Introduction

- Hyperuricemia associated with tumor lysis syndrome is a potentially serious complication most frequently seen during chemotherapy for malignancies with large tumor burden and highly proliferative cells, such as aggressive lymphomas and leukemia.  
  Hyperuricemia usually occurs in association with other metabolic abnormalities, including hyperphosphatemia, hyperkalemia, hypocalcemia, and azotemia, and these metabolites can in turn rapidly exceed the excretory capacity of the kidneys, resulting in renal failure and occasionally death.

- Urate oxidase, an enzyme found in most mammals but not in humans, catalyzes the oxidation of uric acid into water soluble allantoin, which can be more readily excreted and thus normalize uric acid levels. Rasburicase is a recombinant form of urate oxidase that has been approved in the United States for the treatment of pediatric patients with acute leukemia or lymphoma since 2003 to avoid the potentially life-threatening complications of tumor lysis.

- Recent clinical data suggest that rasburicase could be efficacious for adult patients as well. Clinical trials by Pui et al revealed that the administration of rasburicase for 5-7 days to 131 children, adolescents, and young adults with newly diagnosed leukemia or lymphoma significantly decreased their plasma uric acid levels. Within 4 hours of treatment, the mean uric acid level had decreased from 9.7 mg/dL to 1.0 mg/dL (P = 0.0001) in the 65 patients who presented with hyperuricemia, and from 4.3 mg/dL to 0.5 mg/dL (P = 0.0001) in the remaining 66 patients. Toxicity was negligible and none of the patients required dialysis.

- In a randomized comparative trial, rasburicase was found to be more effective than allopurinol in the control of uric acid levels in pediatric patients with acute leukemia or lymphoma (Table 1). The use of rasburicase for the prevention and treatment of hyperuricemia in adult patients with leukemia or lymphoma has only recently been investigated. This article presents the results of the recently published clinical trials by Bosly et al and Coiffier et al on rasburicase for the prevention and treatment of hyperuricemia in pediatric and adult patients with leukemia or lymphoma.

The International Compassionate Use Trial

Study Design

The international compassionate use trial conducted by Bosly et al from January 1999 to December 2001 provided access to rasburicase for patients in 9 countries who were at risk for tumor lysis syndrome during the initiation of chemotherapy. The characteristics of the patients enrolled in the study are presented in Table 2. Both pediatric and adult patients with leukemia and lymphoma were treated intravenously with rasburicase 0.20 mg/kg/day on days 1-7. Patients with high risk for hyperurice-
mia were treated twice a day for the first 72 hours. The median treatment duration among pediatric patients was 5 days, regardless of uric acid levels at presentation.

The median treatment duration for hyperuricemic adult patients was 6 days, and for nonhyperuricemic adult patients it was 5 days. Among the total patient population, 24% of adult patients and 39% of pediatric patients with high risk of tumor lysis syndrome received 2 daily doses of rasburicase at least once in the first 72 hours of the treatment.

All patients who received at least one dose of rasburicase were included in the safety analysis. Patients for whom pretreatment and posttreatment uric acid levels were available were included in the efficacy analysis. Plasma uric acid levels > 7.5 mg/dL for adults and 6.5 mg/dL for children indicated hyperuricemia.

Results

For the efficacy analysis, 122 pediatric patients and 97 adult patients were evaluable. The mean plasma uric acid levels were significantly decreased ($P < 0.001$) in both pediatric and adult patient populations, regardless of whether they were hyperuricemic at presentation. The treatment response rate with rasburicase was 100%. Following treatment with rasburicase, the mean plasma uric acid levels were significantly reduced from 11.3 mg/dL to 0.2 mg/dL in hyperuricemic pediatric patients (Table 3). Similarly, the mean plasma uric acid levels for adult patients with hyperuricemia were decreased from 13.1 mg/dL to 0.3 mg/dL. Patients who presented with nonhyperuricemia, the plasma uric acid levels reduced significantly (from 4.2 mg/dL to 0.5 mg/dL in pediatric patients and from 4.9 mg/dL to 0.3 mg/dL in adult patients) after rasburicase administration.

No major adverse events were documented as drug toxicity. The only drug-related adverse events in > 1% of patients were headache (1.8%), fever (1.4%), and rigors (1.1%).

A Phase II Open-Label Trial of Rasburicase in Adult Patients with Lymphoma

Study Design

A phase II open-label trial published recently by Coiffier et al from Groupe d’Etude des Lymphomes de l’Adulte examined the efficacy of rasburicase in adult patients undergoing cytoreductive chemotherapy.7 Eligible patients presented with previously untreated histologically proven, aggressive non-Hodgkin’s lymphoma, including diffuse large B-cell, peripheral T cell, Burkitt, and anaplastic large-cell lymphomas, and transformation of indolent lymphoma into more aggressive subtypes. All patients were at risk of hyperuricemia with either large tumor volume ($\geq 5$ cm in diameter), elevated levels of creatinine, uric acid and/or lactate dehydrogenase (LDH), electrolyte abnormalities, or low urine volume. In addition, patients were required to have at least 1 adverse prognostic factor of the International Prognostic Index (stage III/IV disease, performance status $\geq 2$, elevated LDH, aged $> 60$ years, or $> 1$ extranodal disease site). Patients with a history of asthma, hypersensitivity to urate oxidase, or prior treatment with rasburicase were ineligible for the study.

Rasburicase was given at a dose of 0.2 mg/kg/day for 3-7 days, starting either before induction of chemotherapy or the same day. Chemotherapy regimens included ACVBP8 (doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone; 43%), CHOP9 (cyclophosphamide/doxorubicin/vincristine/prednisone; 44%), ACE10 (doxorubicin/cyclophosphamide/etoposide; 6%), COP-COPADEM11 (cyclophosphamide/vincristine with steroid therapy plus methotrexate/cyclophosphamide/vincristine/doxorubicin/prednisone/cytarabine; 44%), and ESHAP12 (etoposide/methylprednisolone/cytarabine and a platinum agent; 3%); and 20% of patients received rituximab as well.

A total of 100 patients with a median age of 57 years were enrolled. At presentation, 66 of 100 patients (66%) had elevated LDH and 11 of 100 patients had $> 7.56$ mg/dL uric acid levels. Eighty-
three percent had Ann Arbor stage III/IV disease, and diffuse large B-cell lymphoma was the predominant histology seen in 79% of patients.

**Efficacy**
Response to rasburicase was defined as normalization of uric acid levels. None of the patients had elevated levels of creatinine. Of the 100 patients, 95 patients responded to treatment. Normalization of uric acid levels was achieved within 4 hours of rasburicase administration. None of the patients developed renal failure, and serum phosphorus, calcium, and potassium levels were well controlled in all patients except 1 who became hyperkalemic. The 5 remaining patients who did not receive at least 3 days of treatment were discontinued from the rasburicase treatment because of safety reasons (Table 4).

**Toxicity**
Overall tolerance of rasburicase was excellent. Grade 3 hepatotoxicity was detected during the first 24-48 hours but was rapidly reversible. Rasburicase treatment was discontinued in 1 patient after 2 days of treatment because of non-Hodgkin’s lymphoma–related complications.

**Clinical Relevance**
Taken together the results presented by Bosly and Coiffier confirm the efficacy of rasburicase in preventing hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies.6,7 In nearly all patients from both trials, administration of rasburicase led to a rapid normalization (within 4 hours) of elevated uric acid levels, and effective control was maintained with a 3-5 day course of rasburicase.

**References**