amount of uric acid in blood by means of two different ways: (1) by reducing uric acid production through the inhibition of the enzyme xanthine oxidase (as allopurinol); (2) by increasing uric acid clearance through an inhibition of its renal tubular reabsorption (as probenecid), or through its metabolic conversion to a more soluble compound (as urate oxidase). Allopurinol is rapidly converted in the body to the active metabolite oxypurinol whose total body exposure may be 20-fold greater than that of the parent compound due to a much longer elimination half-life. Allopurinol undergoes several pharmacokinetic interactions with concomitant administered drugs, some of which may be potentially hazardous (especially with mercaptopurine and azathioprine). Probenecid is an uricosuric agent which undergoes extensive hepatic metabolism and whose elimination after high doses may become dose dependent. It may inhibit renal tubular secretion of several coadministered agents, including methotrexate and sulphonylureas. Rasburicase is a recombinant form of the enzyme urate oxidase which catalyzes the conversion of uric acid to the more soluble compound allantoin. Unlike allopurinol, it does not promote accumulation of hypoxanthine and xanthine in plasma, thus preventing the risk of xanthine nephropathy. Rasburicase showed no significant accumulation in children after administration of either 0.15 or 0.20 mg/kg/daily for 5 days. Rasburicase probably undergoes peptide hydrolysis and in in vitro studies was shown neither to inhibit or induce cytochrome P450 isoenzymes nor to interact with several drugs, so that no relevant interaction is expected during cotreatment in patients.

Introduction

Uric acid represents the terminal compound of the catabolic pathway of purine nucleotides which is renally eliminated, but is poorly water soluble at acidic pH due to its low pKa (5.4). Hyperuricemia is a condition which may appear because of a major increase in purine metabolism subsequent to the rapid lysis of malignant cells occurring in patients with large tumour burden, both spontaneously and after aggressive chemotherapy. Additionally, it may also occur as a consequence of an impairment of uric acid renal clearance, as in patients with kidney diseases or iatrogenic adverse events. This metabolic complication may be potentially dangerous since uric acid, by precipitating in renal tubules, may cause acute renal failure. Accordingly, drugs for hyperuricemia are used with the intent of lowering the amount of uric acid in blood, and this may be obtained by means of two different ways: the first is by reducing the production of uric acid through the inhibition of the enzymatic pathway converting its precursors, as in the case of allopurinol; the second is by increasing uric acid clearance, either by enhancing its renal elimination, as in the case of probenecid, or by facilitating its metabolic conversion into a more water-soluble compound, as in the case of urate oxidase.

Allopurinol

Allopurinol is a structural analog of the natural purine base hypoxanthine which may be used to reduce the production of uric acid.

Mechanism of Action

Allopurinol interferes with the catabolism of purines by inhibiting the activity of the enzyme xanthine oxidase which catalyzes the conversion of both hypoxanthine to xanthine and xanthine to uric acid (fig. 1). Interestingly, allopurinol is not only a blocker, but also a substrate of xanthine oxidase, and the deriving metabolite, oxypurinol, is a potent inhibitor of xanthine oxidase itself and may be considered responsible for much of its pharmacological effect [1, 2]. The inhibition of uric acid production lowers its plasma and urinary levels and favors the formation of its precursors hypoxanthine and xanthine. However, it should be noted that whereas hypoxanthine is more water soluble, on the other hand xanthine is even less soluble than uric acid [3], so that allopurinol use may potentially increase the risk of precipitation of xanthine in renal tubules [4]. Indeed, this potential risk of xanthine nephropathy during allopurinol therapy seems moderate, as suggested by the few cases reported in literature [5–9].

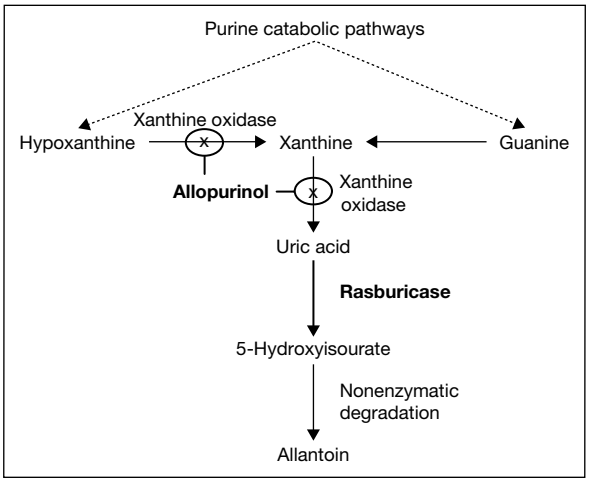

Fig. 1. Mechanisms of action of drugs for hyperuricemia.

Pharmacokinetics

Allopurinol may be administered either orally or intravenously. Oral bioavailability ranges between 67 [10] and 90% [11] with a peak plasma concentration (C_{max}) occurring within one hour and a volume of distribution of 1.6 liter/kg [10]. Allopurinol is rapidly metabolized in the liver by oxidation to the active compound oxypurinol, whose C_{max} occurs within 3–5 h [11]. Neither allopurinol nor oxypurinol are significantly plasma protein bound. Mean elimination half-lives ranges 0.67–1.5 h for allopurinol [12] and 18–40 h for oxypurinol, [10–13] so that during multiple administrations the area under the plasma concentration-time curve (AUC) for oxypurinol may be 20-fold greater than those of allopurinol [13]. Oxypurinol is the main species excreted in the urine (about 70%), whereas the parent compound represents only a minor part (about 12%), and hence, oxypurinol being pharmacologically active, the dosage of allopurinol must be reduced according to creatinine clearance in the presence of renal impairment. Interestingly, in a recent study it has been demonstrated that the pharmacokinetics of allopurinol may change according to aging [14]. After a single 200 mg oral dose, C_{max} was significantly lower for allopurinol (0.64 vs. 1.24 μg/ml) and higher for oxypurinol (5.63 vs. 3.75 μg/ml) in the elderly (n = 10) than in the young (n = 9) subjects. AUC of allopurinol were comparable in the two populations (4.46 vs. 4.38 μg/ml.h), but a much higher total body exposure to oxypurinol was found in the elderly (260 vs. 166 μg/ml.h). This was consistent with a total clearance of similar extent for allopurinol in the two groups (15.7 vs. 15.7 ml/min/kg), but lower for oxypurinol in the elderly (0.24

Table 1. Major drug-drug interactions of agents for hyperuricemia

Drug	Interacting drug
Allopurinol	Mercaptopurine, azathioprine, mycophenolate mophetil, cyclosporin, aluminum hydroxide, theophylline, warfarin
Probenecid	Penicillins, cephalosporins, sulphonylureas, methotrexate, acyclovir, ganciclovir, furosemide, acetominophen, zidovudine, lorazepam, olanzapine
Rasburicase	None known

vs. 0.37 ml/min/kg). Renal clearances of both allopurinol and oxypurinol were decreased in elderly versus young subjects. In both groups, the elimination half-life of oxypurinol (26.65 vs. 26.65 h) was much longer than that of allopurinol (1.54 vs. 1.61 h). The authors concluded that this increased exposure to oxypurinol in the elderly might be responsible for the higher allopurinol toxicity sometimes occurring in the old age.

Drug Interactions

Clinically relevant interactions (table 1) between allopurinol and the chemical analogs of the endogenous purines mercaptopurine and azathioprine have been reported. Mercaptopurine is an anti-neoplastic agent chiefly used in the treatment of acute lymphoblastic leukemia which is metabolized by both thiopurine methyltransferase and xanthine oxidase to inactive metabolites [15]. By inhibiting xanthine oxidase at both the intestinal and the hepatic level, oral allopurinol was shown to cause a marked increase in oral bioavailability of mercaptopurine [16], so that after oral concomitant administration a 4-fold increase in C_{max} and a 5-fold increase in AUC of mercaptopurine was documented [17]. Since this increased systemic exposure to mercaptopurine may lead to severe myelotoxicity and even to death [18–21], allopurinol should be avoided in patients receiving mercaptopurine or, if this is not possible, the dosage of mercaptopurine should be reduced by 75%.

Likewise, severe myelotoxicity may occur even during cotreatment with the immunosuppressive agent azathioprine, which is extensively metabolized to mercaptopurine in the body. Since several cases of toxicity due to systemic overexposure to azathioprine during concomitant administration of allopurinol were reported in the literature [20, 22–27], the coadministration should be avoided or, if this is not possible, the dosage of azathioprine should be reduced by 66%. Interestingly, Cummins et al. [28] in 1996 showed that in a cohort of 24 heart and/or heart-lung transplant patients receiving allopurinol coadministered with azathioprine, despite detailed prescribing guidelines informing

physicians about this potential interaction, the recommended dosage reduction was applied in only 58.3% of cases and a clear relationship between lack of azathioprine dosage adjustment and leukopenia was observed. These findings led the authors to further strengthen the opportunity of reducing azathioprine in patients receiving allopurinol and to suggest that this association should be used only when absolutely necessary. Likewise, very recently it has been hypothesized that bone marrow suppression might be aggravated by using allopurinol in combination even with other immunosuppressive agents which may interfere with purine biosynthesis, namely mycophenolate mophetil, so that their coadministration should be avoided [29].

Some evidences suggest that allopurinol may increase cyclosporin concentrations in patients who received these drugs in combination [30–33], so that in order to avoid cyclosporin-related nephrotoxicity close therapeutic drug monitoring of this immunosuppressive agent has been recommended in these circumstances.

It has been suggested that aluminum hydroxide may interfere with the absorption of allopurinol [34], so that oral allopurinol should be administered at least one hour before or more than 2 h after antacid preparation containing aluminum hydroxide.

Other drug-drug pharmacokinetic interactions involving allopurinol have been reported in the literature, but their clinical evidence is still limited. The coadministration of allopurinol with theophylline may lead to a significant rise of theophylline concentrations [35, 36], and this interaction should be suspected whenever theophylline levels change according to initiation or discontinuation of allopurinol. Likewise, it has been pointed out that allopurinol may interfere with the metabolism of warfarin [37], so that, since an increased anti-coagulation may occur, prothrombin time should be monitored during concomitant administration.

Probenecid

Probenecid is an old drug originally used to delay the renal elimination of penicillin at the time when this antibiotic was introduced in therapy [38].

Mechanism of Action

As an uricosuric agent probenecid acts by competitively inhibiting the renal tubular transport, even if the exact mechanism of action is still unknown. It is believed that the probenecid-related inhibition of the anion exchanger in the renal tubules may substantially reduce the tubular reabsorption of uric acid, and at the same time may also reduce the tubular secretion of some other compounds [39]. As a consequence, the net urinary excretion of uric acid is increased.

Pharmacokinetics

Probenecid is administered orally and its bioavailability is almost complete [40]. It distributes largely through the body and is about 75–90% plasma protein bound [40]. Probenecid undergoes extensive hepatic metabolism through glucuronidation and oxidation-dealkylation [41] and most of its metabolites are pharmacologically active. Its clearance may become dose-dependent at high doses, as documented by the mean terminal half-life increasing from 2–6 h after 0.5–1 g to 4–12 h after 2 g [40, 42, 43]. Probenecid is mainly eliminated through the renal route (about 90%), but only 5–10% in the form of unchanged drug.

Drug Interactions

Probenecid may undergo several pharmacokinetic interactions (table 1) during concomitant administration of other drugs. Most of these interactions are due to its ability in inhibiting the renal tubular secretion/reabsorption processes. Probenecid may reduce the renal tubular secretion of some penicillins [38] and cephalosporins [44–50], and this effect has been used in the past to prolong the permanence of these antibiotics in the body. Potentially hazardous interactions because of the probenecid-induced reduction in renal clearance may occur with sulphonylureas (risk of hypoglycemia) [51], but especially with methotrexate (risk of myelotoxicity and mucositis) [52], so that their concomitant use should be avoided. Likewise, probenecid was shown to increase the total body exposure to both acyclovir [53] and ganciclovir [54] during coadministration of these antiviral agents, but the clinical significance of these interactions in terms of increased toxicity risk still remains to be demonstrated. On the other hand, although probenecid may increase the renal excretion of the active metabolite of allopurinol, namely oxypurinol [55], it was shown that the concomitant administration of probenecid and allopurinol might ensure an additive anti-hyperuricemic effect [56]. Finally, also the renal clearance of nonsteroidal anti-inflammatory drugs (indomethacin, ketoprofen, ketorolac, naproxen) was shown to be lowered by probenecid [57].

Another clinically relevant interaction may occur with furosemide, since probenecid may interfere with the natriuretic effect of furosemide and this loop diuretic may in turn cause hyperuricemia [58].

Although most of the pharmacokinetic interactions of probenecid are due to the inhibition of renal tubular secretion and a potential interference with the renal excretion of many other drugs may be anticipated, however, it should not be overlooked that probenecid may also interfere with hepatic conjugation, as it has been demonstrated with lorazepam [59, 60], acetaminophen [59, 60], furosemide [61], zidovudine [62–64], and recently also with the antipsycotic agent olanzapine [65].

Rasburicase

Urate oxidase is an enzyme which catalyzes the conversion of uric acid to allantoin [66]. This enzyme is endogenous in most mammals but is lacking in primates and humans due to a nonsense mutation that occurred during hominoid evolution [67]. In the form obtained as product of extraction from *Aspergillus flavus*, urate oxidase has been employed for the treatment of hyperuricemia in the past 30 years in France and in Italy, but its use was limited due to the high incidence of severe allergic reactions [68], even if the addition of polyethylene glycol was shown to be useful in reducing this risk.

Rasburicase is a recombinant form of urate oxidase which is obtained by genetic modification of *Saccharomyces cerevisiae* in which the gene for urate oxidase was cloned from *Aspergillus flavus* [69, 70]. Rasburicase is a tetrameric protein formed by identical subunits with a molecular weight of about 34 kDa, and differs from the nonrecombinant urate oxidase in that its structure is completely preserved during the production process and its level of purity is higher [70].

Mechanism of Action

Rasburicase is a highly potent uricolytic agent which, by catalyzing the conversion of uric acid into a five to ten times more water-soluble compound, namely allantoin (fig. 1), readily increases its renal clearance [66]. Unlike allopurinol, which prevents uric acid formation, rasburicase increases uric acid clearance, so that hypoxanthine and xanthine do not accumulate in the plasma. It should not be overlooked that the enzymatic conversion of uric acid to allantoin is accompanied by the production of hydrogen peroxide, the formation of which usually does not represent a major problem since this reactive species is in turn eliminated by endogenous anti-oxidants. However, an increased risk for hemolysis may occur in subjects with a deficiency in glucose-6-phosphate dehydrogenase (G6PD), so that rasburicase is contraindicated in G6PD-deficient patients [71].

Pharmacokinetics

To date the pharmacokinetics of rasburicase has been extensively assessed in children and young adults [72]. In a pharmacokinetic study carried out in 30 patients (age $\leq$20 years) with hematological malignancies, rasburicase disposition was assessed after intravenous infusion for 5 days of either a dose of 0.15 mg/kg/day (n = 11) or 0.20 mg/kg/day (n = 19) [72]. Interestingly, no significant accumulation of rasburicase occurred after 5 days of both the dosing regimen. In patients receiving the 0.15 mg/kg/day dose, the mean ($\pm$ standard deviation) AUC was 32.9 $\pm$ 8.54 and 34.4 $\pm$ 9.05 ng/ml.h on day 1 and 5,

respectively. Likewise, in those patients receiving 0.20 mg/kg/day for 5 days, the mean AUC of rasburicase was 45.2 ± 18.9 and 47.3 ± 21.7 ng/ml.h on day 1 and 5, respectively. Mean C_{max} at the end of the 0.5-hour infusion ranged between 3.13 on day 1 and 3.36 ng/ml on day 5 after the 0.15 mg/kg/day regimen, and between 3.88 on day 1 and 4.5 ng/ml on day 5 after the 0.2 mg/kg/day regimen [72]. The volume of distribution after infusion of 0.20 mg/kg/day ranged between 110 and 127 ml/kg (study ACT2511, ACT2694), suggesting that rasburicase distribution is limited to the vascular space and that is where it exerts its action. Being a protein itself, rasburicase is not expected to bind to plasma protein. The mean terminal elimination half-life was 16.0 ± 6.3 and 21.1 ± 12.0 h for the 0.15 and the 0.20 mg/kg/day dose, respectively [72], so that the steady state condition is expected to be achieved within 2–4 days. Although the metabolic pathway of rasburicase has not been identified, it is expected that, similarly to other proteins, it occurs mainly by peptide hydrolysis. On the other hand, renal elimination is considered a minor pathway for rasburicase, so that both renal and/or hepatic impairments are not anticipated to affect its disposition. However, it should be noted that in patients with renal insufficiency allantoin might accumulate, even if this compound is relatively nontoxic in humans.

Drug Interactions

Although to date no study concerning pharmacokinetic interactions with other drugs in humans has been carried out however, it is worth noting that in in vitro studies rasburicase did not inhibit or induce the most relevant cytochrome P450 (CYP) isoenzymes, namely CYP1A, CYP2A, CYP2B, CYP2C, CYP2E and CYP3A. Additionally, in other in vitro studies rasburicase was not found to interfere with allopurinol, cyclophosphamide, cytarabine, daunorubicin, etoposide, 6-mercaptopurine, methotrexate, methylprednisolone, thioguanine and vincristine [73, 74], so that no major interactions with these agents are expected during concomitant treatment in patients.

Conclusions

Drugs for the treatment of hyperuricemia may act either by preventing the formation of uric acid (allopurinol) or by enhancing its clearance (probenecid, rasburicase). Interestingly, these different mechanisms of action may theoretically allow an additive effect when these drugs are used concomitantly. However, it should also not be overlooked that their potential for drug-drug interaction should be taken into account, since hyperuricemia frequently occurs in heavily cotreated patient. From this point of view,

rasburicase seems a promising agent since, differently from allopurinol and probenecid, interference with the pharmacokinetics of drugs included in the schedule treatment of patients with cancer and/or renal disease seems unlikely.

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Hyperuricemic Syndromes in Cancer Patients

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Abstract

Background/Aims: Tumor lysis syndrome is a challenging complication of cancer therapy. This review focuses on the risk factors and pathologies of patients at risk for hyperuricemic complications. **Methods:** A review of the literature was performed that included original articles and related reviews from MEDLINE (PubMed) and published abstracts of meeting presentations. **Results:** Both host-related and tumor-related factors predispose cancer patients to hyperuricemic syndromes. Host-related factors include low urinary flow, pre-existing hyperuricemia, renal failure, dehydration, acidic urine, and suppressed renal uric acid excretion. Tumor-related risk factors include a high tumor cell proliferation rate, large tumor burden, and tumor chemosensitivity. Acute renal failure may occur after cytoreductive chemotherapy in patients with active disease and a high tumor burden. Patients with advanced Burkitt's leukemia/lymphoma, high-grade lymphoma, or acute leukemia with elevated leukocyte counts are at high risk for complications of hyperuricemia. The use of nonrecombinant (uricozyme) or recombinant urate oxidase to prevent or treat urate nephropathy may improve the outcome of patients. **Conclusion:** Early recognition of metabolic abnormalities in cancer patients at risk for hyperuricemia is essential for proper therapy. Prospective studies to assess the incidence of and risk factors for hyperuricemic syndromes in patients treated with uricolytic agents are needed.

Introduction

In recent years, important advances have been made in the treatment and supportive care of cancer patients. Several novel approaches have been developed, such as new cytotoxic drugs, bioimmunotherapeutic agents, and 'targeted'

therapies. However, the treatment of cancer patients is frequently complicated with hyperuricemic syndromes, including tumor lysis syndrome (TLS). Metabolic abnormalities as complications of cancer therapy have been described since 1870 [1]. In the early 1900s, it was noted that a decrease in the size of the leukemic mass due to irradiation was associated with hyperuricemia [2]. The causative relationship between a high load of free cellular breakdown products and renal toxicity was demonstrated by injecting large amounts of adenine into the peritoneum of mice and causing acute renal failure [3]. TLS was formalized in 1980 with a landmark report of 37 patients with Burkitt's lymphoma [4].

TLS is a potentially fatal metabolic complication of rapidly growing tumors [4–8], caused by spontaneous cytolysis or by maximal tumor cell lysis, beginning a few hours after the initiation of chemotherapy, and usually persisting for 3–7 days. It is characterized by a set of metabolic disturbances, including hyperuricemia, hyperkalemia, hyperphosphatemia, secondary hypocalcemia, metabolic acidosis, and azotemia [9–11]. Despite the improvement of supportive care measures and the availability of novel agents to control uric acid levels, such as the nonrecombinant or recombinant urate oxidase, a subset of patients eventually develop this syndrome and succumb to acute renal failure. This chapter will focus on the pathological risk factors as well as the factors related to mortality and morbidity, in cancer patients with hyperuricemic syndromes.

Risk Factors for Mortality and Morbidity

In some patients, hyperuricemia resulting from the breakdown and rapid release of large quantities of nucleic acids and other intracellular contents in the lysed tumor cells into the bloodstream may lead to life-threatening metabolic abnormalities [9–11]. In addition, renal uric acid excretion increases with hyperuricemia. The precipitation of uric acid crystals and calcium phosphate in the renal tubules and distal collecting system causes intraluminal tubular obstruction and uric acid nephropathy [10, 12–14]. Hyperkalemia may cause serious consequences, such as cardiac arrhythmias. Hyperphosphatemia may result in acute renal failure [15, 16]. Elevated serum phosphorus levels may decrease renal function and further reduce urinary potassium and phosphate excretion. Hypocalcemia resulting from hyperphosphatemia may cause muscle cramps, cardiac arrhythmias, and tetany [17]. TLS is usually reversible, but it may be fatal [18, 19].

The reported risk factors for mortality and morbidity in cancer patients with hyperuricemic syndromes are summarized in table 1 [10, 12, 20]. Both host-related and tumor-related factors can predispose patients to hyperuricemic

Table 1. Hyperuricemic syndromes in cancer patients. Factors associated with increased risk of mortality and morbidity

Host-related	Tumor-related
Decreased urinary flow	Pathology (see table 2)
Pre-existing hyperuricemia	High tumor cell proliferation rate
Pre-existing volume depletion	Tumor sensitivity to therapy
Chronic renal failure	Large tumor burden
Acute renal failure following therapy	Bulky disease
Acidic urine	Advanced stage
Dehydration	Metastatic disease
Poor response to hydration	Elevated LDH levels
Male gender	Intensive cytotoxic therapy
Age <25 years	

Data in part from Arrambide and Toto [10], Flombaum [12], and Altman [20].

syndromes. Host-related risk factors include decreased urinary flow, pre-existing hyperuricemia, renal failure, acute renal failure developing shortly after the initiation of treatment, acidic urine, dehydration, and poor response to hydration [10, 12]. Tumor-related risk factors include a high tumor cell proliferation rate, large tumor burden, sensitivity of the tumor to therapy, elevated pretreatment lactate dehydrogenase (LDH) levels, which indicate a high cell turnover rate, and bulky tumors in patients with lymphoma [21, 22].

Unfortunately, there are no prospective studies focusing on the stratification of cancer patients by risk of developing TLS based on multivariate analyses. Most studies are retrospective and have certain limitations; therefore, their results should be interpreted with caution. For instance, some studies suggest that prognostic factors such as Burkitt's lymphoma, B cell acute lymphoblastic leukemia (ALL), high tumor load at diagnosis and high pretreatment LDH or uric acid levels are not reliable predictors for renal failure or the necessity for dialysis and suggest that the urinary flow rate appears to be a more reliable prognostic parameter [13, 23–25]. Indeed, in children with Burkitt's lymphoma or B cell ALL a lower urinary flow rate in the 24 h following the initiation of chemotherapy predicted renal impairment compared with a higher flow rate in children who did not develop this complication ($p < 0.001$) [24]. However, some recommendations for pediatric patients have been made. The French Society of Pediatric Oncology suggested that the following pediatric patients should be considered high-risk for TLS and should be treated accordingly: (1) patients with ALL or acute myeloid leukemia (AML) with a leukocyte count greater than 100×10^9/liter; (2) patients with stage III/IV Burkitt's lymphoma

and increased LDH levels and/or high uric acid levels, renal involvement, and impaired renal function; (3) patients with L3 leukemia; and (4) patients with stage III/IV lymphoblastic lymphoma and a tumor mass greater than 10 cm and/or pleural effusion and impaired renal function [26].

Bulky Disease

Some studies suggest that TLS develops in patients with bulky disease, although results of studies comparing TLS rates in patients with bulky and non-bulky tumors have not been reported [4, 27–30].

High Blast Cell Counts

Patients with high numbers of circulating leukemic blast cells, leukocyte counts higher than 50×10^9/liter, and a rapid release of cellular breakdown products into the bloodstream owing to the massive lysis of malignant cells that occurs either spontaneously or following anti-neoplastic therapy are at increased risk of TLS [8]. In the past, patients with Burkitt's lymphoma, B cell or T cell ALL, or AML and elevated leukocyte counts often died suddenly of complications of hyperuricemia within 72 h after chemotherapy, but in recent years, earlier diagnosis of TLS and new therapeutic and supportive care strategies have decreased these events.

Pretreatment Uric Acid Levels

Even if their serum uric acid levels are comparable, patients with lymphoid malignancies have been reported to have higher urinary uric acid levels than healthy individuals [31]. Elevated uric acid levels – typically greater than 15 mg/dl – precipitate acute renal failure. In clinical practice, an urinary uric acid to creatinine ratio of greater than one has been used to support the diagnosis of acute uric acid nephropathy associated with TLS [32]. Using that ratio, pretreatment hyperuricemic acute renal failure, a significantly elevated LDH, and a pathologically proven malignancy, investigators in a retrospective analysis of 926 patients, reported that the incidence of spontaneous TLS-induced acute uric acid nephropathy among patients with acute renal failure was 1.08% [31]. It also appears that the relative risk of TLS increases with rising uric acid levels [33]. In a retrospective analysis of 1,198 patients with hematological malignancies treated with chemotherapy, for every milligram per deciliter increase in a patient's serum uric acid level, the odds of the patient developing TLS increased by 1.75-fold [33]. Interestingly, the relative risk of developing TLS increased by 5.5-fold in patients with uric acid levels between 4 and 8 mg/dl compared with patients with uric acid levels less than 4 mg/dL [33].

Hyperuricemic Syndromes and Uricolytic Agents

The use of allopurinol or, more recently, the urate oxidase uricozyme or its recombinant form, rasburicase combined with hydration effectively prevents TLS. To date, randomized studies to compare the mortality and morbidity rates of cancer patients treated with allopurinol with those of patients treated with uricozyme or rasburicase have not been reported. However, early studies have shown that rasburicase is highly effective and safe in the prophylaxis or treatment of children or adults with cancer or chemotherapy-related hyperuricemia [34, 35]. Another study demonstrated that in patients with ALL or B cell lymphoma, treatment with rasburicase resulted in a lower rate of morbidity [36]. In a randomized trial comparing rasburicase with allopurinol in children and young adults with leukemia or lymphoma at high risk for tumor lysis, only 2 patients (0.4%) treated with rasburicase developed new renal complications requiring dialysis. Rasburicase was shown to be superior to allopurinol in controlling and lowering the levels of plasma uric acid rapidly, and it was a safe and effective alternative to allopurinol during initial chemotherapy [33, 37]. In a phase II study, 100 adult patients with aggressive non-Hodgkin's lymphoma (NHL) and at least one risk factor, according to the International Prognostic Index [38], who were at risk for hyperuricemia during the first cycle of chemotherapy received rasburicase. In all patients, rasburicase normalized uric acid levels and controlled the level of creatinine and other metabolites, and no patient required dialysis [39].

The incidence of renal failure in patients with Burkitt's lymphoma, high-grade lymphoma or B cell ALL, treated with allopurinol during induction therapy has been reported to be approximately 20% and the death rate due to metabolic abnormalities is 5% [24, 40, 41]. This incidence appears to decrease (1.7% and no metabolic deaths) with the use of uricozyme [26]. In addition, results from a phase II study suggest that rasburicase can be safely and effectively administered in lymphoma patients treated simultaneously with rituximab [39].

Hyperuricemic Syndromes and Therapeutic Agents

Agents that have potent myelosuppressive activity as well as less intensive therapies such as palliative radiation therapy can cause hyperuricemic complications. The former group includes amsacrine, cisplatin, cladribine, etoposide, fludarabine, paclitaxel, and other cytotoxic drugs [11, 42–45]. Steroids [46], monoclonal antibodies [47–49], interferon-α [50], interleukin-2, tumor necrosis factor-α, tamoxifen [51], and intrathecal methotrexate [52, 53] have also

been implicated in the development of TLS [20]. Radiation therapy, administered either as total-body radiation – part of a preparative regimen for allogeneic bone marrow transplantation in patients with therapy-refractory disease [22] – or as palliative therapy in patients with bulky, diffuse large B cell lymphoma, may also cause TLS [54]. TLS can occur following even 'low-intensity' chemotherapy, which is administered at the initial period of induction in some regimens to prevent hyperuricemic complications [55]. These 'low-intensity' regimens use low-dose corticosteroids prior to combination chemotherapy in ALL or NHL or gradually increased doses of chemotherapy [56].

Nucleoside Analogs

Treatment with nucleoside analogs is associated with a low incidence of TLS [27, 30, 57–59]. In a retrospective review of 6,137 patients with advanced chronic lymphocytic leukemia (CLL) treated with fludarabine, 26 patients (0.42%) were suspected of having TLS, including 20 patients (0.33%) with clinical and laboratory features consistent with this syndrome [30]. Interestingly, the median pretreatment leukocyte count among the 20 patients with confirmed TLS was 109×10^9/liter; 80% of these patients had at least two prior chemotherapy regimens, 89% had lymphadenopathy, 90% had splenomegaly and/or hepatomegaly, and 90% had high-risk CLL. 95% of the patients developed TLS during the first cycle and 5% during the third cycle of fludarabine, after a median of 7 days (range, 5–14 days). Despite the low incidence, the outcome of patients with TLS in this study was poor. 30% of the patients required dialysis, 20% died of renal failure during the first cycle of fludarabine therapy, and another 20% died of sepsis, congestive heart failure, or cardiac arrest. TLS patients had fewer prior regimens than patients without TLS (60 vs. 27%, less than three prior regimens, $p = 0.004$) and were more likely to have baseline hepatomegaly and/or splenomegaly ($p = 0.05$), but baseline leukocyte counts of the two groups did not differ [30]. Some cases of TLS after treatment with nucleoside analogs have been reported anecdotally in patients with CLL [27, 58, 59], prolymphocytic leukemia (PLL) [28], or low-grade lymphoma [29]. Grever et al. [60] reported one case of TLS among 32 patients with CLL treated with fludarabine. In another series of 51 patients with relapsed or refractory CLL, one case of grade 1 TLS was observed. In our series of 68 patients with previously treated CLL who were treated with fludarabine, one patient developed TLS [30, 61]. In another report on 19 patients with refractory CLL treated with fludarabine, one patient developed TLS [62].

Monoclonal Antibodies

Patients with large numbers of antigen-dense cells that have a high mitotic index, such as those with PLL or mantle cell lymphoma, are considered to have

an increased risk of TLS, when treated with monoclonal antibodies. Most data on monoclonal antibodies and TLS focus on rituximab in B cell NHL [39, 47, 63–65]. However, the antibody R24 against GD3 ganglioside (in combination with tumor necrosis factor-α) [49], and the ^{131}I labeled antibody OKB7 [48] may also cause TLS. Of 36,000 patients with B cell NHL treated with rituximab, TLS occurred in 0.04–0.05% within 12–24 h after the first antibody infusion [63]. The risk of TLS appeared to be higher in patients with high numbers of circulating malignant cells. Serious infusion-related adverse drug reactions, most often consisting of cardiopulmonary reactions due to the rapid lysis of large numbers of circulating malignant cells, were fatal in approximately 0.5 per 1,000 treated patients. The major risk factors for TLS included high numbers of circulating malignant lymphoma cells, pulmonary infiltrates or lymphoma involvement of the lung, and prior cardiovascular disease [63].

In another report, 5 patients with B cell PLL (n = 2), CLL (n = 2), or transformed NHL (n = 1) who had a high number of tumor cells in the blood and were previously treated with rituximab developed a unique syndrome of electrolyte evidence of tumor lysis, severe infusion-related reactions, thrombocytopenia, and rapid decrement in circulating tumor cell load [64]. However, this rapid tumor clearance syndrome differed from typical TLS in that potassium, calcium and phosphorus abnormalities tended to be milder and renal impairment was not as severe [64, 65]. Ongoing trials of rasburicase in the USA exclude patients with recent or concurrent rituximab therapy.

Pathologies at Risk

Risk Stratification by Pathology

Pathologies at risk for hyperuricemic syndromes are summarized in table 2 and include mainly hematological malignancies, and less commonly, solid tumors [66, 67]. Patients with lymphoproliferative disorders, in particular high-grade lymphomas [68], Burkitt's leukemia/lymphoma, lymphoblastic lymphoma, B cell and T cell ALL, and AML with high leukocyte counts [42] are at highest risk for the development of TLS [4, 5, 7, 13, 69–71]. Patients with intermediate-risk pathologies for TLS are considered those with low-grade lymphoma, CLL [19, 21, 72, 73] or PLL [18] treated with chemotherapy, radiotherapy, or corticosteroids; multiple myeloma; breast carcinoma treated with chemotherapy or hormonal therapy [51, 74, 75]; small-cell lung cancer [76]; germ cell tumors such as seminoma [74]; and ovarian cancer [77]. Finally, there are also some case reports of TLS in patients with Merkel's cell carcinoma [78], adenocarcinoma of the gastrointestinal tract [79], medulloblastoma [80]; and neuroblastoma [13, 20, 81].

Table 2. Hyperuricemic syndromes in cancer patients. Risk stratification by pathology

High risk	Moderate risk	Low risk
Burkitt's leukemia/lymphoma	Chronic lymphoproliferative disorders	Adenocarcinoma of gastrointestinal tract
Lymphoblastic lymphoma	Low-grade lymphoma	Merkel's cell carcinoma
High-grade lymphomas	Myeloma	Medulloblastoma
B cell or T cell ALL	Breast carcinoma	Neuroblastoma
AML with leukocytes $>50 \times 10^9$/liter	Small-cell lung cancer	
CML in blast crisis	Ovarian cancer	
	Metastatic seminoma	

Data in part from Chasty and Liu-Yin [79].

Patients with solid tumors are at risk of developing TLS if the tumor is sensitive to therapy or if the patient presents with bulky or metastatic disease or has pre-existing risk factors, including azotemia, elevated LDH levels, and hyperuricemia [82]. Although patients with solid tumors have a lower risk of developing TLS than patients with hematological malignancies, the mortality rate was higher in one study in the former group compared with the latter, mainly because awareness of the syndrome was higher in patients with hematological malignancies and prophylactic measures were implemented more often [82].

Incidence by Pathology

The incidence and presentation of TLS in hematological malignancies have been reviewed in some retrospective studies. In a study of 788 patients with NHL, ALL or AML from Belgium, the Netherlands, Spain and the United Kingdom, hyperuricemia and TLS were noted in 18.9 and 5.0% respectively of previously untreated patients who received induction therapy; and in 12.9 and 4.3% respectively of patients in the salvage therapy setting [56]. In that study, approximately 20% of the patient population was treated using an adapted chemotherapy schedule in which treatment onset was slowed to decrease the rate of tumor lysis [56]. The overall death rate of patients with TLS-related complications was 1.9%. Of the 40 patients with TLS, 45% developed acute renal failure, 25% required dialysis or hemofiltration, 13% had cardiac arrhythmias, 5% had cardiopulmonary failure, 10% had fluid retention/effusion, 15% died due to TLS and 37% died from all causes [56].

Burkitt's Leukemia/Lymphoma

In a landmark study, Cohen et al. [4] reported azotemia in 14 of 37 patients (38%) with Burkitt's lymphoma. All patients had abdominal tumors. Azotemia

preceded chemotherapy in eight patients (22%). Dialysis for control of azotemia and/or uric acid nephropathy was required in five patients (n = 2 before and n = 3 after chemotherapy). Tumor lysis complications were associated with very large tumors, high LDH levels and inadequate urinary output. Evidence of ureteral obstruction by intravenous pyelography was noted in seven of 22 patients (32%) with advanced-stage lymphoma [4].

In another study of 24 children with Burkitt's lymphoma treated with alternating high-dose cyclophosphamide and methotrexate, two patients (8.3%) developed metabolic abnormalities after rapid-onset TLS [83]. In a prospective study of 40 children with Burkitt's lymphoma and B cell ALL, 10 patients (25%) developed acute renal failure (n = 2 before and n = 8 after chemotherapy) [24]. Children with renal impairment had a significantly lower urinary flow rate in the 24 h following initiation of chemotherapy, but no difference in LDH or uric acid levels and response rates compared with others [24]. In a series of 1,192 pediatric patients with lymphoma enrolled on the Berlin Frankfurt Munster (BFM) NHL trials, the incidence of impaired renal function and/or TLS before or during initial therapy was 5.3% (n = 63) [25]. Among these 63 patients, 98% had Burkitt's lymphoma or B cell ALL, 92% had advanced stages of disease and high levels of LDH, 68% had impaired renal function at admission, and 40% required dialysis. The most common cause of impaired renal function was hyperuricemia. The death rate among the 63 patients with TLS and/or impaired renal function was 14%. Most of the patients died of sepsis after the first course of therapy, and the rest died within 2 days, of an electrolyte imbalance [25].

In our series of 26 consecutive patients with Burkitt's leukemia/lymphoma treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine, four patients (15%) developed TLS during the induction phase [84]. These patients required dialysis and with recovery of renal function were treated with reduced doses of chemotherapy in subsequent courses [84]. A similar incidence of TLS (15%) was reported in another study in children with B cell ALL or Burkitt's lymphoma and elevated LDH levels [85].

NHL

In a series of 102 patients with high-grade NHL, the incidence of TLS based on laboratory tests was 42%, but clinical tumor lysis occurred in only 6% of patients [23]. In that analysis, TLS occurred more frequently in patients with pretreatment renal insufficiency than in patients with normal renal function (36 vs. 2%, respectively; p = 0.01) [23]. Patients with all types of moderate- to high-grade NHL were at risk, but clinically significant TLS was rare in patients receiving allopurinol [23].

Myeloma

Hyperuricemia is a common characteristic complication of multiple myeloma. Although clinically significant hyperuricemia is uncommon, it may contribute to renal impairment. The development of TLS has been associated with advanced stage, anaplastic, or rapidly proliferative myeloma, high plasma cell load, and the presence of isolated plasmacytomas [13, 14].

Conclusions

Hyperuricemic complications occur more often in patients with advanced Burkitt's leukemia/lymphoma, other aggressive lymphomas with bulky disease, baseline impaired renal function, elevated LDH levels and acute leukemias with leukocyte counts greater than 50×10^9/liter. Awareness also should be high in patients with solid tumors, if the tumor is sensitive to therapy or the patient presents with bulky or metastatic disease or has pre-existing risk factors. Early recognition of metabolic abnormalities in cancer patients at risk for hyperuricemia is essential for proper therapy. The primary aim in the management of such patients should be the prevention of hyperuricemia and achievement of a high urine flow to reduce the probability of TLS and renal failure. Patients at high risk for TLS should be admitted to an intensive care or medical oncology unit, should receive adequate hydration, and should be closely monitored for renal or cardiac complications for at least 72 h after the initiation of therapy. Ongoing trials, including randomized ones, of rasburicase, allopurinol, or combination therapy in patients with leukemia, lymphoma or solid tumors are expected to better assess the safety and effectiveness of these urolytic agents in reducing hyperuricemia and TLS. Prospective studies are needed to determine prognostic models for TLS risk stratification in cancer patients.

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Incidence and Pathogenesis of Tumor Lysis Syndrome

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Abstract

Tumor lysis syndrome (TLS) is a constellation of metabolic disturbances that may be observed in patients with malignancies. Clinically significant TLS can occur spontaneously, but most often is seen 48–72 h after initiation of cancer treatment. The metabolic abnormalities observed in patients with TLS include hyperkalemia, hyperuricemia, and hyperphosphatemia, which leads to secondary hypocalcemia. The precise incidence of TLS is not defined, risk factors being represented by large tumor burden, neoplasms with either high growth fraction or high sensitivity to chemotherapy, and by pre-existing impairment of renal function. Neither racial, nor sex predilection exists. The pathogenesis of TLS is related to the rapid tumor cell turnover or destruction, which may result in release of intracellular ions and metabolic byproducts into the systemic circulation. Acute renal failure (ARF) may frequently complicate TLS and is mainly due to renal tubule precipitation of uric acid, calcium phosphate, or hypoxanthine. Hemodynamic changes reducing glomerular flow due to still-undefined mediators are also involved in TLS pathophysiology. Pre-existing volume depletion or renal dysfunction may worsen metabolic derangements and ARF. A good comprehension of TLS pathophysiology has provided the basis for an effective and rational treatment of this complication, adversely affecting the outcome of cancer patients.

Introduction

Tumor lysis syndrome (TLS) is a serious, sometimes life-threatening complication, occurring in patients with cancer, either before or, more frequently, after beginning of antitumor therapy [1, 2]. It was first reported in 1929 [3] in a group of adults with chronic leukemia. Since then, several studies on TLS have been published [4–10]. TLS can be defined as a pattern of severe metabolic

abnormalities, resulting from either spontaneous or treatment-related destruction of tumor cells, which may lead to the release of intracellular ions and metabolic byproducts into the systemic circulation. All these events represent an oncological emergency characterized by severe electrolyte abnormalities, and may lead to the development of acute renal failure (ARF); occasionally, TLS is also associated with coagulopathy.

In the forms associated with the use of anticancer treatment, TLS has been observed following administration of various chemotherapeutic agents including cisplatin, fludarabine, etoposide, paclitaxel, intrathecal methotrexate, etc. [1, 2]. More recently, cases of TLS following the therapeutic use of monoclonal antibodies, interferon-α and high-dose corticosteroids have been reported as well [11–15].

Incidence of TLS

The incidence of TLS is still not precisely defined. It varies among different malignancies, being more frequent in patients given chemotherapy for high-grade lymphoproliferative disorders, such as Burkitt's lymphoma and T-cell acute lymphoblastic leukemia [7, 8, 16, 17]. However, cases of TLS in patients with solid tumors have also been extensively reported [10, 13, 18, 20]. Not surprisingly, laboratory evidence of TLS has been reported much more frequently than the symptomatic clinical syndrome [21].

As mentioned above, the syndrome typically occurs most often after initiation of anticancer treatment. However, cases of acute spontaneous TLS have been reported rarely, mostly in patients with Burkitt's lymphoma or mature B-cell leukemia, both characterized by very rapid cell turnover rates [18, 22–24]. In a recent study, acute spontaneous TLS, defined by the presence of pretreatment hyperuricemic ARF, ratio of urinary uric acid to creatinine >1.0, and significantly elevated lactate dehydrogenase (>500 units/l), together with a pathologically proven malignancy, was demonstrated to occur in 1.08% of 926 patients with ARF [24]. A key distinction between spontaneous tumor lysis and that occurring after therapy is the lack of hyperphosphatemia in the spontaneous form.

Factors predisposing to the development of TLS include a high growth fraction, high sensitivity to chemotherapy, large tumor burden, elevated lactate dehydrogenase serum levels, extensive bone marrow involvement and decreased urinary flow [1, 2]. Neither racial, nor sex predilection has been reported. Although TLS occurs in all age groups, advanced age leading to impaired renal function may predispose patients to a clinically significant TLS.

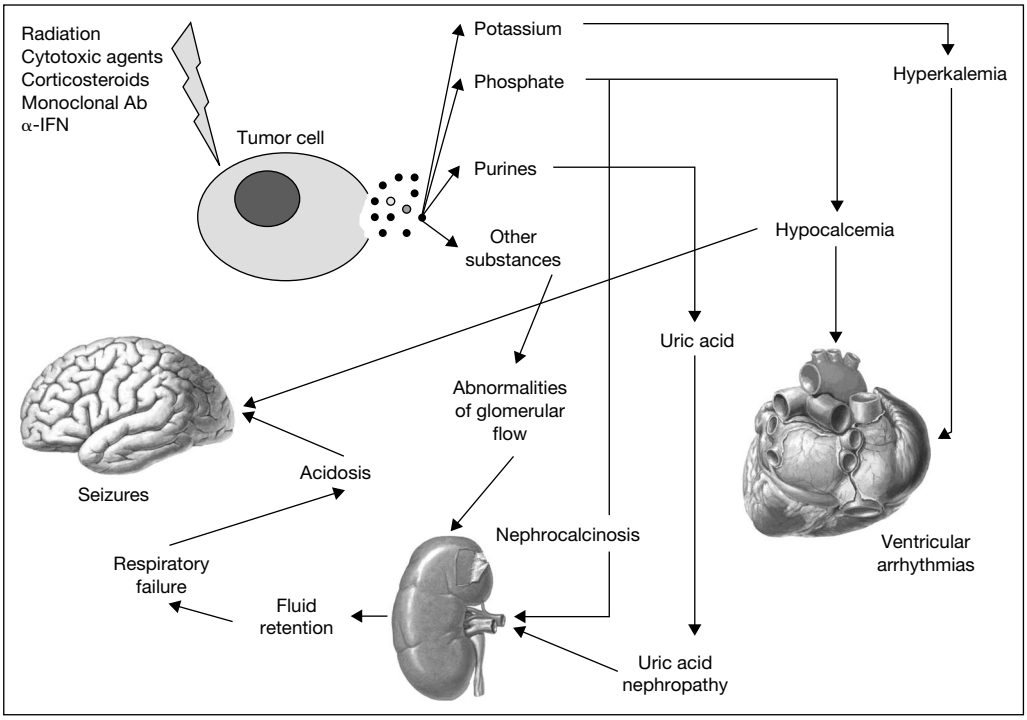

Fig. 1. Pathophysiology of the tumor lysis syndrome.

Pathophysiology, Metabolic and Clinical Consequences of TLS

Pathophysiology of TLS is complex and is derived from a rapid tumor cell turnover and/or destruction, resulting in the release of intracellular ions and metabolic byproducts into the circulation (see also fig. 1). Thus release cannot be compensated by mechanisms of renal elimination and cellular buffering mechanisms, thus leading to numerous, life-threatening metabolic derangements and ARF.

The biochemical hallmarks of TLS are hyperkalemia, hyperuricemia, and hyperphosphatemia with secondary hypocalcemia. All these metabolic derangements may be associated with relevant clinical manifestations, sometimes fatal for the patient (see also table 1 for further details).

Hyperkalemia

Hyperkalemia is often the earliest and most serious laboratory manifestation of TLS and results directly from rapid cell lysis. Co-existing impairment of

Table 1. Electrolyte abnormalities and clinical consequences of TLS

Abnormality	Pathophysiology	Clinical consequences
Hyperkalemia	Release of intracellular K^+ in the circulation due to cell death	Ventricular arrhythmias, weakness, paresthesias
Hyperphosphatemia	Release of intracellular inorganic and organic phosphates in the circulation due to cell death and abnormal renal clearance	Nephrocalcinosis with permanent renal damage and deposits in other body tissues
Hypocalcemia	Precipitation of calcium phosphate crystals due to hyperphosphatemia	Ventricular arrhythmias, weakness, paresthesias, tetany, seizures
Hyperuricemia	Massive release of purines due to cell death, which are metabolized to uric acid	Renal failure
Acidosis	Renal dysfunction and liberation of large amounts of endogenous intracellular acid metabolites	Derangement of vital functions (circulatory, neurological, respiratory, renal, etc.) of varying severity, intravascular coagulopathy

renal function, as well as metabolic acidosis, may worsen hyperkalemia, overwhelming the potassium excretory capacity of the kidney.

Hyperkalemia can lead to electrocardiographic changes and life-threatening cardiac arrhythmia, including asystole. Severe potassium elevation is always associated to electrocardiographic alterations such as peaked T waves, flattened P waves, prolonged PR interval, widened QRS complexes, deep S wave, and sine waves. These electrocardiographic abnormalities must be promptly diagnosed and treated through stabilization of the myocardial cell membrane, intracellular shift of potassium and reduction of total ion load, in order to reduce the risk of fatal, ventricular arrhythmia.

Hyperphosphatemia and Hypocalcemia

Hyperphosphatemia also results directly from rapid cell lysis and usually develops within 24–48 h of anticancer treatment inception [1, 9]. In this regard, it has been estimated that the phosphorus content of leukemic lymphoblasts is three to four times the content of normal lymphocytes [9]. Treatment-induced lysis of tumor cells results in rapid release of phosphorus, which can exceed the renal threshold for phosphate excretion. Calcium phosphate is precipitated

when the in vivo concentration of calcium-phosphate salts exceeds the solubility product of 4.6 mmol/l. Precipitation of calcium-phosphate crystals may occur in several tissues, including the kidney, where it produces nephrocalcinosis. The presence of deposits of calcium in the renal tubules elicits an inflammatory response exacerbating the risk of ARF [1, 2]. Calcium phosphate is less soluble at an alkaline pH, which can exacerbate the risk of deposits of calcium. Overzealous iatrogenic alkalinization of urine in patients with TLS may be associated with an increased risk of nephrocalcinosis and, thus, it must be avoided.

Hypocalcemia is a direct consequence of hyperphosphatemia, with subsequent precipitation of calcium phosphate in soft tissues. Hypocalcemia can lead to the lengthening of QT interval, which predisposes patients to ventricular arrhythmia. Moreover, muscle cramps, tetany and seizures may be favored by the development of an hypocalcemic state.

Hyperuricemia

Hyperuricemia is the increase of uric acid concentration in plasma and it is a constant finding in patients experiencing TLS already present at the time of tumor diagnosis or in any case developing within 48–72 h following initiation of treatment. Neoplastic cells have a very active purine metabolism and a high nucleic acid content. As nucleic acid purines are metabolized to uric acid by hepatic enzyme xanthine oxidase, it is not surprising that the breakdown of tumor cell yields large amount of uric acid. In fact, the purines (adenosine and guanine) are ultimately reduced to the same product, a compound called xanthine, which, in turn, is degraded to uric acid by the enzyme xanthine oxidase. While some animal species have the enzyme urate oxidase which catalyzes degradation of uric acid to allantoin, a much more soluble compound, higher primates, including human beings, have lost, due to nonsense mutation during evolution, this enzyme which favors rapid urate clearance [25]. As blood urate concentration is normally near the saturation level, hyperuricemia facilitates the crystallization of uric acid in the renal collecting ducts and in the deep cortical and medullary vessels, which significantly contributes to the development of ARF in patients suffering from the TLS. With a pKa of 5.75 [2], uric acid precipitation is enhanced by high acidity and high concentration in the renal tubular fluid, becoming less soluble as renal tubule pH decreases. Renal medullary hemoconcentration and decreased tubular flow rate also contribute to uric acid crystallization.

Acute Renal Failure

Renal dysfunction can be severe enough in patients with TLS to require dialysis, but, in the majority of cases, if timely diagnosed and promptly treated

with supportive measures, it is usually reversible. The pathogenesis of ARF in patients with TLS, although more extensively understood in the last years, is still not completely clarified [1, 2]. The kidney is the primary organ involved in the clearance of uric acid, potassium, and phosphate and, thus, it is expected that abnormalities of renal function, characteristic of TLS, predispose patients to worsening of metabolic derangements typical of this syndrome.

There is no doubt that uric acid nephropathy, due to mechanical obstruction by uric acid crystals in the renal tubules, is the major cause of ARF, which is oliguric in nature, leading to volume overload and complications of hypertension and pulmonary edema in patients with TLS. Uric acid crystals form and tend to deposit in the collecting ducts and the deep cortical and medullary vessels due to the high renal intraluminal fluid concentration of urate, acidic distal tubular fluid, reduced tubular flow rate, and hemoconcentration in medullary vessels [24]. Intratubular obstruction causes azotemia/oliguria in acute uric acid nephropathy, and vascular obstruction can contribute to filtration failure.

Uric acid crystallization in the distal tubules/cortical collecting ducts is not the only factor operating in the mechanical obstruction of kidney. In fact, as mentioned above, deposits of inorganic and organic phosphates, released during the processes leading to tumor cell death, with calcium produce nephrocalcinosis and this also significantly contributes to renal injury in acute TLS.

Finally, precipitation of xanthine, which is even less soluble in urine than uric acid, or other purine metabolites, whose urinary excretion is increased by use of allopurinol, may rarely be involved in the development of ARF.

Pre-existing volume depletion (due to poor oral intake, vomiting, diarrhea or fever, frequently observed in patients with cancer) as well as pre-existing renal dysfunction may worsen the clinical and pathogenetic picture associated with TLS facilitating the development of ARF, which has to be considered often multifactorial in its etiology. In this regard, hemodynamic changes, constricting the vasa recta, rather than renal tubular obstruction seem to be implicated in the decreased glomerular filtration frequently observed in patients with TLS. Still-undefined mediators, as well as adenosine released by tumor cells [26, 27], may be responsible for these altered renal vascular vasoconstricting responses, which, by decreasing glomerular filtration rate, play a pivotal role in the development of ARF associated with TLS [2].

Metabolic Acidosis

Both ARF and liberation of large amounts of endogenous intracellular acid metabolites from cellular catabolism may result in metabolic acidosis. This acidemic state, in turn, causes a decrease in serum bicarbonate concentration and a high anion gap acidosis and can worsen the many electrolyte imbalances already present in TLS. In particular, intracellular uptake of potassium is impaired,

uric acid solubility is decreased, and extracellular shift of phosphate is facilitated. Calcium phosphate solubility, however, improves in acidic conditions, this rendering less likely the possibility of deposits of calcium-phosphate crystals in the kidney.

Conclusions

TLS is a complication potentially occurring in any patient, especially in those responding to cancer therapy. It is diagnosed with greater frequency in highly sensitive tumors, especially in advanced stage non-Hodgkin lymphoma (i.e. Burkitt's lymphoma) and in acute lymphoblastic leukemias, whereas it is more rarely observed in the treatment of adult solid tumors. TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia following massive lysis of malignant cells. Complications include ARF and metabolic acidosis. In view of its complex physiopathology and clinical presentation, the myriad of metabolic disorders must be assessed and treated rapidly. Proper fluid management, careful alkalinization of the urine, correction of acidosis, inhibition of the formation of uric acid or destruction of the already circulating uric acid molecules, as well as attention to infections, are mainstays of therapy. The recent availability of a recombinant form of urate oxidase has significantly enriched the therapeutic possibilities for treating this severe and complex disorder to which pediatric hematologists and oncologists must pay great attention in view of its relevant associated morbidity and, in some few cases, mortality.

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Recombinant Urate Oxidase (Rasburicase) in the Prophylaxis and Treatment of Tumor Lysis Syndrome

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Abstract

Spontaneous or treatment-induced tumor lysis syndrome (TLS) can cause significant morbidity and potential mortality. Vigorous hydration, alkalinization and inhibition of uric acid synthesis are the most frequently used methods for prevention of TLS. However, this approach requires hospitalization and tedious nursing care, and fails to prevent renal insufficiency in up to 25% of high-risk patients. With increased intensity and efficacy of cancer therapies, and the current trend to deliver treatment in the outpatient setting, novel approaches at management of TLS are needed. Unlike allopurinol, urate oxidase promptly reduces the existing uric acid pool, prevents accumulation of xanthine and hypoxanthine, and does not require alkalinization, facilitating phosphorus excretion. A recombinant form of urate oxidase, rasburicase, is now available. In this chapter we will present an overview of rasburicase development and discuss the impact of rasburicase in the prevention and management of TLS.

Introduction

Tumor lysis syndrome (TLS) consists of a constellation of metabolic abnormalities that result when the body clearance mechanisms are overwhelmed by the rapid release of cellular contents from tumor cells [1]. The resultant hyperuricemia and electrolyte abnormalities can lead to neurological complications, cardiac arrhythmias, renal failure, and even death. TLS can occur spontaneously, but is exacerbated by anti-neoplastic therapy that results in accelerated tumor cell break down [2]. Historically, TLS has been associated with large tumor burden and rapidly proliferating neoplasms such as mature

B cell malignancies. As cancer therapies become more intensive and effective, TLS is being reported with increasing frequency in other malignancies including breast cancer, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia [3–7]. Although tumor lysis is a desirable effect of the treatment, TLS is an oncological emergency that requires prompt and effective treatment to prevent morbidity, organ damage, and death. In this chapter we will discuss the current approach in the prevention and management of metabolic complications and organs dysfunction in patients at risk of TLS, with emphasis on hyperuricemia.

Historical TLS Management and Its Limitation

When tumor cells break down, they release purine by-products, potassium and phosphorus into the circulation. If the amounts released exceed the clearance capacity of the kidneys, uric acid and other purine metabolites (especially xanthine) can precipitate in the renal tubules, further compromising renal function. This leads to potassium and phosphorus accumulation in the circulation. Phosphorus binds to calcium and precipitates in the kidneys aggravating renal dysfunction. Hyperkalemia and hypocalcemia can lead to tetany, seizures, arrhythmias, and death [1, 2]. Until recently, allopurinol, vigorous hydration and alkalinization have been the standard measures to prevent or treat hyperuricemia in patients with cancer. The advantages and drawbacks of this approach are presented below.

Hydration and Forced Diuresis

It is crucial to maintain adequate urine output in order to facilitate excretion of uric acid, potassium and phosphorus. Intravenous (IV) fluids with no added potassium should be initiated at 3 liters/m^2 per day or more to maintain a urine output of at least 100 ml/m^2/h. Fluid balance should be monitored very closely and diuretics given to prevent fluid retention and maintain adequate urine output. Loop diuretics facilitate potassium excretion in addition to providing forced diuresis. However, the resultant alkalosis may delay phosphorus excretion. Mannitol and renal doses of dopamine may also be used. Hyperhydration requires close monitoring in the inpatient setting, because it can be associated with fluid overload and pulmonary edema, especially in patients with preexisting nephropathy secondary to the disease itself, stones and crystals precipitation, older age, or other coexisting medical problems. Special caution is also warranted in patients with superior vena cava syndrome, or other masses obstructing venous flow, and in elderly patients and patients with cardiovascular diseases.

Alkalinization of Body Fluids

Patients with cancer are susceptible to dehydration and metabolic acidosis secondary to poor oral intake, nausea, vomiting, diarrhea, fever and infections. The crystallization of uric acid in the acidic renal tubular system contributes to the impairment in renal function. Hyperuricemia is one of the most important complications in patients with TLS who develop acute renal failure [1, 8, 9]. The solubility of uric acid is approximately 15 mg/dl in urine with a pH of 5 but increases to 200 mg/dl at pH 7.0 [10]. Adding sodium bicarbonate to the IV fluids increases urine pH, which, in turn, increases the solubility of uric acid, thus minimizing intratubular precipitation of uric acid and its precursors (xanthine and hypoxanthine). In some cases, acetazolamide can be used in addition to sodium bicarbonate to help alkalinize the urine. Urine pH should be monitored closely, and kept between 7 and 7.5. Overzealous alkalinization (urine pH $>$7.5) may exacerbate symptoms of hypocalcemia and facilitate the precipitation of calcium-phosphate salts in body tissues including the kidneys. Hyperphosphatemia can be treated with phosphate binders (aluminum hydroxide, sevelamer, or calcium carbonate in patient with low serum calcium levels). In addition, phosphorus intake should be eliminated or reduced in medications and diet. Hypocalcemia is usually self-correcting if hyperphosphatemia is corrected; IV calcium treatment should be reserved only for symptomatic patients because overzealous replacement of calcium may enhance calcium-phosphorus complex formation.

Allopurinol

Allopurinol is traditionally used in conjunction with vigorous hydration and alkalinization to control hyperuricemia. Uric acid is the end product of purine metabolism in humans. It is produced in the liver by oxidation of xanthine and hypoxanthine. Allopurinol inhibits xanthine oxidase, an enzyme that catalyzes the conversion of hypoxanthine to xanthine, and xanthine to uric acid. Decline in uric acid usually begins 1 or 2 days after the drug is started and reaches a maximum after 7–10 days. Allopurinol is rapidly absorbed after oral administration. Peak levels are reached within 2 h of oral administration before it is rapidly converted to its active metabolite oxypurinol. The half life of oxypurinol is 17–40 h depending on renal function; dosage of allopurinol should be adjusted in patients with renal insufficiency. Allopurinol is well tolerated, and has greatly improved the management of hyperuricemia in patients with malignant diseases. However, despite alkaline hydration and allopurinol, up to 25% of patients at high risk of TLS have been reported to require dialysis, and many cannot receive chemotherapy as planned [11, 12].

While it inhibits uric acid synthesis, allopurinol does not reduce the existing uric acid pool, which still has to be cleared by the kidneys. Allopurinol also

Table 1. Solubility of purine analogs

	pH 5.0, mg/l	pH 7.0, mg/l
Uric acid	150	2,000
Xanthine	50	130
Hypoxanthine	1,400	1,500

Solubility of allantoin – 5,250 mg/l in water.

causes accumulation of xanthine and hypoxanthine by preventing their oxidation to uric acid. Hypoxanthine is more soluble than uric acid, but xanthine actually is less soluble than uric acid (table 1). Indeed, xanthine nephropathy and renal stone have been reported in patients treated with allopurinol [13, 14].

The side effects associated with allopurinol are generally mild-to-moderate, and cutaneous or allergic in nature. Rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Allopurinol is also involved in several drug–drug interactions attributable to competition with renal excretion (e.g., chlorpropamide), inhibition of xanthine oxidase (e.g., mercaptopurine and azathioprine) or unknown cause (e.g., dicumarol, thiazide diuretics, ampicillin and cyclosporine).

IV allopurinol was recently approved for use in the USA, although it has been available for use on a compassionate basis for approximately 30 years for patients unable to tolerate its oral formulation [15, 16]. Both oral and IV formulation have similar safety and efficacy profile. The pharmacokinetics of oxypurinol, the major active metabolite of allopurinol, does not seem to be influenced by the route of allopurinol administration [17–20] indicating that allopurinol IV dose schedule should be the same as that of the oral dosing. Hence, the more expensive IV formulation has no advantage over oral allopurinol, and should be used only in patients who cannot tolerate the oral preparation.

In a retrospective study of 941 patients who received IV allopurinol on a compassionate basis, normalization of serum uric acid levels could not be achieved in 43% of adults and 12% of children [21]. Serum creatinine was normalized in only 29% of the patients and remained elevated in 71%. Among the 216 patients initiating therapy with a normal serum creatinine level, the level increased and remained elevated while on therapy in 13%. There was no response to treatment (i.e., no reduction in uric acid level by 1 mg/dl or more) in 12% of adults and 5% of children.

Hemodialysis

Dialysis is initiated in patients with excessive elevation in uric acid, phosphorus and/or potassium, and in those with deteriorating renal function with uncontrollable volume overload. Data comparing the various dialysis modalities are lacking. In general, hemodialysis is preferred as it can rapidly correct any life-threatening electrolyte abnormalities and results in higher clearance of both uric acid and phosphorus. Peritoneal dialysis is much less efficient than hemodialysis in correcting metabolic abnormalities. The primary aim of TLS treatment is to prevent acute renal failure and the need for dialysis. This in turn will reduce clinical complications, avoid delays in chemotherapy and decrease the length of hospital stay and medical costs.

Recombinant Urate Oxidase

Urate oxidase, a naturally occurring proteolytic enzyme in many mammals, degrades uric acid to allantoin, which is ten times more soluble than uric acid and easily eliminated by the kidneys. Humans lack urate oxidase presumably due to a nonsense mutation during primate evolution [22]. The end product of the purine metabolism pathway in humans is, therefore, the poorly soluble uric acid (fig. 1). In the 1960s, clinical trials with a urate oxidase isolated from cultures of *Aspergillus flavus* demonstrated that the drug significantly reduced blood uric acid levels and increased the excretion of allantoin [23, 24]. Nonrecombinant urate oxidase (Uricozyme) was approved for human use in France in 1975 and in Italy in 1984. Studies conducted in the USA confirmed that urate oxidase is very effective in rapidly reducing uric acid levels and decreasing the need for dialysis in patients at risk of TLS [25]. Hypersensitivity reactions were observed in approximately 5% of patients treated with Uricozyme, generally with the first dose of treatment.

The advent of recombinant technology allowed higher production yield of a highly purified urate oxidase [26]. The cDNA encoding the recombinant product (rasburicase) was cloned from a strain of *Aspergillus flavus*, and expressed in a genetically modified *Saccharomyces cerevisiae* strain. Rasburicase is a tetrameric protein with identical subunits of a molecular mass of approximately 34 kDa, which is similar to that of the native *Aspergillus flavus* urate oxidase. Mean half-life is 21.2 ± 12.0 h. Comparative tests have demonstrated that the recombinant form contains a smaller proportion of isoforms and has 50% more specific activity that of the nonrecombinant form as determined by the conversion of uric acid to allantoin. Rasburicase was approved for clinical use in Europe in 2001 (Fasturtec), and was approved in 2002 by the Food and Drug Administration of the USA for use in pediatric patients (Elitek).

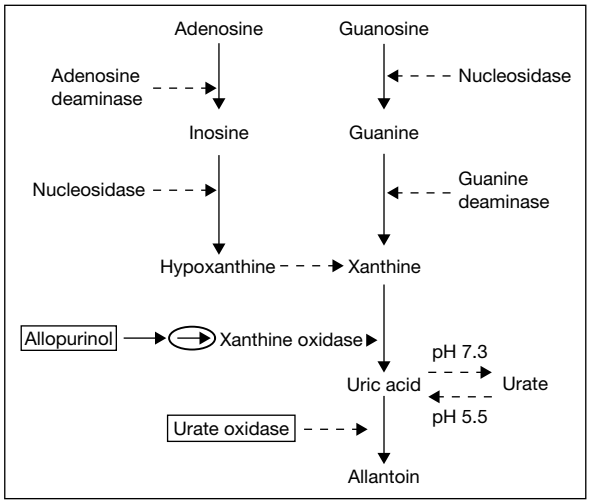

Fig. 1. Purine metabolism pathway.

Clinical Efficacy

In the Phase I trial, 4 healthy adults received rasburicase at each of the four dose levels (0.05, 0.1, 0.15 and 0.2 mg/kg). It was then given as a 5-day course to 4 other healthy adults at each of the three dose levels (0.1, 0.15 and 0.2 mg/kg) [27]. Rasburicase produced a rapid and marked decrease in the plasma concentration of uric acid within one hour after injection. Within 4 h, the decrease in uric acid level was 90–95% in those who received either 0.15 or 0.2 mg/kg. In fact, uric acid was undetectable in many of the volunteers who received the higher doses.

A phase II clinical trial conducted at multiple centers in North America and France enrolled 131 pediatric patients at high risk of TLS [28]. The study consisted of a dose-finding phase which identified 0.20 mg/kg given by IV infusion over 30 min as the effective dose to be used in the dose-validation phase. All patients, including those treated at the lower 0.15 mg/kg dose level, had a significant and rapid decrease in uric acid level within 4 h after rasburicase administration. Rasburicase was well tolerated. None of the patients developed severe TLS or required dialysis.

A phase III study compared the efficacy of rasburicase to that of allopurinol in 52 pediatric patients with leukemia or lymphoma who were at high risk of TLS [29]. Uric acid levels decreased more rapidly and remained lower throughout induction therapy in the rasburicase group as compared to the allopurinol group. The sample size was too small to allow comparison of the frequency of renal failure and hemodialysis between the two groups. Nonetheless, no patient

who received rasburicase including one who presented with renal failure required dialysis, whereas one patient in the allopurinol group did. Also there was a consistent decrease in creatinine and phosphorus levels in the rasburicase group despite initiation of induction therapy, whereas the allopurinol group showed a transient increase in serum concentrations of creatinine and phosphorus during this period.

Compassionate-use trials were initiated in 1999 to provide patients at high risk of TLS with rasburicase before it became commercially available [30, 31]. These trials confirmed that rasburicase is well tolerated and very effective in promptly reducing uric acid levels. Most patients with elevated uric acid levels at baseline have over 80% reduction in uric acid levels as early as 4 h following the first dose and uric acid levels remain low or undetectable for the duration of rasburicase administration and beyond, despite ongoing intensive chemotherapy.

Serum concentrations of uric acid decreased significantly and rapidly in over 98% of patients treated with rasburicase. The majority of patients required rasburicase treatment for only 1–4 days. The median number of doses given and days on treatment was three each. Repeated use of rasburicase has been associated with a similarly good response in spite of a 10–20% incidence of antibody generation, most of which are not neutralizing [26].

In the compassionate-use trial, only 1.5% of children and 5% adult patients required dialysis. This rate is much lower than that of patients with similar diseases treated without urate oxidase (table 2). The median age of patients undergoing dialysis was 50 years. In the dialysis group, 20% required dialysis because of renal failure or hyperphosphatemia. For the remaining 80% of the patients, renal insufficiency was associated with sepsis and other complications that occurred during intensive induction chemotherapy for hematological malignancies. Notably, while these patients presented with multiple clinical problems, all had low uric acid levels after treatment with rasburicase. These data suggest that the administration of rasburicase does not totally eliminate the need for comprehensive management of patients with extensive tumor burden.

Safety

Rasburicase is well tolerated in both pediatric and adult patients. It is not known to interact with other drugs, and does not require dose adjustment according to renal function. However, as one of the by-product of uric acid degradation is hydrogen peroxide, patients deficient in glucose 6-phosphate dehydrogenase are at increased risk of hemolytic anemia or methemoglobinemia and should not receive any preparation of urate oxidase. Other serious adverse reactions attributable to rasburicase are uncommon and include

Table 2. Incidence of dialysis in studies with and without urate oxidase

	Diagnoses	Patients	Dialysis, %	Ref
Studies with urate oxidase				
LMB 89 (urate oxidase)	Advanced B cell NHL and B cell ALL	410	1.7	[35]
Phase II trial (urate oxidase)	ALL	126	0.0	[25]
Phase II trial (rasburicase)	Leukemia or lymphoma	131	0.0	[28]
Phase III trial (Allopurinol vs. rasburicase)	Leukemia or lymphoma	27 (rasburicase)	0.0	[29]
Compassionate use (rasburicase)	Leukemia, lymphoma, solid tumors	278	1.8	[30]
Compassionate use (rasburicase)	Leukemia, lymphoma, solid tumors	1,069	2.8	
GRAAL1	Lymphoma	100	0.0	[36]
Studies without urate oxidase				
St Judes	Advanced B cell NHL and B cell ALL	40	25	[11]
POG	B cell ALL and Stage IV B cell NHL	133	19	[37]
UK CCSG 9003 protocol	B cell ALL and Stage IV B cell NHL	63	15.9	[38]

ALL = Acute lymphoblastic leukemia; NHL = non-Hodgkin's lymphoma.

anaphylaxis, hemolysis, and rash observed in less than 1% of over 1,000 patients treated. Allergic reactions appeared to be more common in patients who had previously received rasburicase and occurred in 9–16% of retreated patients. Symptoms resolved with no sequelae upon discontinuation of rasburicase.

Conclusion

Rasburicase is an effective and safe uricolytic agent available for the prevention and management of hyperuricemia associated with cancer. It is given as a short IV injection over 30 min, does not necessitate urine alkalinization, does not require adjustment for renal impairment, and is not known to interact with other drugs. Rasburicase instantly reduces uric acid levels, improves kidney

function, and prevents delays in initiation of chemotherapy. Cost is the major limitation for using rasburicase and judicious dosing is recommended. Successful treatment can be achieved with a lower dose and duration than those recommended by the manufacturer (i.e., 0.2 mg/kg daily or twice daily for 5–7 days [31–33]. As each vial contains 1.5 mg of rasburicase, doses should be rounded to the nearest 1.5 mg to prevent waste. Successful treatment of hyperuricemia and prevention of severe renal failure can substantially reduce the need of intensive care and hemodialysis; hence, rasburicase is not only medically but also financially cost effective [34].

Allopurinol still has a role in uric acid control in low-risk patients, and can be given following rasburicase in select cases to cut cost. It does not need to be used with rasburicase, and might actually reduce rasburicase efficacy by blocking xanthine and hypoxanthine conversion to uric acid. Repeated courses can be given and are effective, although a higher incidence of allergic reactions was observed in retreated patients. Current studies are ongoing to determine the incidence and duration of antibody formation in retreated patients, and its correlation with allergic reaction and efficacy. In the meantime, rasburicase can be used in patients at high risk of tumor lysis, allowing chemotherapy to be administered in a timely fashion and in a safer way.

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Treatment and Prevention of Tumor Lysis Syndrome in Children

Experience of Associazione Italiana Ematologia Oncologia Pediatrica

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Abstract

Background: Hyperuricemia and tumor lysis syndrome (TLS) are complications that can arise from treatment of rapidly proliferating and drug-sensitive neoplasms. Clinical trials have shown rasburicase, a recombinant urate oxidase to be more effective than allopurinol for the prevention and treatment of malignancy-associated hyperuricemia. We investigated the safety and efficacy of rasburicase in the AIEOP centers' experience. **Methods:** We reviewed the data of 26 children with malignancy at risk for TLS, submitted to treatment (group 1) or prophylaxis (group 2) of acute hyperuricemia with rasburicase (0.20 mg/kg intravenously daily) for a median period of 4 days. **Results:** Rasburicase produced a significant decrease in uric acid concentrations in all the patients. The control of uric acid levels was obtained in both the groups within 24 h of the first dose with a response rate of 100% (group 1) and 93% (group 2). Normalization of creatinine and phosphorus levels was obtained in 5 and 4 days respectively. Tolerance was excellent without toxicity. **Conclusions:** These data confirm that rasburicase is a safe, highly and rapidly effective agent in the treatment and prevention of malignancy-associated acute hyperuricemia and could be considered the treatment of choice to prevent tumor lysis syndrome in children at high risk for this metabolic complication.

Tumor Lysis Syndrome (TLS) is a constellation of metabolic abnormalities that results from the rapid death of tumor cell and release of their contents into the circulation. Malignant cell death may occur spontaneously in tumors with very high cell turnover, but it is mostly associated with cytoreductive therapy, appearing usually 12–72 h from the initiation of it. The classic triad of TLS

Table 1. Risk factors for TLS

Hyperleukocytosis
Large tumor burden
High LDH
Elevated uric acid
Massive organ enlargement
Chemosensitive tumors
Pre-existing renal dysfunction

includes hyperuricemia, hyperkalemia and hyperphosphatemia that can be associated with hypocalcemia.

Children with malignancies have a 70% chance of event-free survival at 10 years with the use of current multimodal and sometimes highly intensive chemotherapy protocols. Therapy-related morbidity and mortality have, for this reason, a substantial impact on the outcome of childhood cancer.

TLS arise more frequently in children with tumor that have a high proliferative fraction, large tumor burden or wide dissemination and high chemosensitivity (table 1).

For these reasons, this metabolic emergency occur most commonly in Burkitt's lymphoma, lymphoblastic lymphoma, B cell acute lymphoblastic leukemia (ALL) and T cell ALL with hyperleukocytosis and extensive extramedullary disease.

In a recent paper Wossmann et al. [1] analyzed the incidence and complications of TLS in 1791 children with non-Hodgkin's lymphoma (NHL) enrolled in the two subsequent multicenter studies NHL-BFM 90 and 95. Out of this group 78 (4.4%) developed a TLS and 42 (2.3%) oligoanuria. Patients with Burkitt's lymphoma or B ALL had a higher incidence of TLS (8.4%) and anuria (4.4%); in particular patients with B ALL had the highest risk to develop a TLS (26.4%) and anuria (14.1%). Of the 790 patients with Burkitt's lymphoma or B ALL, tumor burden as indicated by the plasma level of LDH was the main predictor for the development of both TLS and anuria. The TLS incidence was 1.2, 12.7, 19.1% for patients with LDH level $<$500, 500–1,000, $>$1,000 U/liter, respectively. The incidence of TLS in patients with T lymphoblastic lymphoma and other B cell NHL was below 2% and anuria occurred in less 1%.

TLS has also been documented in childhood solid tumors such as neuroblastoma and medulloblastoma and it is rare in acute myeloid leukemia (AML) despite the high blood cell count. Reviewing the literature, a total of 45, adult (39) and children (6), patients with solid tumor who developed TLS have been reported from 1977 to 2002. Most of the patients presented with metastatic, therapy-sensitive diseases [2]. As more active chemotherapeutic regimens and immunotherapies become available for the management of cancer, previously

untreatable malignancies are becoming highly responsive to treatment and subject to the same precautions seen with the highly proliferate hematopoietic diseases. TLS has also been observed, although rarely, in children treated with agents that do not have a potent cytotoxic action such as interferon-α, interleukin-2, STI-571, intrathecal methotrexate and other various drug therapies, such as corticosteroids, fludarabine as well as radiation in preparative regimens for bone marrow transplantation.

In the pediatric literature there are a few case reports of children who present hyperuricemia and acute renal failure as an initial presentation of occult lymphoproliferative disorder [3].

TLS Prevention and Treatment

The goal of therapy is to implement preventive treatment regimens and, once evident, to correct the metabolic abnormalities immediately. Close monitoring for risk factors, immediate identification and intervention are essential in preventing the life-threatening consequences of TLS.

Prophylactic measures had considerably decreased the incidence of TLS and the morbidity associated with TLS.

The standard prophylaxis of TLS and urate nephropathy consists of hydration, alkalinization, allopurinol and cytoreductive prophase. For most patients, this regime suffices to prevent clinically significant TLS and acute renal failure (ARF). Hydration is the most important aspect of the management and prevention of TLS: increased hydration translates to increased urinary outflow and improved glomerular filtration rate. Aggressive hydration (2.5–3 liters/m^2/day) should start at least 24 h before chemotherapy. Most clinicians felt that urine alkalinization is mandatory because uric acid is more soluble at high pH (>7), so precipitation of uric acid in renal tubules would thereby be avoided. However, there is no scientific proof in the literature that this approach is effective: a study done in 1977 showed that alkalinization did not improve the abnormalities induced by hyperuricemia [4]. Furthermore, in the presence of hyperphosphatemia and hypocalcemia, the use of alkalinization might aggravate manifestations of hypocalcemia and increase the risk for calcium-phosphate deposition in the kidneys. Allopurinol (300 mg/m^2/day), by preventing the conversion of hypoxanthine and xanthine to uric acid, has long been considered the standard pharmacological approach to hyperuricemia and prevention of TLS. However, allopurinol itself may facilitate precipitation of xanthine crystals, has little influence on already-formed uric acid crystals deposited in the kidney and it may take several days for uric acid levels (UAL) to normalize.

Laboratory evaluation of patients at high risk of developing TLS involves frequent clinical laboratory testing (every 12 h for at least 3 days) including complete blood count, serum sodium, potassium, chloride, calcium, phosphorus,

uric acid, BUN, creatinine (in specific cases, creatinine clearance, Ccr, by Schwartz formula or cystatin C) and urinalysis. It is recommended that a nephrologist be consulted at the first sign of TLS for management of any early involvement. The examination of existing therapies for the potential to contribute to electrolyte abnormalities experienced in TLS is crucial. Exogenous potassium source, ACE inhibitors, potassium-sparing diuretics and drugs known to interfere with aldosterone should be avoided.

In some cases a conventional management would be unable to prevent metabolic instability and ARF.

An alternative approach to managing severe hyperuricemia included the administration of Uricozyme®, a nonrecombinant urate oxidase present in many different organisms, but not in the higher primates, which converts uric acid to allantoin, a readily excretable metabolite five to ten times more soluble at normal tubular pH. This enzyme extracted from *Aspergillus sp*. has been available since 1975 in France and since 1984 in Italy [5], where it was routinely used for the treatment and prophylaxis of severe hyperuricemia following chemotherapy.

Rasburicase, an urate oxidase recombinant form produced by a genetically modified strain of *Saccharomyces cerevisiae* expressing cDNA cloned from a strain of *Aspergillus flavus*, available in Europe, Australia and the USA over the last 2 years, has been defined as a well-tolerated and potent urolytic agent for the treatment and prophylaxis of malignancy-associated acute hyperuricemia and also in order to prevent renal failure [6]. Recombinant DNA techniques and new biochemical processes applied for purification result in a pure and stable product compared with the enzyme extracted from *Aspergillus flavus* used in Uricozyme®, potentially translating into a reduced risk of allergic reaction [7]. Rasburicase has been reported to be significantly more effective than allopurinol in lowering UAL in patients at high risk of TLS. Pui et al. [8] and Goldman et al. [9] compared the use of urate oxidase with standard allopurinol and alkalinization in children with leukemia and Burkitt's lymphoma, confirming the ability of urate oxidase to decrease the UAL faster and more reliably than has been shown for allopurinol. From three prospective studies, Goldman et al. [10] also reviewed the safety and efficacy of rasburicase to both treat and prevent hyperuricemia in 246 children with acute leukemia and NHL at risk for TLS, which showed substantial reduction in the UAL with an excellent efficacy/toxicity ratio in both groups of patients. Efficacy of rasburicase has also been documented by Macfarlane in three children with extreme hyperleukocytosis (WBC $>200{,}000/mm^3$) for ALL [11]. A schedule of rasburicase at a dose of 0.2 mg/kg given intravenously once daily for 5–7 days has been recommended in patients at risk of TLS, but successful treatment with shorter duration of use has also been reported [12]. Anselm et al. [13] presented three children with

ALL and hyperuricemia who received rasburicase as a single dose just prior to the start of chemotherapy. This was followed by rapid reduction of UAL within 24 h, remaining low throughout induction therapy while allopurinol and hydration therapy, without urinary alkalinization, ensued. Probably a shorter course of treatment would be feasible and improve the cost-effectiveness profile of rasburicase.

TLS and ARF

ARF can result from urate, xanthine or calcium phosphate kidney precipitation as well as from tumor involvement in the kidney. As reported by Stapleton et al. [14], ARF continues to be a major in children with advanced stage of Burkitt's lymphoma and B ALL. Ten out of 40 patients (25%) developed ARF 0–132 h following initiation of cytotoxic chemotherapy, for whom 1–4 hemodialysis treatments were required. Ten years later, Seidemann et al. [15], by a retrospective analysis of 1192 patients registered in the NHL-BFM trials, confirmed that, in pediatric NHL-patients, Burkitt's lymphoma and B ALL appear to be the commonest cause of metabolic complications early in chemotherapy. In particular, patients with an advanced stage, large tumor mass (92%, LDH >500 U/L) and signs of impaired renal function at admission (69%) are at high risk for renal failure.

In pediatric literature, there are several case reports suggesting that urate oxidase could be helpful to avoid dialysis in patients with hematological malignancies who develop TLS with ARF. Using Uricozyme, the French pediatric NHL group reported a very low incidence of dialyses (1.7%) during induction chemotherapy for Burkitt's lymphoma or B ALL [16]. This compares favorably to data from the USA (21%) and the United Kingdom (14.3%), where no urate oxidase, but the same chemotherapy regimen was used [17]. Wossmann et al. [1] analyzed, moreover, the incidence and complications of TLS in children with B ALL or stage III/IV Burkitt's lymphoma and an LDH level ≥500 U/L before and after the introduction of protocol amendment (1997) to use Uricozyme for the prophylaxis of TLS, demonstrating that for patients with B ALL, who had the highest risk of developing ARF, there was a significant reduction in anuria reported after introduction of urate oxidase. Finally, a steady improvement of renal function was seen during rasburicase prophylaxis for children with leukemia/lymphoma in a study reported by Pui et al. [18]: renal function was within the normal range in all patients by day 6 of treatment and none required dialyses.

Prospective and more accurate studies on renal function prior to and during therapy are required in order to develop a clinical profile detecting patients at risk for developing ARF and subsequent complications. The beneficial effects of rasburicase on the renal response and the secondary possibility to

Table 2. Patient characteristics

Total	26	
Sex (M/F)	15/11	
Age median (range)	7 (1–18)	
Malignancies		
ALL	11 (42%)	
NHL	8 (31%)	
AML	4 (15.5%)	
Solid tumor	3 (11.5%)	
Groups	Hyperuricemic	Nonhyperuricemic
Cases	12 (46%)	14 (54%)
UAL (mg/dl)	13.73 ± 3.42	3.98 ± 1.68
Creatinine (mg/dl)	1.23 ± 0.52	0.52 ± 0.15
Azotemia (g/liter)	0.80 ± 0.30	0.24 ± 0.08
Phosphorus (mg/dl)	5.6 ± 1.53	4.6 ± 0.75

continue or restart chemotherapy more rapidly may anyway have a favorable impact on overall survival in patients at high risk for TLS.

Experience of Associazione Italiana Ematologia Oncologia Pediatrica

In a recent study conducted by some centers of Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) the efficacy of rasburicase, Fasturtec® is reported, in reducing plasma UAL in children with malignancies at risk for developing TLS and who are submitted to treatment or prophylaxis of acute hyperuricemia. AIEOP centers which participate into the study: Bologna (A. Pession), Pavia (F. Locatelli), Bari (N. Santoro), Modena (P. Paolucci), Brescia (F. Porta), Genova (A. Garaventa), Padova (S. Cesaro) and Parma (G. Izzi).

We retrospectively reviewed 26 patients (15 males, 11 females) who had been submitted to treatment or prophylaxis of malignancy-associated hyperuricemia from January to September 2003. Baseline characteristics of the patients are shown in table 2.

Rasburicase was given daily at 0.15–0.20 mg/kg intravenously in 50 ml normal saline solution over 30 min. The drug was administered in 19 patients (73%) at the first induction chemotherapy, starting 0–48 h before the initiation of antiblastic infusion (concomitantly in 10 cases) and in 7 patients (27%) during the chemotherapy treatment. The response to treatment was defined as maintenance or reduction of UAL $\leq$6.5 mg/dl at 48 h post-treatment and control of hyperuricemia under treatment. Response to the first dose was defined as maintenance or reduction of UAL with respect to the basal value at 24 h after

the start of treatment. A supplementary daily dose was indicated for patients at an especially high risk for hyperuricemia or uncontrolled UAL in the first 72 h.

At presentation no patients showed significant history of atopy or G6PD deficiency.

UAL was measured at the clinical laboratories before drug administration and then daily until at least 48 h after the last dose of rasburicase. Handling procedures and temperature conditions were observed during blood collection in all cases. Physical examination, complete blood counts, serum chemistries were performed daily. None of the patients had received previous treatment with Uricozyme® or Rasburicase.

Patients who were hyperuricemic at presentation were analyzed separately from those who were not hyperuricemic. Comparison of pre- and post-treatment UAL was computed with paired t-test. Descriptive summary statistics (N, mean, median, SD) were computed for each group.

The primary endpoint of our study was to test the efficacy of rasburicase in controlling acute hyperuricemia during the induction or consolidation chemotherapy appropriate for the specific disease. All patients submitted to treatment or prophylaxis with rasburicase showed a highly significant ($p < 0.001$) decline of UAL, maintained 48 h after the last dose. The mean UAL ± SD after treatment was 0.71 ± 0.64 mg/dl for *group 1* and 1.18 ± 1.14 mg/dl for *group 2*. The response rate was 100% for both groups. Uric acid concentrations remained low during the entire course of treatment, with a median and a maximum value not exceeding 2.84 mg/dl and 6.40 mg/dl, respectively, on any day. Only a 5-month-old nonhyperuricemic child (presenting UAL: 4.6 mg/dl), affected by AML, had a transient increase in UAL (from 0.10 mg/dl at 24 h to 6.4 mg/dl at 48 h), decreasing to 0.10 mg/dl 72 h after the first dose, showing, however, a good response to treatment.

The second objective of our study was to test the rapidity of the control of UAL after a single dose of rasburicase. The urate oxidase produced a rapid and significant ($p < 0.001$) decrease in UAL within 24 h after the first injection in all our patients, except for a nonhyperuricemic patient at presentation (nonresponder at the first dose). After the first dose the mean UAL ± SD was 0.51 ± 0.39 mg/dl in *group 1* and 1.83 ± 1.07 mg/dl in *group 2*, with a response rate of 100 and 92.9% for *groups 1* and *2*, respectively. One patient, a 13-year-old girl affected by NHL, submitted to prophylaxis of acute hyperuricemia (presenting UAL: 5 mg/dl), had an increase of UAL 24 h after the first dose (UAL_1: 5.8 mg/dl), decreasing to 5 mg/dl 4 days after the start of treatment, anyway showing a response, even though not significant.

The decline in UAL was more evident for the hyperuricemic patients (fig. 1).

The median (range) treatment duration was 4 (1–11) days. No patients needed supplementary treatment to control UAL.

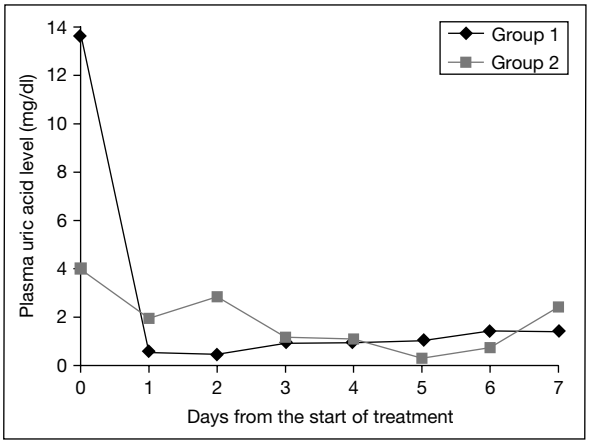

Fig. 1. Comparison of plasma UAL during treatment with recombinant urate oxidase and chemotherapy in Group 1 (treatment; n = 12) or Group 2 (prophylaxis; n = 14).

Four of 5 patients (all from the group 1) with elevated serum creatinine levels at presentation (mean ± SD: 1.86 ± 0.47 mg/dl) showed a progressive decrease in creatinine concentrations from the 3rd day onwards with completely normal values 5 days after the start of treatment (mean ± SD: 0.85 ± 0.13 mg/dl) and did not develop renal failure or hypertension or require dialysis. A six-year-old girl, affected by Wilm's tumor, developed ARF with progressively increasing serum creatinine levels, which was then corrected by pharmacological treatment only. The 3 patients (all from the group 1) with elevated serum phosphorus concentrations at the onset (mean ± SD: 7.8 ± 0.48 mg/dl) had a decrease in phosphorus hematic levels with completely normal values 4 days after the start of treatment (mean ± SD: 3.7 ± 0.46 mg/dl). Serum potassium and calcium concentrations were relatively stable throughout the treatment course in all cases.

Rasburicase was very well tolerated in all our patients. No patients showed even mild hypersensitivity reactions during or after infusion. Other drug-related adverse events such as headache, fever, rigors and hemolysis were not observed.

In all cases the treatment with urate oxidase was associated with hyperhydration (2–3 liters/m^2 daily), and in 19 cases (73%) with urine alkalinization.

Our data demonstrate that rasburicase is a safe and highly effective drug for the prevention and treatment of hyperuricemia, with a marked decline in UAL 24 h after the first injection. The time over which the control of UAL occurs has not been evaluated in this limited set of patients; however, studies on both adults [19] and children [20] have demonstrated that UAL is reduced to normal values within 4 h after the first injection in the majority of the patients.

In our study, patients presenting with hyperuricemia showed a greater response to treatment than nonhyperuricemic patients at baseline. On the basis of the results of important international studies which show a similar response rate in hyperuricemic and nonhyperuricemic patients [21], our data would be anyway supported by other prospective studies comparing the response rate in the two groups of patients.

Considering the duration of treatment, even if literature advises a mean number of 4 doses to control acute hyperuricemia in children [8], our study suggests that, in some patients, even hyperuricemic, with normal renal function, one dose could be sufficient. This confirms the need of individualizing treatment schedule according to the patient's clinical characteristics such as the type and the burden of malignancy, the anticancer treatment and, hence, the duration of tumor cell lysis.

The steady improvement of renal function during treatment with urate oxidase in the patients with impaired renal function at presentation, none of whom required dialysis, is remarkable in considering literature data. Hyperphosphatemia with consequent hyperphosphaturia is another important cause of ARF due to tumor cell lysis. Rasburicase may obviate the need of urine alkalinization, facilitating phosphorus excretion. The last consideration cannot be analyzed in our study considering that only 27% of our patients did not receive sodium bicarbonate infusion. Rasburicase was very well tolerated in all the patients, demonstrating the absolute safety of the recombinant urate oxidase, in particular considering the hypersensitivity reactions which occur after nonrecombinant urate oxidase infusion. Additional studies are needed to test the safety of rasburicase in patients with a history of allergy.

However, as with other oxidative agents, it should not be used in patients with known G6PDH deficiency. Hydrogen peroxide, one of the by-products of breakdown of uric acid to allantoin, can induce hemolytic anemia or methemoglobinemia in patients with G6PDH deficiency.

The pharmacoeconomics of rasburicase and its administration should be considered too. In this study we have not evaluated the pharmacoeconomic benefits or collected treatment-related costs. The low incidence of renal failure and metabolic complications, associated with the absence of toxicity, may, however, suggest a pharmacoeconomic benefit in the use of this drug as suggested by the devoted literature [22]. In conclusion Rasburicase is a safe and highly effective agent for the prevention and treatment of acute hyperuricemia, in particular, in the patients at high risk for developing TLS.

Recommendations for TLS Prevention and Treatment in Children

On the basis of our experience and literature data we could advance some recommendations regarding the optimal use of human recombinant urate oxidase in children defining risk stratification for developing TLS (table 3).

Table 3. Criteria to define the risk for TLS in children with malignancies

High Risk		Low Risk
At least one of the following clinical and/or laboratory criteria		No High
Clinical criteria	Laboratory criteria	
ALL with leukemia/lymphoma syndrome	WBC ≥50,000 m^3	
B ALL – FAB L3	UAL ≥7 mg/dl	
Stage III and IV NHL	LDH ≥2 times over the normal range	
Bulky disease	Phosphoremia ≥6.5 mg/dl	
Renal impairment at diagnosis	Creatinine or Ccr over the normal range for age	

Precocious identification of patients at high risk to develop TLS is critical. To define children at high risk of TLS, one of the following clinical or laboratory criteria is needed and sufficient:

Clinical criteria:

(1) ALL with leukemia/lymphoma syndrome: the presence of mediastinal enlargement or lymph node involvement or high WBC count plus T immunophenotype or normal Hb level or normal platelet counts are criteria to recognize this clinical profile at high risk for chemosensitivity and large tumor burden.

(2) B ALL FAB L3: B mature ALL is constantly associated with FAB L3 (vacuolated cells) category characterized by high chemosensitivity.

(3) NHL stage III and IV: high tumor cell death, both spontaneous and chemotherapy induced, are present in advanced NHL stages.

(4) Bulky disease: all cases with lymphoproliferative disorder with the presence of a large mass at onset have to be considered as high risk for TLS.

(5) Renal impairment at diagnosis: apart from renal function failure, the involvement of kidneys in children at the onset represent a rare but relevant risk factor.

Laboratory criteria:

(1) WBC ≥50,000/m^3

(2) LDH ≥2 times over normal range

(3) UAL ≥7 mg/dl

(4) Phosphoremia ≥6.5 mg/dl

(5) Creatininemia or Ccr (cm × 0.55/creatinemia) over normal range for age

The remaining population is at low risk to develop TLS.

Patients at high risk of TLS will receive rasburicase (0.20 mg/kg/day) for 5 days in addition to hyperhydration (2.5–3 liters/m^2 G5% plus electrolytes).

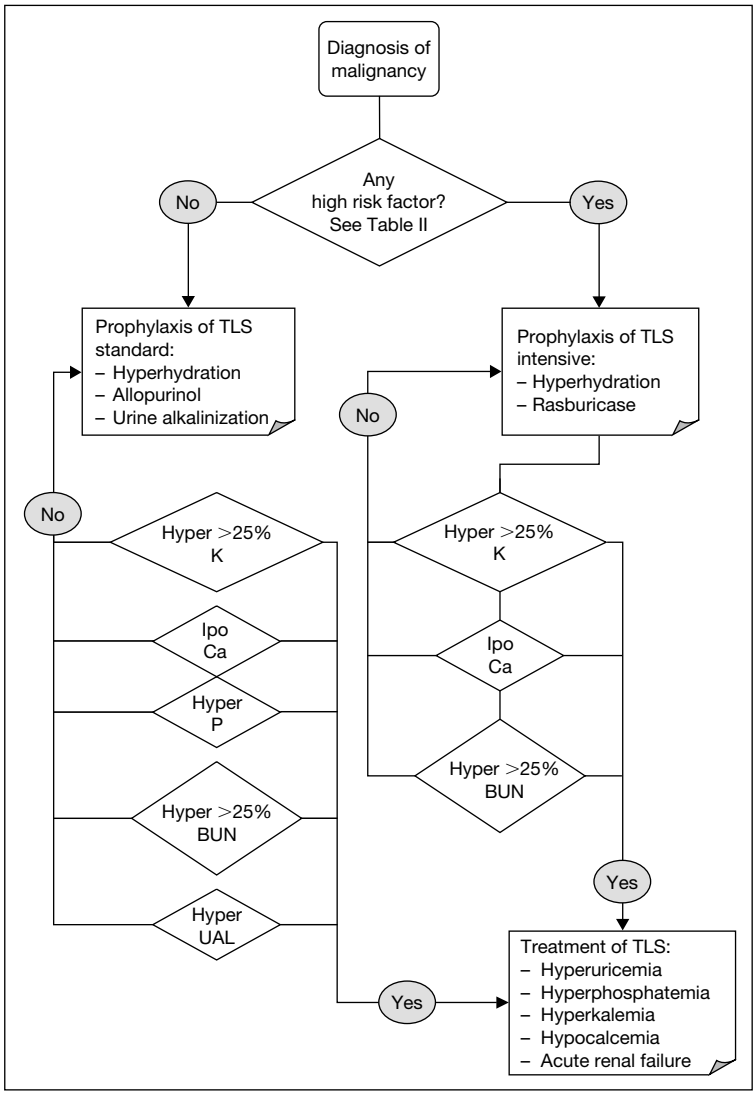

Fig. 2. Algorithm for TLS prevention and treatment in childhood.

Instead, patients at low risk, will be treated with the standard therapy: allopurinol (300 mg/m^2) in addition to hyperhydration (2.5–3 liters/m^2 G5% plus electrolytes) and urine alkalinization (pH >7).

Regarding the use of rasburicase, we recommend the start of treatment at the dosage of 0.2 mg/kg/day just before (4 h) beginning chemotherapy and then

continuing for as long as tumor lysis persists for duration of at least 4 days under chemotherapy. The elevated urinary allantoin excretion during the first 4 days of treatment, which reflects an ongoing generation of uric acid from tumor lysis, supports the need to continue rasburicase treatment for this duration: shorter treatment duration might increase the risk of failure. However, a single dose of rasburicase would be taken into account for the treatment of patients at low risk of TLS.

In patients at high risk of TLS levels of LDH, uric acid, sodium, potassium, creatinine, BUN, phosphorus and calcium would be monitored every 12 h for the first 3 days and subsequently every 24 h. Probably, in same specific cases, a precise evaluation of the renal function would be done by Schwartz formula (Ccr) or cystatin C, but a multidisciplinary approach to evaluate this aspect of treatment is needed before considering it as a standard evaluation.

An algorithm for the management of children with malignancy is reported in figure 2. In these schema criteria to choose a standard or an intensive preventive treatment of TLS is integrated with the laboratories' criteria to eventually decide to proceed with specific electrolyte correction and/or treatment of ARF.

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Intensive Chemotherapy in Patients with Lymphoma

Management of the Risk of Hyperuricemia

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Abstract

Intensive chemotherapy with stem cell autograft is a well-established salvage treatment for relapsed/refractory lymphoma patients aged less than 65 years and it is also an effective treatment option for high-risk patients at diagnosis. Clinical applicability of autograft has been greatly amplified by the use of peripheral blood progenitor cells (PBPC), whose administration is simple and feasible, and results in lower toxicity. In addition, the development of several prophylactic measures preventing extrahemopoietic toxicities has markedly improved the feasibility and tolerability of the approach. In particular, the risk of nephrotoxicity is no more a major problem in the autograft setting since the use of proper treatments for the management of hyperuricemia, including forced hydration along with urinary alkalinization and the administration of the recombinant urate oxidase drug rasburicase. The high-dose sequential (HDS) chemotherapy program is a typical example of an intensive chemotherapy with PBPC autograft. A 15-year experience with the HDS approach in 240 lymphoma patients is reported here. The results demonstrate the clinical efficacy of HDS, with prolonged survival both in relapsed/refractory patients (54% alive) and in those treated frontline (72% alive). In addition, a very low incidence of extrahemopoietic toxicities was observed. In particular, nephrotoxicity was almost abolished, with 2 patients displaying only mild and transient renal dysfunction. In conclusion, the reported results demonstrate the therapeutic efficacy of HDS in the treatment strategy for lymphoma and emphasize the importance of delivering intensive chemotherapy with all the prophylactic measures able to minimize nephrotoxicity and other potential extrahemopoietic toxicities.

Introduction

Intensive chemotherapy with autologous stem cell transplantation (ASCT) is extensively employed in the management of chemosensitive tumors, especially lymphomas, where it is now the most frequently employed treatment for relapsed patients aged less than 65 years [1–2]. In the last decade, several studies have shown the superiority of ASCT compared to conventional chemotherapy programs in the salvage treatment of both Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL) [1–6]. There is also recent evidence of the potential efficacy of intensive chemotherapy with ASCT as a first-line approach in both low- and high-grade NHL patients, presenting with high-risk clinical features [7–10]. Indeed, clinical applicability of ASCT has been greatly amplified by the use of peripheral blood progenitor cells (PBPC), whose administration is simple and feasible, and results in lower toxicity and better cost effectiveness than bone marrow (BM) transplantation [11–12].

The first report on the use of PBPC for autograft was published in 1989 [11]. That study reported that: (1) following chemotherapy and growth factor support, a massive amount of hematopoietic progenitor cells are mobilized into the peripheral blood; and (2) these immature elements can be easily collected and are able to assure prompt engraftment when reinfused in autografting procedures. Since then, autograft with PBPC became more and more popular and represents one of the most important therapeutic options in chemosensitive tumors nowadays. Indeed, PBPC allow a faster engraftment compared to BM cells when reinfused during autograft. As a consequence, autograft performed with PBPC implies a dramatic reduction of those toxic complications associated with BM-based procedures [12, 13]. In particular, the advantages offered by the use of PBPC compared to BM cells include a significant reduction of: (1) infectious and hemorrhagic risks; (2) overall treatment-related mortality (TRM); (3) need of transfusional, antibiotic and supportive therapy; (4) duration of hospitalization; and (5) costs of the whole autografting procedure. Probably, the marked reduction of TRM is the most relevant aspect. At present, the reported TRM in large series of patients receiving PBPC autograft does not exceed 1–2% [13–15]. Given the good hematological tolerability of PBPC-supported ASCT and its widened applicability, particular attention should now be paid to the potential extrahematological toxicity, particularly on kidney, heart and liver, in all patients undergoing intensive chemotherapy with autograft.

Several reports suggest that ASCT is most effective when performed after maximal cytoreduction. For instance, all randomized studies favoring the upfront use of ASCT in poor prognosis, aggressive NHL have employed autograft as consolidation therapy after prolonged or intensified induction chemotherapy [9, 10, 15–17]. By contrast, abbreviated standard induction management followed by

early ASCT has proved ineffective [6, 18]. The importance of an intensive debulking prior to autografting has been clearly demonstrated in refractory/relapsed HL as well [19, 20]. Thus, adequate chemotherapy-based debulking is probably the best prerequisite for an optimal use of ASCT. Once again, the improved hematological tolerability of the autograft if performed with adequate amounts of PBPC, now allows the inclusion of very intensive debulking schedules, without any adverse effect on the rapid hematological recovery following PBPC autograft [21].

The high-dose sequential (HDS) chemotherapy regimen is based on the concept of early high-dose (HD) chemotherapy followed by autograft [12, 15, 21]. The peculiarity of the cycle stems in the delivery of HD drugs since the early beginning, with a final autograft performed with PBPC collected in the HD phase. Since 1989 we have treated high-risk lymphoma patients with this approach [22]. Following the initial experience with the first generation HDS, we then developed the 'second and third generation' HDS regimens, characterized by a more effective early intensification. We illustrate here the evolution of the HDS approach in the recent past, along with the overall toxicity and efficacy of the HDS approach, based on the long-term follow-up of a wide, though heterogeneous, patient population. The issue of potential renal toxicity following an intensive program such as HDS will be addressed with particular emphasis.

Schedule of HD-Chemotherapy Administration and ASCT in the HDS Program

The HDS approach is a typical example of an intensive chemotherapy program specifically designed for lymphoma patients. Details of the various HDS schedules that have been developed so far are shown in figure 1. The initial experience started in 1989 with the original HDS (o-HDS) regimen [23]. Following a very short debulking with one reduced-dose APO course (doxorubicin + vincristine + prednisone), original-HDS then included the sequential administration at 10- to 15-day intervals of: (1) cyclophosphamide (CY) at 7 g/sqm intravenous (i.v.); (2) methotrexate (8 g/sqm) plus vincristine (2 mg i.v.); and (3) etoposide (VP16) at 2 g/sqm i.v.; PBPC harvest was scheduled at hemopoietic recovery following CY. The regimen ended with a myeloablative treatment and PBPC autograft, using total body irradiation plus L-PAM or HD-L-PAM alone as the conditioning regimen.

Later on, 'second generation' HDS regimens were developed. In particular, two novel schemes were designed in order to further increase the efficacy in poor prognosis, aggressive NHL (C-HDS) and to develop a suitable schedule for patients with indolent lymphomas (intensified-HDS; i-HDS) [8, 24]. While designing second generation HDS regimens, the main goal was to

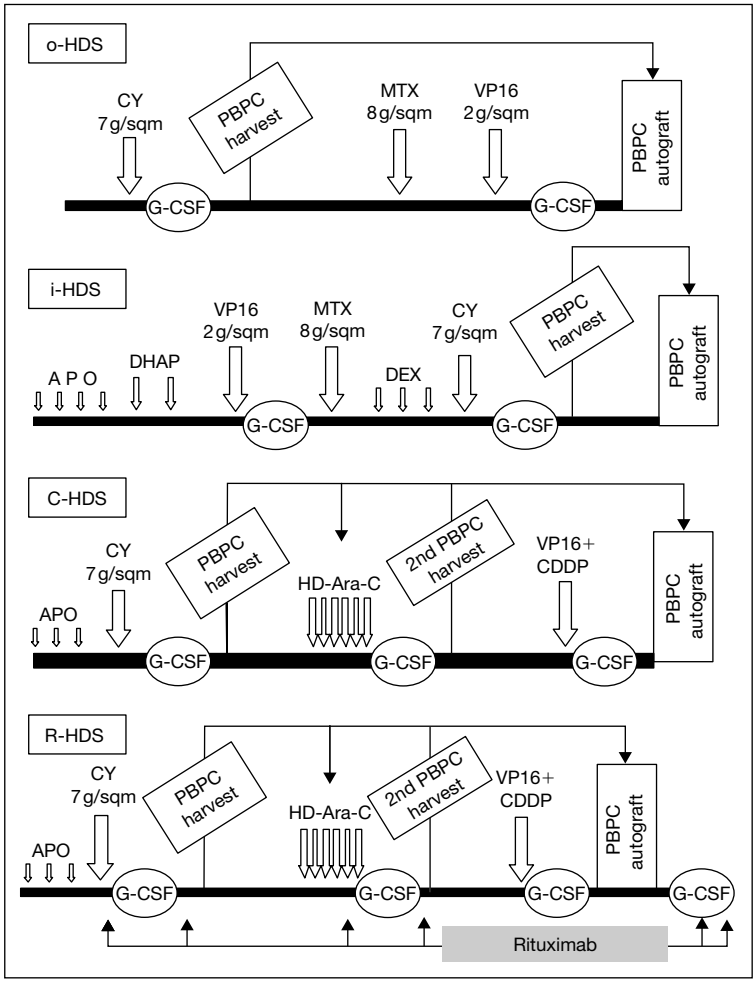

Fig. 1. Development of the first, second and third generation HDS regimens. o-HDS = Original HDS; i-HDS = intensified HDS; C-HDS = HD-Ara-C-HDS 2 g/sqm every 12 hrs for 6 consecutive days; R-HDS = rituximab-supplemented HDS; CY = cyclophosphamide; MTX = methotrexate; VP16 = etoposide; MITO = mitoxantrone; L-PAM = melphalan; APO = adriamycin-prednisone-vincristine; DHAP = dexamethasone-HD-Ara-C-cisplatin; CDDP = cisplatin; PBPC = peripheral blood progenitor cells.

minimize the risk of tumor contamination on cell harvests by exploiting a sort of purification (in vivo purging) operated by chemotherapy [25]. As illustrated in figure 1, i-HDS includes a prolonged debulking with APO and dexamethasone-HD-Ara-C-cisplatin (DHAP) courses [8]. The whole HD sequence is then

scheduled and PBPC (or BM) harvest is postponed to the end of the HD-drug delivery. The C-HDS has only recently been developed [22, 24]. It was specifically studied for aggressive (i.e., high-grade) NHL. For this reason, HD Ara-C has been included. In order to reduce hematological toxicity, $1–3 \times 10^6$ CD34/kg are infused following Ara-C. In addition a second progenitor cell harvest is scheduled following Ara-C, with the dual aim to collect less contaminated cells due to the extensive in vivo purging operated by two consecutive HD-drug delivery and to collect as many progenitors as possible. In both schemes, the final myeloablative consolidation does not include total body irradiation in order to minimize postgraft side effects [26–27]. The conditioning regimen generally includes the combination of high-dose mitoxantrone and melphalan (L-PAM) [15].

The most recent, third generation, HDS schedule takes advantage of the availability of a very effective new drug, the anti-CD20 rituximab [28]. The introduction of rituximab has represented a major advance in the management of B cell lymphoma. The efficacy of conventional chemotherapy can be enhanced by rituximab, as shown by several recently reported studies [28, 29]. The addition of rituximab may also improve the ASCT programs by intensifying both the anti-tumor activity of chemotherapy and the in vivo purging effect prior to PBPC harvesting. Thus, rituximab has been included in our 'third generation' HDS programs for all NHL of B cell phenotype [30, 31]. As shown in figure 1, rituximab has been placed immediately before PBPC harvesting in order to maximally exploit its in vivo purging effect. Our preliminary experience with rituximab-supplemented C-HDS has given promising results in both the salvage and the first-line treatment of high-risk lymphoma [30, 31]. Ongoing multicenter studies will clarify whether rituximab-supplemented ASCT may substantially improve the outcome of B cell NHL patients that otherwise would have a poor life expectancy if treated with conventional chemotherapy.

Prophylactic Measures to Minimize Nephrotoxicity of HD-Chemotherapy and ASCT

Besides hematological toxicity, intensive treatments are associated with potential side effects on extrahemopoietic organs. Renal failure is a frequent and harmful complication following HD-chemotherapy administration and ASCT and its etiology may be multifactorial [32, 33]. Renal dysfunction may be a consequence of direct nephrotoxicity from several chemotherapeutic agents; moreover, it may result from uric acid-induced nephropathy. Although this dysfunction is usually reversible, all therapeutic maneuvers able to minimize

Table 1. Standard treatments to prevent nephrotoxicity of high-dose chemotherapy administration in patients managed with the HDS approach

Therapeutic approach	Procedure
Aggressive i.v. hydration	Equal volumes of isotonic saline (0.9% NaCl) and 5% Dextrose at 2.5–3 L/24 h/sqm KCL 20–30 mEq/L of fluids
Urinary alkalinization	$NaHCO_3$ 30 mEq/L of fluids acetazolamide 250 mg p.o., q.i.d.
Serum uric acid reduction	Recombinant urate oxidase (rasburicase) at 0.10 mg/kg/day i.v.*

*Rasburicase provides a safe and effective alternative to allopurinol for lowering uric acid levels and preventing uric acid nephropathy (see text for details about dosage).

this risk should be included in treatment protocols for patients receiving HD-chemotherapy and ASCT. The main prophylactic measures to prevent nephropathy in patients treated with the HDS program are summarized in table 1.

Chemotherapeutic agents such as cisplatin, cyclophosphamide, methotrexate and melphalan have a well-known potential nephrotoxicity and may induce acute renal failure. In programs such as HDS, these drugs are administered as a single agent at very high doses, with the exception of cisplatin, which is given at standard dose in the DHAP courses. The only effective prophylactic measure to prevent drug-induced nephropathy is an adequate intravenous hydration [33]. As shown in table 1, all patients undergoing HDS receive forced intravenous hydration with 2.5–3 L/sqm/day, starting 12 h before and maintained up to 2–3 days after each HD-drug administration. The forced intravenous input is maintained to ensure a urine output of 100–150 mL/h.

Besides anti-neoplastic chemotherapeutic drugs, other nephrotoxic agents, namely antibiotics, anti-fungal and anti-viral agents, may be required in patients undergoing intensive treatment and ASCT. Omission of the most nephrotoxic drugs should always be carefully considered. However, if highly nephrotoxic agents are required, such as aminoglycoside, glycopeptide, amphotericin B, or anti-CMV agents, i.e. gancyclovir and/or foscavir, the drug dosage must be adjusted on the blood creatinine clearance and, when feasible, serum drug levels should be monitored daily. Again, adequate fluid intake should be maintained.

Forced hydration is also the basic measure to prevent uric acid-induced nephropathy [34]. Rapid cell lysis with consequent hyperuricemia is a common feature of cytotoxic therapy of hematological malignancies [35]. The risk of

acute uric acid nephropathy is particularly high in patients with chemosensitive disease receiving HD-chemotherapy. Furthermore, maximal risk occurs in the early treatment phases, when the high tumor burden undergoes a rapid cytoreduction, with the consequent occurrence of the tumor lysis syndrome which leads to acute renal dysfunction [36, 37]. A lower risk of nephrotoxicity is associated to the late treatment phase, including ASCT. In fact, ASCT is effective if performed after extensive tumor reduction and very often its main objective is the elimination of minimal residual disease. Thus, the correct management of hyperuricemia is a critical issue in the beginning of any intensive chemotherapy program [34, 38].

Prevention of uric acid-induced nephropathy involves forced alkaline diuresis. As detailed in table 1, this may be accomplished by aggressive intravenous hydration, associated with infusion of sodium bicarbonate and acetazolamide orally, in order to maintain a urine pH of 6.5–7.5 and thus prevent uric acid precipitation. Daily monitoring of serum creatinine and electrolytes is highly recommended along with control of urine volumes every 6 h and monitoring variation of body weight twice daily. This careful monitoring will direct adjustments in electrolyte intake and diuretic administration.

Besides aggressive hydration, treatments aimed to reduce the serum uric acid levels can also be added. For instance, a decrease of uric acid production can be achieved by allopurinol, 300–600 mg orally. However, several factors limits the applicability and efficacy of allopurinol, including: (1) the latency period of 2–3 days required to achieve a sustained activity in vivo; (2) the risk of worsening an underlying mild renal insufficiency; (3) the frequent hypersensitivity reactions, ranging from a minor skin rash up to diffuse exfoliative dermatitis with fever and renal and hepatic injury; (4) the potential interaction with some chemotherapeutic agents. For these reasons, allopurinol has almost never been employed in patients treated according to HDS programs.

Recently, a novel drug, rasburicase, has been made available for patients with hyperuricemia [39]. Like allopurinol, rasburicase is able to reduce serum uric acid levels, although its mechanism of action does not imply inhibition of uric acid production but transformation of uric acid into the less toxic allantoin catabolite. Compared to allopurinol, rasburicase is rapidly active after intravenous administration and it is associated with less side effects [40]. Thus, since its availability, rasburicase has been included in the HDS programs, although its use is limited to the patients presenting with high tumor burden and/or high serum uric acid level. As detailed in table 1, the aggressive hydration with urine alkalinization is always included in the treatment protocol. This induced us to deliver rasburicase at a lower dosage compared to that commonly recomended (0.10 vs. 0.20 mg/kg/day) and for a reduced period (3–5 vs. 5–7 days).

Table 2. Main clinical features and long-term outcome of 240 lymphoma patients treated with the HDS program and autograft

Parameter	Disease status	
	Refractory/relapsed (n = 74)	At diagnosis (n = 166)
Age (years), median (range)	41 (16–69)	46 (18–64)
Sex (M/F)	42/32	96/70
Histology		
HL, n (%)	30 (41)	0
Low-grade NHL, n (%)	20 (27)	71 (43)
High-grade NHL, n (%)	24 (32)	95 (57)
Patients alive, n (%)	40 (54)	120 (72)
Median follow up, years, (range)	46 (7–144)	63 (5–162)
Patients alive in CCR, n (%)	40 (54)	102 (61)
Median follow up, years, (range)	45 (6–140)	58 (5–162)
Acute nephrotoxicity, n (%)	0	2 (1.2)
Chronic nephrotoxicity, n (%)	0	0

HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma

The 15-Year Experience with the HDS Approach in 240 Lymphoma Patients: Prolonged Disease-Free Survival with a Very Low Incidence of Extrahemopoietic Toxicities

Since 1989, 240 lymphoma patients have been treated at our institution with HDS and autograft, and can be evaluated for treatment tolerability and long-term outcome [22]. Most patients were aged less than 60 years, few were between 60 and 65 years. They were eligible for HDS if they presented with: (1) HL or NHL and refractory or relapsed disease after conventional therapy, or (2) NHL at diagnosis and poor prognostic features. The main patient characteristics are summarized in table 2.

Overall, there were seven fatal toxic events during the autografting phase, accounting for a TRM of 2.9%. The toxic events were due to: sudden cardiac arrest (one patient), prolonged pancytopenia after postgraft abdominal irradiation (one patient), massive cerebral hemorrhage (one patient) and infectious

complications (4 patients). No severe nephrotoxicities were observed neither during the HD-phase nor following autograft. Only 2 patients displayed mild and transient renal dysfunction, preventing the delivery of the second DHAP course and of the HD-Methotrexate, respectively. Four more patients had severe renal failure, which was related to massive abdominal disease progression. At present, 160 patients are long- term survivors and none of them show signs of renal function impairment. Indeed, a very low incidence of extrahemopoietic toxicities was observed at long term and no late fatal toxicities have been observed so far.

Patients treated for refractory/relapsed disease did well: 54% are currently alive and disease free, as detailed in table 2. The result is particularly satisfactory if compared with the poor prognosis of refractory/relapsed patients managed with conventional salvage programs. HDS proved to be feasible and of some benefit both in HL and NHL patients. Indeed, a recent survey on 102 HL patients treated by fourteen Italian members of the Intergruppo Italiano Linfomi has shown evidence that HDS with PBPC autograft is an effective rescue program for refractory/relapsed HL patients [20]. In that study, the 5-year overall survival and event free survival projections were 64 and 53%, respectively. A similar multicenter, retrospective analysis has been performed in refractory or relapsed diffuse large B cell and T cell lymphoma, treated with HDS and ASCT. The 3-year estimates of overall survival and event-free survival were 47 and 44%, respectively [41]. Again, the retrospective study showed that salvage treatment using HDS had relatively low toxicity and was associated with remarkable response rates. Both studies confirm that intensive therapy with ASCT is now the first choice of treatment for both HL and NHL with recurrent disease.

In our series, most patients received HDS as first-line therapy for either aggressive (43%) or indolent (57%) NHL. They entered the intensive program due to poor prognosis, most often identified as intermediate-high IPI score. As shown in table 2, 72% are currently alive and 61% survive disease free. Patients with aggressive NHL had a better outcome than those historically reported with conventional chemotherapy. The HDS program was also very effective in indolent NHL patients, as reported in a recent study on a large series of patients, including follicular, mantle-cell and small lymphocytic lymphoma [42]. The reported results show that a high proportion of follicular lymphoma patients may attain a durable clinical and molecular remission following HDS. Indeed, achievement of clinical and molecular remission was associated with prolonged survival in the absence of disease recurrence. This suggests that cure is a reasonable treatment goal in follicular lymphoma also, a disease historically considered incurable with conventional chemotherapy approaches. In order to increase the proportion of patients achieving molecular remission, the inclusion of the

anti-CD20 monoclonal antibody rituximab into intensive chemotherapy programs is currently being investigated [30, 31].

In conclusion, disease progression remains the main cause of failure after intensive chemotherapy and ASCT. The use of PBPC combined with careful prophylactic measures to prevent extrahemopoietic toxicities has made the ASCT a feasible, widely applicable and effective treatment approach for high-risk lymphoma patients. In particular, the risk of nephrotoxicity is no more a major problem in the autograft setting since the use of forced hydration along with urine alkalinization and the administration of drugs like rasburicase, which is able to markedly reduce serum uric acid levels.

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Hyperuricemia and Bone Marrow Transplantation

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Abstract

Blood uric acid levels and purine metabolism are affected in many ways after bone marrow transplantation (BMT). Although BMT is usually performed when patients have a low residual disease burden, a proportion of them are still at risk of tumor lysis syndrome, even with limited disease or after nonmyeloablative conditioning regimens; moreover, an alteration in uric acid turnover can also be observed in patients with persistently normal uric acid blood levels. Apart from this obvious complication, multiple physiopathological events occurring after transplantation may derange uric acid homeostasis. Although there is only indirect evidence (derived from obstetric eclampsia and experimental gout arthritis), a transplant-related increase in cytokine production (particularly TNF, IL-1 and IL-6) may activate xanthine oxidase which, in turn, may be responsible for a further cytokine bout: deranged cytokine homeostasis is involved in the pathogenesis of some of the main acute post-BMT complications, such as hepatic veno-occlusive disease (VOD) and acute graft-versus-host disease (aGVHD). Hyperuricemia is also a well-known side effect of cyclosporine A, the reference drug for the prevention of post-BMT GVHD, which may affect uric acid turnover by reducing glomerular filtration and/or affecting tubular handling; the available evidence favors the former explanation. Hyperuricemia is found in long-term transplanted patients as part of a metabolic pattern reminiscent of the so-called 'X' or 'metabolic' syndrome related to insulin resistance: there is still no precise interpretation of this post-transplant complication nor any definite data concerning its real incidence and outcome. Hyperuricemia is frequently regarded as a marginal finding in the context of X syndrome, but it is pathogenetically linked to the other component of the syndrome and has proved to be autonomously responsible for tissue and vessel damage. Finally, BMT is a possible therapeutic strategy for some inherited forms of hyperuricemia, particularly Lesch-Nyhan disease, although there is still some perplexity concerning the possibility of preventing the development of neurological impairment.

Introduction

Blood uric acid levels and purine metabolism are not uncommonly altered in bone marrow transplantation (BMT) patients. Although BMT should usually be performed when patients are in complete remission or at least have a low residual disease burden, a variable proportion are at risk of tumor lysis syndrome, and alterations in purine metabolism have been observed in BMT patients with limited disease. Furthermore, multiple physiopathological events occurring after transplantation may derange uric acid homeostasis. Hyperuricemia is also a well-known side effect of cyclosporine A (CsA) treatment and may also follow the use of other drugs except chemotherapeutic agents. Hyperuricemia may also be found in long-term transplanted patients as part of a metabolic pattern reminiscent of the so-called 'X-syndrome' or 'metabolic syndrome.'

In the last part of this review, brief mention will be made of BMT as a treatment of choice for some inherited forms of hyperuricemia, particularly Lesch-Nyhan disease.

Hyperuricemia as a Complication of BMT

BMT is usually performed after a myeloablative conditioning regimen in order to prolong disease-free survival in complete remission patients at high risk of relapse. However, it is also frequently used as a rescue therapy in patients with progressive disease and some neoplasias, such as chronic myeloid leukemia or myelodysplastic syndromes, do not necessarily require a significant pre-transplant cytoreduction. Moreover, BMT has recently been performed after reduced intensity conditioning regimens, a strategy that primarily relies on the 'graft versus tumor effect' to eradicate neoplastic disease. Such patients often have refractory or even active disease, and are, therefore, at risk of tumor lysis syndrome.

No extensive studies of altered purine metabolism in BMT patients have been recently published, probably because it is common practice to combine uricemia-lowering agents and hyperhydration with diuretics and urine alkalinization before and during conditioning, which clearly hinders the evaluation of baseline uric acid production and excretion [1]. Nevertheless, a crude 1–2% rate of severe iatrogenic hyperuricemia has been reported as a consequence of tumor lysis syndrome after myeloablative conditioning [1, 2], and this complication is sometimes reported even in patients receiving a reduced intensity preparative regimen [3]. In particular, subjects with chronic lymphoproliferative disorders are at risk of developing tumor lysis syndrome because of the increased susceptibility of lymphoid tissue to the cytolytic effect of anti-tumoral agents [2, 4].

It should be remembered that serum uric acid is a poor indicator of uric acid turnover [1, 5] because the kidney excretion of urate markedly increases after the delivery of a conditioning regimen even in the presence of low serum uric acid levels. Uric acid excretion may be so high that it raises the question as to whether allopurinol should be considered the drug of choice in preventing and managing secondary nephropathy because, when the amount of xanthine coming from the use of allopurinol exceeds its urine solubility, there is a risk of xanthine urolithiasis [1]. Moreover, as allopurinol does not affect preformed uric acid, BMT recipients risk early urate nephropathy in the first days after the delivery of a conditioning regimen; furthermore, allopurinol treatment can rarely induce a life-threatening syndrome of desquamative erythrodermy accompanied by hepatic and renal failure. For all these reasons, treatment with uricase (which leads to the production of highly soluble allantoin) should be considered in the patients at some risk of tumor lysis syndrome because of residual disease or an underlying lymphoproliferative disorder. It has been shown that rasburicase is more effective and probably less toxic than other uricases.

Uric acid production and urinary excretion decrease over the days following BMT [6]. Subsequently, serum uric acid levels decrease as part of the consumption of total serum anti-oxidant potential, a well-known complication of BMT that is considered to be a predisposing condition for the development of hepatic veno-occlusive disease and acute graft-versus-host disease (aGVHD) [7, 8]. However, other events may derange uric acid homeostasis after BMT, although only indirect evidence is available from observations of obstetric eclampsia, in which cytokines cause an increase in uric acid production, and experimental gout, in which tissue uric acid stimulates cytokine production [9–12]. An increase in C-reactive protein is a common finding during the course of BMT, and may lead to an increase in uric acid production and even uric acid blood levels in the presence of an inadequate urinary output of the metabolite [11, 12]. The thyroid is a target of post-BMT toxic and immunological events and, in combination with the effects of CsA and other drugs, thyroid dysfunction may lead to hyperuricemia [13, 14].

An increased and deranged production of many cytokines is common after a BMT conditioning regimen. Some cytokines contribute to the development of tissue damage, the expression of major and minor histocompatibility antigens, and the regulation and polarization of lymphocyte subpopulations, a sequence of events involved in the development of aGVHD. The relationships between many cytokines and uric acid homeostasis after BMT are far from clear. Under different clinical and experimental conditions tumor necrosis factor, (TNF), Interleukin-1 and -6 have been reported to activate xanthine oxidase, thus stimulating uric acid production [9, 15–18]. Even in the absence of an increase in blood uric acid level, this effect may lead to further cytokine activation and

indirectly contribute to the development of tissue damage and possibly aGVHD [19]. A relationship has also been observed between high TNF levels and insulin resistance, which may further affect blood uric acid levels [17, 18].

Hyperuricemia Secondary to CsA and Other Non-Cytotoxic Agents

The evaluation of post-BMT uric acid turnover is made more intriguing by the interference of drugs other than cytotoxic agents. Increased serum uric acid levels characteristically follow treatment with CsA, the standard immunosuppressive agent used to prevent GVHD, which has multiple effects on renal function [5]. In some patients, hyperuricemia may simply mirror renal damage in the same way as increased serum urea and creatinine levels, but CsA-related hyperuricemia is more frequently a side effect that is not directly related to renal damage [5, 20].

CsA reduces renal blood flow mainly by constricting the afferent arteriolar bed, and also interferes with proximal tubular function. CsA-related hyperuricemia may be an expression of reduced glomerular filtration decreasing the amount of filtered uric acid, or may be related to the drug's interference with the tubular handling of uric acid [21]. The currently available evidence favors the first explanation [5]. It is commonly held that CsA-related hyperuricemia is a reversible phenomenon that disappears within 30 days unless some form of irreversible renal damage has been established [22].

In BMT patients, parenteral nutrition could be another factor affecting uric acid turnover, mainly by counteracting the effects of CsA. Intravenous amino acid administration increases urinary uric acid excretion [23–25], whereas some imbalances in the nutrition schedule may lead to molybdenum deficiency, which is an essential component of the xanthine oxidase enzyme that produces uric acid [26].

The relationships between serum uric acid levels and other immunosuppressive agents (with or without CsA) have not been thoroughly investigated. Corticosteroids may potentiate CsA-induced renal function damage and, indirectly affect uric acid by having a negative influence on renal blood flow and increasing the risk of renal damage. Tacrolimus, another antagonist of calcineurin, is frequently used in transplanted patients to avoid the side effects of CsA, such as nephrotoxicity, neurotoxicity or vascular damage. It does not significantly modify uric acid levels in patients pretreated with CsA [27], whereas there is a significant decrease in serum uric acid levels after the switch to mycophenolate or sirolimus [28, 29].

Increased serum uric acid levels have been observed after treatment with hematopoietic growth factors that stimulate cell turnover, and the sudden

increase in neutrophil count after granulocyte colony stimulating factor therapy is a potential inducer of xanthine oxidase, thus leading to hyperuricemia. This laboratory finding should be taken into account before starting hematopoietic stem cell mobilization, even though it is often clinically irrelevant [30, 31].

Post-BMT 'X-Syndrome' or 'Metabolic Syndrome'

After BMT, hyperuricemia may be observed later as a consequence of chronic toxic renal damage or, more rarely, chronic GVHD requiring long-term CsA therapy [32]. However, the most interesting cause of late hyperuricemia recalls the so-called 'X-syndrome' or 'metabolic syndrome'. In everyday clinical practice, its clinical and laboratory pattern is characterized by overweight, increased insulin, triglyceride, VLDL and uric acid levels and by a decrease in HDL levels [33]. It can be considered an expression of insulin resistance and is commonly observed in middle-aged subjects who are at risk of developing type II diabetes mellitus, atherosclerosis and major vascular events. Hyperuricemia is another finding, although its relevance is overshadowed by other clinical and laboratory aspects [34].

A similar 'X-syndrome' is sometimes observed in long-term cancer survivors treated with chemotherapy at conventional doses. Particular attention has been paid to pediatric patients with testicular cancer, in whom it has been speculated that a deranged sexual hormone pattern related to the disease and its therapy may contribute to the development of 'X-syndrome' [35].

Laboratory findings indistinguishable from 'X-syndrome' have also been reported in long-term survivors of both autologous and allogeneic BMT [36–38]. This raises the question as to whether it may represent a further risk factor for the development of late cardiovascular effects, although there are surprisingly few studies of this aspect in the setting of the late effects of BMT [39, 40]. There is still no accurate interpretation of this post-transplant complication nor is there any definite data concerning its real incidence and outcome [34, 38]. Thyroid dysfunction, sex hormone derangement, corticosteroid therapy, adrenal insufficiency, a reduced number of beta pancreatic islet cells, chronic GVHD and persistently high TNF levels are well known long-term effects of BMT which, mainly on the basis of indirect evidence, can affect insulin resistance and/or uric acid turnover, and may, therefore, be involved in the pathogenesis of post-BMT 'X-syndrome' [12, 17, 18, 32, 41, 42]. However, they have not been thoroughly investigated in this regard. It can also be speculated that, in some patients, the progressive replacement of nonhematopoietic tissue by donor cells may be directly responsible for the transmission of donor-type molecular or metabolic patterns that can contribute to the development of 'X-syndrome' [43–46].

It can be argued that hyperuricemia is in any case a marginal finding in the background of 'X-syndrome', an observation that deserves some comment. A negative relationship between high serum uric acid levels and life expectancy has been observed in cohorts of apparently healthy adults regardless of other possible risk factors [47]. It has recently been postulated that leptin may be the metabolic link between insulin resistance and hyperuricemia [48, 49]. Furthermore, there is some evidence supporting the view that, in patients with 'X-syndrome', hyperuricemia may play an autonomous role in accelerating tissue damage and atherogenesis by means of cytokine and monocyte activation [49, 50]. In BMT recipients, the development of 'X-syndrome', hyperuricemia and vascular damage may be the consequence of a pathogenetic sequence involving TNF, insulin resistance, leptin, hyperuricemia and cytokine activation [17, 18, 49, 50].

In conclusion, an 'X-syndrome'-like picture can be seen as a physiopathological entity that is not uncommon in BMT recipients. A better understanding of its epidemiology, risk factors and outcome seems to be essential as it could provide insights into possible preventive and therapeutic measures.

BMT as a Treatment of Lesch-Nyhan Disease

Lesch-Nyhan disease is an inherited X-linked disorder caused by a defect in the hypoxanthine guanine phosphoribosyl transferase (HPRT) enzyme and characterized by the association of hyperuricemia and neurological symptoms, including mental retardation and attempts at self-injury. The link between hyperuricemia and such neurological manifestations is not completely understood, but patients with a variant disease in which HPRT activity is as little as 1% of normal do not show neurological symptoms [51].

This last observation prompted some authors to test the feasibility of BMT because it may be effective in supplying sufficient donor cell replacement in the recipient organism to achieve the goal of $\geq$1% HPRT [52, 53]. Interestingly, the replacement of host microglia by means of donor cells may also deliver sufficient HPRT activity in the central nervous system [43]. There are few published experiences of BMT in Lesch Nyhan disease; the busulfan-cyclophosphamide combination is probably the preferred conditioning regimen, and CsA combined with methotrexate is generally used as GVHD prophylaxis [54].

The first transplanted Lesch-Nyhan patient was a young adult who experienced an increase in HPRT activity but no improvement in neurological symptoms [55, 56]; the obvious explanation of this failure was that the relatively advanced age of the recipient had allowed full-blown brain damage to develop. However, even in patients of pediatric age, BMT has failed to correct nervous impairment [54]. These disappointing results led to the speculation that

brain damage in Lesch-Nyhan syndrome may already be established at birth, or that the blood-brain barrier may in some way prevent its correction [51].

Similar findings have come from experimental BMT in HPRT-deficient mice whose clinical picture closely mimics that of humans. Once again, BMT was unable to revert the intracerebral neurotransmitter derangement and behavioral disturbances characteristic of HPRT deficiency [51].

There are only a few published studies of BMT in Lesch-Nyhan disease, but more recently, cord blood has also been explored as an alternative source of hematopoietic stem cells [57].

Gene therapy may be an alternative to BMT as it could allow autografting and thus overcome the risk of transplant-related complications that negatively affect the outcome of allogeneic BMT. In experimental models, retroviral vectors have been found to be effective in inducing HPRT activity in Lesch-Nyhan bone marrow cells. Transfected bone marrow cells have a proliferative advantage over resident HPRT-negative cells, and thus achieve the target of increasing HPRT to more than 1%. Unfortunately, the promising results obtained using animal models have not been confirmed in clinical practice [58–60].

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Rasburicase Therapy in Acute Hyperuricemia and Renal Dysfunction

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Abstract

Neoplastic disorders may be complicated by acute renal failure (ARF). Different tumors may cause ARF: solid tumors involving the kidney, solid tumors not of hematological origin and not primarily involving the kidney or, more frequently, rapidly developing hematological tumors. The pathogenesis of ARF is different depending on the type of cancer, but the most frequent clinical feature is the acute tumor lysis syndrome, characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia and acute, frequently oliguric, ARF. The presence of a neoplastic disorder and associated acute illness may sometimes lead to the presence of immunodysfunction, septic complications and multiple organ dysfunction. In these settings patients develop systemic inflammation and diffuse endothelial damage, related to different mediators. Among these substances, in cancer patients, high circulating levels of uric acid are a common finding. Hyperuricemia is caused by the increase of purine metabolism, which is result of the increased cellular turnover or the aggressive cancer chemotherapy regimens that worsen cell lysis and release of purine metabolites. Even if hyperuricemia is not the first insult to the kidney, its development might represent a concomitant factor aggravating other previous or simultaneous insults. The most efficient therapy for lowering uric acid is rasburicase, a recombinant form of urate oxidase, a nonhuman proteolytic enzyme that oxidizes uric acid to allantoin. It is efficacious in reducing serum uric acid levels with associated diuresis more effectively and much faster than allopurinol, and to correct renal dysfunction more rapidly than allopurinol.

Introduction

Cancer patients can often be affected by acute impairment of renal function. The pathogenesis of acute renal failure (ARF) related to a neoplastic disorder depends very much on the type of cancer: solid tumors involving the kidney may cause ARF by obstruction, parenchymal disruption and vascular thrombosis; solid tumors not of hematological origin and not primarily involving the kidney may cause ARF especially in the context of the tumor lysis syndrome (TLS), which can be spontaneous or secondary to therapy [1]. Acute, spontaneous TLS is an extremely rare disease but requires prompt recognition and aggressive management because it is fulminant at its outset, associated with severe metabolic derangement, and can be potentially reversible. Among the type of solid tumors that may cause TLS we may list small cell lung cancer, metastatic breast cancer, metastatic medulloblastoma, metastatic seminoma, ovarian cancer and hepatoblastoma [2]. However, TLS occurs more frequently after chemotherapy in rapidly developing high-grade non-Hodgkin's lymphoma, acute lymphoid leukemia, acute myeloid leukemia and chronic myeloid leukemia in the blastic phase, especially during hemolytic crisis [3]. Paraproteinemia might represent another important disorder leading to renal dysfunction during multiple myeloma [4].

Acute TLS occurs when neoplastic cells die and the intracellular contents are released into the circulation. From a clinical point of view, TLS is characterized by hyperphosphatemia, hyperkalemia, hyperuricemia, hypocalcemia and acute, frequently oliguric renal failure. Low urine output and pre-existing hyperuricemia and/or renal failure may worsen the clinical features [5], and the standard treatment usually aims to clear high plasma levels of potassium, uric acid and phosphorus and to correct acidosis.

In TLS as well as in other hyperuricemic disorders, when urate crystals precipitate in the kidney, it may cause two different types of damage: obstruction of the tubular lumen and/or inflammation and edema of the interstitial tissue. Frequently, an imbalance of phosphate metabolism, with the formation of calcium phosphate and its precipitation in the renal tissue, may be correlated. All these events may contribute to an acute renal dysfunction. However, the mechanisms by which renal parenchyma can be damaged include hemodynamic changes and the presence of circulating toxins. The additional presence of obstruction or compression may further contribute to the syndrome. Whatever is the primary cause of the renal insult, a final common pathway leading to ARF includes intrarenal vasoconstriction and medullary ischemia, tubular obstruction, decreased glomerular filtration and back-leak of ultrafiltrate in the interstitial space. Several other mechanisms may take part in the process of renal damage including loss of cellular polarity, loss of tight junction gate function, loss of cell substrate adhesion, exfoliation of viable cells from the tubular basement

membrane, and aberrant cell-cell adhesion. Finally, the presence of altered gene expression and the process of cellular dedifferentiation lead to lethal cell injury by the mechanisms of necrosis and apoptosis [5].

The mechanisms of cell necrosis in ARF are: a severe depletion of ATP stores, a reduced activity of membrane transport, cell swelling, increase in intracellular free calcium, activation of phospholipases and proteases. Apoptosis may also be enhanced in ARF due to the increased concentration of physiological activators, the loss of renal growth factors, the impaired cell matrix adhesion and the loss of cell-cell adhesion. The presence of cytotoxic agents such as reactive oxygen species, intracellular free calcium, pharmacological agents and chemotherapy or the effect of physical factors such as hyperthermia or irradiation, may further contribute to enhance the cellular apoptotic patterns.

Pathogenic Role of Uric Acid: Is It a New Toxin?

The presence of a neoplastic disorder and associated acute illness may sometimes lead to the presence of immunodysfunction, septic complications and multiple organ dysfunction. In these settings the patient becomes critically ill and the clinical picture is sustained by a series of circulating biochemical mediators of inflammation and endothelial damage. Among these substances, in cancer patients, there is a higher chance of finding high circulating levels of uric acid [6].

Hyperuricemia is a potentially serious complication in patients with neoplasms characterized by rapid cell proliferation and destruction.

Hyperuricemia is caused by the increased purine metabolism due to the enhanced catabolism of nucleic acids, a result of the increased cellular turnover (primary TLS), or by the aggressive cancer chemotherapy regimens that worsen cell lysis and release of purine metabolites (secondary TLS).

Renal uric acid excretion increases with hyperuricemia. Urinary uric acid is higher in individuals with lymphoid malignancies than in normal subjects with comparable serum uric acid levels. Uric acid crystals form and tend to deposit in the collecting ducts and the deep cortical and medullary vessels due to the presence of renal intraluminal fluid concentrations, acidic distal tubular fluid, reduced tubular flow rate and hemoconcentration in medullary vessels. Intratubular obstruction causes hyperazotemia/oliguria in acute uric acid nephropathy and a vascular obstruction can contribute to filtration failure [7]. Then, hyperuricemia may represent an important cause of ARF through different mechanisms (fig. 1). Moreover, uric acid can exert a direct toxicity on renal tubular cells, related to a direct endothelial damage mediated by nitric oxide, an increased local oxidant stress on renal tissue and an abnormal platelet activation. Finally the potential effect of high levels of uric acid on local and systemic

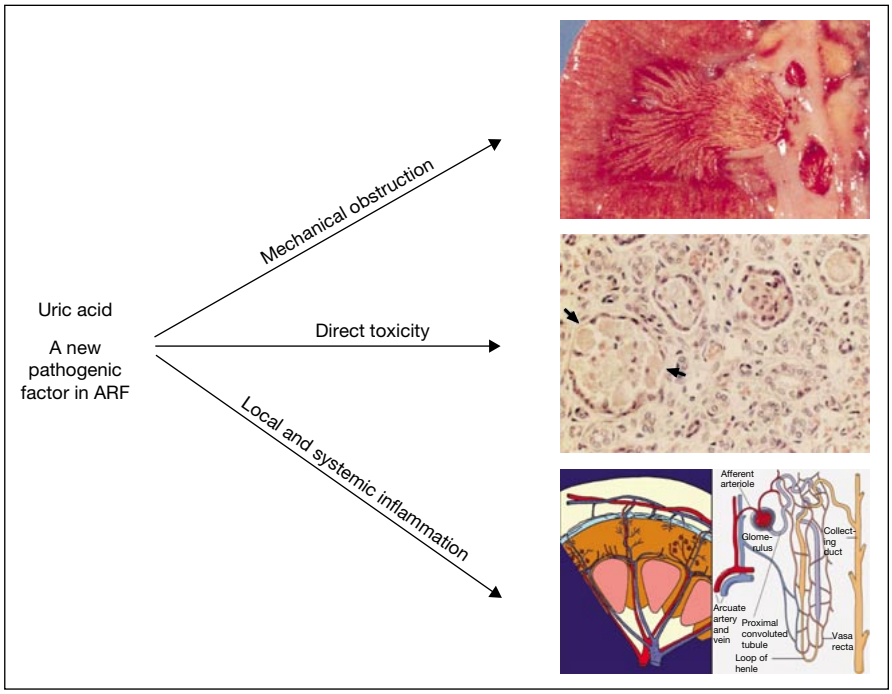

Fig. 1. Uric acid is involved in acute renal damage by three different mechanisms: mechanical obstruction of the tubular lumen, direct toxicity on renal cells and the induction of inflammatory response.

inflammation is another emerging pathway: uric acid levels correlate with cytokine levels, they stimulate the synthesis of monocyte chemoattractant protein 1 and they stimulate the activation of monocytes with increased production of tumor necrosis factor and interleukin 1 β (table 1).

Furthermore, it has been demonstrated that uric acid is able to prevent the inactivation of superoxide dismutase by hydrogen peroxide, which contributes to oxidant stress in vivo; high uric acid levels dramatically increase the vascular homeostasis of superoxide dismutase [8]. In vitro, uric acid is effective in scavenging free radicals and can chelate transition metal ions. It has also been hypothesized that uric acid might be an evolutionary antioxidant substitute for the loss of the ability to synthesize ascorbate. Hence, the overall functional importance of urate in vivo remains unknown.

However, beneficial effects of uric acid as antioxidant molecule is still controversial: paradoxically, uric acid has been reported to increase oxidative damage, to enhance platelet adhesiveness and to stimulate vascular smooth muscle cell growth [9].

Table 1. Uric acid: A new pathogenic factor in ARF

Tubular obstruction (precipitation of urate crystals)
Tissue damage
– Endothelial dysfunction (NO mediated)
– Oxidant stress and cell disruption
– Platelet activation
Acute inflammation
– Correlates with circulating cytokines
– Stimulates synthesis of monocyte chemoattractant protein 1
– Stimulates monocyte production of Il-1b and TNFα

Treatment of Hyperuricemia: Rasburicase

Even if hyperuricemia is not the first insult to the kidney, its development might represent a concomitant factor aggravating other previous or simultaneous insults. For this reason, all efforts should be made to protect the kidney from multiple insults and thus to prevent hyperuricemic states [10]. Prevention and treatment of hyperuricemia include different steps of intervention: we first need to identify patients at risk, then to actuate preventive measures and finally to start a therapeutic plan rapidly in the early phases of the syndrome. Among the preventive measures, mainly fluid resuscitation for maintaining blood volume and pressure is important, because it ensures the perfusion of the kidney even in the presence of a loss of autoregulation. In the second step, the maintenance of urine flow is important to reduce the chance of obstruction and tubular damage. In spite of their satisfactory results in animal models, most renoprotective drugs do not appear to be efficacious in human clinical conditions. Finally, the therapy plan may include the utilization of drugs lowering uric acid concentration: allopurinol and urate oxidase.

Allopurinol blocks the production of new uric acid by inhibiting the enzyme xanthine oxidase but it does not degrade the uric acid already present; for this reason, it may induce the accumulation of uric acid precursors, xanthine and hypoxanthine, that are potentially toxic. Furthermore, it inhibits the degradation of chemotherapeutic agents 6-mercaptopurine and azathioprine, thus increasing their chemotoxicity and the related risk of worsening ARF. As observed by Hsu et al. [7], allopurinol introduction before anti-tumor therapy seems to reduce, but does not eliminate, acute uric acid nephropathy incidence. Consequently, aggressive measures to inhibit uric acid production and maintain adequate urine output, seems to fail in preventing acute uric acid nephropathy in most patients.

Urate oxidase is a nonhuman proteolytic enzyme that oxidizes uric acid to allantoin, that is five to ten times more soluble than uric acid at urinary pH.

Such enzyme is not present in humans and other primates. It has been extracted from *Aspergillus flavus* in 1968, and has been commercialized in France since 1975 and in Italy since 1984 as Uricozyme®. Urate oxidase has been demonstrated to be efficacious in reducing serum uric acid levels with associated diuresis more effectively than allopurinol, and to correct renal dysfunction more rapidly than allopurinol. However, urate oxidase is a nonrecombinant enzyme, and is associated with acute hypersensitivity reactions (urticaria, bronchospasm and/or hypoxemia occur in 5% of patients, even in those without a history of allergy) and has a production process with a low yeild [11].

Rasburicase is the recombinant form of urate oxidase. The recombinant version has been obtained from a modified *Saccharomyces cerevisiae* and has recently been commercialized as Fasturtec®.

It is well tolerated at a dose of 0.2 mg/kg/day intravenously. (T1/2 of 21.2 ± 12 h). Rasburicase has been shown to decrease uric acid from 9.7 to 1.0 mg/dl after one injection. Less allergic reactions than Uricozyme® have been reported. Nevertheless, caution is suggested in patients with a history of severe allergies. When using this new drug, there is no need of urine alkalinization. The molecule should be avoided in pregnancy and G6PDH deficiency syndromes [12].

Figure 2 illustrates the mechanism of action of urate oxidase and the structure of its molecule.

Rasburicase has been shown to reduce the levels of uric acid much faster than allopurinol and it seems to have an uricolytic effect, correlat with the dose (fig. 3). The drug when tested in children with malignancies showed it to be 6 times more efficient than allopurinol [10, 13].

Allantoin excretion increases in parallel with the reduction of uric acid concentration. The amount of allantoin excreted in the urine is a direct measure of the removal of both the plasma uric acid present before chemotherapy as well as the removal of any additional uric acid produced by chemotherapy-induced TLS.

The drug appears to be beneficial as well in preventing an increase in the concentration of uric acid. Furthermore, it has been shown to have an effect on the creatinine levels as well when compared to allopurinol (fig. 4).

Dialysis

Prompt dialysis is necessary when vigorous conservative measures fail to normalize the electrolytes or establish urinary flow. Hemodialysis efficiently removes excess circulating uric acid and electrolytes, but requires a prompt initiation following the development of oliguria inorder to reduce the uric acid and electrolyte plasma levels. Many years ago it has a correlation was shown

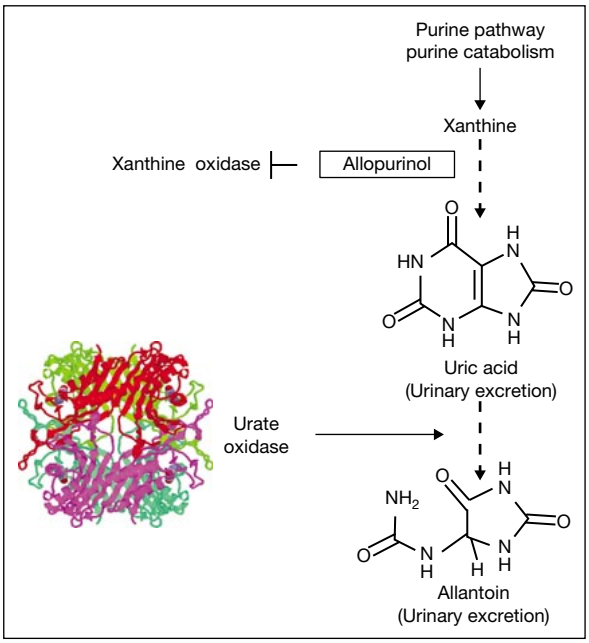

Fig. 2. Urate oxidase is the enzyme that oxidizes uric acid into allantoin, which is five to ten times more soluble than uric acid. Instead, allopurinol inhibits xanthine oxidase, which catalyzes the conversion of xanthine into uric acid.

between the length of oliguria postdialysis initiation and length of oliguria postdialysis [14], however a more recent study failed to demonstrate this correlation, probably because of the development of long-term oliguric or advanced tubular necrosis [7]. Institution of the standard therapeutic approach, that is, intermittent hemodialysis, is not always indicated because of the frequent hemodynamic instability. Instead, continuous venovenous hemofiltration or continuous venovenous hemodialysis is effective in the control of serum uric acid, potassium, urea nitrogen, phosphorus, and extracellular fluid volume.

In another study, Berghmans et al. [15] treated cancer patients affected by ARF with continuous venovenous hemodiafiltration. Continuous venovenous hemodiafiltration seems effective in the treatment of ARF in cancer patients. Most of the patients were affected by ARF associated to multiple organ failure, and the number of organ failures was found as the only significant prognostic factor for hospital mortality; it is remarkable that both elevated phosphate level and cancer characteristics seems to be poor predictive factors for survival, as well as the general gravity scores such as Apache score.

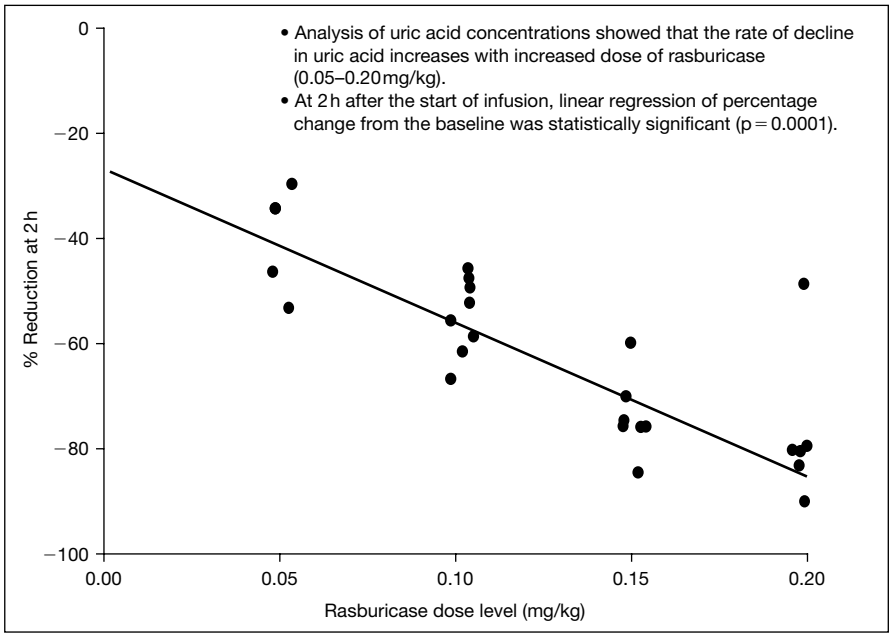

Fig. 3. Urate oxidase has a dose-dependent mechanism of action. At 2 h after the administration of 0.2 mg/kg of rasburicase, the reduction rate of uric acid was 80% from the baseline.

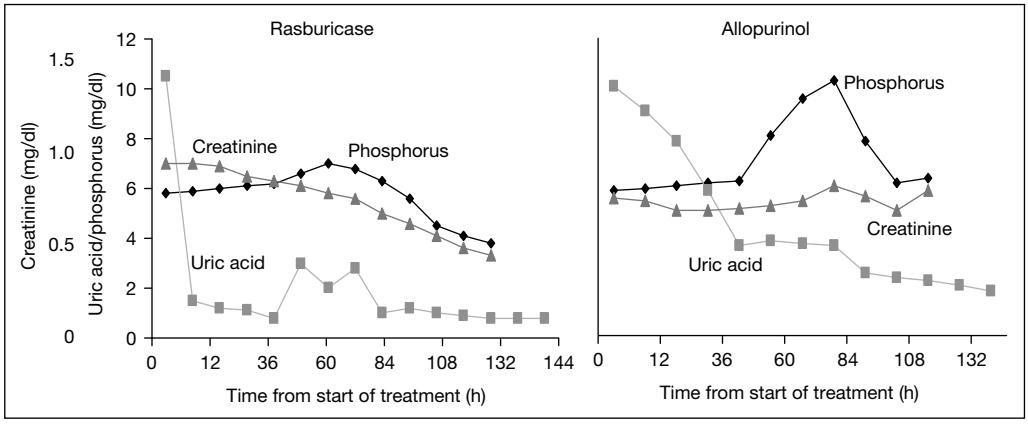

Fig. 4. Urate oxidase is more efficient than allopurinol in reducing uric acid plasma levels. Moreover, urate oxidase does not induce hyperphosphoremia and is associated with an ameliorated renal function in the first 5 days after treatment start. Modified from Pui CH, Semin Hematol 2001.

Conclusion

The presence of elevated concentrations of uric acid seems to represent an additional risk factor in acute renal failure or in the case of initial renal dysfunction. The early treatment of hyperuricemic states appears to be beneficial on renal function and we might hypothesize that such an approach may represent an important protective measure for the kidney. The experience of extracorporeal therapies in the treatment of ARF in cancer patients is still limited, and the current guidelines do not help in the choice of a more effective technique.

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Hyperuricemia in Kidney Transplantation

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Abstract

Hyperuricemia is a common problem among renal transplant recipients. Its prevalence is clearly attributable to cyclosporine (CsA) use, although individual patients may have other risk factors as well. CsA lowers the urinary clearance of uric acid. The specific mechanism for this is unknown, but may involve alteration in tubular transport. Hyperuricemia may add on to several other factors in contributing to progressive deterioration of graft function and ultimately graft loss. The therapy of hyperuricemia may be particularly challenging in transplant patients.

In the last three decades, the progress in transplantation has been impressive. Thanks to the advances in surgery and medical treatments, and the development of new immunosuppressive drugs, more and more patients can be transplanted successfully. Recently, a progressive improvement of allograft survival, in particular, kidney transplants, has been reported [1]. This improvement, however, was seen only in recipients who never had an acute rejection episode, emphasizing the recipient's alloimmune response as a major determinant of the overall outcome of the transplant. Nevertheless, this therapy is not entirely satisfactory because the recipient must be treated with immunosuppressive agents that trade the morbidity and mortality of organ failure for the risk of infection and cancer. These drugs are also likely to contribute to increased mortality from cardiovascular disease, the major cause of premature death in kidney transplant recipients [2].

In addition, there is the problem of chronic rejection or chronic allograft nephropathy (CAN), the second most common cause of late graft loss, which results in a slow progressive deterioration in the graft function [3].

One recognized complication of renal transplantation is hyperuricemia. As many as 55–80% of the transplant patients taking cyclosporine (CsA) become hyperuricemic [4, 5], and approximately 10% develop gout [6, 7]. The observation that longstanding hyperuricemia is associated with intrarenal vasoconstriction and chronic tubulointerstitial injury [8], raises the possibility that it might contribute to CAN. Moreover, since hyperuricemia is associated with hypertension and vascular disease, elevated uric acid could be a risk factor for cardiovascular diseases in kidney transplant recipients, eventually dictating an unfavorable outcome for graft and/or patient.

Pathophysiology of Hyperuricemia in Renal Transplantation

Uric acid, a product of purine metabolism, is freely filtered by the glomerulus. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by an urate/anion exchanger and a voltage-sensitive urate channel [9]. Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter, whereas several substances, including probenecid and benziodarone, have opposite effects [10]. Thus, uric acid levels in the blood may rise in patients with lactic acidosis or ketoacidosis. Uricemia also varies significantly as a result of factors that increase uric acid generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease its urinary excretion. Hyperuricemia is usually defined as >6.5 or 7.0 mg/dl in men and >6.0 mg/dl in women.

Several factors may contribute to the high prevalence of hyperuricemia among renal transplant patients [11]. Renal uric acid excretion may be impaired simply on the basis of poor graft function. However, a correlation between serum creatinine or creatinine clearance and serum urate levels has not always been found [6, 12]. These data suggest that renal failure is not the major or the only determinant of the rise in serum uric acid. Both loop and thiazide diuretics may induce hyperuricemia [13]. They cause a certain degree of hypovolemia, that increases proximal tubular reabsorption of urate, ultimately enhancing the level of serum urate [14]. Loop diuretics may also compete with uric acid for secretion by the proximal organic acid transporter. Nevertheless, a large number of patients not receiving diuretics still develop post-transplant hyperuricemia. When uric acid handling was examined in patients with functioning kidney transplants in the preCsA era, no consistent abnormalities in fractional

reabsorption or excretion of uric acid emerged. This argues against any specific impairment in uric acid excretion inherent to transplantation itself [15]. In some patients, hypouricemia and hyperuricosuria were reported and attributed to the uricosuric effect of steroids [16] or to proximal tubular dysfunction [17].

Most data support the notion that the risk of hyperuricemia attributable to CsA is greater than that of any other factor in renal transplantation [12, 18, 19]. The adverse effects of CsA on the handling of renal uric acid were recognized shortly after the drug came into widespread clinical use. The mechanisms by which these effects occured have been the subject of considerable investigation, but as yet they remain ill defined. Cohen et al. [20] found that among CsA-treated transplant patients, hyperuricemia was mainly related to a reduced glomerular filtration rate, but also an impairment of urate secretion and proximal reabsorption was documented. Nevertheless, the majority of studies tend to implicate the altered tubular handling of uric acid as a key mechanism in hyperuricemia of adult and pediatric transplant patients given CsA [21, 22]. Evidence is available that CsA inhibits probenecid, which stimulates urate tubular secretion [21]. In other studies, however, uric acid reabsorption was found to be increased by CsA [22]. The relationship between CsA and hyperuricemia is also supported by the correlation found between blood trough CsA and serum uric acid levels [23] and by the observation of hyperuricemia among heart transplant recipients as well as patients with autoimmune diseases receiving CsA [24, 25]. The effect on uric acid handling is, however, not specific for CsA, but probably relates to the calcineurin-inhibitor drug class, since tacrolimus has also been found to cause hyperuricemia [26].

Hyperuricemia as a Risk Factor of CAN

Hyperuricemia has long been associated with renal disease. Approximately 20–60% of patients with gout have mild or moderate renal dysfunction [27]. Before the availability of uric acid-lowering agents, as many as 10–25% of patients with gout developed end-stage renal disease [28]. Despite the association of gout with renal disease, controversy exists as to whether uric acid has an etiological role [8, 29]. However, studies have found that hyperuricemia is an independent risk factor for progression in IgA nephropathy [30]. Furthermore, in a cohort of 6,400 screened subjects with normal renal function, a serum uric acid of >8.0 mg/dl when compared with serum uric acid level of <5.0 mg/dl was associated with a 2.9-fold increased risk for developing renal insufficiency within 2 years in men and a 10-fold increased risk in women [31]. This increased risk was independent of several other risk factors including age, systolic blood pressure, proteinuria and hematuria [31]. Experimental evidence also indicate

that hyperuricemic animals developed glomerular afferent arteriolopathy that occurred independently of changes in blood pressure, due in part by direct uric acid effect which induces vascular smooth muscle cell proliferation and by activation of the renin-angiotensin and COX-2 systems [32, 33]. Moreover, uric acid may contribute to endothelial dysfunction, stimulates monocyte chemoattractant protein-1 in rat vascular smooth muscle cells and of IL-1β, IL-6, TNF-α in human mononuclear cells [34], ultimately sustaining a proinflammatory environment in the kidney. All together these observations suggest that uric acid is a potentially important mediator of renal disease progression [34] and highlight the possibility that hyperuricemia participates in the progressive renal scarring of CAN. This is supported by the fact that the histological lesion of 'gouty nephropathy' consists of glomerulosclerosis, interstitial fibrosis, and renal arteriosclerosis [28], all features shared by CAN. Although the relationship between hyperuricemia and transplant failure has not been proven so far, studies have documented different kidney graft survival whether patients were normo- (83.3%) or hyperuricemic (68.8%) over a 5-year follow-up [35].

CAN is one of the leading causes of late renal allograft loss and represents the most prevalent reason for patients to re-enter the already long waiting list for renal transplantation [3]. The pathogenesis of deteriorating renal function post transplantation is poorly understood, but involves both antigen-dependent and independent mechanisms [3]. Among the antigen-independent factors, chronic CsA nephrotoxicity plays a significant role, which in turn is due to the capability of CsA to enhance the production of vasoactive and growth factor mediators [36, 37]. Recent studies in rats showed that an increase in serum uric acid exacerbated CsA nephropathy [38]. The mechanisms did not involve intrarenal uric acid crystal deposition, but the activation of renin-angiotensin system and inhibition of intrarenal nitric oxide production have been claimed to play a role. Thus, in kidney transplant setting the possibility exists that hyperuricemia, besides exerting direct deleterious effects on the graft, may potentiate the chronic renal disease induced by CsA, further contributing to late graft loss.

Hyperuricemia as a Cardiovascular Risk Factor in Renal Transplantation

Epidemiological studies show the continuous relationship of serum uric acid with blood pressure, which is stronger in younger subjects [39, 40]. Hyperuricemia is also an independent risk factor for predicting the development of hypertension [41]. On the other hand, many studies, but not all, have found that uric acid is not an independent risk factor for cardiovascular disease after controlling other risk factors such as hypertension or renal disease [42, 43].

The reason why uric acid may not always be an independent cardiovascular risk factor could be that the beneficial antioxidant actions of uric acid may partially counteract its potential detrimental effects on vascular smooth muscle cell proliferation [34]. Whether renal transplant-associated hyperuricemia opens patients up to an increased risk of cardiovascular events still remains ill defined. Nevertheless, in transplant recipients the uric acid might cause cardiovascular disease as a consequence of causing hypertension or renal disease. Studies need to be performed in humans to prove or disprove this possibility.

Anti-Hyperuricemic Therapy for Renal Transplant Recipients

Generally no therapy is required for mild asymptomatic hyperuricemia. In a typical patient population control of hyperuricemia may be accomplished in either of two ways: attenuating the production of uric acid with allopurinol, or increasing the uric acid excretion through the use of uricosuric agents. Allopurinol reduces the metabolism of purines to uric acid by inhibiting the activity of the enzyme xanthine oxidase. This is particularly critical for transplant patients given azathioprine as a part of their anti-rejection therapy. Indeed, as azathioprine is metabolized to its inactive products by xanthine oxidase, the concomitant use of allopurinol and azathioprine causes the accumulation of 6-mercaptopurine, which can lead to a severe suppression of the bone marrow, with neutropenia, thrombocytopenia and anemia. Extreme care should, therefore, be exercised when introducing allopurinol to the regimen of a patient receiving azathioprine [44]. Thus, in transplant patients with moderately elevated asymptomatic hyperuricemia or symptomatic hyperuricemia on azathioprine therapy, consideration should be given at first to the alkalinization of urine with sodium bicarbonate. Nevertheless, in the case of concomitant administration of allopurinol, the dosage of azathioprine must be reduced to 50–75% of the usual amount or the patient should be switched to mycophenolate mofetil. Mycophenolate mofetil has replaced azathioprine for prophylaxis of acute graft rejection in many protocols. The pharmacological benefit of this agent also resides in its ability to alter purine metabolism. It is much more selective in this regard than allopurinol, which only inhibits the de novo pathway of purine synthesis. For this reason, in addition to the absence of an effect of allopurinol on mycophenolate metabolism, these two drugs are easier to use safely in combination than are allopurinol and azathioprine [45]. Uricosuric agents, such as probenecid or sulfinpyrazone, are less effective than allopurinol and become even less effective in patients with significant graft dysfunction. Moreover, uricosuric agents may favor urate stone formation. Thus, fluids should be forced and urine pH should be kept at 6 when under uricosuric treatment. CsA withdrawal may be

considered for transplant patients with recurrent, severe gout that cannot be managed safely or effectively with colchicine. The hyperuricemia due to CsA generally reverses upon discontinuation of the drug [46]. The risks and utility of this maneuver, however, warrant careful consideration by both patient and transplant clinicians.

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Uric Acid Elimination in the Urine

Pathophysiological Implications

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Abstract

Uric acid, a weak organic acid, has very low pH-dependent solubility in aqueous solutions. About 70% of urate elimination occurs in urine, the kidney standing as a major determinant of plasma levels. The complex renal handling results in a fractional clearance of less than 10%. Recently identified urate-specific transporter/channels are involved in tubular handling and extracellular transport. Extracellular fluid, rather than urine output, is the main regulator of urate excretion. A number of interfering agents, including widely used drugs such as aspirin, losartan, diuretics, may decrease or increase urate elimination. Hyperuricemia induced by hypouricosuria often accompanies the metabolic syndrome, and insulin resistance has been hypothesized as the common underlying defect. Hyperuricosuria, associated with dehydration or exercise, results in acute uric acid nephropathy, and causes an obstructive acute renal failure (ARF). This reversible ARF can be prevented by forced hydration with bicarbonate or saline solutions. Renal hypouricemia, due to mutations of urate transporter, is a rare cause of exercise-induced ARF. The existence of chronic urate nephropathy, gouty nephropathy, is still under discussion. Uric acid nephrolithiasis results from supersaturation, strongly influenced by low urine pH, rather than altered urate turnover. Alkali and fluid intake prove successful in managing uric acid stones.

Introduction

Uric acid is a weak organic acid of molecular weight 168 Daltons, with dissociation constants $pK_{a1} = 5.75$ and $pK_{a2} = 10.3$ [1]. Therefore, at physiological serum pH, almost all the urate species are in the form of monovalent-anion. The solubility of urate in serum is about 7.0 mg/dL, above which it may deposit in tissues as monosodium-urate-monohydrate. Only about 4–5% of urate is bound to plasma proteins. Relative to other mammals, humans have high urate levels in

plasma, ranging between 3.5 and 7.5 mg/dL (200–450 μmol/L), men having 1.2 times greater urate levels than healthy females.

Uric acid is an endproduct of purine metabolism. Contrary to other mammals, humans have lost the capacity to metabolize urate by hepatic uricase, due to mutational silencing of the enzyme [2]. In addition, a peculiar renal handling, featured by relevant tubular reabsorption, sets plasma levels at these high levels. A fascinating hypothesis, supported by some experimental works, justifies this high concentrations with urate acting as an effective scavenger against reactive oxygen species, namely hydroxyl-radicals and peroxynitrite in micro-vascular endothelium and in encephalic structures [3–5]. However, in both plasma and urine, uric acid species may exhibit increases as high as to reach saturation, with an ensuing risk of gout in plasma, and urolithiasis in urine.

Urate body pool is about 1–1.2 g, daily turnover being 0.6–0.7 g. Two third of the newly produced uric acid is excreted in urine, while the remaining one third has a biliary or intestinal elimination or undergoes bacterial uricolysis. It emerges, therefore, that the kidney is the main regulator of uric acid balance. Urate elimination is the result of a four-component system, and has potential pathophysiological implications. These will be the objects of the present article.

Renal Handling of Uric Acid

Most of the uric acid generated daily is excreted by the kidney, which accounts for about 70% of urate elimination, with some 30% made by the intestine. Normally, excretion depends on plasma levels over a wide range of urate concentrations, from less than 1 mg/min at plasma urate below 5 mg/dl to more than 5 mg/min at plasma urate above 15 mg/dL [6]. Upper limits of normal urate excretion have been established at 750 mg daily for women and 800 mg for men, but the reference range should be normalized for body weight or size. As mentioned before, less than 10% of urate filtered at the glomerulus is excreted in the urine, because of an efficient tubular reabsorption. However, the amount of urate eliminated in the final urine is the result of a four-component renal handling, including glomerular filtration, early tubular reabsorption, tubular secretion and postsecretory reabsorption [7].

Because only a negligible fraction of urate is protein bound, virtually all of it is filtered at the glomerulus and as many as 8–9 g daily are delivered to the renal tubules. The tubular handling is rather complex, as it consists of a three-phase process which starts with reabsorption of the majority of the filtered urate, followed by tubular secretion and finally by a more distal post-secretory reabsorption. The sequential interplay between these three phases is influenced by a number of factors, but basically depends on lumen-to-cell and cell-to-peritubular

Table 1. Renal handling of uric acid in healthy individuals

	Our own	Pak et al. [64]
Plasma UA, mg/dL	4.13 ± 1.22	5.3 ± 1.1
Plasma creatinine, mg/dL	0.91 ± 0.10	1.0 ± 0.2
Urine UA, mg/24 h	538 ± 185	716 ± 243
Clearance UA, mL/min	9.4 ± 3.6	9.9 ± 3.2
Clearance creatinine, mL/min	107 ± 21	124 ± 32
FE-UA, %	8.8 ± 3.5	8.0 ± 2.9

space gradients of urate concentrations. This issue has been object of much controversy, because of the difficulty to separate the single phases of urate renal handling. Most of the results were based on studies using drugs known to interfere with either reabsorption (i.e. sulfinpyrazone and probenecid) or secretion (pyrazinamide) by which, however, the relative contribution of early or post-secretory reabsorption remained unclear. The recent suggestion that pyrazinamide could act by facilitating reabsorption rather than inhibiting secretion of urate, might advocate reconsideration of this complex matter [8].

Practically, the fractional excretion of uric acid (FE-UA) can be easily calculated as the ratio between uric acid and creatinine clearances. In our institution mean FE-UA from 50 normal subjects on a free home diet was below 10% of glomerular filtration (table 1).

FE-UA is profoundly influenced by the extracellular volume, in that, expansion increases whereas, contraction decreases the urate excretion. This applies independently of urine flow rate. In fact, high flow rates, as in case of nephrogenic diabetes insipidus or diuretic administration, decrease urate excretion; conversely, patients with Syndrome of inappropriate antidiuretic hormone secretion, who have reduced urine volume but expanded extracellular fluid, show high FE-UA and hypouricemia. The increase of urate plasma levels with age is inversely related to progressing decrease of FE-UA occurring in adulthood. Systemic respiratory or metabolic acidosis, exercise and alcohol abuse reduce FE-UA, because accumulated organic acids, such as lactate and beta-hydroxybutyrate, compete with urate transport systems. Finally, a number of pharmacological agents may interfere with urate renal handling, resulting in either increased or decreased urate excretion, thereby, inducing changes in its plasma levels (table 2).

The recent identification of a urate-anion transporter in the kidney has contributed to a better understanding of the tubular handling of urate [9]. This urate-anion exchanger, named URAT1 was identified in human kidney, being encoded by a gene (SLC22A12) located in chromosome 11q13. URAT1, which

Table 2. Pharmacological agents interfering with urate renal handling

Uricosuric	Antiuricosuric
Probenecid	Pyrazinamide
Sulphynpirazone	Salicylates (low dose)
Salicylates (high dose)	Ethambutol
Ascorbic acid (high dose)	Thiazides
Mannitol	Furosemide
Phenylbutazone	Lead intoxication
Radiocontrast media	Berillium intoxication

belongs to the family of organic anion transporters, is encoded by a 1,659 bp cDNA, and has a predicted secondary structure composed of 12 transmembrane domains, six intracellular loops, and one large extracellular loop interposed between the C- and N-terminus. The identification of a renal-specific urate transporter in mouse, which shares 74% identity with URAT1 [10] has allowed to further clarify function and localization of the urate transporter. URAT1 is involved in the reabsorption of urate from the lumen to cytosol, all along the proximal but not the distal tubule. In fact, immuno histochemical studies have shown that protein is expressed apically in the brush border of the proximal tubule, starting from the exit of Bowman's capsule [10]. Functional analysis after injection of cRNA in xenopus oocytes suggests that URAT1 operates as a Na^+ independent anionexchanger, stimulated by an outwardly directed Cl^- gradient. Urate uptake of transfected oocytes was inhibited by several organic anions, including L-lactate, succinate, ketoglutarate, and by drugs known to increase urate excretion such as benzbromarone and probenecid. Conversely, uptake was stimulated by substituting L-lactate for chloride in the culture medium, as well as by the addition of pyrazinamide [9, 10]. In summary, the aforementioned experimental results indicate that URAT1 is involved in and may explain most of the features of renal handling of urate. Mutations of the encoding gene were shown to cause hereditary renal hypouricemia, as will be mentioned below [11].

Other genes have been reported to influence the urate renal handling, including the UMOD gene, which encodes for the uromodulin/Tamm-Horsfall glycoprotein [12], and the UAT gene, encoding for the urate transporter/channel [13]. The former was hypothesized to have some effects on urate renal handling based on the observation that mutations of UMOD were found in patients with familial juvenile hyperuricemic nephropathy, an autosomal-dominant disease characterized by abnormal tubular handling of urate and subsequent appearance of chronic interstitial nephropathy leading to renal failure [14]. Hyperuricemia and hypouricosuria, which are primary features in familial

juvenile hyperuricemic nephropathy, are unexpected in the face of altered expression and function of the Tamm-Horsfall protein, which is only produced in the thick ascending limb of Henle's loop (TAL). It has been hypothesized that urate renal handling might be altered by a decrease in NaCl reabsorption in the thick ascending limb of Henle's loop, with consequent contraction of extracellular fluid and increased urate reabsorption in the proximal tubule. Alternatively, UMOD could interfere with the still unclear basolateral pathways of organic anions or in more distal postsecretory reabsorption of urate. The UAT gene (1,545 bp cDNA) encodes a protein of 322 aminoacid residues which has been designed as a specific urate transporter/channel [13]. UAT mRNA was expressed in multiple tissues, including kidney and intestine, and the corresponding protein was shown to act as a voltage-sensitive urate-selective ion channel when fused in lipid bilayers. UAT, also designated as galectin 9, was recently shown to be not only involved in urate transport, but also in eosinophil-chemotaxis, cell apoptosis, thimocyte-epithelial interactions [15]. It was suggested that the natural function of UAT, which is present in at least 4 isoforms, is the extracellular transport of urate produced intracellularly by purine catabolism, so as to maintain urate concentration below the solubility limits and to prevent intracellular crystallization. UAT was also shown to act as a urate transporter/channel in polarized epithelial cells, where it is expressed in both apical and basolateral membranes, promoting urate secretion, blocked by pyrazinoate, in both kidney and intestine [16].

Altered Renal Handling of Urate

As mentioned above, a number of endogenous and pharmacological agents may alter urate generation and renal elimination. Elevated plasma levels of urate which increase the filtered load, induce corresponding increases in urate renal excretion. Therefore, settings inducing a higher generation of urate are most often associated with hyperuricosuria. The issue of hyperuricemic states caused by abnormalities in the purine metabolism is treated elsewhere in this book and is out of the aim of this article.

There are, however, clinical disorders in which abnormal plasma levels of urate are caused by an altered renal handling leading to either hypouricosuria or hyperuricosuria.

Hypouricosuria

Hyperuricemia may be caused by decreased renal excretion of urate. In this subset, renal clearance and FE-UA are significantly decreased. Factors inducing reduced urate excretion are listed in table 2. Virtually all diuretic

agents, while leaving urate clearance unchanged or only mildly increased acutely, induce hyperuricemia over longterm administration [17], and this is essentially due to the contraction of extracellular fluid. Similar, though less significant effects, can be induced by beta-blockers [18]. The widely used aspirin has a dual action on urate renal handling, with retention on low dosages and uricosuria at high dosages (>3 g daily). Recently, it was reported that mini-dose aspirin, as that generally used for platelet aggregation inhibition (75–150 mg daily), induced a 15% decrease in uric acid excretion rate in elderly people, and this effect was enhanced by diuretics and hypoalbuminemia [19].

Insulin has been known for a long time to interfere with renal handling of sodium and potassium [20]. Subsequently, it was also shown that urate renal handling is influenced by insulin. Physiological hyperinsulinemia was induced in healthy individuals a 20 to 30% decrease in net and fractional clearances of urate, which was directly correlated with concurrent changes in sodium renal handling [21, 22]. The effects of insulin maintained in patients with insulin resistance [23], hypertension and obesity [24]. In patients with varying degrees of the metabolic syndrome, insulin sensitivity, assessed by means of euglycemic clamp, was inversely related to plasma levels of uric acid [23]. These studies provide evidence that a chronic state of hyperinsulinemia due to insulin resistance represents the basis for the clustering of hyperuricemia with obesity, dislipidaemia, hypertension and diabetes mellitus, which are landmarks of the metabolic syndrome [25, 26]. In this setting, high plasma levels of urate are caused by chronic reduction in urate excretion, but the mechanisms whereby insulin affects urate renal handling are still unknown. Similarly, it is not clear whether this hyperuricemic state is of clinical significance in the cardiovascular manifestations of the metabolic syndrome [27]. Finally, it has been recently reported that patients with uric acid nephrolithiasis often manifest features consistent with the metabolic syndrome, and that a possible pathophysiological explanation of this association could be an effect of insulin on urinary ammonia and pH [28].

Lead and Gouty Nephropathy

Lead is known to reduce uric acid excretion, and the consequent hyperuricemic state is of clinical relevance, namely as it concerns the relationship between chronic lead-intoxication and gouty-nephropathy. The association between gout and chronic renal failure was classically attributed to a tubulointerstitial damage induced by tophaceous precipitation of monosodium urate in the renal interstitium. However, it was subsequently argued against the presumed nephrotoxic action of urate per se: gouty patients followed for more than 20 years did not exhibit renal failure [29], urate deposition was often found in non gouty patients with renal failure or unrelated nephropathies [30], treatment of hyperuricemia did not change the natural course of renal function [31]. It was therefore

suggested that the renal damage in these settings was secondary to other factors complicating gout such as hypertension, metabolic syndrome, drug abuse [32], and gouty nephropathy was defined as a '*vanishing syndrome*' [33]. Conversely, long-glasting exposure to and accumulation of lead, ascertained by means of the EDTA mobilization test, were found in most patients presenting with hyperuricemia and renal-failure due to chronic interstitial nephropathy [34, 35]. The reduction of urate elimination, leading to hyperuricemia, was held as a secondary consequence of lead intoxication, and the resulting nephropathy viewed as a lead nephropathy [36]. Until recently, chronic environmental lead poisoning was suspected to be a widespread problem, which advocates that diagnosis of lead nephropathy be pursued by either the EDTA lead mobilization test or by X-ray fluorescence in all the patients presenting with gout, renal failure and hypertension [37].

Hyperuricosuria

As mentioned above, hyperuricemia is a major cause of elevated renal elimination of uric acid, since it increases the filtered load of urate. Some of the many other uricosuric agents are listed in table 2. In addition to these, there are other subsets characterized by uricosuria.

Losartan, a subtype1 angiotensin II receptor antagonist was reported to increase the uric acid elimination, showing a probenecid-like effect [40]. Renal clearance of urate was three-fold increased by losartan in both normal and uremic rats [41]. Hypertensive patients and patients with renal transplant exhibited 17 to 25% increase in urate renal clearance, with only minor changes in plasma urate [42, 43]. Losartan proved beneficial to decrease thiazide-induced hyperuricemia in hypertensive patients [44]. Uricosuria did not induce adverse renal events because of a concurrent increase in urine pH induced by the drug [44, 45]. However, a case of ARF probably induced by exercise was reported in a patient with renal hypouricemia treated with losartan and trichlormethiazide [46]. Renal failure regressed upon substitution of losartan for candesartan, and renal biopsy showed that kidney was recovering from acute tubular necrosis. It should be noted that the renal effects of losartan were not shared by other drugs of the same class, such as eprosartan [42], irbesartan and valsartan [47]. In summary, losartan, but not other AT1 receptor blockers, affects renal handling of urate. While appearing safe for the kidney, unless pre-disposing factors be present, these effects may help to oppose hyperuricemia that often accompanies hypertensive states.

Renal hypouricemia was recently characterized as a heterogeneous inherited defect associated with increased renal clearance of urate. This syndrome was shown to be caused by mutations of the gene encoding for URAT1, an anion transporter specific for urate [9]. Gene mutations were identified in 30 out of 32 Japanese patients presenting with renal hypouricemia, 24 homozygotes or

compound heterozygotes and 6 heterozygotes [11]. All these patients presented with serum urate levels below 2 mg/dL (mean 0.93 ± 0.49 mg/dL) and very high urate renal clearance (68.3 ± 31.6 mL/min) and fractional excretion (58.4 ± 26.4%). Genotype-phenotype correlations showed that the defect was more severe in homozygotes and compound heterozygotes than heterozygotes. Exercise-induced renal failure and uric acid nephrolithiasis occurred in 9.4 and 12.5% of these patients, respectively.

Hyperuricosuria was reported in other clinical settings. A familial syndrome featured by hyperuricosuria, hypercalciuria, persistent hematuria associated with either calcium oxalate or uric acid crystalluria or nephrolithiasis, was reported to occur in 12 patients from 5 families [48]. Renal hypouricemia was reported to occur in a few patients with a generalized defect of the proximal tubule characterized by low molecular weight proteinuria, glycosuria, aminoaciduria and hypercalciuria inherited with an autosomal recessive pattern, and with no genetic linkage with the X-linked hypercalciuric syndromes [49].

Clinical Consequences of Hyperuricosuria

The main consequence of high concentrations of urate in the urine is the risk of crystallization due to the very poor solubility of the undissociated species. The solubility product of uric acid ($K_{sp,UA}$) in urine was estimated to be about 96 mg/L (0.6 mmol/L) [38]. Therefore, when urine pH approaches the pK_{a1} of 5.75 and about 50% of urate is in the undissociated form, the risk of uric acid precipitation is significant at very low urine concentrations. pK_{a1} was even fixed at values lower than 5.75, that is, 5.47 [39] and 5.35 [38]. If so, at given total urate concentrations and urine pH, the undissociated fraction is correspondingly higher and the risk of crystal formation augmented.

The pathological events caused by excessive uric acid elimination are acute uric acid nephropathy and uric acid nephrolithiasis. The third uric acid/urate related renal disorder is referred to as gouty nephropathy. It has been outlined above that an etiological link between urate and a chronic interstitial-nephropathy has not so far been established. This issue will not be discussed further.

Acute Uric Acid Nephropathy

A massive increase in uric acid production and the consequent increase in renal elimination is the main cause of this renal disease, which often occurs in patients with underlying malignancies undergoing therapies aimed at reducing the tumoral mass. The exceedingly high production of uric acid from purine catabolism brings serum levels of urate to higher than 12–15 mg/dL, with corresponding increases in its tubular concentration [6]. Overwhelming amounts of

urate, resulting from both reduction of reabsorption and increase in secretion, are delivered more distally where urine pH becomes more acidic. In these physicochemical conditions, the fraction of undissociated uric acid increases and exceeds its solubility and massive intratubular precipitation occurs. These events lead to an ARF due to intratubular obstruction. Contraction of ECF and dehydration worsen this condition, whereas high fluid administration is able to prevent it.

ARF was also reported to occur in patients with renal hypouricemia after physical exercise [11, 50, 51]. Diagnosis of renal hypouricemia was made after recovery of renal function, since renal failure had of course masked hypouricemia. Some authors claimed that renal hypouricemia might be overlooked as a cause of ARF. In fact, while renal hypouricemia and exercise-induced ARF had estimated incidences of 0.12% and 9.4% respectively in Japan, the reported cases of ARF associated with renal hypouricemia were only 70 worldwide [11, 52]. Recovery of renal function was quite always complete, but recurrences of ARF occurred in about 30% of these patients. Renal biopsy showed signs of tubular necrosis and in only few cases intratubular uric acid crystals (fig. 1). The mechanisms whereby uricosuric hypouricemia account for renal failure after exercise are still unclear: an increase of urate production during exercise [53] or a defective scavenger effect of urate against an exercise-induced production of free radicals [54] were put forward as likely explanations. Urine pH was also reported to be severely acidic in most patients with renal hypouricemia, and this could represent an important risk factor for the development of ARF induced by exercise [55].

Acute uric acid nephropathy was also reported in a patient treated with sulfinpyrazone. In this setting, ARF was thought to be caused by both hyperuricosuria and acute reduction of renal blood flow due to inhibition of renal prostaglandin synthesis [56].

Treatment of Uric Acid Nephropathy

Allopurinol and its metabolite oxypurinol will act as effective competitive inhibitors of xanthine-oxidase. In case of massive uricosuria, allopurinol must be used at higher than usual dosage, that is 600–900 mg/daily, to accomplish a more complete reduction of urate production. The amount of fluids infused to prevent this acute obstructive nephropathy can be estimated by assuming a distal intratubular pH of about 5.5 and an expected uric acid elimination of up to 5 g/day [6]. In these conditions a urine volume of 1 mL/min yields twelve-fold supersaturation, whereas a theoretical urine flow rate of about 10 mL/min would be necessary to approach saturation [57]. Increasing intratubular pH accomplishes undersaturation at considerably lower flow rates; for instance, at pH of 6.5 a flow rate of only 2 mL/min is sufficient to obtain under saturation at the given urate

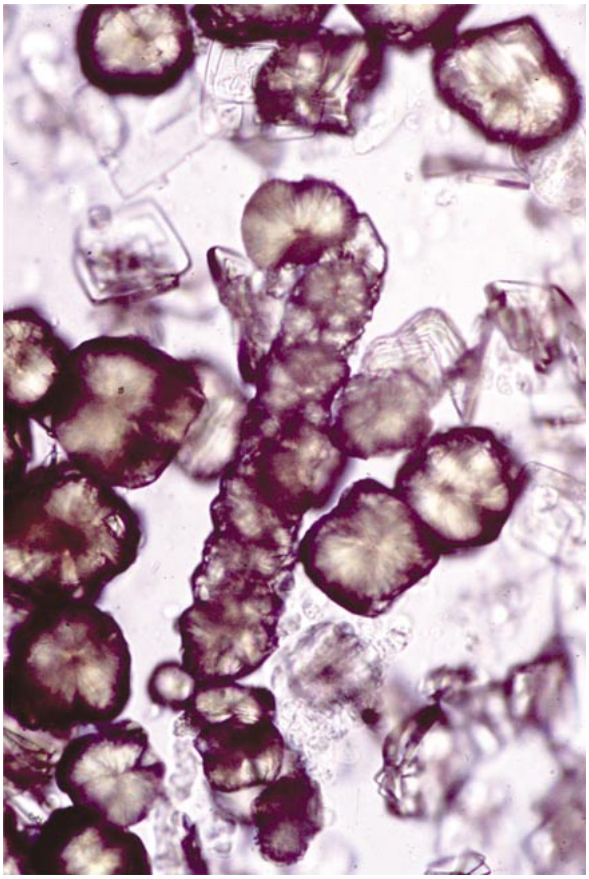

Fig. 1. Casts in urinary sediment with inclusions of brown uric acid crystals in a patient recovering from acute obstructive uric acid nephropathy.

excretion of 5 g daily. Intratubular pH should be therefore increased by infusing sodium bicarbonate alone or in association with 0.9% sodium chloride solutions.

Uric Acid Nephrolithiasis

Uric acid stones account for about 5 to 10% of all kidney stones in western countries and Japan [58–61]. The stones can be composed of uric acid alone or admixed with calcium oxalate. Sex distribution indicates a male to female ratio of more than one, which tends to diminish in the post-menopausal age. While it is widely agreed that uric acid supersaturation accounts for the occurrence and clinical severity of uric acid stone [62], the incidence and role of altered uric acid elimination in this setting has not been confirmed. Several

studies reporting on metabolic evaluation of kidney stones, including ours, have failed to find hyperuricosuria as the main risk factor [63, 64]. Similarly, the association between hyperuricemia and uric acid nephrolithiasis is far from being clear. Earlier reports indicated that uric acid nephrolithiasis had a prevalence significantly higher among gouty patients than normal individuals [31, 65]. However, a consistent portion of stones in gouty patients was found to be calcium-containing stones [66]. The latter observation was subsequently assumed as the basis to hypothesize a causal role of uricosuria in the pathogenesis of calcium oxalate stones [67, 68]. Paradoxically, whereas the role of elevated uric acid in urine is of lesser importance in case of uric acid nephrolithiasis, it may represent a risk factor for calcium oxalate stone formation. Coe et al. [68] speculated that hyperuricosuria can cause calcium oxalate nephrolithiasis by promoting the formation of monosodium urate or uric acid crystals, thereby acting as seed crystals for calcium oxalate or adsorbing macromolecular inhibitors of calcium oxalate crystallization. They observed that urine from calcium oxalate stone-formers were supersaturated with respect to monosodium urate or uric acid more frequently than other stone formers or normal individuals. Based on this, allopurinol was challenged in the treatment of hyperuricosuric calcium stone formers and was found to be effective in the prevention of stone recurrences, which decreased from 0.26 per patient per year in the placebo group to 0.12 in the allopurinol group [69].

Conversely, uric acid elimination was reported to be comparable, only mildly increased or even lower in uric acid stone formers compared to controls [64]. Uric acid supersaturation plays a key role in stone formation: in this regard, the major risk factor is not uricosuria but abnormally low urine pH [64, 69, 70]. Figure 2 illustrates the changes of uric acid saturation (βUA) in samples at different total urate concentration by varying pHs: it is shown that at pH between 6.0 and 6.5, even as high urate concentrations as 1 g/L yield undersaturation. Table 3 compares main chemistries from 98 uric acid stone formers and 50 controls from our institution. It is shown that the main differences between the two groups are represented by urine pH and, consequently, by undissociated uric acid concentration. This results in supersaturation with respect to uric acid in stone forming, but not in nonstone forming urines. Our results are well comparable with those reported by others [64, 70], who not only failed to find differences in uric acid elimination and renal handling in patients with uric acid nephrolithiasis, but even found values lower than controls.

Therefore, not elevated uric acid, but lower pH, appears to discriminate stone forming from nonstone forming urine. Why urines in uric acid nephrolithiasis are abnormally acidic is still matter of discussion. It was formerly suggested that these patients had a defective renal production and excretion of ammonium, with a consequent decrease in the titration of protons normally

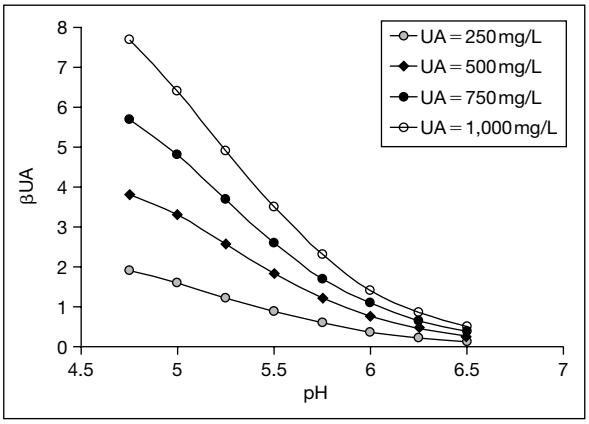

Fig. 2. Dependence of uric acid saturation (βUA) on urine pH. βUA was calculated at different total urate concentrations and varying pHs, by means of a computer system [LithoRisk, ref. 57]. Other urine components kept constant.

secreted in the distal tubule [71, 72]. However, these findings were not universally confirmed, in that, urinary NH_4^+ excretion was shown to be normal under both chronic- and acute-acid loading tests [73, 74]. It was also proposed that low urine pH could be caused by different defects and that these patients could be classified in at least three subgroups [69]. The issue of defective ammonia genesis was recently reviewed by Pak and co-workers [70], who found that patients with either pure uric acid or mixed uric acid and calcium oxalate stones had a lower ammonia to net acid excretion ratio compared to both normal and calcium oxalate stone formers. Moreover, the increase in ammonia genesis in response to an acute acid load as NH_4Cl was five to seven-fold higher in controls than in uric acid stone formers. They also noted that among the latter there was a significant fraction of patients with insulin resistance and hypothesized an association between the two defects. In a recent study, it was shown that insulin resistance assessed by glucose disposal rate during a hyperinsulinemic euglycemic clamp, was associated with excessively low pH, due to defective ammonia excretion [75]. It was suggested that insulin might be involved, either directly or through its action on electrolyte handling, in renal production of ammonium, and that resistance to its action could also explain, besides other metabolic abnormalities typical of the metabolic syndrome [25], the excessively low urine pH of uric acid nephrolithiasis.

Treatment of Uric Acid Nephrolithiasis

Uric acid stones can not only be prevented but even be dissolved by vigorous medical intervention. Therapy is aimed at decreasing saturation well

Table 3. Main urine chemistries and state of saturation (ß) in idiopathic uric acid stone formers and healthy controls

	Controls	UA-SF	p
Males/Females	41/9	78/20	n.s.
Volume, mL/24-h	1,284 ± 468	1,562 ± 537	0.002
Clearance creat, mL/min	107 ± 21	95 ± 24	0.005
Total uric acid, mmol/24-h	3.2 ± 1.1	3.8 ± 1.4	0.038
Clearance UA, mL/min	9.4 ± 3.6	8.5 ± 4.6	n.s.
Cl UA/Cl Cr, %	8.38 ± 3.5	8.9 ± 4.1	n.s.
Urine, pH	6.03 ± 0.45	5.43 ± 0.45	<0.001
Undissociated UA, mmol/L	0.47 ± 0.33	1.13 ± 0.66	<0.001
ßUA	0.79 ± 0.56	1.92 ± 1.12	<0.001
ß Sodium urate	4.83 ± 3.02	2.82 ± 2.42	<0.001

below the solubility product and this is substantially accomplished by decreasing the concentration of undissociated uric acid. High fluid intake should be encouraged by possibly using alkaline mineral water for its ability to increase urine pH. Alkalinization must also be pursued by using bicarbonate or citrate salts, at dosages adequate to accomplish a pH equal to or higher than 6.5. Potassium citrate, 60 to 80 mEq/day, was reported to increase urine pH from 5.3 to 6.2 on average; thereby decreasing undissociated uric acid to less than 50% of the baseline values. Correspondingly, stone recurrence rate declined from 1.20 to 0.01 stones/year [76]. In our own patients, potassium citrate (alone or in association with allopurinol, 150 mg daily) reduced un-dissociated uric acid concentration from 1.15 ± 0.6 mmol/L pretreatment, to 0.59 ± 0.53 mmol/L posttreatment ($p < 0.001$). In patients poorly compliant with or exhibiting untoward effects for potassium citrate, this can be substituted for bicarbonate salts, to be used at similar dosages expressed as mEq/day.

Allopurinol, 150 to 300 mg daily, should be used in the setting of elevated uric acid excretion, taking into account that at pH higher than 6.25 urine is undersaturated with uric acid concentration up to 750 mg/L. It is conceivable, though not definitely confirmed, that trials aimed at dissolving uric acid stones in the urinary tract should be carried out by using both alkali and allopurinol together with high fluid intake, to maximally reduce saturation. If meticulously practiced, medical intervention succeeds in undersaturating urine with uric acid and this invariably results in stable remission of stone activity. This contention only partially applies to patients who form mixed calcium-uric acid stones, a subset characterized by unusually frequent stone relapses, in which treatment for uric acid lithiasis may require concomitant correction of calcium disorders [77].

Conclusions

Recent interesting studies have contributed to understanding in more depth the complex renal handling of urate. Similarly in other fields of renal physiology, molecular genetics stands as an invaluable tool to explain the fine mechanisms involved in the renal regulation of urate levels in body fluids. Most investigators are deeply concerned with a possible finalistic explanation of why urate plasma levels are curiously high in humans, compared to other mammals. In fact, in addition to the loss of a significant uricase activity, a depressed renal elimination of this endproduct concurs to fix plasma levels quite close to the solubility product. The recent discovery of urate-specific transporter/channels is now viewed as a device to maintain safe concentrations of urate intracellularly in the face of continuing metabolic generation [13]. Conversely, elevated levels in the extracellular environment could contribute to the antioxidant potential against reactive oxygen species, if a scavenging action of urate will be confirmed [5]. If so, hyperuricemia that often accompanies the so-called metabolic syndrome, should be viewed as a protective rather than harmful feature.

In any case, the kidney is a primary regulator of urate turnover. The recent identification and characterization of the URAT1 anion transporter have not only explained the mechanisms of rare inherited defects of urate excretion, but also help to share light on its renal handling [9–11]. The pathophysiological consequences of urate elimination appear to be substantially caused by its low solubility in urine, and in an only negligible way, if any, by elevated concentrations in renal interstitium. The ability to maintain urate homeostasis exposes the kidney to the trade-off of urate-related clinical disorders.

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Pharmacological Treatment of Acute and Chronic Hyperuricemia in Kidney Diseased Patients

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Abstract

Several trials argued the possibility that hyperuricemia may have a direct effect on cardiovascular and renal disease. It has been shown that an elevated serum uric acid concentration is a predictor of cardiovascular events such as myocardial infarction. It also predicts the development of hypertension and in hypertensive patients, hyperuricemia is associated with increased cardiovascular morbidity and mortality. Hyperuricemia is a complication often seen in patients with chronic and acute renal disease. The relationship between serum uric acid level and the appearance or progression of renal dysfunction has been debated in the last years. During chemotherapy for hematological malignancies or more rarely for solid tumors, acute renal failure, secondary to a sudden marked increase in uric acid, is not such a rare complication. The therapeutic intervention includes hyper hydration, urinary alkalinization, and the use of uric acid decreasing agents such as allopurinol and rasburicase, a recent recombinant-urate oxidase. In our personal experience, patients with acute renal failure due to hyperuricemia, showed a better renal prognosis with rasburicase than allopurinol.

Chronic hyperuricemia is also associated with chronic tubulo-interstitial disease with glomerular sclerosis, and renal dysfunction. Experimental trials showed that uric acid can affect kidneys through different mechanisms at glomerular, tubulo-interstitial and vascular level. Although allopurinol is often the drug of choice, caution must be used to avoid serious side effects. New therapeutic options, for treating hyperuricemia are needed in patients with renal dysfunction for slowing the progression to end stage kidney disease.

Introduction

The kidney represents the primary route for the excretion of urate, since one-third of total excretion is via the intestinal route and once transported into

the lumen, it undergoes uricolysis by microbial action [1]. Uric acid is freely filtrated at the glomerulus, then it is almost completely reabsorbed (99%) in the proximal tubule, and undergoes significant tubular secretion. Tubular secretion is dependent on an anion-exchange transport system and a voltage-sensitive pathway in the proximal tubule [2]. Indeed, one of the most important mechanisms responsible for uric acid elevation is related to inhibition of tubular secretion and it occurs when the anion-exchange transport system is inhibited by lactate or ketoacids. Interference with this transport system can result in acute changes in uric acid levels. Lactate generations, for example, are responsible for acute hyperuricemia observed in patients after intense exercise or alcohol ingestion, and ketoacid generation may account for the increase in serum uric acid level observed with fasting [3–4]. Elevated concentrations of serum uric acid are present in different conditions, most of them are considered cardiovascular risk factors, like essential hypertension, renal failure, obesity, aging, glucose intolerance, alcohol, lead intoxication, cyclosporine, diuretics and eclampsia [5]. In hypertensive patients, the common presence of hyperuricemia can be explained by the inhibition of the anion-exchange system. It has been shown that hypertension induces intrarenal ischemia, and generates lactates, due to tissue hypoxia, that as previously indicated, interferes with the tubular anion-exchange system involved in the secretion of urate. Furthermore, local hypoxia might lead to increased uric acid, because ischemia is associated with increase in both substrate and enzyme associated uric acid generation [6]. For this reason, 25 to 50% of hypertensive patients are hyperuricemic [7]. The relationship between uric acid and the kidney is controversial. Indeed, hyperuricemia can lead to acute renal failure in some instances, but in other situations elevated levels of serum uric acid are not associated with renal damage. In chronic renal failure (CRF), enteric excretion is actively involved in extra-renal excretion of urate, thus maintaining the urate homeostasis [8]. Inspite of an important reduction in renal failure, the absence of significant hyperuricemia and low incidence of gout has been observed in CRF for different mechanisms; these include enhanced extra renal excretion, diminished biosynthesis, and/or increased degradation of uric acid and marked reduction of hepatic, renal, jejunal, ileal, and colonic xanthine oxidase activity. This marked reduction may be due to a depressed tissue urate production than to a reduced total quantity of the enzyme [9].

Treatment in Acute Uric Acid Nephropathy

Acute uric acid nephropathy is characterized by a sudden increase in uric acid which is responsible for acute renal failure. The precipitation of uric acid crystals within the tubules of distal nephrons, induces the pathological damage.

When uric acid or urate reaches the collecting ducts, it precipitates out because of decreased solubility in the acid medium. Subsequently, water reabsorption and progressive acidification of tubule fluid as urate reaches the distal tubules, and due to the relative insolubility of non-ionized uric acid in this acid milieu, makes the stage set for the development of a microcrystalline 'intrarenal hydronephrosis'. Tubular ingestion of crystals leads to tubular necrosis, inflammation and acute renal failure. At light microscopy, the collecting tubules contain large amounts of uric acid and urates, characterized by amorphous mass or doubly refractile, radially disposed crystals. Urate may be present in the interstitium. Other changes are dilatation of glomerular spaces and pre-obstruction of tubules with edema of the cortical interstitium (figure 1 and 2) [10]. On ultrasound, kidneys are enlarged and very bright.

Tumor lysis syndrome, is responsible for acute uric acid nephropathy. It is considered as an oncological emergency, due to the rapid lysis of malignant cells. The consequence is the rapid release of intracellular contents into the systemic circulation, which exceeds the normal renal excretory and physiological buffering mechanisms [11].

There are several conditions that are at risk of developing tumor lysis syndrome. Some of them are large tumor burden, rapid tumor growth rate or high tumor growth fraction, the sensitivity of the tumor to chemotherapy and pre-existing impaired renal function. Some tumors are at higher risk for the increased ability to rapidly proliferate and their high sensitivity to chemotherapeutic agents; the main tumors involved are Burkitt's lymphoma, lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia and acute myeloid leukemia [12]. The chemotherapeutic agents that have been associated to the tumor lysis - syndrome are: cisplatin, etoposide, fludarabine, intrathecal methotrexate and paclitaxel [13]. Other tumors have also been associated with tumor lysis syndrome because of their increased antitumor activity rather than a direct toxicity of renal tubules [14]. There are other diseases that can determine acute uric acid nephropathy; these are the Lesch-Nyhan syndrome of complete hypoxanthine-guanine phosphoribosyl-transferase deficiency in which there is a great overproduction of urate. Overproduction of urate and acute renal failure may also be seen in rhabdomyolysis, crush injuries, prolonged immobility etc, although in these situations, the relationship between renal involvement and hyperuricemia is not clear [5].

There are two different orders of therapeutic intervention in the acute uric acid nephropathy. One is prevention, that is considered the key to the management of tumor lysis syndrome and the other is the treatment of hyperuricemia.

The correction of hyperkalemia, which occurs from 6 to 62 h after starting chemotherapy, must be done rapidly before potentially fatal ventricular arrhythmias occur, since they are considered the most serious manifestations of tumor

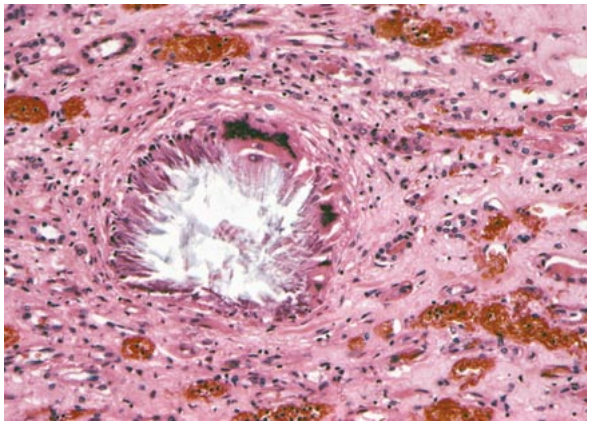

Fig. 1. Uric acid crystals in the renal medulla are surrounded by histiocytes and multinucleated giant cells. The crystals, which represent dissolved uric acid, formed initially in collecting duct lumen, disrupted the wall and extended into the interstitium. (With courtesy from Arthur H Cohen, MD. CSMS UCLA, Los Angeles).

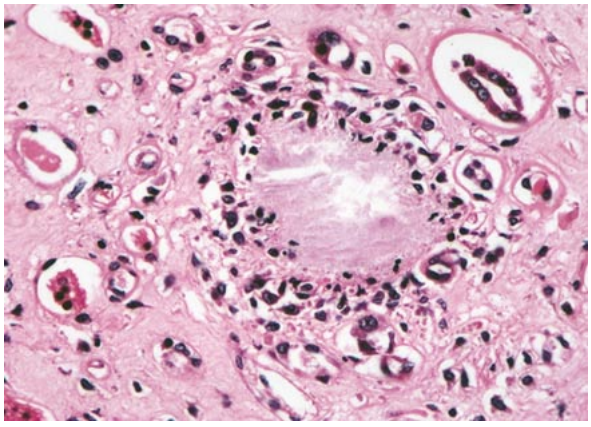

Fig. 2. Amorphous urate mass in the medullary interstitium surrounded by histiocytes. (With courtesy from Arthur H Cohen, MD. CSMS UCLA, Los Angeles).

lysis syndrome [15]. The pathophysiology of hyperkalemia is due to the rapid expulsion of K^+ from intracellular into extracellular fluid due to cell lysis. Treatment options of hyperkalemia are directed to counteract the effect on myocardium, stabilize cardiac membrane (calcium gluconate) and prevent life-threatening cardiac arrhythmias; another intervention is directed to reduce

potassium level (glucose with insulin, sodium bicarbonate, inhaled beta agonist, K-binding resins, and in some instances, also dialysis). Hyperphosphatemia and hypocalcemia are common in this syndrome. Indeed, phosphatemia increases due to cell lysis, which induces the release of intracellular phosphate together with impaired renal function, whilst hypocalcemia is due to precipitation of the calcium-phosphate complex for the rapid increase of phosphate. It has to be mentioned, that malignant hematological cells have contents of phosphate four times higher than normal mature lymphoid cells [15]. In both cases, the consequences range from muscle cramps to serious events like tetany, arrhythmias, seizures and acute renal failure due to nephrocalcinosis. Treatment to reduce phosphatemia with phosphate binders or dialysis with consequent improvement of hypocalcemia needs to be started early to prevent the development of the previously indicated clinical consequences. The use of calcium gluconate, in absence of hyperkalemia, is indicated only for symptomatic hypocalcemia.

The prevention and treatment of hyperuricemia represents the major goal of the treatment of patients with acute renal disease, because it prevents the subsequent development of end stage renal disease. The standard treatment of hyperuricemia includes hydration, urine alkalinization and allopurinol. Adequate prophylaxis concerns hydration that should be initiated before chemotherapy and continued for several days after the last dose of chemotherapy. With the exception of patients at risk for volume overload, intense fluid administration must be recommended in all patients at risk for tumor lysis syndrome [16]. The rationale of this intervention is to reduce the concentration of solutes in tubules, thus decreasing the chance of urate to precipitate and determine tubular obstruction. Another mechanism to reduce the precipitation of urate in the tubules is, urine alkalinization with sodium bicarbonate. Indeed, it improves uric acid solubility through an increased percentage of ionized uric acid in the urine [17]. The use of allopurinol, which should be started before treatment, does not seem to add any beneficial effects. Indeed allopurinol blocks uric acid formation by inhibiting the enzyme, xanthine oxidase, which converts xanthine and hypoxanthine to uric acid, thus decreasing both serum and urinary uric acid concentrations. It has to be mentioned that this mechanism involves only the new generation of urate without any actions on preexisting uric acid. It determines increasing levels of the precursor of uric acid, xanthine and hypoxanthine, which have been reported to be responsible for allopurinol-related xanthine nephropathy [18]. Another treatment option for prevention or treatment of hyperuricemia is urate oxidase. Urate oxidase is an endogenous enzyme, present in most mammals but not in humans due to a nonsense mutation in the gene-coding region [19]. Previous studies with a nonrecombinant form of urate oxidase (Uricozyme®, Sanofi-Synthelabo Inc., Paris, France), showed a high efficacy as uricolytic agent, but its effect was associated

with hypersensitivity reactions in 5% of patients, manifested mainly by bronchospasm [20]. It has to be mentioned that the addition of polyethylene glycol has reduced this risk. Since 1996, recombinant urate oxidase, also called rasburicase (Fasturtec from Sanofi-Synthelabo, Paris, France/Elitek from Sanofi-Synthelabo Inc., New York N.Y., USA) showed better results compared to allopurinol for treating hyperuricemia and demonstrated a lower toxicity profile than the non-recombinant form of urate oxidase in several clinical trials [20–24]. Rasburicase does not require adjustment with decreased creatinine clearance [21]. The risk of hypersensitivity reactions, including anaphylaxis, is lower with rasburicase than with nonrecombinant form of urate oxidase. Nausea and vomiting have been rarely reported in patients on rasburicase [20].

A study performed on 131 patients with newly diagnosed acute lymphoblastic leukemia or stage III/IV non-Hodgkin's lymphoma demonstrated a rapid decrease of plasma uric acid concentrations after receiving recombinant urate oxidase. None of the patients required dialysis, and serum creatinine levels also decreased significantly [22]. In another trial, which compared, in a randomized fashion, recombinant urate oxidase and allopurinol in children with newly diagnosed acute lymphoblastic leukemia or stage III/IV non-Hodgkin's lymphoma, the results showed a significant lower plasma uric acid concentration and a more rapid decline in serum creatinine level in 27 patients treated with recombinant urate oxidase, than in the 25 subjects who consumed allopurinol. In the rasburicase group, renal failure, requiring dialysis, did not occur [23]. A retrospective analysis on 245 patients (173 children and 72 adults), who received this agent in a compassionate-use program, showed an important dramatic reduction of uric acid concentration in all subjects [24].

We, retrospectively, analyzed the data of 10 patients, with hyperuricemia as a complication of tumor lysis syndrome secondary to treatment of different types of tumors (B-cell lymphomas, lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia, and acute myeloid leukemia) treated in our department with rasburicase and compared these results with those of other series of patients (12 subjects) treated in the past with allopurinol in similar clinical situations. Our preliminary data showed that the combined treatment of hyperuricemia with hyperhydration and rasburicase successfully resolved or prevented the development of renal damage. We did not observe any allergic reactions, and any other serious adverse events. The maximum decrease in uric acid was obtained after the first day of therapy, whilst in the allopurinol group the improvement of hyperuricemia was slower (fig. 3). Moreover, in the group of patients treated with allopurinol (12 patients) three of them (25%) underwent dialysis because of development of acute renal failure.

Follow-up at third year of these patients showed that chronic renal failure developed in two of them. We are currently following the group of patients

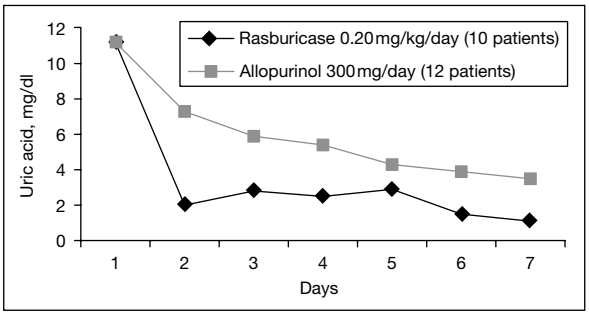

Fig. 3. Mean of serum uric acid in the two group of patients in the first week of therapy.

treated with rasburicase. Preliminary data did not show any changes in renal function after the 18 ± 6 months of treatment with rasburicase. Till now, these results have demonstrated the efficacy of rasburicase in lowering uric acid levels, in hyperuricemic patients and preserving renal function.

Treatment in Chronic Nephropathy

The pathological damage associated with hyperuricemia in chronic kidney disease occurs in the interstitium of the medulla along the collecting duct in which precipitation has taken place. For example, patients (25 to 40% of cases) with gout may have a typical pattern of renal disease called 'gout nephropathy' which is characterized by tubulo-interstitial fibrosis with arteriolosclerosis and glomerulosclerosis, and with the presence of focal urate deposits in the tubules and in the interstitium in the medulla [10]; in renal specimens crystals of urate can be observed, penetrating the tubular wall and inciting a giant-cell reaction. Nevertheless, other patients with many years of gout have hypertension and/or are older and their renal disease is compatible with hypertension or with aging.

The possible pathogenetic role for chronic hyperuricemia in inducing and accelerating renal disease has been proposed [25].

A hypothetical beneficial function is related to the antioxidant function of uric acid. Indeed, uric acid may prevent the degradation of extracellular superoxide dismutase, an enzyme involved in maintaining endothelial and vascular function [26]. On the other hand, the negative effects reported for uric acid were related to the stimulation of vascular smooth cell proliferation and the induction of endothelial dysfunction [25]. The stimuli for proliferation is mediated by organic anion transporters that allow urate uptake in vascular smooth muscle cells, that activate COX-2, leading to synthesis of thromboxane, thus

inducing platelet derived growth factor (PDGF) and platelet derived growth factor-receptor secretion, that stimulate cell proliferation. Moreover, the secretion of MCP-1, induced by hyperuricemia, can lead to inflammation [25]. Recently, some authors tried to investigate the role of uric acid in renal disease, developing a rat-model of hyperuricemia. This model resulted in mild hyperuricemia without intrarenal crystal deposition. The renal damage, characterized by interstitial renal injury was associated with activation of the renal angiotensin system and the development of hypertension. Moreover, immunohistochemical studies showed an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Treatment with enalapril or L-arginine reduced both the renal injury and hypertension. This model, showed how a mild hyperuricemia causes hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system [27]. Another experimental model showed how progression of renal disease could be accelerated by hyperuricemia. Renal injury in the rats after remnant kidney surgery (5/6), occurred via a mechanism linked to hypertension and COX-2-mediated, with thromboxane-induced vascular disease, giving a direct correlation of hyperuricemia and progression of renal damage [28].

Glomerular size studied by computer image analysis and structure reviewed in hyperuricemic rats showed a 30% increase in glomerular filtration area. Glomerular hypertrophy was prevented by treatment with ACE-inhibitor, but not by hydrochlorothiazide, which normally prevents hypertension induced by hyperuricemia [29].

This suggests that glomerular hypertrophy was not mediated by hypertension, but by activation of renal angiotensin system. This mechanism was confirmed by another experimental model of cyclosporine nephropathy, which showed increases in renal renin content and acceleration of renal damage characterized mainly by afferent arteriolopathy which occurred independent of changes in blood pressure [30].

Although, in MDRD study [31], uric acid was not found to be a risk factor, the pathogenetic role of uric acid in the renal lesion, observed in clinical and experimental studies led many clinicians to reduce urate production with allopurinol, also in non-gouty patients. Some evidences raised many questions about the dosage. In particular, in chronic kidney diseased patients, especially treated with thiazide diuretics, the accumulation of this drug together with its metabolite oxypurinol can lead to serious risks of bone marrow depression or other serious adverse events. For this reason, it has been suggested that the dose of allopurinol be reduced to 100 mg/day or three times weekly [32].

Hyperuricemia has been suggested as an important factor for the appearance and progression of renal dysfunction in hypertensive patients [33]. The

target of serum uric acid level has been debated. Some authors recommend the use of uric acid-decreasing agents in patients with gout or when uric acid levels are markedly elevated (>10 mg/dl in women and >13 mg/dl in men) [34]. The treatment of moderate hyperuricemia (between 7 and 10 mg/dl) is not accepted by many authors [35].

The management of hyperuricemia in patients with chronic kidney disease still remains debated. Of course diuretics should be limited, if possible, for their ability to increase uric acid levels. The activation of the renal angiotensin system found in experimental models explain the renal protective effect of angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist in hypertensive subjects with hyperuricemia [27–30].

Moreover losartan, an angiotensin II receptor antagonist, also demonstrated to reduce uric acid serum levels, for a mechanism independent on its action to block angiotensin II [36]. Indeed its hypouricemic effects are due to the ability of interfering with urate transport by the anion exchange pathway in the proximal tubule [2].

In conclusion, it has been shown that an elevated serum uric acid concentration is a predictor of cardiovascular events such as myocardial infarction [37–38]. It also predicts the development of hypertension and in hypertensive patients, hyperuricemia is associated with increased cardiovascular morbidity and mortality [39]. Although with all these evidences, it is not clear whether serum uric acid can be considered a true cardiovascular risk factor or simply an indirect marker since these patients have other well-established risk factors for cardiovascular diseases such as, renal disease, hypertension, dyslipidemia etc. The role of serum uric acid in the development of acute and chronic urate nephropathy has been debated in the last years. Although acute renal failure caused by sudden marked hyperuricemia, during chemotherapy for hematological malignancies or more rarely for solid tumors is a complication widely accepted [11], the idea that prolonged hyperuricemia (such in patients with gout), may induce or accelerate the progression of CRF is more controversial. It has to be mentioned that renal-damage associated with hyperuricemia may accelerate the progression to the end stage renal disease in IgA nephropathy [40] and in type II diabetes [41]. For this reason we need to use all the therapeutic options in hyperuricemic patients for establishing a better renal prognosis. Up to now, we have used allopurinol for treatment of hyperuricemia in acute and chronic renal disease. Since its active metabolite, oxypurinol, is actively reabsorbed by the kidney, in patients with renal dysfunction, oxypurinol retention can lead to adverse effects and, as a consequence, it is not considered the ideal drug in patients with CRF. Therefore, in patients with CRF, that are admitted to a nephrology unit for rapid declining of renal function, associated with elevated serum uric acid level, we suggest short courses of rasburicase, in order to avoid

the possible side effects of allopurinol accumulation and a more rapid reduction of urate, before they can precipitate in the medulla or can induce glomerular hemodynamic changes. Of course, this suggestion needs to be validated by clinical trials in humans to explain whether a rapid lowering of uric acid may slow the progression of renal disease.

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Pharmacological Treatment of Acute Renal Failure in Intensive Care Unit Patients

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Abstract

Uric acid nephropathy is a potentially reversible cause of acute renal failure resulting from diffuse urate crystal depositions in the tubules in the setting of excessive uricosuria. Hyperuricemia is frequently encountered in ICU patients with acute renal failure of any etiology, but it is rarely a prominent feature or a major pathophysiological element in the renal failures of nonhematology/ oncology patients. It can, nevertheless, be severe in some pathologies associated with massive tissue destruction such as rhabdomyolysis. The most frequent clinical context is, nevertheless, hematological, when patients with large tumor burden and rapid cell turnover develop acute tumor lysis syndrome (ATLS). The purpose of this chapter is to review the pharmacological tools currently available and their optimal use in the treatment of patients admitted in intensive care unit with hyperuricemia and severe acute renal failure.

Characteristics of Acute Renal Failure Admitted in ICU

Hyperuricemia and Severe Acute Renal Failure

The incidence of hyperuricemia-related acute renal failure (ARF) is largely unknown in nonhematological patients due to the rarity of this syndrome, mainly encountered in inborn errors of metabolism and long-term treatments with drugs inducing hyperuricemia/hyperuricosuria. Hyperuricemia is, nevertheless, a common finding in most patients with ARF of any cause, especially in catabolic states such as rhabdomyolysis. The medical literature provides much more data regarding its incidence during acute tumor lysis syndromes (ATLS) occurring

during the induction of hematological malignancies, but significant variations can be found, essentially depending on the type of population studied (high risk or low risk), and the countries where the studies have been conducted, since incidences of severe ATLS-related ARF is lower in countries where urate oxidase has been available for many years such as France and Italy. In most series, reported incidence of ATLS-related ARF varies between 16 and 40% [1–5], but the incidence in France, even in a high-risk pediatric population is much lower, estimated at 3.5% in the study by Patte et al. [6–7], with less than 1.7% of these patients requiring dialysis [vs. 16–21% in similar patients in the United Kingdom and USA; 8, 9].

The Spectrum of ARF in ICU

The pathophysiology of hyperuricemia-related ARF is multifactorial, particularly in ATLS:

– the main mechanism is the occurrence of an acute urate nephropathy caused by tubular precipitation of uric acid massively excreted in the urine. The two main aggravating factors are volume depletion (with subsequent decreased glomerular filtration and high urate concentrations in the distal tubule, reaching the precipitation threshold), and acidic urine pH, which lowers the crystallization threshold. Severe acute urate nephropathy has become rare in countries where urate oxidase has been available and systematically used for a long time, such as Italy and France, as confirmed in the aforementioned comparative study of two comparable high-risk pediatric cohorts [7].
– the second mechanism in ATLS is hyperphosphatemia, which can lead to acute nephrocalcinosis through diffuse tissular precipitation of calcium phosphate complexes in the renal interstitial and tubular system. This second mechanism has infrequently been reported as a cause of ARF in ATLS [10–12] since most of the literature about ATLS has been published by teams who did not have access to urate oxidase, but is now the leading cause of severe ARF requiring dialysis in ATLS in Saint Louis Hospital, a tertiary care reference center for hematological malignancies in Paris (France), where urate nephropathy has virtually disappeared since a systematic prevention of ATLS with a urate oxidase-based regimen has been the rule for over 15 years [unpubl. data].
– in addition, many cancer patients admitted in ICU cumulate several additional factors contributing to severe renal dysfunction: they have often been exposed to nephrotoxic drugs such as aminoglycosides, glycopeptides, ACE inhibitors, or have undergone diagnostic procedures with injection of contrast media. Some have compression of the urinary tract or tumoral infiltration of kidneys.

Pharmacological Treatment of ARF with Hyperuricemia in ICU

Acute urate nephropathy is a condition in which ARF is primarily due to the diffuse deposition of urate crystals in kidneys and is essentially associated with rapidly progressive hematological malignancies, but the differential diagnosis include other renal conditions with elevated uricemia as a result of ARF from any cause, but particularly in the setting of dehydration and treatments with diuretics, low dose of salicylate, ethambutol, vitamin A and other drugs known to cause hyperuricemia/hyperuricosuria [13].

Moreover, other conditions associated with massive tissue breakdown and cellular lysis can cause hyperuricemia that can be hard to distinguish from acute urate nephropathy, such as rhadomyolysis, crush syndromes and extensive burns [14]. The measurement of the urinary urate/creatinine ratio can be of great help in nonanuric patients, since it has been shown that it exceeds one in acute urate nephropathies [15]. Nevertheless, ARF can be multifactorial and acute urate depositions can contribute to the aggravation of any ARF from other causes making the decision process to specifically treat hyperuricemia sometimes difficult.

ARF-Related Hyperuricemia

Although mild-to-moderate hyperuricemia is frequently encountered in ARF, especially when oligo-anuric, and the extent to which urate participates in the genesis of renal dysfunction is unknown, its role is probably minor. However, some acute hyperuricemic states arise in massive tissue destruction-related ARF, but plasma uric acid levels are generally lower than in ATLS [15]. Nevertheless, collecting convincing evidence of the role of uric acid in the pathogenesis of ARF is made difficult by its solubility in fixating solutions, especially formalin. Urate depositions can, therefore, not be visualized upon examination of tissue sections from biopsies or autopsies.

Theoretically, high uric acid plasma levels have the potential to cause tubular obstruction if urine flow is maintained, whatever the main initial renal injury mechanism may have been, and to aggravate the ARF or delay its recovery, but there is no definitive proof of such a role of urate in non-ATLS-related ARF. Nonetheless, there is accumulating recent evidence that uric acid can cause injuries by other mechanisms, especially local inflammatory response, direct glomerular and tubular cell toxicity through endothelial dysfunction, oxidant stress, and platelet activation. It has also been demonstrated that hyperuricemia accelerated cyclosporine-induced renal disease [16] and that reducing uric acid levels in rats with allopurinol reduced the incidence of renal disease [16, 17].

Nevertheless, there are no convincing data in the literature to currently advocate the systematic treatment of hyperuricemia in the general population of patients with ARF [18].

The nonrecombinant urate oxidase, obtained by extraction from *Aspergillus fumigatus* cultures, and formerly available in France and Italy had been approved for ATLS-related hyperuricemia, but has been occasionally used for hyperuricemia in other settings, especially when allopurinol could not be used because of its interaction with immunosuppressive drugs [19, 20]. Scarce data are available regarding its use in cardiac transplant recipients with ARF-related, severe hyperuricemia [21], but are largely insufficient to establish recommendations in this particular population or in any ICU population.

In addition, so far, rasburicase use has only been approved in the prevention and treatment of hyperuricemia associated with high-tumor burden hematological malignancies, and not in any other form of hyperuricemia. Allopurinol would, therefore, be the only pharmacological compound that could be used in this setting, but no study currently supports its administration in ARF-related hyperuricemia to limit its severity or to hasten its recovery. Even if allopurinol has been shown to reduce cardiovascular complications following coronary bypass surgery [22], further human studies are needed in this field to examine the potential beneficial effect of lowering uric acid level in ARF.

On theoretic grounds, urine alkalinization (pH above 7.0) using sodium bicarbonate could be considered as an adjuvant tool in the treatment of non-ATLS-related hyperuricemia if diuresis has been maintained. In the absence of hyperphosphatemia, it increases the solubility of uric acid [14] and can contribute to an increase in its renal clearance without exposing the patient to an increased risk of acute nephrocalcinosis. Nevertheless, in the setting of critically ill patients with altered renal functions, the metabolic consequences of sodium bicarbonate administration on the homeostasis of blood pH can be deleterious, especially in patients with chronic respiratory failure or during the weaning process of mechanically ventilated patients. In experimental models of acute hyperuricemia, the simple increase of urinary flow with crystalloid infusions has been proven to be as effective in increasing uric acid excretion as alkalinization [23] and should be favored at least in this aforementioned ICU population.

In massive rhabdomyolysis in which hyperuricemia can be encountered, alkalinization and mannitol are currently recommended by most authors in addition to volume resuscitation, since acidic urine pH and tubular obstruction by debris have been shown to be cornerstones in the pathogenesis of these ARF. But their efficacy has never been formally proven in prospective randomized trials. In a recent small-scale study in 24 patients admitted in ICU with rhabdomyolysis-related ARF, Homsi et al. [24] showed no differences in renal parameters in patients treated with saline alone or a combination of saline, mannitol and sodium bicarbonate. The use of these two agents in patients admitted in ICU with ARF can, therefore, only be suggested with caution, especially in oliguric patients.

Other pharmacological compounds that are currently under investigation in the prevention or treatment of ARF also have to prove their efficacy in larger studies. This is the case for the atrial natriuretic peptide, a potent natriuretic and diuretic compound, that have been found to improve renal blood flow and glomerular filtration rate in a small-scale study of ARF after cardiac surgery, but whose action on uric acid levels has not been reported [25].

Hyperuricemia-Related ARF

Obstructive ARF

Urate calculi have been exceptionally described in acute urate nephropathy [26] and most cases of ureteral obstructions by urate calculi are seen in patients with chronic hyperuricemia with or without inborn errors of metabolism. The management of such cases of ARF does not significantly differ from other types of obstructive ARF, urine derivation (generally with a JJ ureteral catheter, or if necessary, by nephrostomy) being the priority. The recovery of previous renal function is usually obtained after urine derivation, with the exception of prolonged obstructions or previously, severely altered kidneys in the setting of advanced chronic urate nephropathies. Nevertheless, in these patients, plasma levels of uric acid can be very high upon presentation, much higher than their usual chronic hyperuricemia, due to renal failure. Not only is urate oxidase not approved in this type of hyperuricemia, but its use anyway cannot be recommended unless the intensivist or the nephrologist in charge believe that an acute uric acid nephropathy is associated and significantly contributes to the alteration of the renal function. Rapid decrease of the hyperuricemia is usually obtained by the restoration of the urine flow, and in these patients, urine alkalinization is indicated in the absence of severe hyperphosphatemia. Neither injectable allopurinol nor recombinant urate oxidase are appropriate or approved in this indication, and normalization of uric acid levels with a long-term oral allopurinol-based treatment is the cornerstone of the management of these patients.

Anecdotally, dissolution of uric acid calculi in the ureters has been reported with continuous alkalinization with intravenous infusion of 14‰ sodium bicarbonate [27], but for obvious reasons this type of management should not be attempted in any obstructive ARF in place of urine derivation, even if uric acid lithiases are suspected.

ATLS-related ARF

Adequate prevention of ATLS is the hallmark of a quality management when the induction therapy of acute hematological malignancies is initiated

and a specific chapter deals with this topic elsewhere in this book. When prevention was nonexistent, inadequate or insufficient, severe ARF requiring ICU admission can occur.

Patients admitted in ICU with ATLS-related ARF are almost always hematology patients with already identified malignancies, mainly high-grade non-Hodgkin's lymphomas and acute leukemias. Nevertheless, spontaneous inaugural ATLS has been described sometimes associated with arthropathy [28] or even in metastatic solid tumor [29] and can be of particular severity because of the delay in the diagnosis and the absence of preventive measures [30–35].

In most cases of severe ARF, hemodialysis or hemofiltration will be required because of threatening metabolic disturbances and/or fluid overload, and this topic is covered in the previous chapter. Apart from extracorporeal renal replacement, the pharmacological management of these patients is very similar to the measures that can be recommended for non-ICU patients, and mainly depends on the availability of the two specific drugs for hyperuricemia, and of the presence of hyperphosphatemia.

Experience with Allopurinol

Most of the published cases of severe ATLS-related ARF have been managed with oral or IV allopurinol [36, 37] (100 mg/m^2 every 8 h on average), since urate oxidase has been available only in France and Italy until the recent commercialization of the nonrecombinant form of urate oxidase. Allopurinol is a xanthine oxidase inhibitor, and although it has demonstrated its efficacy in the prevention and treatment of malignancy-associated hyperuricemia [36–38], it carries several drawbacks that should now make it a second-line choice, at least in ICU, where the most severe cases of ATLS are managed.

Firstly, it blocks the synthesis of uric acid from xanthine but does not degrade the uric acid that has accumulated before the treatment, often abundantly in ICU patients, and is, therefore, unable to rapidly lower uric acid levels in patients already hyperuricemic upon presentation or admission in ICU. It usually takes 2–3 days before a significant reduction in plasma uric acid levels can be obtained, assuming normal renal function, which is never the case in this type of ICU patients. Secondly, it leads to the accumulation of uric acid precursors such as xanthine and hypoxanthine, which are poorly soluble and can precipitate in renal tubules, causing the rare but unwanted xanthine nephropathy [39–41]. Thirdly, its active metabolite, oxypurinol, is normally excreted in urine. In case of ARF, it accumulates and dose reduction of allopurinol is necessary, especially since none of these two compounds are readily removed by hemodialysis [42]. Lastly, allopurinol inhibits the degradation of other purines, including 6-mercaptopurine, making the handling of patients receiving allopurinol difficult, with necessary approximate dose reductions. For all these

reasons, allopurinol will no longer be the first-line choice for the treatment of severe hyperuricemia especially in ICU patients, and rasburicase should be preferred. It will, nevertheless, probably remain an acceptable alternative whenever the administration of a urate oxidase will not be possible, whether for allergic reason or because of a glucose-6-phosphate dehydrogenase deficit, which contraindicates the use of rasburicase [43].

Experience with Urate Oxidase

Most of the clinical experience of the handling of urate oxidase has been acquired over the past 25 years with the nonrecombinant urate oxidase (Uricozyme®), which was only commercialized in France and Italy, but has been enriched with the recent experience gained with rasburicase, the recombinant form [6, 7, 44–48]. Urate oxidase degrades uric acid into a highly soluble compound, allantoine, which is readily excreted in urine. Unlike xanthine, a metabolite that accumulates during allopurinol therapy, allantoine does not precipitate into the renal parenchyma, even when its excretion is impossible, like in anuric patients. Urate oxidase is effective in the prevention of hyperuricemia, but both the recombinant and the nonrecombinant urate oxidase have been shown to be more effective than allopurinol in the treatment of hyperuricemia in hematology patients [47, 49, 50].

Specific ICU experience with this drug has never been described, since most published series are from countries where no urate oxidase was available, and do not report separately on patients with severe renal impairment or those admitted in ICU. In fact the incidence of ICU admission for dialysis is extremely low when urate oxidase is used: in a randomized study versus allopurinol in 52 high-risk pediatric patients, Goldman et al. [50] reported no renal failure requiring renal replacement in the phase II and III studies, only one patient developed renal failure while on rasburicase therapy [45, 51]. The comparison of the need for dialysis of children treated in England (UKCCSG protocol) and in France (LMB89 study) with similar protocols for the same diseases show a 3% incidence of ARF requiring dialysis in children treated with a urate oxidase versus 16% in children receiving allopurinol [7]. Scattered reports specifically describing single or small numbers of ATLS requiring hemodialysis have been published [30, 52, 53], but none with the administration of urate oxidase.

Nevertheless, pharmacokinetic studies show that urate oxidase is not metabolized or excreted by the kidneys and that dose reduction is not necessary whatever the severity of renal failure [43, 44]. Therefore, all patients with renal dysfunction severe enough to require ICU admission, or combined with other organ failure compromising renal perfusion should benefit from a full dose urate oxidase-based treatment (Rasburicase, 0.2 mg/kg/day in one daily intravenous injection), as long as biological markers of ongoing tumor lysis are

elevated, even if they are being dialyzed in parallel. This enzyme is rapidly active with low levels of uric acid being achieved within 4 h and failure with full doses being exceptional. In massive ATLS, uric acid levels should, nevertheless, be checked and a second injection prescribed 12 h later if plasma levels are still high [46]. In the era of a worldwide availability of rasburicase, there is no longer any place for an allopurinol-based treatment in these severe forms of ARF, this latter being less rapidly active, less efficacious and potentially responsible for xanthine nephropathy [39–41]. Concomitant or preceding treatment with allopurinol is also not necessary when rasburicase is used, especially since rasburicase cannot metabolize uric acid precursors that will accumulate if allopurinol is used before the initiation of the urate oxidase.

Use of Diuretics

The administration of diuretics, whatever the class, should be withheld in these patients with severe hyperuricemia-related ARF. Firstly, because in this obstructive nephropathy context with high plasma and urine urate concentrations, forced diuresis is obviously inappropriate and will not alleviate tubular obstruction in any way. Secondly, precocious deaths in severe ATLS are related to metabolic disturbances or multiorgan failure, none of these two situations being indications for diuretic-based therapy, which may even potentially worsen prognosis in critically ill patients [54]. Delaying renal replacement therapy in patients with looming hyperkalemia and impending calcium phosphate precipitation may jeopardize not only their odds for survival but also their renal prognosis. Even the use of acetazolamide that might seem more appropriate because of its capacity to alkalinize urine, should be discouraged for the same reasons.

Pharmacological Management of Calcium-Phosphate Disturbances

In hospitals where a urate oxidase-based prevention is the rule, intensivists have acquired a slightly different point of view about patients admitted in ICU for an ATLS-related ARF: urate oxidase invariably leads to a dramatic decrease in plasma uric acid level and urate nephropathy has become rare in the ICU, the majority of these patients being admitted with low or undetectable uric acid but with hyperphosphatemia/hypocalcemia and acute nephrocalcinosis-related ARF. The key point in their management is then to avoid any therapeutic measure that could aggravate this condition, especially alkalinization. Indeed, massive amounts of organic phosphorus are released during ATLS due to the important phosphate content of lymphoid blasts [55]. Diffuse calcium phosphate precipitation can occur causing ARF through acute nephrocalcinosis [56–59], especially when the calcium-phosphate products exceeds 4.6 $(mmol/l)^2$ [60]. This phenomenon has been described as the main mechanism leading to ARF in patients with ATLS but low uric acid levels [11, 12, 61–63], and is favored by

alkaline pH that lowers the crystallization threshold and by exogenous calcium administration. Moreover, alkinization also lowers the threshold for symptoms of hypocalcemia.

In anuric patients, extrarenal support and fluid restriction are the rule and IV alkalinization is then rarely administered. But the bicarbonate load induced by dialysis bath or reinjection fluid during continuous hemofiltration is often overlooked. When dialysis is initiated for a patient with severe hyperphosphatemia, the composition of the dialysate fluid should be modified whenever possible to minimize the risk of calcium-phosphate precipitation.

In patients with maintained diuresis, rasburicase administration should be systematic because it obviates the need to alkalinize the urine, and high urine flow should be maintained with the sole use of nonalkaline crystalloid solutions.

Considering the phosphate load in these patients, control of severe hyperphosphatemia by phosphate binders (aluminium hydroxide, or even sevelamer-Renagel®) is illusory. These pharmacological measures should be considered as adjuvant tools in the management of moderate hyperphosphatemia and should certainly not delay the initiation of renal replacement therapy.

Asymptomatic hypocalcemia should also not be corrected for the same reason of potential exacerbation of calcium-phosphate precipitation and brief administration of minimal doses of IV calcium gluconate should be reserved for poorly tolerated symptomatic hypocalcemia while preparing the patient for extracorporeal renal replacement therapy, which is the only way to rapidly lower plasma phosphorous while correcting calcemia at the same time. Symptoms of hypocalcemia generally disappear with the correction of hyperphosphatemia.

Prognosis of Hyperuricemia-related ARF in ICU

Prognosis of ATLS-related ARF is particularly difficult to determine based on the available literature. The series were small, mortality was generally not reported, and when reported, most authors only mention immediate ATLS-related mortality. ATLS survival is high with precocious death being rare and related to acute metabolic disturbances such as hyperkalemia (6–20% ARF-related mortality) [2–4]. But with closer examination of the literature, one can estimate that the one-month mortality of dialysis-requiring ATLS is much higher [64], exceeding 40% for Cohen et al. [4] and Atra et al. [8], most of the cases being associated with multiorgan failure. The main survival prognosis factor for severe ARF from ATLS, therefore, appears to be the presence of other organ failures rather than the severity of the ARF in itself. Indeed, for patients surviving ICU, the renal prognosis seems excellent with discontinuation of dialysis in all reported cases and excellent recovery of renal function in most cases [1, 2, 64].

Regarding acute severe nephrocalcinosis, although probably bound to be more and more frequent in ICU patients, its prognosis is currently unknown. A few cases reporting complete reversibility, including with normalization of echographic findings, have been published [61, 62, 65] but further investigation of these type of ATLS-related ARF is needed.

Economic Evaluation of the Pharmacological Treatment of ATLS

Pharmacoeconomic evaluation of the cost-effectiveness of this type of treatment should be considered when highly effective but expensive new drugs such as rasburicase are made available to physicians. Beyond survival, all aspects of the costs but also the benefits of a prophylactic management should then be assessed, including reduction of hospital stays, costs of dialysis and ICU stays, but also potential alteration in quality of life and functional status caused by delayed chemotherapies or hazardous dose adjustments due to impaired renal function [66]. Considering the cost of the recombinant urate oxidase, a cost-effectiveness study has already been conducted in Europe [67], establishing that a rasburicase-based preventive strategy is costeffective in all type of hematological malignancies in children, and in adults with non-Hodgkin's lymphoma and acute lymphoblastic leukemias, the beneficial effect being lower for acute myeloid leukemias where short average life expectancy and lower baseline risk of ATLS limit its cost-effectiveness. Further larger studies within the next few years, both in North America and in Europe, should shed a more precise light on this matter.

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