COMMENTARY

Managing tumor lysis syndrome in 2010

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In this issue of *Leukemia and Lymphoma*, Darmon et al. report that patients with renal injury manifest by an acute rise in serum creatinine or the development of oliguria without a rise in the serum creatinine (presumably insufficient time has elapsed for creatinine to accumulate in the serum) have a significantly shorter survival than patients who develop tumor lysis syndrome but maintain adequate renal function. All patients with acute renal injury in this study had a serum creatinine, at ICU admission, of greater than 126 µmol/L of creatinine (serum creatinine >1.4 mg/dL). At 6 months, patients with acute renal injury had a survival of 35% compared with 85% in the no acute renal injury group. This cohort is not representative of all patients with tumor lysis syndrome because milder forms were cared for outside of the intensive care unit and were excluded from this study [1].

Tumor lysis syndrome is characterized by the acute development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and renal injury after chemotherapy [2]. The development of tumor lysis syndrome has three prerequisites. The tumor mass needs to be high; the tumor itself needs to be highly sensitive to systemic chemotherapy, and a high fraction of cells must be destroyed by systemic chemotherapy. Tumor lysis syndrome was first described in the management of Burkitt lymphoma, a consequence of the high sensitivity of this malignancy to treatment with cyclophosphamide [3]. The prevalence of tumor lysis syndrome has been rising as more effective systemic chemotherapies have been developed. The majority of patients have a hematologic malignancy because the majority of patients with solid tumors have an insufficient fraction of highly chemotherapy-sensitive cells. The tumors, most commonly associated with tumor lysis syndrome today, are acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and a fraction of high-grade lymphomas. Clinical parameters predicting a high risk of tumor lysis syndrome include: elevation of the lactate dehydrogenase and a white blood cell count over 50 000/μL. The dangers associated with tumor lysis syndrome include the metabolic disturbances associated with acute hypocalcemia and hyperphosphatemia that can lead to frank tetany [4], as well as cardiac arrhythmias precipitated by the combination of hypocalcemia and hyperkalemia. The most devastating complication is the development of oliguric renal failure related to uric acid nephropathy.

Historically preventative therapy necessitated alka-linization of the urine and the administration of allopurinol, an inhibitor of xanthine oxidase, preventing the conversion of hypoxanthine and xanthine, normal purine metabolites, from being converted into uric acid. As xanthine and hypoxanthine are far more soluble than uric acid, their precipitation in the renal tubule is less likely, although xanthine urolithiasis can occur [5]. Although allopurinol sharply reduced the risk of post chemotherapy hyperuricemia, the inhibition of xanthine oxidase does nothing to reduce the level of uric acid at presentation. The introduction of rasburicase has altered the natural history of this syndrome. Rasburicase has altered the natural history of this syndrome. Rasburicase is a recombinant urate oxidase and catalytically degrades uric acid. Rasburicase oxidizes uric acid, converting it to allantoin, which is 10-fold more soluble than uric acid and does not precipitate as crystals. Rasburicase is produced after the proteolytic hydrolysis of *Aspergillus flavus* urate oxidase, which permits the formation of oligodeoxynucleotide probes that are used to obtain DNA
fragments from *Aspergillus* cDNA in a genomic library [6]. Urinary alkalinization is contraindicated when rasburicase is being used. Although rasburicase is approved for use for five consecutive days, single doses have resulted in reduction of the serum urate level – a mean of 90% at substantial cost savings [7].

The spectrum of diseases prone to tumor lysis syndrome has expanded as the efficacy of therapy has improved. With the introduction of purine analogs, bendamustine and monoclonal antibodies higher response rates have been achieved in chronic lymphatic leukemia, and the rapid cell killing has resulted in an increasing risk of tumor lysis syndrome [8]. The introduction of imatinib has increased the risk of tumor lysis syndrome in chronic myelogenous leukemia [9]. Tumor lysis syndrome has been reported in breast cancer following therapy with gemcitabine and cisplatin as well as fluorouracil, epirubicin, and cyclophosphamide. Both patients had hepatic metastasis, which may have increased their risk. Hyperkalemia is typically managed with standard glucose solutions and orally or enterally administered phosphate binders, and calcium is replaced parenterally.

When renal failure or oliguria is established at presentation of tumor lysis syndrome, it is estimated that as many as 3% of patients (1.5% of pediatrics and 5% of adult patients) will require dialysis for management [10]. In the study reported in this month’s issue, 40 of 63 patients required intermittent hemodialysis, half of those without renal injury and three-quarters of those with renal injury.

In conclusion, the presence of tumor lysis syndrome with acute renal injury at the time of admission to an intensive care unit is associated with a higher in hospital and 6-month mortality compared to those patients without renal injury. Pre-emptive measures to reduce the risk of the development of acute renal failure using rasburicase are indicated, if the patient is considered to be at high-risk before chemotherapy [11].

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**References**