Tumor lysis syndrome: current perspective

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Tumor lysis syndrome is characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood following the rapid lysis of malignant cells. It is observed most frequently in patients with hematologic malignancies such as acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma after the initiation of chemotherapy, although it may also occur in other malignancies, both hematologic and solid tumors. These malignancies share the characteristics of a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.[1-5] In some cases, tumor lysis syndrome can lead to acute renal failure and even death. The key to the management of tumor lysis syndrome includes awareness of its causes, identification of high-risk patients, implementation of appropriate prophylactic measures, vigilant monitoring of electrolyte levels in patients undergoing chemotherapy, and initiation of more active treatment measures when necessary.

Pathophysiology

In tumors with a high proliferative rate, a relatively large mass and a high sensitivity to cytotoxic agents, the initiation of therapy often results in the rapid release of intracellular anions, cations, and the metabolic products of proteins and nucleic acids into the bloodstream.[4,6-9] The increased concentrations of uric acid, calcium, phosphates, potassium, and urea can overwhelm the body's homeostatic mechanisms to process and excrete these materials and result in the clinical spectrum associated with tumor lysis syndrome.[10] Hyperuricemia and its associated complications are the most frequently recognized manifestations of tumor lysis syndrome, and predispose to many of the other clinical derangements. Hyperuricemia results from rapid release and catabolism of intracellular nucleic acids. Purine nucleic acids are catabolized to hypoxanthine, then xanthine, and finally to uric acid by xanthine oxidase (Figure 1).[11-14]

Hyperphosphatemia results from the rapid release of intracellular phosphates from malignant cells, which may contain as much as four times the amount of organic and inorganic phosphates as normal cells.[9,15] Hyperphosphatemia can lead to the development of acute renal failure after precipitation with calcium in renal tubules during tumor lysis syndrome. The serum concentration of calcium rapidly decreases as precipitation with phosphate occurs. Hypocalcemia is one of the most serious clinical manifestations of tumor lysis syndrome and has been associated with the development of severe muscle cramping, tetany, and cardiac arrhythmias. Hyperkalemia may also be a life-threatening consequence of tumor lysis syndrome. Hyperkalemia results from the kidneys' inability to clear the massive load of intracellular potassium released by lysed tumor cells. Neuromuscular signs and symptoms may include muscle weakness, cramps, paresthesias, and possible paralysis. Cardiac manifestations may include asystole, ventricular tachycardia or fibrillation, syncope, and possible sudden death.[5,15]

Increases in blood urea nitrogen and creatinine levels occur as a result of renal impairment associated with acute uric acid crystal nephropathy, calcium-phosphate crystals and nephrocalcinosis, or a combination of both, leading to an acute obstructive uropathy syndrome. Acute clinical manifestations may include uremia, edema, hypertension, congestive heart failure, and exacerbations of metabolic disturbances.

Definition

While the set of metabolic abnormalities comprising tumor lysis syndrome is generally agreed upon, there is currently no universally accepted system for classifica-

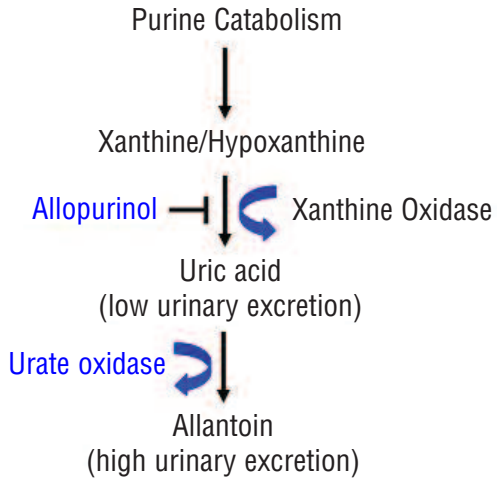

Figure 1. Purine catabolism pathway.

Table 1. Cairo-Bishop definition of laboratory tumor lysis syndrome.[17]

Uric acid	≥476 μmol/L (8 mg/dL) or 25% increase from baseline
Potassium	≥6.0 mmol/L (6mEq/L) or 25% increase from baseline
Phosphorous	≥2.1 mmol/L (children) or ≥1.45 mmol/L (adults) or 25% increase from baseline
Calcium	≤1.75 mmol/L or 25% decrease from baseline

Table 2. Cairo-Bishop definition of clinical tumor lysis syndrome.[17]

(1) Creatinine: ≥1.5 ULN (age adjusted)
(2) Cardiac arrhythmia/sudden death
(3) Seizure

tion and grading. Hande and Garrow developed a classification system based on defining laboratory (LTLS) or clinical tumor lysis syndrome (CTLS).[16] This system distinguishes between patients who do not require therapeutic intervention versus those experiencing life-threatening clinical abnormalities. In order to address the shortcomings of this classification system, Cairo and Bishop developed a system for defining CTLS and LTLS based upon modifications to the Hande-Garrow classification.[6] Under this definition, LTLS is considered to be present if two or more serum values of uric acid, potassium, phosphate or calcium are above or below normal at presentation, or if they change by 25% within 3 days before or 7 days after the initiation of treatment (Table 1). CTLS requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 2). Under this system, LTLS is considered to be either present or absent, while the grade of CTLS is defined by the maximal grade of the clinical manifestation (Table 3).[6,7]

Risk factors

Certain intrinsic tumor-related factors have been associated with an increased risk for the development of tumor lysis syndrome, including high tumor cell proliferation rate, large tumor burden, tumor chemosensitivity, and increased lactate dehydrogenase (LDH) levels.[17-19] However, the overall incidence of tumor lysis syndrome is not well established and has been closely studied only in high-grade non-Hodgkin's lymphomas (NHL).[15,19,20] In a retrospective study of 102 patients with high-grade NHL, the incidence of tumor lysis syndrome was reported to be 42% as determined by serial laboratory testing. The incidence of clinically significant tumor lysis syndrome was only 6% in the same group of patients. It is extremely important to recognize that tumor lysis syndrome can occur spontaneously, before any intervention.[21-23]

Management

The identication of patients at risk for the development of tumor lysis syndrome is the most important aspect of management so that prophylactic measures may be implemented before the initiation of therapy. Most of the complications can be readily managed when they are recognized early. However, delay in recognition and initiation of treatment of tumor lysis syndrome can be life-threatening. In addition, a recent cost analysis looking at acute renal failure, length of stay and total cost, demonstrated that those patients who went on to develop acute renal failure requiring dialysis had up to 2 to 3 times the length of stay and more than 5 times the cost.[24,25]

Serum creatinine, blood urea nitrogen, sodium, potassium, calcium, phosphorous, LDH and uric acid levels should be determined before therapy and every 4-6 hours for the first 48-72 hours after the initiation of tumor therapy. Patients should have a baseline electrocardiogram and continuous cardiac monitoring until the completion of treatment. Ideally, all patients should receive intravenous hydration 24-48 hours before the initiation of tumor therapy.[26]

Fluids and hydration

Aggressive hydration and diuresis are fundamental to the prevention and management of tumor lysis syndrome.[27,28] In general, patients should be hydrated with approximately 3 L/m^2/day. Administration of mannitol may be considered if sufficient diuresis cannot be

achieved with intravenous hydration alone. The use of sodium bicarbonate to alkalinize the urine has traditionally been recommended as part of tumor lysis syndrome prevention and management strategies.[29] However, while alkaline urine promotes the excretion of uric acid, it does not substantially increase the solubility of xanthine and hypoxanthine.[27-29] Moreover, xanthine has low solubility (5 mg/dL at pH 5.0 and 13 mg/dL at pH 7.0).[13] In situations in which levels of these metabolites are increased, such as after allopurinol treatment, this can lead to the precipitation of xanthine crystals in renal tubules, potentially resulting in xanthine obstructive uropathies. Based upon the potential complications associated with alkalinization, such as metabolic alkalosis and calcium phosphate precipitation, and the lack of clear evidence of benefit, the use of sodium bicarbonate for the prevention and treatment of tumor lysis syndrome is currently not recommended.

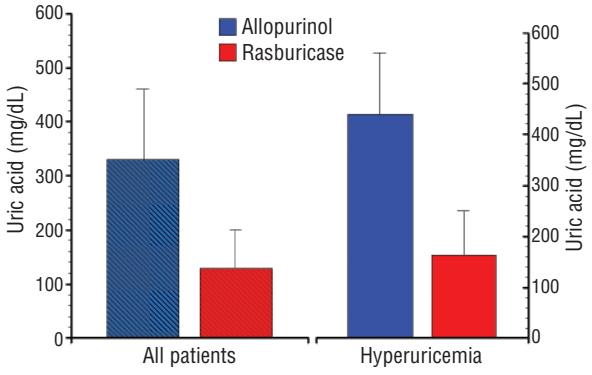

Figure 2. Uric acid AUC 0-96hr mg/dL/hr by treatment comparing all patients versus a subgroup with hyperuricemia.

Allopurinol

In addition to hydration, it is necessary to administer a hypo-uricemic agent, either allopurinol or rasburicase, before the initiation of therapy. Allopurinol is a potent inhibitor of xanthine oxidase and blocks the conversion of hypoxanthine and xanthine to uric acid.[13] Although allopurinol prevents new uric acid formation, it does not reduce the amount of uric acid already present. Thus, allopurinol needs to be initiated 2-3 days before the initiation of cytotoxic therapy. Allopurinol is generally given at a dose of at least 300 mg/m^2 day.[30] It is known to interfere with the degradation of 6-mercaptopurine, 6-thioguanine, and azathioprine through inhibition of the p450 pathway. Thus the dose of allopurinol should be reduced 50-75% in patients receiving these chemotherapeutic agents.

Recombinant urate oxidase (Rasburicase)

An alternative to inhibiting uric acid formation is to promote the catabolism of uric acid to allantoin by uric acid oxidase. Allantoin is 5 to 10 times more soluble in the urine than uric acid. The gene encoding urate oxidase has now been cloned from *Aspergillus flavus*, allowing production and purification of the recombinant enzyme (rasburicase). Although initial studies were performed using rasburicase daily for 5-7 days, subsequent studies have demonstrated that less frequent dosing is sufficient. A median of three doses were administered per patient on the North American compassionate use trial.[31]

In a multicenter trial, 52 pediatric patients with

Table 3. Cairo-Bishop grading system for tumor lysis syndrome.

	*Grade 0**	*Grade I*	*Grade II*	*Grade III*	*Grade IV*	*Grade V*
LTLS	-	+	+	+	+	+
Creatinine‡	1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 UNL	Death§
Cardiac arrhythmia‡	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death§
Seizure‡	None	---	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which is prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death§

**No laboratory TLS; ‡Not directly or probably attributable to a therapeutic agent; §Attributive probably or definitely to CTLS. TLS=tumor lysis syndrome; LTLS=laboratory tumor lysis syndrome; ULN=upper limit of normal; CHF=congestive heart failure; ADL=activities of daily living; CTLS=clinical tumor lysis syndrome. ©Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification (2004). Originally published in British Journal of Haematology, Blackwell Publishing Ltd. 127, 3-11.*

hematologic malignancy at high risk for tumor lysis syndrome were randomly assigned to receive allopurinol or rasburicase. Uric acid levels significantly decreased by 85% with rasburicase compared with 12% with allopurinol within 4 hours of drug administration. The mean area-under-the-curve (uric acid plasma concentration versus time) was significantly lower for patients treated with rasburicase (128 mg/dL/hour ±70) compared to those receiving allopurinol (329 mg/dL/hour±129) (p<0.0001), for a 2.6 fold decrease in uric acid exposure in the rasburicase versus allopurinol treatment groups (Figure 2).[11]

Pui *et al*. administered rasburicase IV at doses up to 0.2 mg/kg in 131 pediatric patients with newly diagnosed leukemia or lymphoma. They found rapid decrease in uric acid levels from 9.7 to 1 mg/dL within 4 hours of treatment in patients with hyperuricemia and a further decrease to 0.5 mg/dL within 24 hours after rasburicase administration. Serum phosphorous and creatinine concentrations also decreased significantly within 1-3 days.[11,32-34]

The *Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma* (GRAAL1) study evaluated the efficacy and safety of prophylactic rasburicase therapy in 100 adult patients with aggressive NHL during the first course of chemotherapy.[35] Rasburicase was given to all subjects and uric acid levels were then measured at 4 hours. All of the patients responded to rasburicase with normalization of uric acid and none exhibited increased creatinine levels or required dialysis.

Additional management

Attempts should be made to correct fluid overload, dehydration, electrolyte and acid-base abnormalities, and to establish adequate urinary output before the initiation of therapy. Hyperkalemia and hyperphosphatemia should be treated expediently according to standard measures. Treatment of asymptomatic hypocalcemia is generally not recommended. In patients with symptomatic hypocalcemia, intravenous calcium gluconate (50-100 mg/kg per dose) may be administered to correct the clinical symptoms. However, this may increase the risk of calcium phosphorus deposition and acute obstructive uropathy. For patients who have acute renal failure, signicant uremia, or severe electrolyte abnormalities associated with tumor lysis syndrome, hemodialysis should be initiated as soon as possible. Continuous hemofiltration has been used to correct fluid overload and electrolyte abnormalities associated with tumor lysis syndrome in children.[36] Any delay in starting hemodialysis for acute renal failure may turn a potentially reversible clinical situation into an irreversible one.[6]

Future considerations

In this issue of the journal, Montesinos *et al*. have published a single center review analyzing the incidence and outcomes of tumor lysis syndrome in 130 adult patients with AML.[37] This is the largest study to date of this population and highlights the importance of continuing to recognize patients outside the usual defined risk groups. In their review, 17% of the patients had tumor lysis syndrome, 5% meeting criteria for CTLS. Importantly, their data shows that 25% of the patients met laboratory or clinical criteria prior to the initiation of chemotherapy, emphasizing the wider recognition of spontaneous tumor lysis syndrome as a significant entity.

The authors go on to develop a predictive model to identify high-risk patients who need more aggressive measures, such as rasburicase and/or hemodialysis. This scoring system is based upon the definitions of LTLS and CTLS already proposed here, but with significant changes. Most importantly, the authors suggest that creatinine >1.4 be used as a criteria for LTLS rather than CTLS and that only oliguria or hemodialysis be used as clinical criteria for renal complications. In fact, care must be taken in limiting renal complications to oliguric renal failure as many patients with high output renal failure may be missed. Additionally, a rise in creatinine above baseline is often the earliest clinical indicator of worsening renal dysfunction. Therefore, patients with significant changes above baseline should be considered as having CTLS and managed accordingly. This is supported by the presented data that elevated creatinine is an equal risk factor for both LTLS and CTLS. In addition, their data supports the need to identify CTLS early as this was shown to increase induction mortality rates among patients. Their findings, that elevated LDH and uric acid levels at presentation remain important risk factors for CTLS, corroborate previously published data linking high uric acid with the development of renal impairment.[38] It is important that groups continue to examine risk factors and outcomes for tumor lysis syndrome, especially in the age of rasburicase when complications from tumor lysis syndrome should remain limited.

Summary

Successful management and treatment of tumor lysis syndrome is highly dependent on the prompt identication of clinical and laboratory characteristics, signs and symptoms of patients at risk. Establishment of vascular access and the initiation of prophylactic measures, especially hydration and administration of allopurinol or rasburicase, are vital. The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with tumor lysis syndrome.

References

1. Ajzensztejn D, Hegde VS, Lee SM. Tumor lysis syndrome after treatment with docetaxel for non-small-cell lung cancer. J Clin Oncol 2006;24:2389-91.
2. Alavi S, Arzanian MT, Abbasian MR, Ashena Z. Tumor lysis syndrome in children with non-Hodgkin lymphoma. Pediatr Hematol Oncol 2006;23:65-70.
3. Chan JK, Lin SS, McMeekin DS, Berman ML. Patients with malignancy requiring urgent therapy: CASE 3. Tumor lysis syndrome associated with chemotherapy in ovarian cancer. J Clin Oncol 2005;23:6794-5.
4. Jeha S. Tumor lysis syndrome. Semin Hematol 2001;38[4 Suppl 10]:4-8.
5. Milano GM, De Sio L, Cozza R, Donfrancesco A. Tumor lysis syndrome and neuroblastoma. Med Pediatr Oncol 2003;41:592.
6. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004; 127:3-11.
7. Del Toro G, Morris E, Cairo MS. Tumor lysis syndrome: pathophysiology, definition, and alternative treatment approaches. Clin Adv Hematol Oncol 2005;3:54-61.
8. Rampello E, Fricia T, Malaguarnera M. The management of tumor lysis syndrome. Nat Clin Pract Oncol 2006; 3:438-47.
9. Yarpuzlu AA. A review of clinical and laboratory findings and treatment of tumor lysis syndrome. Clin Chim Acta 2003;333:13-8.
10. Howard SC, Pui CH. Pitfalls in predicting tumor lysis syndrome. Leuk Lymphoma 2006;47:782-5.
11. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001; 97:2998-3003.
12. Gutman AB, Yu TF. Uric acid nephrolithiasis. Am J Med 1968;45:756-79.
13. Klinenberg JR, Goldfinger SE, Seegmiller JE. The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. Ann Intern Med 1965;62:639-47.
14. Rieselbach RE, Bentzel CJ, Cotlove E, Frei E 3rd, Freireich EJ. Uric acid excretion and renal function in the acute hyperuricemia of leukemia. Pathogenic therapeutic uric acid nephropathy. Am J Med 1964;37:872-83.
15. Locatelli F, Rossi F. Incidence and pathogenesis of tumor lysis syndrome. Contrib Nephrol 2005;147:61-8.
16. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med 1993;94:133-9.
17. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004; 127:3-11.
18. Navolanic PM, Pui CH, Larson RA, Bishop MR, Pearce TE, Cairo MS, et al. Elitek-rasburicase: an effective means to prevent and treat hyperuricemia associated with tumor lysis syndrome, a Meeting Report, Dallas, Texas, January 2002. Leukemia 2003;17:499-514.
19. Wossmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. Ann Hematol 2003;82:160-5.
20. Arseneau JC, Canellos GP, Banks PM, Berard CW, Gralnick HR, DeVita VT Jr. American Burkitt's lymphoma: a clinicopathologic study of 30 cases. I. Clinical factors relating to prolonged survival. Am J Med 1975;58:314-21.
21. Barquero Romero J, Catalina Fernandez I, Hernandez Saez C, Jimenez Morales JL, Garcia de la Llana F. Spontaneous tumor lysis syndrome in a patient with non-Hodgkin's lymphoma. An Med Interna 2005;22:387-9.
22. Hsu HH, Huang CC. Acute spontaneous tumor lysis in anaplastic large T-cell lymphoma presenting with hyperuricemic acute renal failure. Int J Hematol 2004;79:48-51.
23. Tufan A, Unal N, Koca E, Onal I, Aksu S, Haznedaroglu I. Spontaneous tumor lysis syndrome in a patient with diffuse large B cell lymphoma and Richter syndrome. Ann Hematol 2006;85:183-4.
24. Annemans L, Moeremans K, Lamotte M, Garcia Conde J, van den Berg H, Myint H, et al. Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. Leuk Lymphoma 2003;44:77-83.
25. Candrilli S, Bell T, Irish W, Morris E, Goldman S, Cairo MS. A Comparison of Inpatient Length of Stay and Costs Among Patients With Hematological Malignancies (Excluding Hodgkin?s Disease) Associated With and Without Acute Renal Failure. In press, Clinical Lymphoma and Myeloma, 2007.
26. Pession A, Barbieri E. Treatment and prevention of tumor lysis syndrome in children. Experience of Associazione Italiana Ematologia Oncologia Pediatrica. Contrib Nephrol 2005;147:80-92.
27 Andreoli SP, Clark JH, McGuire WA, Bergstein JM. Purine excretion during tumor lysis in children with acute lymphocytic leukemia receiving allopurinol: relationship to acute renal failure. J Pediatr 1986;109:292-8.
28. Jones DP, Mahmoud H, Chesney RW. Tumor lysis syndrome: pathogenesis and management. Pediatr Nephrol 1995;9:206-12.
29. Ten Harkel AD, Kist-Van Holthe JE, Van Weel M, Van der Vorst MM. Alkalinization and the tumor lysis syndrome. Med Pediatr Oncol 1998;31:27-8.
30. Bessmertny O, Robitaille LM, Cairo MS. Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. Curr Pharm Des 2005;11:4177-85.
31. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia 2005;19:34-8.
32. Pui CH, Jeha S, Irwin D, Camitta B. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. Leukemia 2001;15:1505-9.
33. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients With leukemia or lymphoma. J Clin Oncol 2001;19:697-704.
34. Ribeiro RC, Pui CH. Recombinant urate oxidase for prevention of hyperuricemia and tumor lysis syndrome in lymphoid malignancies. Clin Lymphoma 2003;3:225-32.
35. Coiffier B, Mounier N, Bologna S, Ferme C, Tilly H, Sonet A, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol 2003;21: 4402-6.
36. Agha-Razii M, Amyot SL, Pichette V, Cardinal J, Ouimet D, Leblanc M. Continuous veno-venous hemodiafiltration for the treatment of spontaneous tumor lysis syndrome complicated by acute renal failure and severe hyperuricemia. Clin Nephrol 2000;54:59-63.
37. Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent M, Martínez D, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica 2007; 93:67-74.
38. Cairo MS. Both normal and elevated uric acid (UA) levels are independantly and significantly correlated with both tumor lysis syndrome (TLS) and renal events in patients admitted for induction chemotherapy for hematological malignancies. ASCO Proceedings 2002;21:271b[abstract].