Tumor Lysis Syndrome

(Amended July 2006)

1. Background

Tumor lysis syndrome (TLS) results from massive lysis of rapidly proliferating malignant cells, and is characterized by hyperuricemia, hyperkalemia, and hyperphosphatemia. Hyperphosphatemia may lead to hypocalcemia with resultant tetany or other potentially life-threatening complications. TLS usually develops shortly after the start of effective cytotoxic therapy and may lead to acute renal failure and death. Renal tubular precipitation of uric acid is a major, but not the only factor, leading to renal failure in TLS [1,2] .

Risk factors for development of TLS include: 1) malignancies with a large growth fraction (i.e. B-cell lymphomas/leukemias, T-cell lymphomas/leukemias); 2) large tumor bulk; 3) use of effective cytolytic chemotherapy; 4) preexisting renal insufficiency; 5) kidney involvement; 6) ureteral or bladder obstruction by tumor; and, 6) pre-treatment metabolic abnormalities.

Traditionally, the standard prevention or treatment of TLS has consisted of vigorous hydration to ensure a high rate of urine flow, urinary alkalinization with sodium bicarbonate to prevent precipitation of uric acid, and use of allopurinol to decrease uric acid formation - via inhibition of xanthine oxidase. Use of allopurinol, however, results in increased production and urinary excretion of uric acid precursors, xanthine and hypoxanthine[3]. Xanthine has poor solubility even in alkaline urine, and one report has suggested that hyperxanthinuria had a pathogenic role in the renal failure of patients with lymphoma receiving allopurinol for prevention of TLS[2].

An alternative to allopurinol is the use of the uricolytic agent **urate oxidase**. This compound induces enzymatic oxidation of uric acid to allantoin, a metabolite which is 5- to 10-fold times more soluble than uric acid. Recombinant urate oxidase (**Rasburicase**, Sanofi-Synthelabo) is now commercially available and has been found to be safe and effective for prevention and treatment of hyperuricemia in children with leukemia or lymphoma [4]. The main problem with the routine use of this drug is its high cost compared to that of oral allopurinol.

Hyperkalemia is the most life-threatening manifestation of TLS. Recent reports in the literature indicate that albuterol (or salbutamol), administered intravenously or by nebulizations, is an effective, rapid, and safe treatment for moderate hyperkalemia in neonates and children [5]. It lowers the serum potassium level by inducing a shift of K into the intracellular compartment, which results from increased 3'5'-cyclic AMP and secondary changes in the sodium/potassium-ATPase pump. One report suggested that nebulizations may be more efficacious than the IV route[6]. In this study, side effects were mild and transient, and included tremors, tachycardia, and flushing.

2. Prevention and Treatment of Tumor Lysis Syndrome

2.1 Patients with High-Risk for Tumor Lysis Syndrome (HR-TLS)

2.1.1 Definition (*)

(Amended June, 2006)

2.1.1.1 Patient with leukemia with a WBC > 100, 000/µL

2.1.1.2 Patient with a WBC of > 50,000 but < 100,000/µL and elevated uric acid levels less than 2x the upper limits of normal, without normalization of uric acid level after 24 hr of hydration and allopurinol

2.1.1.3 Patient with leukemia and uric acid level which is at least 2x the upper limits of normal and no clinical or laboratory signs of dehydration

2.1.1.4 Patient with Stage III-IV Burkitt lymphoma or B-cell ALL

2.1.1.5 Patient with bulky T-cell lymphoblastic lymphoma/leukemia with uric acid level above the upper limits of normal, without normalization of the uric acid level after 24 hours of hydration and allopurinol.

2.1.1.6 Patient with bulky leukemia or lymphoma and serum creatinine level which is at least 50 % above the upper limits of normal for age, regardless of uric acid level or WBC, and which does not normalize after 24 hours of IV hydration.

2.1.1.7 Patient with leukemia, WBC > 50,000/uL, and *nephromegaly* , regardless of uric acid and serum creatinine levels.

2.1.1.8 Patient has 2 or all 3 laboratory features of TLS prior to treatment, without normalization of laboratory values after 24 hours of IV hydration and PO allopurinol.

(*) Note: *If patient does not fully meet any of the above outlined criteria and you are contemplating use of* ***rasburicase****, discuss case with Drs. Alvarado or Keller at the Egleston campus or Drs. Bergsagel or Lew at the Scottish Rite campus, before writing Rasburicase orders.*

2.1.2 Laboratory/Imaging Guidelines/Consults

2.1.2.1 Renal function panel and uric acid Q 3-6 hr, depending upon risk of TLS and the patient's clinical condition. Measure lactic acid on patients with otherwise unexplained metabolic acidosis.

2.1.2.2 ***For patients with bulky leukemias or lymphomas and those with renal insufficiency prior to starting therapy, u***ltrasound of abdomen and kidneys *should be done to* assess kidney size and rule out renal masses, hydronephrosis, hydroureter or bladder compression or distention.

2.1.2.3 Consult with Nephrology service if patient has a low creatinine clearance (by Schwartz formula or GFR).

2.1.2.4 Consult with Urology service if imaging studies show obstructive uropathy

2.1.2.5 Consult with Radiation Oncology if imaging studies show nephromegaly ***for possible need of radiation to the kidneys***

2.1.2.6 G-6-PD screening for patients at risk for G-6-PD deficiency , i.e. male patients of African and Mediteranean ancestry.(See 2.1.1.5 for rationale)

2.1.3 Prevention Guidelines

2.1.3 1 Patients with HR-TLS are candidates for treatment with *Rasburicase*

2.1.3.2 IV hydration: 3000 cc/m^2/24 hr D5W ¼ NS (if < 1 yr old) or D5W½ NS (if ≥ 1 yr old).
Goal: Achieve and maintain urine output of 2500 cc/m^2/24 hr and urine specific gravity of ≤ 1010.

2.1.3.3 *Do not* add potassium to IV solution

2.1.3.5 *Do not* use sodium bicarbonate routinely –unless it is needed to control significant metabolic acidosis.

Rationale for this recommendation : 1) significant hyperuricemia is unlikely to occur when *Rasburicase* is used, thus urine alkalinization is not necessary; 2) *Rasburicase* does not prevent hyperphosphatemia - and phosphorus is less soluble in alkaline urine.

…2.1.4 Clinical Monitoring

2.1.4.1 Strict I & O

2.1.4.2 Check weight BID

2.1.4.3 Check urine output Q 4-6 hr.

2.1.4.4 If urine output < 60 % of intake within the first 4 hours of IV hydration and there are no signs of volume overload (e.g. hypertension, tachypnea, hypoxemia, S_3 gallop), give normal saline boluses (10 cc/kg x 2). If there is no response, may give furosemide (lasix) 1-2 mg/kg Q 6-8 hr. (Do not write any of these as standing orders).

2.1.4.5 Consult with Nephrology.

2.1.5. Treatment Guidelines

2.1.5.1 ***Rasburicase*** 0.15 mg/kg/dose (round down to multiple of 1.5 mg vial size) (*) IV. Repeat dose q. 12-24 hr as necessary to keep uric acid ≤ normal limits.

(*) *For overweight patients use ideal body weight*

2.1.5.2 After first dose of rasburicase, start ***allopurinol*** 300 mg/m2/day (or 10 mg/kg/day) PO divided TID.

2.1.5.3 Give first dose of Rasburicase as soon as HR-TLS criteria for elevated uric acid are met, even if therapy is not to start **immediately**.

2.1.5.4 If uric acid is not elevated at diagnosis, give first dose about 4 hours prior to starting chemotherapy.

2.1.5.5 When patient is on treatment with Rasburicase, blood samples for uric acid measurements **should be kept in ice** until analyzed, to prevent continuing ex-vivo degradation of uric acid by rasburicase and thus, falsely low uric acid levels.

2.1.5.6 ***Contraindication***: Rasburicase is contraindicated in patients with known G-6-PD deficiency for it may cause hemolysis. Patients at higher risk for G-6-PD deficiency (i.e. male patients of African and Mediteranean ancestry) should ideally be screened prior to starting Rasburicase.

2.1.5.7 Start chemotherapy when good urine ouput is established and uric acid is ≤ normal limits, regardless of urine pH.

2.1.5.8 If patient has moderate to severe renal dysfunction at diagnosis (i.e. e stimated GFR < 50 %), consider renal dialysis prophylactically.

2.2 **Patients with Low-Risk for Tumor Lysis Syndrome (LR-TLS)**

2.2.1 Definition: Patients who do not meet criteria for HRTLS. (See section 2.1.1)

Most of these patients can be safely managed with IV fluids and PO allopurinol

2.2.2 Laboratory and Imaging Guidelines

2.2.2.1 Monitor renal panel and uric acid Q 8 - 12 hr

2.2.2.2 Imaging studies as noted above

2.2.3 Prevention Guidelines

2.2.3.1 Hydration: IV fluids: 3000 cc/m^2/24 hr as D5 W ¼ NS (< 1 yr old) or D5 ½ NS (≥ 1 yr old).
Do not add potassium or sodium bicarbonate to IV fluids.

2.2.3.2 Start chemotherapy when good urine output is established

2.2.3.3 ***Allopurinol***: 300 mg/m^2/ day (or 10 mg/kg/day) PO divided TID.

2.2.3.4 If patient is unable to take PO, consider use of **IV allopurinol 200 mg/m^2/day (max 600 mg/day) divided Q 8 hr.**

3. Management of Common Electrolyte Problems In *TLS*

3.1 Hyperkalemia

3.1.1 Definition: Serum potassium > 5.5 mEq/L

3.1.2 General recommendation: EKG rhythm strip - rule out peaked T waves, widening of PR or QRS, ventricular arrhythmia's.

3.1.3 If serum K > 5.5 but <6.0 mEq/L

3.1.3.1 Albuterol nebulization 2.5 mg if < 30 kg, 5 mg if > 30 kg. May repeat treatment in 2 hours if necessary.

3.1.4 If serum K > 6.0 - 6.5 mEq/l and EKG is normal:

3.1.4.1 Consult Renal service for potential need for dialysis. Initiate one or more of the following measures:

3.1.4.2 Kayexalate 0.5 -1 gm/kg with 25 % sorbitol PO or PR.

3.1.4.3 Albuterol by nebulization as per 3.13. May repeat in 2 hr.

3.1.4.4 Insulin: Regular insulin 0.1 U/kg in 2 cc/kg (= 0.5 gm/kg)of 25 % Dextrose IV over 30 minutes.

Caution: If patient is hypoglycemic, omit insulin or use lower doses.

3.1.4.5 If serum bicarbonate ≤ 28 mEq/L, serum Na < 145 mEq/L, and serum calcium > 8 mg/dL, may give 8.4 % sodium bicarbonate (1 mEq = 1 ml) 1 - 2 mEq/kg IV over 5-10 minutes.

3.1.4.6 *Dialysis should be done if there is no response to the above management.* See Appendix I for indications for dialysis.

3.1.5 If serum K > 6.5 mEq and EKG is abnormal: Consult Renal and Critical Care Medicine services for possible emergent dialysis. Initiate one or more of the following temporazing measures:

3.1.5.1 Give 10 % calcium gluconate 0.5 ml/kg IV over 3-5 minutes with careful heart rate (HR) monitoring. STOP infusion if HR < 60/min. May repeat in 10 minutes

3.1.5.2 Albuterol nebulization as per 3.13

3.1.5.3 Insulin with hypertonic glucose as per 3.14

3.1.5.4 Sodium bicarbonate as per 3.14

3.2 **Hypocalcemia**

3.2.1 Definition: Serum ionized calcium < 4.4 mg/dl.

3.2.2 Use IV calcium only if patient has *symptomatic* hypocalcemia (i.e. tetany, seizures): Give 0.5- 1.0 ml/kg (or 50-100 mg/kg/dose) of 10 % calcium gluconate IV (or 10 mg/kg elemental calcium), slowly over 3-5 minutes with careful monitoring of the heart rate. STOP infusion if the heart rate is < 60/min.

3.2.3 If patient is not symptomatic, treat with *oral* calcium.

3.2.4 When patient is no longer symptomatic and hypocalcemia has been corrected, may give calcium orally (i.e. *Tums*). If patient cannot take PO, may add calcium gluconate to IV solution (which *should be bicarbonate-free*), to provide 100 mg of elemental Ca/kg/24 hr.

• *Warning*: Extravasation of calcium can result in severe tissue necrosis. Except in extreme emergencies, *IV calcium should always be administered via a central line*.

3.3 **Hyperphosphatemia**

3.3.1 Definition: Serum phosphorus > 5.9 or >6.5 mg/dL -depending upon age of patient.

3.3.2 Give aluminum hydroxide (*amphogel*) 50 - 150 mg/kg/day PO divided TID, with meals. (This is a slow acting treatment and intended only for binding dietary phosphorus in the G.I. tract; neither this nor any other medication will remove phosphorus from the body).

3.3.3 Consider discontinuing alkalinization because precipitation of phosphate is enhanced at pH >6.0.

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7. Appendices: 1

8. Approval by **Date**

APPENDIX I

TUMOR LYSIS SYNDROME: INDICATIONS FOR DIALYSIS

- Renal Failure: Creatinine rising inexorably or 10 x normal

- Hyperkalemia: Serum K > 6 mEq/L, in presence of rising creatinine and falling urine output, with inadequate response to conservative treatment

- Hyperuricemia: Uric acid >10 mg/dl, in presence of rising creatinine and falling urine output, with inadequate response to conservative treatment

- Hyperphosphatemia: Serum Phosphorus > 10 mg/dl, in presence of rising creatinine and falling urine output, with inadequate response to conservative treatment.

- Hypocalcemia, *symptomatic* (tetany, seizures), with inadequate response to conservative treatment

- Fluid overload unresponsive to diuretics.

APPENDIX II

(ADDENDUM: April, 2005)

CHEMOTHERAPY GUIDELINES FOR PATIENTS WITH SEVERE RENAL FAILURE OR ANEPHRIC PATIENTS ON DIALYSIS

General Principles. In patients with severe renal failure, the administration of conventional doses of drugs that are primarily excreted by the kidney (i.e platinum compounds, methotrexate, etoposide) can result in significant toxicity; thus, dose reduction is necessary. Drugs that are primarily excreted by other routes can be given in standard doses (i.e. vincristine, vinblastine, dactinomycin) or at slightly reduced dosages (i.e. cyclophosphamide) in patients with renal failure.

For children with severe renal failure or anephric children undergoing dialysis, consider the following:

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> **Cyclophosphamide (CYC)'** main clearance is hepatic; renal clearance is low. Dose should be adjusted based on creatinine clearance (CrCl). CYC and its metabolites can be removed by hemodialysis . In patients on hemodialysis, CYC has been tolerated at doses similar to those used in patients with normal renal function. In one report, [1] an anephric child with multiply relapsed Wilms tumor received 3 g/m^2 as preparative regimen. A 42-yr old patient with AML and end-stage renal disease on hemodialysis was successfully transplanted after TBI and CYC (60 mg/kg/day x 2) [2].

When to dialyze after cyclophosphamide?: The anephric child [1]was dialyzed 2 hours after CYC infusion, whereas in the adult AML patient hemodialysis (x 6 hr) was initiated 14 hours after completion of CYC infusion. Based on CYC pharmacokinetic data in patients with autoimmune diseases and renal failure Haubitz et al recommended [3] that dialysis not be initiated earlier than 12 hours after CYC infusion to avoid excessive drug removal (and thus, lessening treatment efficacy).

>**Etoposide (VP-16)** is normally eliminated by renal (60%) and hepatic (40%) mechanisms. It is not extensively dialyzed (peritoneal or hemodialysis) because it is highly protein bound. Thus, timing dialysis to chemotherapy administration is not relevant. Dose adjustment is recommended in moderate and severe renal failure (see Table. The anephric child [1] in Dager's report received 400 mg/m2 as preparative regimen .

> **Carboplatin**'s major route of elimination is glomerular filtration and tubular secretion. It can be used in patients with renal failure. It is not cleared by peritoneal dialysis but it is removed by hemodialysis [4] .

In patients with renal failure, dose of carboplatin should be calculated using the Calvert formula, as follows :

Dose *(mg) = target AUC** x (GFR+25)

AUC: area under the curve
* the dose of carboplatin is expressed as milligrams (not mg/m2)

** Target AUC values of 4 to 6 mg/ml/min are most commonly used in pretreated patients.

When to dialyze?. Hemodialysis was performed 16 after the infusion in a patient with ovarian cancer who also received paclitaxel [5]. Other investigators have performed hemodialysis 12-18 hours [7] or 24 hours after carboplatin [6].

>**Cisplatin** has been used in patients with renal failure on hemodialysis [7]. In anephric patients, clearance of free platinum is five times lower than in individuals with normal renal function. Five patients with lung cancer on hemodialysis were treated with escalating doses of cisplatin (40 mg/m2 day 1, then 80 mg/m2 day 1) and VP-16 (first 50 mg/m2 on days 1,3, and 5, then 100 mg/m2). Dialysis was performed three times a week and soon after completion of therapy.

Dose Modifications for Other Commonly Used Chemotherapy Drugs in Severe Renal Failure [see Table 61-11, Ref. 8]

TABLE 61–11. Antineoplastic Agents

Drug, Toxicity, Notes	Dose for Normal Renal Function	Method	Adjustment for Renal Failure GFR, mL/min		Supplement for Dialysis
			10–50	*<10*	
Bleomycin (9)	10–20 U/m²	D	75%	50%	Hemo: None CAPD: Unlikely CAVH: Unknown
Busulfan (10)	4–8 mg/d	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Carboplatin (11)	400–500 mg/m²	D	50–75%	50%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Chlorambucil	0.1–0.2 mg/kg/d	D	Unknown	Unknown	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Cisplatin (12)	20–120 mg/m²	D	75%	50%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Cyclophosphamide (13) Hemorrhagic cystitis, bladder fibrosis and bladder cancer (SIADH)	1–5 mg/kg/d	D	100%	75%	Hemo: Dose after dialysis CAPD: Unknown CAVH: Unknown
Cytarabine (14) Increased risk of neurotoxicity with high-dose therapy (2–3 g/m²) in patients with renal insufficiency	100–200 mg/m²	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Daunorubicin	30–45 mg/m²	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Doxorubicin (15)	60–75 mg/m²	D	100%	100%	Hemo: None CAPD: Unlikely CAVH: Unlikely
Etoposide (16)	35–100 mg/m²/d	D	75%	50%	Hemo: None CAPD: Unlikely CAVH: Unlikely
Fluorouracil	12 mg/kg/d	D	100%	100%	Hemo: Dose after dialysis CAPD: Unknown CAVH: Unknown
Hydroxyurea	20–30 mg/kg/d	D	50%	20%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Idarubicin	12 mg/m²	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Melphalan (17)	6 mg/d	D	75%	50%	Hemo: Unlikely CAPD: Unlikely CAVH: Unlikely
Methotrexate (18)	Low dose 15–30 mg/d, high dose 12 g/m² (with leucovorin rescue)	D	50%	Avoid	Hemo: None CAPD: None CAVH: Unlikely
Mitomycin C Hemolytic uremic syndrome	20 mg/m² q 6–8 wk	D	100%	75%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Nitrosureas	Varies	D	75%	25–50%	Hemo: None CAPD: Unlikely CAVH: Unlikely
Tamoxifen	10–20 mg bid	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Vinblastine	3.7 mg/m²	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown
Vincristine	1.4 mg/m²	D	100%	100%	Hemo: Unknown CAPD: Unknown CAVH: Unknown

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