

REVIEW

Elitek™–rasburicase: an effective means to prevent and treat hyperuricemia associated with tumor lysis syndrome, a Meeting Report, Dallas, Texas, January 2002

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Renal precipitation of uric acid associated with tumor lysis syndrome (TLS) is a major complication in the management of leukemia, lymphoma, and other drug-sensitive cancers. Management of hyperuricemia has historically consisted of administration of allopurinol, hydration, alkalization to maintain pH between 7.0 and 7.3, and in some cases diuresis. Allopurinol, a xanthine analogue, blocks xanthine oxidase and formation of uric acid. Urate oxidase converts uric acid to allantoin, which is 5–10 times more soluble than uric acid. *Homo sapiens* cannot express urate oxidase because of a nonsense mutation. Urate oxidase was initially purified from *Aspergillus flavus* fungus. Treatment with this nonrecombinant product had been effective in preventing renal precipitation of uric acid in cancer patients, but was associated with a relatively high frequency of allergic reactions. This enzyme was recently cloned from *A. flavus* and is now manufactured as a recombinant protein. Clinical trials have shown this drug to be more effective than allopurinol for prevention and treatment of hyperuricemia in leukemia and lymphoma patients. This drug has been approved in Europe as well as the US and several clinical trials are in progress to further determine its clinical utility in other patient subsets. The purpose of this meeting was to discuss usefulness of recombinant urate oxidase, also known as rasburicase, Fas-turtec[®], and Elitek[™], for the management of TLS in certain cancer patients.

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Introduction

Definition of tumor lysis syndrome (TLS)

TLS is a set of complications that can arise from treatment of rapidly proliferating and drug-sensitive neoplasms, particularly those of hemopoietic origin.^{1–10} Untreated, TLS can lead to life-threatening complications such as acute renal failure.^{11–31} While TLS may occur prior to administration of chemotherapy in leukemia and lymphoma patients, especially those with

advanced-stage Burkitt's lymphoma and B-cell leukemia, it is usually induced by chemotherapy. Chemotherapy causes rapid destruction of tumor cells, which leads to release of intracellular substances into the bloodstream. These substances and their by-products are eliminated by renal excretion.

Metabolic disturbances associated with TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.^{1–31} Abnormally high levels of potassium, phosphorus, and nucleic acids are released from lysed cells into the bloodstream following aggressive cytotoxic chemotherapy.^{1–31} Hyperphosphatemia in turn leads to hypocalcemia. Nucleic acids are broken down, which leads to hyperuricemia. Uric acid crystals can block renal tubules. Calcium phosphate salts can also precipitate in renal tubules to further contribute to renal failure (Figure 1).

Factors predisposing patients to TLS

Patients with decreased urinary flow, pre-existing hyperuricemia, renal failure, dehydration, or acidic urine are at increased risk for TLS. All these host-related factors suppress renal uric acid excretion. There are also tumor-related risk factors for this complication, which include high tumor cell proliferation rate, tumor size, and tumor chemosensitivity. While advanced Burkitt's lymphoma and B-cell acute lymphoblastic leukemia (ALL) are associated with the highest risk for TLS, this complication also occurs occasionally in patients with large solid tumors.

TLS patients typically present with hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These biochemical abnormalities can affect the function of many organs, and result in cardiac and neurological complications. Elevated serum lactate dehydrogenase level is a biochemical marker for tumor lysis, but has no clinical consequence.

The pK_a of uric acid is 5.7. In plasma, where pH is higher, uric acid is ionized. In the acidic environment of renal tubules, uric acid becomes nonionized and less soluble. As uric acid levels increase from TLS, deposition of uric acid crystals in renal tubules becomes more likely. Upon development of uric acid nephropathy, symptoms of renal insufficiency develop. Uric acid crystals are often detected on urinalysis. Urine output decreases markedly and blood urea nitrogen (BUN) and creatinine levels rise.

This critical Review has been written on the basis of data and discussions presented at the Meeting on Rasburicase, Dallas, Texas, January 2002.

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Tumor Lysis Syndrome and Kidney Dysfunction

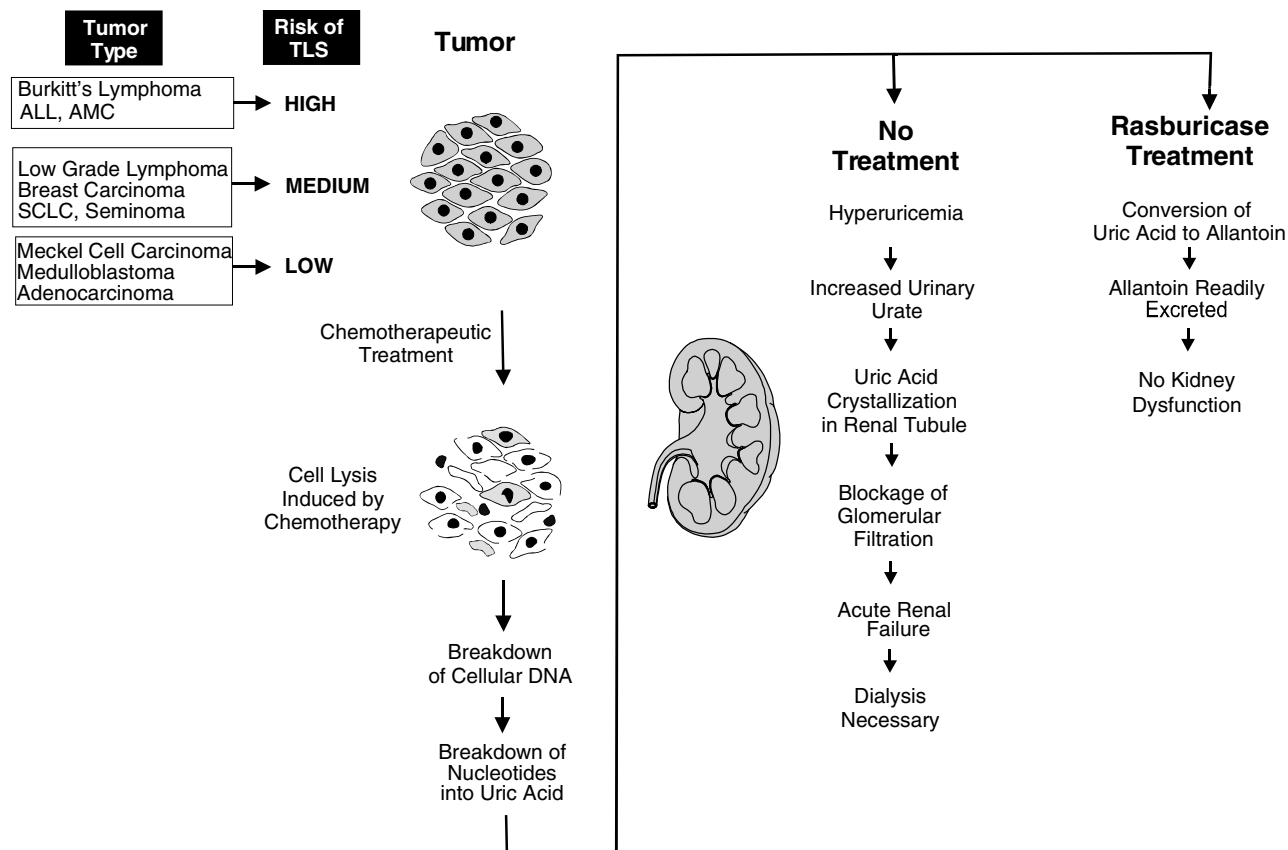


Figure 1 Tumor lysis syndrome (TLS) and kidney dysfunction. This diagram provides an overview of the effects of TLS on kidney function and the effects of no treatment vs rasburicase treatment.

Patients with TLS and those at risk of developing it must be monitored to determine the electrolyte levels. By monitoring serum levels of these compounds every 4–6 h during the initial 48–72 h, electrolyte imbalances may be rapidly corrected by appropriate treatment.

Sodium bicarbonate administration increases urinary pH. Urinary pH between 6.5 and 7.0 can keep uric acid ionized and prevent its crystallization in renal tubules. However, urinary alkalization may predispose patients to urinary calcium phosphate precipitation, resulting in decreased glomerular filtration. Allopurinol treatment decreases uric acid production, but increases levels of its precursors hypoxanthine and xanthine, both of which have higher solubility in alkaline urine. Unlike hypoxanthine, xanthine is less soluble than uric acid, even in alkaline urine. Therefore, occasional cases of xanthine nephropathy or xanthine renal stones have been reported.^{32–35} Figure 2 outlines hepatic catabolism of purine nucleotides. Xanthine oxidase catalyzes conversion of hypoxanthine to xanthine as well as xanthine to uric acid.

Hydration, urine alkalization, and diuresis may decrease risk of renal uric acid deposition. Uric acid levels are further lowered by allopurinol (Figure 3). Allopurinol is a xanthine analogue converted *in vivo* to an active metabolite, oxypurinol. Oxypurinol binds and inhibits xanthine oxidase.

Allopurinol [Zyloprim™; Zyloric®; Aloprim™] combined with alkaline hydration has been the primary treatment for hyperuricemia until recently. Allopurinol is usually administered orally at doses ranging from 300 to 600 mg per day in adults and 300 mg/m² per day in children. It can also be administered

intravenously at a recommended dose of 200–400 mg/m² per day. Skin rashes are the most frequent side effects of allopurinol, which in rare instances can be life threatening. If allergic side effects occur, allopurinol treatment should be discontinued immediately. Since there is pre-existing uric acid before allopurinol treatment is initiated and allopurinol cannot break down uric acid, 2–3 days are generally necessary for uric acid levels to decrease after initiation of allopurinol treatment.

The primary function of urate oxidase is to catabolize uric acid formed by purine catabolism. Urate oxidase catalyzes conversion of uric acid to allantoin via a 5-hydroxyisourate intermediate (Figure 2). Since allantoin is readily water soluble, its elimination by urinary excretion is less problematic than xanthine or uric acid. The reactive by-product of this reaction, hydrogen peroxide (H₂O₂), is neutralized by catalase to yield oxygen and water.

Meeting Report – plenary speakers

Allopurinol and urate oxidase for TLS treatment

Recombinant urate oxidase is produced by genetically modified *Saccharomyces cerevisiae* that express urate oxidase cDNA cloned from a strain of *A. flavus*.^{36,37} The generic name of the drug is rasburicase. The trade name used by Sanofi-Synthelabo is Fasturtec® in Europe and Elitek™ in the United States.^{38,39} Hyperuricemia results from the breakdown of purines and pyrimidines released by tumor cells lysed by chemotherapy.

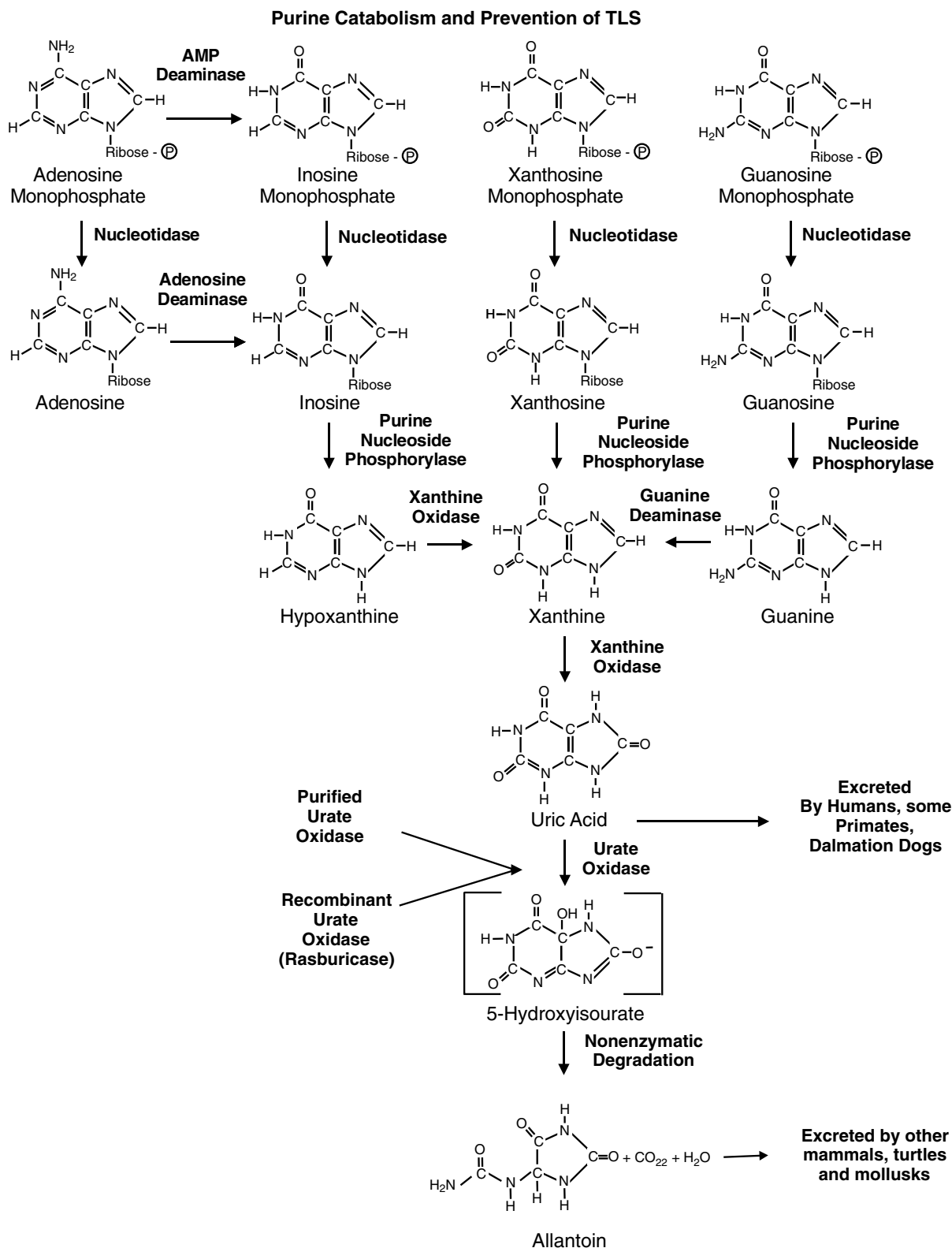


Figure 2 Purine catabolism and prevention of TLS. This diagram depicts biochemical pathways responsible for the degradation of purines following rapid cell lysis induced by chemotherapy. This diagram also illustrates the ability of either purified or recombinant urate oxidase to convert uric acid to allantoin.

Uric acid produced by catabolism of purines and pyrimidines may precipitate in renal tubules.

Management of elevated uric acid levels in the United States generally consists of hydration, alkalinization to maintain

urinary pH between 7.0 and 7.3, and in some cases diuresis to facilitate uric acid excretion. Alkalinization is not necessary if rasburicase is administered, thus facilitating phosphorus excretion.

Allopurinol, an Inhibitor of Xanthine Oxidase

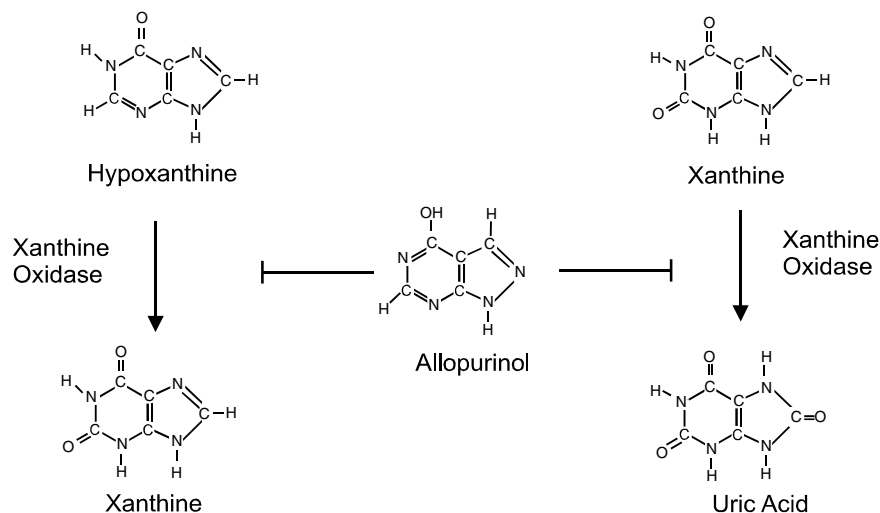


Figure 3 Allopurinol, an inhibitor of xanthine oxidase. This diagram depicts inhibition of xanthine oxidase by allopurinol to prevent conversion of hypoxanthine to xanthine and conversion of xanthine to uric acid.

Allopurinol prevents uric acid formation by inhibiting xanthine oxidase. Allopurinol has been available for oral use since 1966 (Figure 3), and an intravenous preparation became available in the United States in 1999. The intravenous formulation was available on a named patients basis in many countries outside the United States, but was withdrawn in Europe upon arrival of rasburicase. Nonrecombinant urate oxidase (Uricozyme[®], Sanofi-Synthelabo) has been available in France since 1975, and in Italy since 1984. It is produced by extraction from *A. flavus*. Rasburicase is a recombinant form of urate oxidase approved in 2001 for use in Europe.

Allopurinol has a number of limitations. First, although allopurinol prevents uric acid formation, patients must still excrete pre-existing uric acid. Also, there is a potential for xanthine nephropathy. By blocking xanthine oxidase, the patient accumulates hypoxanthine and xanthine. Xanthine is very insoluble and has a solubility even less than that of uric acid. There have been case reports of xanthine stone formation since the early 1970s. Moreover, 3% of patients will develop hypersensitivity reactions to allopurinol, and some patients develop a severe allergic reaction manifested as Stevens-Johnson syndrome. If the patient has renal impairment at diagnosis, allopurinol dosage must be reduced. Additionally, allopurinol usefulness is further limited because it interacts with many drugs such as chlorpropamide, 6-mercaptopurine, azathioprine, dicumarol, cyclosporine, and thiazide diuretics.

A recent study of compassionate-use intravenous allopurinol showed that it normalized uric acid in only about half of adult patients and about 88% of children.⁴⁰ Children responded rapidly with a mean response time of 1 day. However, adults responded slower with a mean response time of 5 days. Importantly, renal function decreased in 15% of patients treated with intravenous allopurinol. In contrast, deterioration of renal function in patients treated with urate oxidase was rarely observed, as is described below.

At St Jude's Hospital in Memphis, TN, USA, studies of upfront high-dose methotrexate before initiation of conventional remission induction therapy have been conducted in newly diagnosed ALL patients since 1991. Initially, allopurinol was used for prevention and treatment of hyperuricemia. However, in 1994 it was observed that allopurinol inhibited *de novo* purine

synthesis, which would confound interpretation of methotrexate pharmacodynamic data. Indeed, white blood cell (WBC) counts dropped because allopurinol had a small antileukemic effect.⁴¹

Since 1994, Uricozyme[®] had been used in the St Jude's study to avoid this confounding factor. Consecutive use of allopurinol and Uricozyme[®] allowed the efficacy of each drug to be compared. These consecutive cohort patients had comparable ages and similar clinical and presenting features such as WBC counts and levels of LDH, uric acid, phosphorus, BUN, and creatinine.

In this retrospective comparison, Uricozyme[®] was significantly more effective than allopurinol for reducing uric acid levels.⁴² Uricozyme[®] also improved renal function as demonstrated by lower BUN and creatinine levels. Similar results have subsequently been observed in patients receiving recombinant urate oxidase (rasburicase).^{43,44} Phosphorus levels were similar between the two treatment groups. Since patients in the St Jude study were treated with high-dose methotrexate as an upfront treatment, bicarbonate was given to prevent methotrexate precipitation, regardless of whether they received allopurinol or Uricozyme[®]. Administration of bicarbonate to patients in this study may have reduced their phosphorus excretion and may explain why phosphorus levels did not differ between the two treatment groups. In most treatment protocols, however, high-dose methotrexate is not a component of early remission induction treatment. In other studies without use of upfront high-dose methotrexate, patients treated with rasburicase demonstrated better control of phosphorus levels.^{43,44}

Hypersensitivity reactions were observed in nearly 5% of patients treated with Uricozyme[®]. Allergic reactions occurred within 1–17 min after beginning infusion of the first dose. These symptoms were manifested mainly as bronchospasm, urticaria, and, in some patients, angioedema. One African-American boy developed methemoglobinemia and was subsequently found to have glucose-6-phosphate dehydrogenase (G6PD) deficiency. It should be noted that methemoglobinemia and hemolytic anemia are known complications of treatment with urate oxidase in patients with G6PD deficiency. H₂O₂, a strong oxidizing agent produced as a by-product of uric acid breakdown, causes these complications in this set of patients.

Therefore, urate oxidase is contraindicated in individuals deficient in G6PD.⁴⁵

There are also a number of other limitations associated with nonrecombinant urate oxidase. The preparation contains multiple uncharacterized impurities that may contribute to allergic reactions. 8-Azaxanthine, a stabilizing agent used in the production process, is not a standard excipient. Production of nonrecombinant urate oxidase from *Aspergillus flavus* is slow, and the yield is low, which limits supply. Nonrecombinant urate oxidase contains a cysteine adduct resulting from its process of purification that lowers its activity.⁴⁶ In contrast, the molecular structure of rasburicase is preserved by its process of production.⁴⁶

Dr Pui further reviewed frequency of acute renal failure in patients with advanced B-cell malignancies such as stage III/IV lymphoma and B-cell ALL. Allopurinol was administered to 230 patients in three studies conducted by the Pediatric Oncology Group (POG),⁴⁷ UK Children's Cancer Study Group,⁴⁸ and St Jude's.⁸ Of these, 20% developed acute renal failure and 5% died.

These results were compared with six trials that used urate oxidase. Two studies used nonrecombinant urate oxidase^{42,49} and the other four employed the recombinant enzyme.^{43,44,50,51} Of 219 patients, only 3% developed acute renal failure and no fatalities were reported. However, Dr Pui cautioned against interpretation of data by retrospective comparison.

Preliminary results of a study performed at St Jude's Hospital to investigate pharmacology of an initial high dose of methotrexate were summarized. Clearance of methotrexate from patients treated with rasburicase or allopurinol was compared. Patients treated with rasburicase had better renal function and significantly better methotrexate clearance.⁵² Administration of rasburicase not only controlled uric acid accumulation, but also facilitated renal clearance of other metabolites or drugs.

Incidence of TLS

The exact incidence of TLS is unknown. In a retrospective analysis of approximately 40 patients with high-grade non-Hodgkin's lymphoma, TLS was recognized in approximately 40% of the patients, as defined by a 25% decrease in calcium or a 25% increase in either potassium or uric acid. It is most commonly associated with hematologic malignancies, particularly acute leukemias and high-grade lymphomas, but it also has been observed in a variety of solid tumors.

Hematologic malignancies associated with TLS include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), non-Hodgkin's lymphoma (NHL), plasma cell disorders such as multiple myeloma (MM) and amyloidosis, as well as myelofibrosis and myelodysplastic syndrome (MDS). The risk of TLS among acute leukemia patients increases as their WBC count increases. This has also been observed in CLL and bulky adenopathy, and in patients with advanced forms of CML. In NHL, it has primarily been observed in patients with high-grade NHL. In MM, TLS has primarily been associated with more advanced myelomas with a high plasma cell load, and also in patients with isolated plasmacytomas. TLS has been observed in advanced MDS. TLS has also been recognized in a few patients with refractory anemia and refractory anemia with ringed sideroblasts.

Solid tumors that have been reported to have TLS associated with their treatment include breast cancer, testicular cancer,

medulloblastoma, Merkel cell carcinoma, both small cell and nonsmall cell lung cancer, melanoma, choriocarcinoma, hepatocellular carcinoma, vulvar carcinoma, colorectal cancer, germ cell tumors, neuroblastoma, and teratoma. It is more commonly observed in patients with either testicular cancers or nontesticular germ cell tumors with high tumor burden that have high proliferative rates and respond to cytotoxic therapy.

TLS has been primarily observed with the administration of cytotoxic chemotherapy, but has also been observed with a variety of other treatment modalities. Some correlations have been reported between more aggressive cytotoxic treatment and TLS, but this probably reflects more the biology of the disease and the necessity to treat it in an aggressive manner rather than the treatment modality or treatment regimen itself. TLS has been observed with the administration of corticosteroids alone and also after treatment of certain cancers with hormonal agents such as letrozole and tamoxifen. TLS has been observed after treatment of certain cancer patients with biologic response modifiers such as interferon and interleukin-2. TLS has been observed with administration of immunotherapeutic agents, such as rituximab. More recently, TLS has been observed after treatment of patients with small molecular weight inhibitors. Two patients with Philadelphia chromosome-positive ALL developed TLS after treatment with STI-571, which is better known as Gleevec.⁵³

TLS directly results from rapid release of intracellular ions and metabolites from malignant cells after the initiation of cytotoxic therapy. This becomes problematic when the body is unable to handle increased concentrations of these ions and metabolites, which are primarily cleared by urinary excretion, which results in characteristic metabolic abnormalities. Metabolic disturbances associated with TLS can lead to a variety of life-threatening complications, which are reviewed below.

The most common abnormalities associated with TLS include hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, and uremia. Hypocalcemia is somewhat deceiving, because after initiation of cytotoxic chemotherapy, calcium levels tend to rise. Then calcium binds with released phosphate. Cardiac arrhythmias can result from decreased serum calcium levels.

The most important concern with TLS is the development of hyperuricemia. Malignant cells contain a concentration of purines that are four to five times that of normal cells. Purines are catabolized to uric acid. In most mammals, with the exception of humans, urate oxidase will convert uric acid to allantoin. Allantoin is four to five times more soluble than uric acid. Hence, uric acid is not precipitated within kidneys if urate oxidase is present.

The most important aspect in the management of TLS is early recognition of at-risk patients. Patients at highest risk for TLS include those with tumors that have a high proliferative rate, patients with tumors with a high sensitivity to cytotoxic therapy, patients with large tumor masses, patients with pre-existing renal insufficiency, and finally patients who present with a high-serum LDH. Patients with high-serum LDH may be at highest risk for the development of clinically significant TLS.

Therefore, it is important to identify those patients at risk. These patients should be admitted either to a medical intensive care unit or to a hematology/oncology unit with sufficient staff and support that can recognize and treat multiple complications associated with TLS. Adequate venous access should be established in all patients, and, if possible, tumor therapy should be delayed in order to initiate adequate hydration to prevent complications. A baseline electrocardiogram should be ob-

tained and patients should ideally be on continuous cardiac monitoring for at least the first 72 h after therapy initiation. Levels of LDH, uric acid, sodium, potassium, creatinine, BUN, phosphorus, and calcium should be determined. These should be monitored every 4 h during the first 24 h of treatment and every 6–8 h subsequently.

The most important aspect of TLS prevention is intravenous hydration. This should be achieved with either a hypotonic solution or an isotonic saline solution at approximately 2500–3000 ml/m² per day, or about 100–125 ml/m² per hour. One can administer allopurinol at 300–400 mg/m² per day orally or recombinant urate oxidase (rasburicase, Elitek™) at 0.2 mg/kg per day intravenously. Either allopurinol or rasburicase should be given for 5–7 days, preferably starting 24 h before the initiation of therapy. Urinary alkalization is often employed, although this remains controversial. Urine alkalization can be achieved by administration of acetazolamide or an isotonic solution consisting of 50–100 mEq sodium bicarbonate added to half-normal saline.

Alkalinization is controversial for two reasons. First, alkalinization leads to precipitation of calcium and phosphate. Calcium phosphate precipitation can lead to increased renal failure and lead to other abnormalities following deposition in other organs. Of particular concern is deposition of calcium phosphate within the heart. Secondly, alkalization is inadequate for xanthine solubility. If one uses allopurinol, inhibition of xanthine oxidase can increase xanthine levels. Xanthine has a pK_a of approximately 7.4. Thus, it is important to exceed a urinary pH of 7.4 in order to prevent xanthine precipitation that may contribute to renal failure. It is advantageous to administer urate oxidase rasburicase, Elitek™, which converts uric acid into allantoin, which is far more soluble. Thus, rasburicase prevents these complications.

The major emphasis should be placed upon trying to prevent TLS. However, if it occurs, how should it be treated? One of the major complications that can occur is decreased urinary output that can result from a number of physiological problems. It can result from urate, xanthine, or calcium phosphate precipitation as well as from tumor involvement in the kidney. Clinical manifestations in this situation include overt renal failure and fluid overload. As mentioned before, one can remove fluid through diuresis. Furosemide or Bumex are not very effective if the renal tubules are affected with urate precipitation. Mannitol may be administered at doses from 200 to 500 mg/kg, but mannitol is not effective in most situations. Immediate hemodialysis should be considered.

The primary concern with hyperkalemia is the development of arrhythmias. Potassium-binding resin can be administered at any time during the development of hyperkalemia, but the physician should consider hemodialysis if it does not appear that this will reverse the arrhythmia, especially if it appears to be a malignant arrhythmia. For patients who develop severe hyperkalemia and/or malignant arrhythmia, the acute treatment is an infusion of calcium gluconate.

Uremia can cause pericarditis and platelet dysfunction. Uremia is generally not life threatening, but uremic syndrome and platelet dysfunction can adversely affect the patient later on, especially during a period of aplasia. Again, if uremia does develop or the BUN rises above 80 mg/dl, hemodialysis should be performed.

Cytotoxic therapy may also cause hypocalcemia. Hypocalcemia results from calcium binding to phosphate released from tumor cells and may lead to significant arrhythmia. One must be cautious with calcium replacement with calcium carbonate, because additional calcium may bind with phosphate

causing further exacerbation of symptoms and there is little chance of reversing this process. Management of this situation includes antiarrhythmics and, again, hemodialysis should be considered.

Hyperuricemia and hyperphosphatemia are important effects of TLS. Deposition of uric acid in renal tubules is the most significant cause of kidney dysfunction resulting from TLS. Allopurinol may prevent uric acid crystallization, but may also cause renal deposition of xanthine crystals. The second most common cause of kidney dysfunction in TLS patients is deposition of calcium phosphate precipitates in distal tubules. Conservative treatment is to administer 1–2 g of aluminum hydroxide orally every 4 h. Again, hemodialysis must be initiated early if renal function declines.

It is important to identify patients at risk for TLS. They include patients with advanced hematologic malignancies, high-grade NHL such as Burkitt's NHL, acute leukemias such as ALL and AML, those with a high tumor burden, and those with tumors having a high proliferative rate or high sensitivity to cytotoxic chemotherapy. It is important that intravenous fluids be initiated and that diuresis is established.

One can administer either allopurinol or urate oxidase 24 h prior to initiation of chemotherapy to prevent uric acid precipitation. Unfortunately, this is not possible in most situations because of the urgent need to treat patients. In these cases, it is started simultaneously with chemotherapy. Urine alkalization, again, is a controversial part of management because of the concern that it may lead to calcium phosphate precipitation and is relatively ineffective for the prevention of xanthine precipitation.

Development of rasburicase

Purines such as adenine and guanine are degraded to hypoxanthine, then xanthine, and finally to uric acid (Figure 2). This is the end product of purine metabolism in humans. At some point in human evolution, a premature stop codon was introduced into the gene for urate oxidase preventing its expression in humans.

Xanthine oxidase converts hypoxanthine to xanthine and xanthine to uric acid. Allopurinol is a xanthine analog that blocks both of these reactions. Urate oxidase converts uric acid to allantoin, which is more water soluble than uric acid. This enzymatic reaction also liberates H₂O₂, which is a potential source of oxidative stress. This has important clinical significance because patients with G6PD deficiency may be at increased risk of either methemoglobinemia or outright hemolysis. Urate oxidase is a tetrameric protein composed of four 34 kDa monomers. It is a relatively large protein with a very low renal clearance. Elimination of this enzyme does not correlate with renal function.

The rationale for rasburicase development resulted from the use of nonrecombinant urate oxidase. Urate oxidase has been used effectively in France and Italy since the 1970s and 1980s, respectively. Urate oxidase was isolated from wild-type fungal cultures by a relatively laborious process. Purification of urate oxidase involved extraction procedures that cause some oxidative degradation of the enzyme.⁴⁶ Since this process was developed over 25 years ago, the drug was stabilized with agents that have never been fully characterized.

Urate oxidase cDNA was isolated with oligonucleotide DNA probes generated after amino acid sequencing of purified urate oxidase. Urate oxidase cDNA was cloned from *Aspergillus*, the same organism in which the enzyme was initially purified from.

Urate oxidase cDNA was subcloned into a high-expression yeast vector and is expressed in *Saccharomyces*. The yield of rasburicase per kilogram of total cellular protein is about 100 times higher than that of nonrecombinant urate oxidase from *Aspergillus*. Moreover, recombinant urate oxidase produced by this process has a higher activity and purity than that of the nonrecombinant process.⁴⁶ Although Sanofi-Synthelabo has been interested in rasburicase for the treatment of both pediatric and adult patients, it has initially been used primarily by pediatric physicians.

A phase I study demonstrated that rasburicase has linear pharmacokinetics and pharmacodynamics. The mean half-life is 18 h, which is appropriate for a drug administered once per day. The mean volume of distribution is similar to blood volume, which is evidence that rasburicase is confined to the vascular compartment. Vascular distribution of rasburicase is desirable given its mechanism of action. Finally, rasburicase clearance is independent of renal or hepatic function. Rasburicase is degraded by peptide hydrolysis. Rasburicase amino acids are reincorporated into other proteins. This does not cause problematic metabolic interactions. This protein does not alter the cytochrome P-450 system and no drug interactions have been reported.

A human study with nonhyperuricemic volunteers investigated the dose–response relation for rasburicase. Rasburicase elicited dose-dependent conversion of uric acid to allantoin. Thus, patients with a higher load of uric acid may require higher doses. In a study of healthy volunteers, there were few side effects. A few patients reported headaches, but that was the only noticeable side effect documented. A dose of 0.2 mg/kg was chosen because a phase II study demonstrated that this dose provided better uric acid control than 0.15 mg/kg without an increase in side effects.

Urinary allantoin excretion was measured. Each mol of uric acid is converted to 1 mol of allantoin. Thus, the amount of uric acid that would have been generated without treatment was calculated. The most allantoin excreted by a patient was 8.2 g/day, which would correspond to about 9 g/day of uric acid. Since normal human uric acid production is about 700 mg per day, intravascular uric acid levels would have been about 13 times normal. Of the patients tested, 70% had acute leukemia, primarily ALL, and 20% had lymphomas. Patients with solid tumors represented only 4.6% and the remainder had diseases such as MM.

A TLS risk classification system was designed to decide what types of patients would participate in these studies. TLS risk was estimated to be high, intermediate, or low. Patients with certain leukemias with a WBC count less than 25 000/mm³ were classified as low risk. If these patients had WBC counts in excess of 50 000/mm³, they were classified as high risk. With lymphoma patients, if LDH levels were less than two times the upper limit of normal, they were considered low risk. However, it should be noted that adult lymphoma patients may still be at high risk for TLS. Lymphoma patients with LDH levels more than five times the upper limit of normal were classified as high risk. Any patient hyperuricemic before treatment was also classified as high risk.

In randomized studies analyzed, 60–70% of patients were considered high risk. In the European study, in which a dose of 0.15 mg/kg was chosen, only 23% of patients were high risk. Patients were divided into the treatment and prophylaxis populations. Treatment was given to anyone who was hyperuricemic at baseline, prophylaxis was given to those who were not. Approximately 30% of patients were in the treatment population and 70% were in the prophylaxis population. TLS

risk within the prophylaxis population was evenly distributed among low, intermediate, and high risk. Baseline renal dysfunction was present in 25% of the treatment population, but only 4% of the prophylaxis population.

Main end points were pharmacologic end points. These included uric acid response rate in hyperuricemic patients, AUC, exposure to uric acid over the first 96 h, uric acid reduction in 4 h, and the time for maximum drop in uric acid levels. Additionally, other clinical end points were also followed.

With allopurinol-treated patients there was a gradual decline in uric acid levels. In contrast, all patients treated with rasburicase had a very low uric acid level after 4 h, despite the fact that some of these patients were hyperuricemic at baseline. Uric acid levels followed an M-shaped curve with peaks at 48 and 72 h separated by a trough at 60 h. Uric acid peaks corresponded to periods of maximum tumor lysis. There were some isolated escapes in patients at the 24 h time point between 2 and 3 days of dosing when the patient was undergoing maximum lysis.

Occasional escapes were observed at 5–7 days in patients whose rasburicase treatment was discontinued because it was assumed that hyperuricemia risk had ceased. In each of these situations, another dose of rasburicase brought uric acid levels back down.

Two phase II studies were discussed. In both studies, uric acid levels were well controlled for 7 days. Rasburicase was given for 5–7 days in these studies. During the first 4 days, allantoin levels peaked on days 2–3 and then gradually tapered off, although some patients were still generating significant levels of allantoin.

Examples of patients treated with allopurinol were discussed. Upon treatment with allopurinol, uric acid levels decreased slowly. Plasma calcium levels dipped at 84 h. There was massive hyperphosphatemia that was a mirror image of the calcium curve. Simultaneously, creatinine levels increased dramatically. There are other cases of pediatric patients with Burkitt's lymphoma treated with allopurinol that had an immediate uric acid decrease, but required dialysis because of hyperphosphatemia. Other patients treated with allopurinol had renal dysfunction because of calcium phosphate deposition even though their uric acid levels were effectively controlled.

Some patients received rasburicase but continued to have their urine alkalized. It is essential to provide adequate hydration of patients either with or without rasburicase treatment. Without adequate hydration, urine in the medullary portion of the distal tubule becomes concentrated resulting in crystal formation. Alkalinization has been used to increase uric acid excretion because its pK_a is 5.3. However, calcium phosphate becomes less soluble in an alkaline environment. Although rasburicase prevents renal uric acid accumulation, there still is phosphate reabsorption and calcium phosphate deposition remains a concern.

Dr Pui described a retrospective review of published studies of European pediatric patients receiving the LMB NHL regimen.⁴⁹ There were 152 stage IV patients. All received urate oxidase and 2.6% went on dialysis. In the UK, the exact same chemotherapy regimen was used in the same stage patients. The only difference was that they used allopurinol instead of urate oxidase. There may have been different trigger points for British and French nephrologists for initiation of dialysis that could account for the difference. Nevertheless, 16% of British patients underwent dialysis in comparison with 2.6% of French patients. The POG had the same population of patients, but more aggressive chemotherapy was used. There were

123 patients treated with allopurinol. In all, 23% of patients receiving allopurinol underwent dialysis. In the randomized trial of rasburicase vs allopurinol, one patient treated with allopurinol required dialysis, whereas none of the patients treated with rasburicase required dialysis. No statistically significant difference in dialysis frequency was shown between the two treatment groups because of the low patient number. Thus, data currently available do not definitively prove that less dialysis events occur in rasburicase vs allopurinol-treated patients. Currently, Dr Sima Jeha at MD Anderson has started a randomized trial in high-risk patients comparing allopurinol vs rasburicase with clinical outcomes as primary end points.

Rasburicase is very well tolerated. The most important concern is allergic reactions to rasburicase that occur because humans do not express urate oxidase. In this study, two patients had severe allergic reactions, which was an incidence of 0.5%. These reactions tended to occur in the first 10 min of infusion. In total, 15% of patients produced detectable antirasburicase antibodies. It is not known whether they were neutralizing antibodies. Sanofi-Synthelabo has a study ongoing in France involving retreatment of patients with rasburicase to evaluate the safety and efficacy. It is likely that there is some increase in allergic events in patients who have been retreated multiple times. However, it is also very likely that rasburicase can be successfully readministered. Nausea, fever, and vomiting are three types of adverse events with a frequency more than 5%. In healthy subjects receiving up to a week of treatment infrequent headaches were the only adverse side effects.

Of 347 patients in the database, there were five discontinuations of the treatment that may have been drug related. Dr Pui described a patient with methemoglobinemia. There has been mild-to-moderate hemolysis detected with retrospective confirmation that the patient was G6PD deficient. In addition, there was one patient with acute renal failure that was resolved without dialysis, which did not appear to be related.

Randomized clinical trials comparing rasburicase and allopurinol

Dr Cairo summarized studies published by Dr Pui and colleagues in the *Journal of Clinical Oncology*.⁴⁴ It was shown that nonrecombinant urate oxidase decreased uric acid levels to a greater extent than has been achieved with allopurinol. In the original phase I study, 90% of patients had elevated LDH levels and about half of the patients were hyperuricemic. Many patients had elevated creatinine levels when this study was initiated. Uric acid levels ranged from 1.4 to 34 mg/dl and had a mean of 6.5 mg/dl. Most patients had pre-B-ALL and the remainder had T-cell ALL, B-NHL, and B-ALL.

Uric acid levels of nonhyperuricemic patients administered rasburicase decreased within 4 h. Although there was a small increase in uric acid levels as time passed, these levels remained significantly lower than baseline. Patients who were hyperuricemic at diagnosis in this phase I/II trial had a median level of uric acid level of nearly 10 mg/dl. Within 4 h of rasburicase administration, there was a dramatic drop in uric acid levels. This decrease in uric acid levels was maintained as rasburicase treatment continued. These studies demonstrated significant success in reducing serum uric acid levels with rasburicase.

Dr Pui and colleagues have published initial results of an ongoing compassionate-use rasburicase study in *Leukemia*.⁵⁰ There were 173 children and 72 adults in this initial group of patients. This is the largest number of adults yet reported in

a rasburicase study. Rasburicase was used either for prophylaxis or for treatment depending upon whether they were hyperuricemic or not. The majority of the patients had ALL or NHL. Hyperuricemic patients had uric acid levels ranging from 24 to 34 mg/dl. WBC counts and LDH levels were fairly high in most patients. This group of hematologic malignancy patients had a high risk of TLS.

Dr Pui and colleagues observed a dramatic decrease in uric acid levels following rasburicase treatment. Uric acid levels of children in the prophylactic group decreased from 4.7 to 0.5 mg/dl. Uric acid levels in children in the hyperuricemic group decreased from 9.7 to 0.4 mg/dl. Moreover, rasburicase was equally effective in reducing uric acid levels in adults from 4.0 to 0.7 mg/dl and from 12.0 to 0.6 mg/dl in prophylactic and hyperuricemic groups, respectively. Adverse events were rare. Of nine adverse events that occurred among 245 patients, all were grade I or II, except for one grade III fever.

Dr Cairo discussed a randomized study published in May 2001 in *Blood* in which patients with leukemia and lymphoma at risk of TLS were treated randomly with either rasburicase or allopurinol.⁴³ This was a multicenter trial to test the hypothesis that rasburicase decreases TLS-induced hyperuricemia in patients with hematological malignancies better than standard allopurinol therapy. The objectives of the study were to compare efficacy in controlling hyperuricemia as well as safety and tolerability of these two agents. Patients were stratified prior to treatment based upon whether they had normal or elevated uric acid levels and upon what type of hematopoietic cancer was being treated.

This study was limited to patients under 21 years of age and included NHL patients having stage III or greater disease by Murphy classification, ALL patients with a WBC count greater than 25 000/mm³, or patients with leukemia or lymphoma having hyperuricemia. Patients selected were required to have a life expectancy of greater than 4 weeks and were stratified by the type of cancer and uric acid level. Patients were classified as hyperuricemic if their plasma uric acid level exceeded 8 mg/dl.

Rasburicase was given over a period of 5–7 days. If patients presented with normal uric acid levels, chemotherapy was initiated within 24 h. If they presented with hyperuricemia, chemotherapy was initiated within 48 h. A single 30 min rasburicase infusion was administered daily at 0.2 mg/kg per day, except during the first 2 days when the daily amount could be split into two doses every 12 h if desired. Allopurinol was given in standard doses with hydration. The decision of whether or not to alkalinize was left to the individual investigators.

An important issue to consider is how samples were handled prior to analysis. Samples obtained were immediately cooled to 0–4°C to block *ex vivo* enzymatic degradation by any rasburicase present in serum. This is an important consideration for both clinical rasburicase study design as well as measurement of serum uric acid levels of patients receiving rasburicase in clinical practice. Serum uric acid levels were examined from 0 to 96 h for each of the patients.

There were 52 patients with a variety of leukemias and lymphomas. More males than females were treated because B-NHL is more common among males. Median age was 7 years in both treatment groups. LDH levels were significantly elevated in both groups but were not different from each other. Hyperuricemia incidence was not significantly different between the two groups, although lymphoma patients receiving rasburicase did have a slightly higher hyperuricemia incidence. Creatine, phosphorus, calcium, and potassium levels did not significantly differ between the two groups at presentation. Uric acid levels decreased in patients treated with either allopurinol or rasbu-

case. These levels were decreased to a greater extent in patients treated with rasburicase than allopurinol.

All patients treated with rasburicase had decreased uric acid levels within 4 h, even those who were initially hyperuricemic. In contrast, allopurinol elicited a slower decrease in uric acid levels. Hyperuricemic patients treated with allopurinol remained hyperuricemic 4 h after treatment. Only after 24 h of treatment did uric acid levels dip below 8 mg/dl in patients treated with allopurinol.

At 4 h after rasburicase treatment, there was an 80% reduction in plasma uric acid levels, compared to only a 15% reduction in patients treated with allopurinol. There were a number of adverse events in both groups, but these were not related to either of the drugs. Incidence of adverse effects was not statistically different between patients treated with rasburicase or allopurinol.

The study was not designed to assess differences between frequency of renal events or assisted renal support. There was only one patient who required dialysis. This was a 12-year-old Burkitt's lymphoma patient treated with cyclophosphamide, vincristine, and prednisone. This patient was receiving allopurinol. The patient recovered after 6 days of hemodialysis for severe hyperphosphatemia.

Serum creatinine levels in rasburicase- and allopurinol-treated patients were compared. By day 4, adjusted serum creatinine levels in patients treated with rasburicase were down to baseline, whereas creatinine levels of patients treated with allopurinol, if anything, were beginning to increase.

The frequency of hypersensitivity reactions has been measured. In the 510 patients who have received rasburicase, the incidence is very low, at about 1% of patients. There were patients who developed antibodies directed against rasburicase. These patients have responded well to rasburicase retreatment.

Development of renal complications requiring dialysis is an important consideration. Only two of 510 patients developed renal complications requiring dialysis. This was an incidence of about 0.4%.

Dr Cairo reviewed the use of intravenous allopurinol, which has historically been considered an alternative therapy. He summarized clinical studies occurring over about 20 years involving 210 children and 250 adults treated for TLS or its prevention. These patients could not tolerate oral allopurinol. Intravenous dose varied between 40 and 150 mg/m² over 8 h, which was at the discretion of each investigator. It was somewhat difficult to obtain efficacy data, because treatment outcomes were defined only as complete remission (CR) or a partial remission (PR). CR was achieved if serum uric acid became and remained normal and PR was achieved if serum uric acid decreased by at least 1 mg/dl, but did not reach normal. In the prophylactic setting, efficacy was defined simply as no increase in serum uric acid. These definitions differed from what had been previously described for rasburicase.

In adults, 42% did not achieve a CR. Children presenting with hyperuricemia responded better with a failure rate of only 12%. Between 7 and 8% of patients treated with prophylactic allopurinol developed hyperuricemia. Allergic reactions occurred in about 2% of patients treated with intravenous allopurinol.

In contrast, rasburicase was well tolerated. Approximately 1% of patients treated with rasburicase had hypersensitivity reactions and about 5% exhibited antibody formation. Rasburicase treatment reduced plasma uric acid levels by 90% within 4 h of administration. In a randomized prospective multicenter trial, rasburicase was more effective than allopurinol for the reduction of plasma uric acid levels in patients at risk for TLS. There

was only a 0.4% risk of developing renal complications requiring dialysis among all patients without pre-existing renal abnormalities treated with rasburicase. Rasburicase is the drug of choice for reduction of uric acid levels in patients with hematological malignancies at risk for TLS.

Dr Cairo also described a new clinical study conducted by the Children's Oncology Group. Drs Cairo and Goldman are directing this study to investigate children with newly diagnosed advanced B-NHL, which includes Burkitt's and large B-cell lymphoma and B-ALL. Patients presenting with hyperuricemia will receive rasburicase once per day for up to 3 days before chemotherapy. At the time that therapy with cyclophosphamide, vincristine, and prednisone is initiated, each investigator has the option of administering one or two doses of rasburicase, depending on uric acid levels. Several more doses will then be administered over the next 8 days.

Case reports and discussion of TLS patients

Dr Stan Goldman presented two illustrative cases of TLS in pediatric leukemia and lymphoma. In contrast to adult NHL, NHL is almost always high-grade in children. Most NHLs have one of the three histologies. The first is large cell lymphoma, which includes anaplastic large cell (T-origin) and diffuse large cell (B-origin) lymphomas. The second is lymphoblastic lymphoma that is generally a high-grade rapidly expanding lymphoma of T-cell origin in continuum with T-ALL. The third histology is small noncleaved cell and mature B-cell lymphoma, which includes Burkitt's and Burkitt's-like lymphomas as well as L3-ALL.

Owing to cooperative advances in the treatment of childhood cancers in the past 10 years, the cure rate in NHL even with advanced disease is approaching 70–90%. Death from TLS during induction therapy or other complications is certainly a major loss, especially in cases with a high cure rate. Radiation has little or no role in therapy of pediatric NHL, in distinction to Hodgkin's disease.

What differences in etiology and treatment exist between pediatric and adult leukemia? Acute leukemia is much more common than chronic leukemia in children. The reverse is true in adults. The most frequent acute leukemia is precursor B-cell ALL, which is most common from 2 to 6 years of age in industrialized countries. The cure rate of precursor B-cell ALL is approaching 80–90% in industrialized countries. In all, 25% of precursor B-cell ALL patients present with a WBC cell count above 25 000/mm³, which gives this patient population a high TLS risk.

T-ALL in continuum with T-cell NHL is distinct from precursor B-cell ALL. T-cell ALL occurs most often in teenage boys. Patients affected often have massive tumor burdens and mediastinal masses as well as high TLS risk.

Case 1

The first illustrative case discussed by Dr Goldman was a 5-year-old Hispanic boy brought to the emergency room for a swollen neck, fever, and shortness of breath, which developed suddenly. Initially, it appeared that this child had suffered an allergic reaction. However, the child was febrile with a temperature of 39°C and had a high respiratory rate of 46. His exam displayed diffuse cervical adenopathy, significant plethora to his face, and positional respiratory distress.

The patient on presentation had severe superior vena cava (SVC) syndrome. Although potassium, calcium, and phosphorus levels were normal, creatinine and uric acid levels were elevated at 1 and 15 mg/dl, respectively. His WBC count was 58 000/mm³ with 90% L2 lymphoblasts on the peripheral blood smear. Platelets and hemoglobin were relatively normal, although slightly anemic. The chest X-ray showed an anterior mediastinal mass. Peripheral blood was sent for flow cytometric analysis, which revealed that this child had T-cell ALL. Prognosis for cure in this 5-year old with T-lymphoblastic leukemia is up from less than 50% before the 1990s to between 66 and 75% today.

This 5-year old had renal failure. Creatinine levels in young children are much different than in adults and translation of these levels into a glomerular filtration rate varies. A creatinine level change as little as 0.1 mg/dl is statistically significant in children. If the patient is prepubertal, mean creatinine is normally lower than 0.7 mg/dl. A creatinine level of 1 mg/dl is inappropriately high in prepubertal patients, whereas it would not be abnormal in a 16-year-old male. Interpretation of creatinine levels must be based on mean and upper limits of normal values specific for age and gender of each patient.

This patient was enrolled in a phase III trial for advanced lymphoblastic lymphoma, including T-ALL, which randomized patients to both high-dose methotrexate during consolidation as well as a cardioprotectant, Zinecard[®]. The patient began therapy with vincristine, prednisone, doxorubicin, and asparaginase.

How should TLS be prevented in this child with allopurinol? Administration of fluid must be based upon the body surface area calculated from height and weight of the patient. This child's body surface area was 0.75 m². A rate of 3 l/m² per day corresponds to approximately 100 ml/h. It is important to maintain a urinary pH of greater than 6.5 to promote uric acid excretion when utilizing allopurinol for uric acid control. Therefore, intravenous sodium bicarbonate would be administered if using allopurinol. However, this child had a very swollen neck and had impending respiratory failure due to SVC syndrome. Hydration would increase risk of exacerbating facial plethora and respiratory distress.

Rasburicase was administered at 0.2 mg/kg every 24 h. The uric acid level 4 h after the first dose was 0.5 mg/dl. Fluid was initially administered at 3 l/m² per day, but was decreased because rasburicase had lowered the uric acid levels. By 5 days, there were no circulating blasts, his creatinine level was 0.5 mg/dl, his WBC count was 1200/mm³, and he had recovered.

Case 2

The second illustrative case discussed by Dr Goldman was a 16-year-old boy. At 1 week prior to admission to the emergency room, the boy was perfectly well. At the time of admission to the emergency room, the patient complained that every time he ate, he just got full. Normally, the child liked to eat a large amount of food, but was now unable to because his stomach felt full. During the preceding 12 h, he complained of shortness of breath, pleuritic chest pain, and some mild respiratory distress.

The child weighed 75 kg and was mildly tachypneic and tachycardic. He had a tense and enlarged abdomen. There were no bowel sounds and breath sounds were diminished. A bone marrow biopsy, spinal tap, and complete blood count were all normal. His abdominal X-ray was quite remarkable. In spite of tremendous abdominal distension, there was very little bowel gas. CT scan of the chest, abdomen, and pelvis showed bilateral

pleural effusion, liver enlarged with tumor, and that his pancreas was also full of tumor. There was also diffuse abdominopelvic adenopathy. His kidneys were normal.

Initial chemistries were determined. His LDH level was high at 4500 U/l. His creatinine was 1.2 mg/dl, which was slightly high for his age. His phosphorus level was elevated at 9 mg/dl. His calcium level was normal and his uric acid level was 19 mg/dl.

How would one make a diagnosis in this patient, now that bone marrow, spinal fluid, and complete blood count were unrevealing? Would one perform pleural fluid analysis? Would one perform open abdominal surgery, laparoscopic abdominal surgery, or CT-guided needle biopsy of an easily assessable area of tumor? Any of these would be acceptable, depending on what could be done most quickly as well as available expertise and facilities. An initial bedside pleural fluid analysis was negative in this patient.

The child went to the operating room. After abdominal fluid removal and insertion of a double-port, enough tumor was removed by laparoscopy for cytogenetics, biology studies, and flow cytometry. He was diagnosed with Burkitt's lymphoma, which has a cure rate over 75%.

At 6 h after surgery and flow cytometry results were received, he was enrolled in the Burkitt's trial as well as the compassionate use rasburicase trial. Rasburicase was dosed every 12 h for the first four doses, then every 24 h thereafter. He was also administered aluminum hydroxide. Alkalinization was not done because he was not acidotic and his potassium level was normal. Additionally, calcium phosphate precipitation was a concern because his phosphorus level was 9 mg/dl. He was administered half-normal saline at 3 l/m² per day to promote urine flow.

This patient illustrates the importance of maintaining proper urinary pH. Uric acid produced by tumor lysis is eliminated by renal excretion. However, precipitation of uric acid may occur in the acidic environment of renal tubules. Bicarbonate is administered to prevent uric acid precipitation. However, phosphorus is also released by tumor lysis and eliminated by renal excretion. Alkalinization promotes renal precipitation of calcium phosphate. Urinary pH should not exceed 8 for prolonged periods.

Case 3

Dr Larson reviewed a case of a 23-year-old female noted by her dentist to have gingival hypertrophy and pallor. Her primary care physician noted petechiae on her legs and palpated her spleen 3 cm below her left costal margin. That physician drew blood for tests and then sent her home. This patient illustrates a pressing need for specialists in hematologic oncology who can rapidly identify and treat cases such as these.

This young woman had a WBC count of 155 000/mm³ consisting predominantly of blasts. Auer rods were absent from her blood smear. She was anemic and thrombocytopenic. Her potassium level was slightly elevated. Her creatinine level was markedly elevated at 4.2 mg/dl. Her uric acid, calcium, and phosphorus levels were 16, 8.2, and 7 mg/dl, respectively. Her LDH level was three times above normal.

She was afebrile but tachypneic. Importantly, her mentation was still normal. Upon re-examination, her physical exam and laboratory findings were unchanged, and she had urinated at least 100 ml in the previous 2 h. Her chest radiograph revealed a diffuse bilateral reticular infiltrate. A peripheral blood smear revealed what appeared to be undifferentiated myeloperoxidase

negative monoblasts. Peripheral blood was sent for flow cytometry analysis to determine if she had monoclonal leukemia as well as for cytogenetics to aid in treatment planning. In addition, a renal ultrasound showed that her kidneys were within the upper limits of normal for someone in her age group.

She had peripheral cyanosis including blue fingertips. For that reason, she was given supplemental oxygen in the intensive care unit. Funduscopic examination also revealed evidence of ischemia. Retinal cotton-wool spots and focal hemorrhages were observed, which were complications of leukostasis and ischemia in distal capillary beds. Leukapheresis was performed. Intravenous hydration was performed first with concomitant administration of allopurinol. Additionally, hydroxyurea was administered.

It may be hazardous to transfuse someone while they have a high WBC count. For a young patient that walked in under her own power, red blood cell transfusion should not be given until her WBC count is reduced to avoid increasing the blood viscosity.

This patient received intravenous allopurinol and oral bicarbonate. She was treated before rasburicase was available. Although uric acid becomes increasingly soluble at higher pH values, one must be wary of making the patient too alkalotic. In this case, optimal urinary pH would be between 7 and 8.

Following two cycles of leukapheresis and 48 h of hydroxyurea treatment, her WBC count was reduced by about 75% to 47 000/mm³. She remained thrombocytopenic, but was not bleeding. Following transfusion, her hematocrit increased to approximately 26%. Her potassium level was 4.5 mEq/l and her creatinine level had improved with hydration. She had continued renal dysfunction that likely resulted, at least in part, from anemia. Her uric acid level decreased, but remained elevated at 9 mg/dl. She was urinating adequately and her urinary pH was 7.

There had been inadequate improvement to allow standard remission induction chemotherapy to begin. Treatment was continued with hydroxyurea to provide steady cytorreduction until renal function improved. There was concern that the bulk of disease was in her bone marrow, which would put her at risk for TLS once intensive chemotherapy began. If she were to suffer severe TLS, hemodialysis might be required.

After her renal function improved further, a standard remission induction program was initiated on her fifth hospital day. Hemodialysis was not required. Complete remission was achieved and she has remained in remission for more than 3 years. After treatment, it was revealed that this patient had a t(9;11) chromosomal translocation.

Dr Larson discussed hazards of hyperleukocytosis in AML. This is a problem for patients with increased numbers of myeloblasts. This complication most often occurs when there are over 100 000 myeloblasts per mm³. Complications associated with hyperleukocytosis include leukostasis, endothelial infiltration, vascular injury, and hypoxemia. Patients with hyperleukocytosis often present with pulmonary or CNS symptoms and renal failure. Rasburicase should impact standard management of these patients.

Dr Sima Jeha from MD Anderson Cancer Center at Houston presented cases of MM and an elderly patient with advanced-stage lymphoma and impaired renal function.

Children have more aggressive cancers than adults that respond much better to chemotherapy. These factors help explain why TLS is perceived to affect children more than adults. In reality, adults have a higher risk for TLS than children because more adults have cancer than children. As anticancer

therapies improve, it is likely that more TLS will be observed in adults because more effective therapies may produce more lysis.

Children are very resilient. They have excellent kidney function that can handle the amount of fluid hydration necessary to prevent TLS. With adult patients, many different clinical problems are presented such as hypertension as well as cardiac and renal problems that complicate TLS prophylaxis and treatment.

Case 4

The next case was an 85-year-old male with bulky stage III large cell lymphoma. He had a history of prostate cancer, renal stones, and hypertension. Laboratory results revealed high tumor burden as well as compromised renal function with a creatinine level of 3.1 mg/dl, an elevated uric acid level of 16 mg/dl, and a high LDH level.

The patient received rasburicase and a full dose of CHOP on the first day of admission. On the next day, his uric acid level had dropped rapidly to less than 0.7 mg/dl. In contrast, levels of creatinine and LDH were elevated, which probably resulted from initiation of chemotherapy before renal function had recovered.

He was treated for 5 days with daily doses of rasburicase, which kept his uric acid level at 0.7. His creatinine level decreased despite his history of hypertension and renal stones. BUN was still high at this stage and LDH was still decreasing, but remained elevated.

On day 7, 48 h after discontinuing rasburicase treatment, his uric acid level remained low. It had increased from 0.7 to 2.7 mg/dl. Continued lysis was evidenced by his elevated LDH level. On day 14, his creatinine level was 0.8 mg/dl, dialysis was unnecessary, and he was discharged from the hospital.

MM can present with renal failure. Historically, TLS incidence with MM has been very low. However, TLS incidence is higher in advanced cases of MM, especially if high-dose chemotherapy is administered or if bone marrow transplantation has been performed.

Case 5

An MM patient discussed was a 50-year-old female with long-standing hypertension aggravated by her disease and anemia. Ultrasound analysis revealed enlarged kidneys. Initial laboratory reports indicated high levels of immunoglobulin proteins, calcium, uric acid, and creatinine.

TLS incidence depends upon the severity of MM. TLS has been reported to occur in 5–15% of patients with early-stage MM. In advanced MM, TLS incidence is close to 20%. Less than 5% require dialysis. This low rate of dialysis among MM patients largely results from adequate hydration and other support. In some cases, cancer treatment can be altered to prevent renal impairment.

She began chemotherapy and rasburicase treatment simultaneously. Chemotherapy consisted of dexamethasone, doxorubicin, and vincristine. By day 2, her uric acid level dropped from 11.0 to 0.7 mg/dl. She received treatment for a total of 7 days. Her uric acid level was less than 0.7 mg/dl on day 9 and then increased to 5.3 mg/dl by day 12. Her uric acid level then gradually increased to 6.0 mg/dl by day 19 and 7.0 mg/dl by day 28. Overall, she responded well to treatment with decreases in both calcium and protein levels.

A lesson illustrated by these two cases is that rasburicase is as effective in adults as it is in children. It can prevent dialysis and uric acid levels do not rebound after discontinuing rasburicase unless significant tumor lysis continues. After a response is observed, rasburicase treatment can be stopped and allopurinol treatment is unnecessary.

Cases 6 and 7

Dr Shanholtz from the University of Maryland discussed two cases of severe TLS in intensive care unit patients. The first case he presented was a 48-year-old homeless man with fever and a dental abscess. He had fever for 3 days prior to admission. The dental abscess was there for a week prior to admission. He was unresponsive, dyspneic, and his liver and spleen were palpable. He had bilateral axillary lymphadenopathy. He had a WBC count of 252 000/mm³, of which 90% were monocytic blasts. His BUN, creatinine, and uric acid levels were 63, 6, and 29.1 mg/dl, respectively, which were all above upper limits of normal. A chest X-ray revealed diffuse pulmonary infiltrates consistent with leukostasis. He had monocytic leukemia with profound leukocytosis.

He was intubated and placed on mechanical ventilation. He was leukapheresed and administered hydroxyurea and allopurinol. He required dopamine for vasopressor support. He was also treated with imipenem and required daily hemodialysis. Almost any critically ill patient with multiorgan system failure requiring vasopressor support has a greater than 80% mortality rate.

His uric acid level was nearly 30 mg/dl and his creatinine level was 6 mg/dl. Leukapheresis and hydroxyurea treatment lowered his WBC count during the first 24 h. He received emergency compassionate release rasburicase. Within 2 h after rasburicase administration, uric acid was undetectable and remained undetectable for several days. Chemotherapy was withheld a few days until his WBC count plateaued. It was possible that residual hydroxyurea was present and active because of renal failure. When the patient received remission induction chemotherapy, his uric acid level began to increase. The 7-day period for emergency compassionate release rasburicase had expired, so he was treated with allopurinol. He continued to improve over the next few weeks. His renal function returned to normal and his uric acid level fell.

He required tracheostomy for prolonged mechanical ventilation, but his respiratory failure resolved. By hospital day 38, he was discharged. He was breathing spontaneously with a tracheostomy collar and was dialysis independent with a normal creatinine level.

Dr Shanholtz discussed a second case, which was a 61-year-old man who had received a heart transplant 10 years previously because of viral cardiomyopathy. He was admitted with fulminant lymphoblastic lymphoma. He had involvement of his mediastinum, retroperitoneal nodes, liver, stomach, cecum, and kidneys. He also had lactic acidosis and renal insufficiency.

Following EPOCH chemotherapy, his LDH level increased to nearly 45 000 U/L. His uric acid level began to rise the day chemotherapy was initiated, but decreased to undetectable levels within 2 h of receiving his first dose of compassionate release rasburicase. He did require three dialysis treatments in the intensive care unit, but his creatinine level plateaued and later began to decrease. After 7 days of treatment, he became dialysis independent and was transferred out of the intensive care unit. He was dialysis independent for over a week, until he had to return to the intensive care unit with sepsis and septic

shock. Although rasburicase is effective for the treatment of renal failure caused by hyperuricemia, it is not useful for the treatment of renal failure caused by shock.

He received dialysis treatment. However, complications included febrile neutropenia, atrial fibrillation, gastrointestinal hemorrhage, and septic shock requiring two vasopressors. Although he was dialysis independent and transferred out of the intensive care unit on hospital day 19, he had to return and unfortunately expired because of septic shock.

Poor prognostic factors among intensive care unit patients include advanced age, hematologic malignancy, renal failure, cardiovascular failure, and shock. Each of these have been described as risk factors for mortality in heterogeneous populations of intensive care unit patients.

Acute renal failure is independently associated with risk of mortality among intensive care unit patients. This has been best examined among intensive care unit patients with multiorgan system failure. Although logistic regression analysis has shown that acute renal failure is independent of any other organ failure, it is associated with a threefold higher mortality. Of patients who present with hematologic malignancy or any other critical illness, mortality increases threefold if acute renal failure requiring dialysis develops.

Multiple organ system dysfunction is lethal in critically ill patients. Acute renal failure from TLS greatly increases morbidity and mortality of critically ill patients with hematologic malignancies. Rasburicase may be beneficial in the treatment of acute renal failure due to TLS in the intensive care unit setting.

Case 8

Dr John Leonard from the Weill Medical College of Cornell University addressed TLS in adults with NHL. The first case discussed was a 63-year-old male with diffuse large B-cell lymphoma presenting with fatigue, mild low back pain, and abdominal bloating. He had mild hypertension, but was otherwise in good health. Physical examination revealed axillary lymphadenopathy in the 3–4 cm range, some abdominal fullness, and inguinal adenopathy. His BUN, creatinine, and LDH levels were elevated at 40 mg/dl, 1.4 mg/dl, and 825 U/L, respectively. His uric acid level was also elevated and his phosphorus level was at the upper limit of normal.

Axillary lymph node biopsy revealed diffuse large B-cell lymphoma. Diffuse large cell represents about a third of lymphomas in adults. Diffuse large cell lymphomas are also referred to as intermediate grade or aggressive NHL. This patient had diffuse lymphadenopathy up to 5 cm, a somewhat enlarged spleen, a sacral mass of extranodal disease, and a negative bone marrow evaluation.

This patient was treated with CHOP and rituximab. Without rasburicase, this patient would likely be admitted and receive allopurinol and fluids to prevent TLS. Elevation of LDH level or worsening of renal function would further signify an increased TLS risk. Some physicians, however, might manage him as an outpatient with close supervision. If rasburicase was available, management of this individual as an outpatient becomes more likely.

How should TLS be managed in a patient such as this? Initially, he does not have clinically evident TLS. LDH and uric acid levels were decreasing when the second cycle of chemotherapy began. Allopurinol would likely be discontinued; however, some might continue administering allopurinol during the second cycle of chemotherapy. This is a short-term problem, assuming the disease is under control.

As primary therapy, this patient was admitted and given CHOP-rituximab chemotherapy, allopurinol, and intravenous fluids. Suddenly, one day after chemotherapy, his condition began to worsen. Creatinine, uric acid, and LDH levels were 1.8 mg/dl, 15 mg/dl, and 1300 U/l, respectively. The patient had TLS. Fortunately, he was tolerating fluids well. He did not display any evidence of congestive heart failure. In cases such as this, rasburicase may be able to reverse TLS that could not be adequately controlled by allopurinol.

Case 9

The final patient discussed was a 70-year-old female with follicular lymphoma. Follicular lymphoma accounts for about a third of lymphomas. It is the most common indolent lymphoma. Follicular lymphoma patients have a relatively low risk of TLS. The patient had fatigue, lymphadenopathy, night sweats, and some other medical problems such as chronic obstructive pulmonary disease, diabetes, and osteoarthritis. She had 2 cm lymph nodes and 4 cm inguinal nodes. She was anemic and had mild renal insufficiency. BUN, creatinine, and uric acid levels were 35, 1.3, and 8 mg/dl, respectively. Her LDH level was normal. She had diffuse follicular small cleaved-cell NHL. Finally, she had splenomegaly and bone marrow involvement.

She was treated with cyclophosphamide, vincristine, and prednisone chemotherapy. She would likely be administered allopurinol for TLS prophylaxis in an outpatient setting and checked in 2 days for signs of tumor lysis. Rasburicase would be a viable alternative to allopurinol.

There are a number of key issues concerning TLS in adults with lymphoma. It is important to identify patients at high risk for TLS, particularly those with indolent lymphomas where TLS is less common but can occasionally occur. Rasburicase may be a useful prophylactic in those adults with lymphoma who are at high risk for TLS. Hyperuricemia is primarily an acute problem and not a major issue after the bulk of tumor lysis has occurred. Rasburicase would also be useful to treat lymphoma patients with TLS that worsens despite hydration and allopurinol administration. Value of rasburicase for prophylaxis in patients at lower risk for TLS remains undefined.

Roundtable Discussion

At the end of this meeting there was a roundtable discussion of key points. Questions submitted by the audience were asked by Dr Richard Larson.

RICHARD A LARSON, MD: In both of the patients that you presented, rasburicase reduced the uric acid level, but the creatinine did not change for more than 7 days. Is there an explanation for that?

CARL B SHANHOLTZ, MD: The only explanation I can think of is that rasburicase was not given as prophylaxis. It was given as treatment after renal failure had already occurred. The remarkable thing from my standpoint is that these patients had reversal of renal dysfunction, considering how sick they were. Usually, somebody who is in an ICU on a ventilator and on pressors receives dialysis for a lot longer.

RICHARD A LARSON, MD: Can rasburicase reverse pre-existing uric acid nephropathy? Does anyone know how reversible nephropathy is?

TILLMAN E PEARCE, MD: There are two case reports in the literature of patients who had renal failure associated with urate nephropathy, where they actually catheterized the ureter. The

patients were on allopurinol and they could actually see crystals coming out of the ureteral fluid and then they put them on nonrecombinant urate oxidase in France. Within 48 h, the crystals were dissolved and there was a higher outflow of urine.

RICHARD A LARSON, MD: Does rasburicase get filtered in the glomerulus and find its way into the urine?

TILLMAN E PEARCE, MD: Rasburicase is a low renally excreted drug. I think it is in the medullary part of the nephron. Rasburicase is probably dissolving the crystals in those small capillaries around the medulla improving the function and allowing better excretion.

RICHARD A LARSON, MD: There have been several questions provided by the audience about the possible use of this drug in patients with gout, either management of chronic gout or treatment of acute gouty arthritis. Is there any information available on that?

TILLMAN E PEARCE, MD: We have not done a study in patients with chronic gout. There is one case report of a patient from Arkansas who had a very advanced case of chronic gout and large, visible tophi. This patient was refractory to allopurinol therapy. This patient started receiving weekly doses of rasburicase, which lowered the uric acid. They were able to manage the uric acid in this patient by weekly administration of rasburicase for about 3 months and then they were able to spread it out to every 2 weeks, every 3 weeks, and over a period of about 6 months the tophi regressed. The patient became ambulatory and sensitive to allopurinol. Once they got rid of that major burden the patient became sensitive to allopurinol.

CHING-HON PUI MD: Patients with gout have received nonrecombinant urate oxidase in France. But results of these cases have not been compiled and published.

RICHARD A LARSON, MD: In this era of evidence-based medicine, have there been randomized clinical trials on the supportive care aspects of TLS, particularly the use of mannitol, for example, or the early use of hemodialysis?

MICHAEL R BISHOP, MD: That is a three-part question. Number one, no, there have not been any randomized trials looking at any form of these supportive modalities. The mannitol trial was part of a phase II trial looking at mannitol in the setting of chemotherapy-induced renal failure, not specifically on TLS. Quality of life issues and supportive care issues have not been looked at except in the nursing literature.

RICHARD A LARSON, MD: What is the utility of following the ionized calcium rather than the total calcium with regard to risk of cardiac arrhythmias?

MICHAEL R BISHOP, MD: In my own clinical experience, I do not find it to be very useful. Luckily, it is not a major component of TLS and I still find the most important aspect is following the LDH levels.

RICHARD A LARSON, MD: Is it possible to administer rasburicase by other than the IV route, for example, intramuscular or subcutaneous dosing? In Europe, some doctors have done so with the nonrecombinant version. Dr Mahmoud, maybe you could give us some information about that.

HAZEM MAHMOUD, MD: Since approval of the nonrecombinant Uricozyme[®] in France and Italy, it has been mostly given by i.m. It is only those patients who have thrombocytopenia or develop bleeding that are given the Uricozyme[®] i.v. and that is one of the reasons they had less allergic reaction than the i.v. administration here in the United States. When we started the i.v. therapy at St Jude, it was mainly because patients had low platelets and leukemia, and clinicians were skeptical about administration of rasburicase i.m. and causing hematoma in treated patients. So we administered it i.v. But in Europe it has been mostly administered i.m. and there has been less allergic

reaction and it is still as effective, although there are no pharmacokinetic studies done. But it was as effective as the i.v. formulation.

RICHARD A LARSON, MD: There were several questions about the most appropriate dosing. Dr Pearce showed us how this was developed through a relatively small phase I trial, but is there any advantage to giving higher doses or more frequent doses and should it be dosed the same in all ages and with all levels of renal function? Again, are there data from the clinical trials that have been done so far that speak to the necessity, perhaps, of q 12 h dosing? Dr Cairo, you have q 12 h dosing built into your proposed COG study for days 1 and 2. Could you comment on the rationale behind this dosing schedule?

MITCHELL S CAIRO, MD: We did not look at it in a randomized way, but when we started the study, we were concerned that there would be patients who might not respond early on or who had very bulky disease. However, when we finished the study, we saw that nearly everybody had a very low uric acid level within 4 h and stayed that way. Therefore, I think the need for q 12 h dosing is probably going to be eliminated.

RICHARD A LARSON, MD: Dr Pui, perhaps from your experience you could comment? Is it more efficacious to use a higher dose or more frequent dosing?

CHING-HON PUI, MD: In the phase I adult volunteer study, we know that there is a linear correlation between the effect and the dosage from 0.05 to 0.2 mg/kg. My answer is that it depends on what kind of patient you are treating. In the European phase II trial, which enrolled a group of not very high-risk cases, the dose of 0.15 mg/kg given once daily was adequate. However, if you are treating somebody with a high tumor burden, like many cases treated in the American phase II study, 0.2 mg/kg is more likely to be an effective dosage. For a patient with a uric acid level as high as 30 mg/dl and a bulky tumor, it may be more appropriate to use a dose of 0.25 mg/kg, which may be needed as often as every 12 h. Therefore, it really depends on the kind of patients that you are treating and the kind of chemotherapy that you are administering. So I think on average, 0.15–0.2 mg/kg is an appropriate dose.

TILLMAN E PEARCE, MD: In terms of the host factors, I can tell you that the pharmacokinetics are not associated with gender and they are not associated with renal function or liver function. They were associated with weight and that is why the choice of a mg/kg dosing adjusts for the weight. So it is really the tumor volume and the amount of TLS that is to be expected.

RICHARD A LARSON, MD: Are there any plans or potential to develop an oral formulation of this enzyme?

TILLMAN E PEARCE, MD: I would have to say at the present time no.

RICHARD A LARSON, MD: Do you recommend screening for different G6PD alleles prior to starting rasburicase, particularly in African Americans, and again, perhaps even more importantly, in other areas in the world where different G6PD isoenzymes are more prevalent?

STANTON C GOLDMAN, MD: No. We just simply ask the families if there is a history of G6PD, recurrent hemolytic anemia, or asthma. Previously, patients with asthma were excluded from our trial, although in our new Burkitt's trial, we are not going to exclude patients with asthma from receiving the drug, but we are going to exclude the known G6PD patients.

RICHARD A LARSON, MD: What are the current guidelines for handling the uric acid specimens? Dr Cairo mentioned that they needed to be kept on ice. What are the differences between iced and noniced specimens? Dr Cairo, has this been looked at?

How stable are these uric acid levels and the rasburicase activity?

MITCHELL S CAIRO, MD: I don't know if there's been a comparison done, since the uric acid drops fairly significantly. I am not sure it is a real clinical issue. If one is going to do a study where that is a primary or secondary end point, I think it is important that if they are on rasburicase that you do not enhance the enzymatic degradation of uric acid and get a falsely lower value. But from a clinical perspective, I do not think it is very important since 90% of it is reduced fairly quickly.

CHING-HON PUI, MD: The drug is so effective that with rare exceptions, virtually everyone will have a very low uric acid after rasburicase. Clinically, it may not be too critical to have a very accurate measurement. But if you are performing a study and you need an accurate measurement, you have to put the sample on ice immediately after it is collected because uric acid will break down *ex vivo* rapidly with the presence of urate oxidase in the serum.

RICHARD A LARSON, MD: What current clinical trials are ongoing or planned for the near future to answer additional questions about the use of rasburicase.

SIMA C JEHA, MD: A question in adults remaining is does uric acid definitely decrease with the rasburicase and does that translate into improvement of renal function? Would that prevent pulmonary hemorrhages and admission to ICU because of fluid overload because the kidney function was better? Would it decrease the need for dialysis because of improvement of kidney function? So what we are going to do at MD Anderson is to randomize all the high-risk patients to be treated either with standard methods for the prevention of tumor lysis and allopurinol, or on an arm that will receive rasburicase, and then we will compare all the clinical outcomes: admission to ICU, days of dialysis, *et cetera*, and we will see if there is a difference or not in that arm.

JOHN P LEONARD, MD: I can think of three major areas with regard to the need for more studies using rasburicase. I think number one is defining the high-risk patient for TLS. Number two, there needs to be more experience in adults who clearly have ongoing TLS, which is worsening despite other measures, to define the potential benefit of rasburicase. We clearly need more information on rasburicase treatment of adult patients with more common tumor types. And third, more information is required on the treatment of high-risk patients as outpatients in order to avoid the inconvenience and expense of hospitalization for TLS prophylaxis and management.

CHING-HON PUI, MD: A study that I am interested in performing is to determine the safety of this drug in patients with a history of atopic allergy or asthma because they represent approximately 10% of the general population. Occasionally, I encountered a patient with a uric acid of 20 mg/dl, but I could not give this patient rasburicase because the patient had a history of significant atopic allergy or asthma. Anecdotally, a few patients received urate oxidase without complications who later were found to have a history of allergy. I suspect that rasburicase can be safely given to many of these patients but a study is needed. Therefore, in collaboration with Dr Jeha and others, we will conduct a study to test the safety of this drug in patients with a history of allergy.

TILLMAN E PEARCE, MD: There are two studies in France by the GELA group, one looking at administration of rasburicase for three to five doses in adult aggressive NHL patients and the other looking at retreatment. Another issue that came up earlier is whether to use prephase dosing or to go straight to full dose ablative treatment.

RICHARD A LARSON, MD: There was a question asked whether changes in the LDH levels could be used to make a decision regarding the number of doses to be given. Does ongoing elevated LDH levels suggest ongoing risk of renal failure and the need to continue the drug longer than 3.9 days?

TILLMAN E PEARCE, MD: No, there is no definitive answer to that question. I think that the best answer that I can give you really came from those allantoin curves where you really saw that the allantoin production started to go down after about day 4 and that M-shaped spike was really pretty reproducible between 48 and 72 h. So I think certainly giving it for at least four doses probably covers most of the patients. But again, it depends on the chemotherapy, the speed at which the lysis occurs, and there were certainly patients who even after 5, 6, or 7 days would have some late escapes who had ongoing lysis. So I think Dr Pui or one of the clinicians can give you their view.

CHING-HON PUI, MD: Based on the result of a compassionate trial, on average, patients only need three doses of rasburicase.

RICHARD A LARSON: There were several questions around the issue of repeated use of rasburicase in patients with relapsed or refractory disease, some of these dealing with the issue of antibodies, the likelihood of forming antibodies while patients were on immunosuppressive therapy or less immunosuppressive therapy, whether the antibodies were neutralizing in their activity. Would someone like to summarize what data are known on the recurrent use of this drug?

TILLMAN E PEARCE, MD: If you look in the healthy volunteers, the majority will generate antibodies. If you look in patients, somewhere between 10 and 20% will generate antibodies. Most of them *in vitro* are not neutralizing, and according to Dr Mahmoud, in many of the patients with the nonrecombinant version who generated antibodies, they still had good uricolytic effects even though they had circulating antibodies. So it seems like most of these are not blocking the effectiveness.

On the other hand, although we see less than 1% allergic reactions on first time usage and we have less data on reuse, it does seem like the allergic manifestations are more than 1% when the drug is reused. Whether these are antibody-related reactions or not I think is not known, but certainly you seem to get more allergic reactions with rechallenge and you also have antibodies. So they may in fact be related in some way to allergic side effects that seem not so clearly to be resulting in decreased efficacy.

CHING-HON PUI, MD: Of the 18 patients who received the repeated doses, 17 had very good response with serum uric acid decreased to a level below normal or not measurable. The only failure was a patient with chronic lymphocytic leukemia in blast crisis who presented with a uric acid level of 7.2 mg/dl and had a level of 7.4 mg/dl after one dose of treatment. But, she was given only one dose for a reason unknown to me. Dr Pearce is correct. There was a somewhat higher incidence of allergic reactions in patients receiving repeated courses of rasburicase. However, the reactions consisted generally of rashes of grade I or II degree.

RICHARD FISHER, MD: I think we have to be a little cautious that as the drug gets approved and is used, it will be used in less and less critically ill patients as it replaces allopurinol. The fact that there is a 100% incidence in the normal volunteers whereas there is a very low incidence in the very sick patients, it is probably a statement about the nature of the immunosuppression in the sick patients. Therefore, if more immunocompetent patients are treated there will probably be an increased

incidence of antibodies and perhaps even different kinds of antibodies. I think that we will be asked to be very careful on the surveillance of that issue and some of the comments that have applied in the population as tested will not apply once it is generally released.

Summary of meeting

Complications of TLS can be prevented by either allopurinol or rasburicase treatment. This meeting summarized the results of recent clinical trials designed to prevent TLS by either allopurinol or rasburicase treatment. Clearly, rasburicase is more effective and rapid in reducing uric acid levels because of TLS than allopurinol. As a result of the cloning of urate oxidase and the subsequent manufacturing of this recombinant protein, clinicians will be able to treat potential TLS patients with this drug, rasburicase. Proper identification of patients of high risk for TLS and their subsequent treatment with rasburicase will reduce renal problems associated with TLS. Adverse immune reactions resulting from administration of a foreign protein may develop if cancer patients are retreated with rasburicase. However, this may not be a major problem if patients are cured of their cancer after a single treatment. Rasburicase is an intriguing example of how basic science can be applied to prevent a disease. A recombinant enzyme absent in humans is infused to catabolize uric acid that could otherwise accumulate to toxic levels in certain disease states.

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