Prevention in TUMOR LYSIS SYNDROME

Hemato-Oncology Department
Tumor Lysis Syndrome

• Caused by rapid & massive tumor cell lysis and release of intracellular contents (potassium, phosphate and nucleic acids) into the bloodstream that overwhelms the kidney’s ability to excrete those products
• Can occur at presentation or more commonly after initiation of chemo for high grade lymphomas (e.g., Burkitt’s) and leukemia
• Can also be precipitated by radiation, steroid or antibody therapy
• Risk of renal failure and life-threatening electrolyte disturbances is caused by the breakdown of nucleic acids -> uric acid, which can precipitate in the renal tubules
• Hyperphostatemia with deposition of calcium phosphate in the renal tubules can also cause renal failure
Common Tumors Associated with TLS

- ALL 63%
- Non-Hodgkin’s Lymphoma 18%
- AML 11%
- Solid Tumors 5% - Neuroblastoma; Medulloblastoma; germ cell tumors; sarcoma
Risk Factors

- Patients with highly proliferative tumors and/or high tumor burden (>10cm diameter; WBC>50,000)
- Pretreatment LDH > 2x upper limit of normal
- Pre-existing renal insufficiency
- Tumor with high sensitivity to treatment
Cairo Bishop Grading System

- Laboratory TLS requires 2 or more abnormal serum values be present 3 days before or 7 days after instituting chemotherapy in the setting of adequate hydration and use of a hypouricemic agent
Cairo Bishop Grading System

- Laboratory tumor lysis syndrome:
  Uric acid $\geq 8$ mg/dL ($\geq 476$ mol/L) or 25% increase from baseline

  Potassium $\geq 6.0$ mEq/L ($\geq 6$ mmol/L) or 25% increase from baseline

  Phosphorus $\geq 6.5$ mg/dL ($\geq 2.1$ mmol/L) or 25% increase from baseline

  Calcium $\leq 7$ mg/dL ($\leq 1.75$ mmol/L) or 25% decrease from baseline
Clinical TLS

• Clinical TLS constitutes laboratory TLS plus at least one of the following:
  – serum Creatinine > 1.5 x ULN
  – cardiac arrhythmia/sudden death
  – seizure
# Clinical TLS

<table>
<thead>
<tr>
<th>LTLS</th>
<th>Grade 0†</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Grade V</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| Creatinine‡ | ≤1.5 × ULN | 1.5 × ULN | >1.5–3.0 × ULN | >3.0–6.0 × ULN | >6 × ULN | Death§  |

| Cardiac arrhythmia‡ | None | Intervention not needed | Nonurgent intervention needed | Symptomatic and incompletely controlled medically or controlled with a device | Life-threatening (e.g., arrhythmia associated with CHF, hypotension, or shock) | Death§  |

| Seizures‡ | None | None | None | One brief, generalized seizure, seizures controlled with anticonvulsant drugs, or infrequent motor seizures | Seizures with impaired consciousness, poorly controlled seizures, generalized seizures despite medical interventions | Status epilepticus | Death§  |
Clinical Manifestations of TLS

- Nausea/Vomiting, diarrhea, anoxeria
- Hyperkalemia $\rightarrow$ weakness, dysrhythmias
- Hyperphosphatemia $\rightarrow$ hypocalcemia, renal failure
- Hypocalcemia $\rightarrow$ muscle cramps, tetany, mental status changes, seizures
- Hyperuricemia $\rightarrow$ “uric acid nephropathy” = oliguria, renal failure
Hyperuricemia

Purine catabolism

Hypoxanthine

\( \text{XO} \)

Xanthine

\( \text{XO} \)

Uric Acid

Exogenous urate oxidase

Allantoin

Allopurinol
Hyperuricemia

URIC ACID (U-pH ≤ 5.4)
Hyperphosphatemia

• Malignant cells contain higher concentration of phosphorus
• Hyperphosphatemia causes hypocalcemia (precipitation in renal tubules/heart is increased when phos*ca product > 60 mg/dL)
• More common cause of renal failure since the use of Allopurinol and UO
<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Burkitt’s lymphoma, lymphoblastic lymphoma, B-cell ALL, ALL if WBC &gt;100 K, AML if WBC &gt;50 K, monoblastic AML</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>DLBCL, ALL if WBC 50-100 K, AML if WBC 10-50 K, CLL if 10-50 K and treated with fludarabine, other malignancies with rapid proliferations and expected rapid response to therapy</td>
</tr>
<tr>
<td>Low risk</td>
<td>Indolent NHL, ALL if WBC &gt;50 K, AML if WBC &gt;10 K, CLL if WBC &gt;10 K, other malignancies</td>
</tr>
</tbody>
</table>

ALL=acute lymphoblastic leukemia; WBC=white blood cell count; AML=acute myelogenous leukemia; DLBCL=diffuse large B-cell lymphoma; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin’s lymphoma.

# Tumor lysis syndrome (TLS) prophylaxis recommendations based on TLS risk

<table>
<thead>
<tr>
<th>Low risk disease (LRD)</th>
<th>Intermediate risk disease (IRD)</th>
<th>High risk disease (HRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most solid tumors</td>
<td>Rare, highly chemotherapy sensitive solid tumors (eg, neuroblastoma, germ cell tumor, small cell lung cancer) with bulky or advanced stage disease</td>
<td>N/A</td>
</tr>
<tr>
<td>MM</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CML</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Indolent NHL</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>HL</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CLL and WBC &lt;50 x 10^9/L treated only with alkylating agents</td>
<td>CLL treated with fludarabine or rituximab, and/or those with high WBC ≥50 x 10^9/L</td>
<td>N/A</td>
</tr>
<tr>
<td>AML and WBC &lt;25 x 10^9/L and LDH &lt;2 x ULN</td>
<td>AML with WBC 25 to 100 x 10^9/L</td>
<td>AML and WBC ≥100 x 10^9/L</td>
</tr>
<tr>
<td>Adult intermediate grade NHL and LDH within normal limits</td>
<td>Adult intermediate grade NHL and LDH &gt; ULN, non bulky</td>
<td>Adult intermediate grade NHL with bulky disease and LDH ≥2 x ULN</td>
</tr>
<tr>
<td>Adult ALCL</td>
<td>Childhood ALCL stage III/IV</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>Childhood intermediate grade NHL stage III/IV with LDH &lt;2 x ULN</td>
<td>Stage III/IV childhood diffuse large B cell lymphoma with LDH ≥2 x ULN</td>
</tr>
<tr>
<td>N/A</td>
<td>ALL and WBC &lt;100 x 10^9/L and LDH &lt;2 x ULN</td>
<td>Burkitt's leukemia</td>
</tr>
<tr>
<td>N/A</td>
<td>BL and LDH &lt;2 x ULN</td>
<td>Other ALL and WBC ≥100 x 10^9/L and/or LDH ≥2 x ULN</td>
</tr>
<tr>
<td>N/A</td>
<td>LL stage I/II and LDH &lt;2 x ULN</td>
<td>BL stage III/IV and/or LDH ≥2 x ULN</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>LL stage III/IV and/or LDH ≥2 x ULN</td>
</tr>
</tbody>
</table>

## Prophylaxis recommendations

<table>
<thead>
<tr>
<th>Monitoring</th>
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<tbody>
<tr>
<td>Hydration</td>
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</tr>
<tr>
<td>±Allopurinol</td>
<td>Allopurinol</td>
<td>Rasburicase*</td>
</tr>
</tbody>
</table>
Prevention - Monitoring

- Follow laboratory parameters (UA, phosphate, potassium, calcium, creatinine, LDH) closely, starting 4-6 hours after initiation of chemo & then every 6 hours thereafter
- Monitor UOP/Intake; monitor for seizures/cardiac arrhythmias
- Monitor for 24-72 hours after initiation of chemo
Prevention - Hydration

- Hydration to produce high urine output
  - Fluid intake = 2-3 L/m²/day (or 200 ml/kg/day for patients <10kg) enhances uric acid excretion, phosphate excretion
  - Goal UOP of 80-100 ml/m² per hour (or 4-6 ml/kg/hr if patient < 10kg)
  - Use isotonic fluid: D5 1/4 NS or NS if hyponatremic
  - Do not add calcium or potassium
- Monitor for fluid overload in patients with underlying cardiac dysfunction or renal insufficiency
Prevention - Urinary Alkalization

- Urine alkalization - add NaHCO₃ to IVF
  - Uric acid more soluble at urine pH = 7.0 vs 5.0
  - Goal of urine specific gravity ≤1.015 and pH 7.0-7.5
  - Caution -- hypoxanthine and Ca-PO₄ stones possible if urine pH >7.5
- Fallen out of favor as no demonstrated advantage; may be appropriate for patients with underlying metabolic acidosis
Prevention - Hypourricemic Agents

- Allopurinol – a hypoxanthine analog that inhibits XO producing more hypoxanthine and xanthine which are more soluble in acidic urine; takes 2-3 days to be effective
- Urate Oxidase/Rasburicase – breaks down uric acid to allantoin which is more soluble in urine; acts within several hours
- UO has significantly reduced the need for rescue dialysis therapy for TLS
Prevention - Allopurinol

- Decrease production of uric acid
  - allopurinol inhibits xanthine oxidase
    - 300 mg/m²/day divided tid PO/IV
    - Dose reduction in renal insufficiency
    - Long-time standard Rx
**ALLOPURINOL:**
- Competitive inhibitor of xanthine oxidase which decreases conversion of purine metabolites to uric acid. Used prophylactically for TLS
- Prophylactic option for patients with a medium risk of TLS
- Limitations:
  ---- 1) ineffective in reducing uric acid levels before chemoTx
  ---- 2) Xanthine and hypoxanthine precipitate → obstructive uropathy
  ---- 3) reduces clearance of some chemoTx (azothiopurine & 6-mercaptopurine)
Prevention - Urate Oxidase

• Present in other mammalian species
• Catalyzes conversion of uric acid to allantoin
  – Allantoin more soluble, easily excreted by kidneys
• Urine alkalinization unnecessary if used
• Recombinant urate oxidase (rasburicase) more effective than allopurinol in prevention and treatment of hyperuricemia
• Contraindicated with G6PD deficiency, asthma
RASBURICASE (recombinant urate oxidase):
- promotes catabolism of uric acid:
Uric acid $\rightarrow$ allantoin (10x more soluble than uric acid)
- 100 adult pt (w/ aggressive NHL) got 3 to 7 days of rasburicase beginning day 1 of chemo:
  1) Uric acid levels decreased w/i 4 hrs of rasburicase
  2) Normalized uric acid levels maintained throughout chemo
  3) No increase in creatinine observed
  4) No patient required dialysis
- One European and one US study showed that rasburicase prophylaxis resulted in net savings in health care costs ($9,978 for 7 day stay VS. $51,990 for 21 day stay w/ HD)
Conclusions

• Pediatric oncology patients experience a broad variety of critical illnesses related to both disease and therapy.
• Long-term survival for many pediatric cancers is improving.
• ICU outcomes for this patient group is improving.
• Good ICU care can benefit children with malignancies.