Rasburicase Fixed Dosing Recommendations
Clinical Initiative

Recommendations
1. It is recommended to implement fixed dosing of rasburicase.
2. Results clinical studies indicate no difference in safety and efficacy for single fixed dosing compared to weight-based multiday dosing.
3. In an analysis from January to December 2015, Centura spent $86,000 on rasburicase. Rasburicase purchases by hospital is as follows:
   a. Littleton ($1200)
   b. Mercy ($5300)
   c. Penrose ($52,000)
   d. Porter ($5800)
   e. St. Anthony ($14,000)
   f. St. Anthony North ($3500)
   g. St. Catherine ($3300)
4. If 50% of the patients are not utilizing fixed dosing, then approximately $29,000 annually could be saved by using this strategy systematically.

Background
Tumor Lysis Syndrome (TLS) is an oncologic emergency characterized by electrolyte and metabolic disturbances, which may lead to renal dysfunction, cardiac dysrhythmias, seizures, prolonged hospitalization, and the need for renal replacement therapy. TLS occurs spontaneously due to lysis of malignant cells when treated with radiation or chemotherapy and results in cellular by-products accumulating in the kidneys leading to impaired function. TLS requires prompt recognition by healthcare providers and aggressive management. TLS can occur independently of anticancer treatment in cancers with a high cell turnover rate. Hallmark symptoms of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

The key to prevention and management of TLS includes awareness of predisposing factors, implementation of appropriate prophylactic measures, vigilant monitoring of electrolytes in patients at risk for TLS, and prompt initiation of active treatment when necessary.

Historically, risk stratification systems had been developed, but they each addressed different entities, criteria, and thresholds and could not be uniformly applied to all patients at risk. An international panel met in 2008 to address this unmet need. (Cairo 2010) The following risk stratification system was developed:

Patients are stratified based on the following three criteria:

- Laboratory TLS (LTLS) defined as elevation in two of following three lab values:
  - Elevated uric acid ≥ 8 mg/dL or 25% or more increase from baseline
  - Potassium ≥ 6 mEq/L or 25% or more increase from baseline
  - Phosphate ≥ 6.5 mg/dL or 25% or more increase from baseline
- Disease type (hematological vs solid tumor, age, stage, bulk disease, WBC, LDH)
- Renal function
Prevention and management strategies for TLS include IV hydration, allopurinol (for prophylaxis) and rasburicase. (Coiffier 2008, Darmon 2010). This review will focus on rasburicase therapy. Rasburicase is a recombinant urate oxidase enzyme produced by a genetically modified *Saccharomyces cerevisiae* strain. It directly breaks down uric acid into its water-soluble metabolite, allantoin, and hydrogen peroxide. Rasburicase is contraindicated in patients with a G6PD deficiency because G6PD is needed to breakdown the peroxide, which can lead to oxidative damage, hemolytic anemia, and methemoglobinemia. G6PD screening should be performed prior to considering rasburicase therapy.

The FDA-approved dosing is 0.2 mg/kg IV once daily for up to 5 days, draw serum uric acid 4 hours post administration of rasburicase and then every 6-8 hours thereafter until resolution of TLS. However, studies have shown that single dose therapy (unlabeled) is efficacious (see Table 1). This dosing is 3-7.5 mg single fixed dose IV one time, draw serum urate every 4-12 hours; second dose to be administered if patient does not have adequate response (normalization of uric acid levels) within 72 hours.

A recent retrospective review suggested tailoring fixed dosing based on uric acid level. Patients with UA greater than 15 mg/dL should receive an initial rasburicase dose of 6 mg; while patients with UA less than 15 mg/dL receive an initial rasburicase dose of 3 mg. See algorithm below. (Herrington 2015) This study and other studies support the single fixed dose treatment recommendations for this initiative.

**Data**

Table 1. Clinical trial and case report summary supporting single-dose therapy and fixed dosing

<table>
<thead>
<tr>
<th>Study design</th>
<th>No. of patients</th>
<th>Malignancy</th>
<th>Rasburicase regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective chart review</td>
<td>11 (adults)</td>
<td>AML, MM, other, lung</td>
<td>6 mg/day x1</td>
<td>12 pts required 1 dose, 1 pt required additional dose</td>
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<tr>
<td>(Hutcherson 2006)</td>
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<tr>
<td>Retrospective chart review</td>
<td>43 (adults)</td>
<td>Plasma cell dyscrasias, NHL, AML, CLL, MDS</td>
<td>3 mg/day</td>
<td>37 pts required 1 dose, 6 pts required 1 additional dose</td>
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<td>(Trifilio 2006)</td>
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<tr>
<td>Retrospective chart review</td>
<td>11 (adults)</td>
<td>NHL, AML, CML, ALL, MDS, Burkitt’s</td>
<td>6 mg x1</td>
<td>UA normalized in 10 pts after 1 dose, 1 pt required additional dose</td>
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<td>(McDonnell 2006)</td>
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<tr>
<td>Retrospective chart review</td>
<td>34 (adults)</td>
<td>AML, ALL, NHL, MM, HD, solid tumor</td>
<td>6 mg x 1</td>
<td>UA normalized to less than 4 mg/dL by day 3, 2 pts required repeat dose</td>
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<td>(Vines 2010)</td>
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<tr>
<td>Retrospective chart review</td>
<td>373 (adults)</td>
<td>Hematologic (AML, lymphoma, MM) or solid tumor</td>
<td>3 mg x 1 (n=38) 6 mg x 1 (n=99) 7.5 mg x 1 (n=43) Wt-based (median 0.16 mg/kg) x 1 (n=193)</td>
<td>UA reported on 319 patients – UA normalized in 313 patients within 24 hours. No statistical significant difference across doses. Study concluded that 6 mg may be most appropriate single dose.</td>
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<td>(McBride 2013)</td>
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Retrospective chart review (Clemmons 2014) 151 (normal, overweight, obese: n=47, 47, 57 respectively) Leukemia, lymphoma, MM, other 1.5 mg (n=1) 3 mg (n=31) 4.5 mg (n=3) 6 mg (n=116) Of 151 patient, 12 required 2nd dose – percentage was not significantly higher in obese/overweight arms. Fixed dosing appropriate in obese patients.

Retrospective chart review (Herrington 2015) 45 patients (adult) (obese evaluated in subset analysis) Acute and chronic leukemia, NHL, HD, MM, other 1.5 mg (n=6) 3 mg (n=26) 4.5 mg (n=1) 6 mg (n=12) UA normalized to less than 8 mg/dL in 80% of patients. Five patients required repeat dose. Greater reduction in UA seen with higher doses of rasburicase. No difference in UA reduction between obese and non-obese.

*This study dosed patients on IBW and if greater than 30% over their IBW, patients were dosed on adjusted body weight.

Chart Review
Compared to other Centura hospitals, Penrose Hospitals have the highest utilization of rasburicase. A chart review of 11 patients treated with rasburicase from January to August 2015 was conducted at Penrose hospital. Five out of eleven patients used the fixed 3 mg dose. Repeat dosing was not required for these patients. Of the other six patients, the average rasburicase dose was 9 mg. None of these patients had a uric acid level over 15 mg/dL.

Table 2. Dosing

| Non-obese adult and Obese adult with uric acid \( \leq 15 \) mg/dL | RASBURICASE 3 MG IV IN 50 ML NS OVER 30 MIN ONCE | PRIOR TO ORDERING EACH REPEAT DOSE OF RASBURICASE, A URIC ACID LEVEL SHOULD BE EVALUATED. REORDER STAT URIC ACID 12 HOURS AFTER THE RASBURICASE DOSE THEN DAILY UNTIL WBC WNL | MAY REPEAT RASBURICASE 3 MG DOSE IN 24 HOURS IF URIC ACID LEVEL OVER 8 MG/DL. Pharmacist must verify plasma uric acid results prior to preparation of each dose of rasburicase. |
| Obese adult (\( >20\% \) over IBW) with uric acid level \( >15 \) mg/dL | RASBURICASE 6MG IV IN 50 ML NS OVER 30 MIN ONCE |  | |
| Child | Pediatric dosing differs from adult (0.05-0.2mg/kg/dose daily for 1-7 days, depending on risk) refer to product literature for more detailed information. It is recommended to consult with a Pediatric Hem/Onc specialist from Helen DeVos Children’s Hospital prior to ordering |  | |

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Reviewed by: Julie Prince, PharmD, BCPS (Centura Health)
Version date: January 2016
Algorithm

<table>
<thead>
<tr>
<th>Low-Risk Features</th>
<th>High-Risk Features</th>
</tr>
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<tbody>
<tr>
<td>• Normal serum creatinine</td>
<td>• Elevated serum creatinine (≥ 1.5 mg/dL)</td>
</tr>
<tr>
<td>• Uric acid &lt; 10 mg/dL</td>
<td>• Uric acid ≥ 10 mg/dL</td>
</tr>
<tr>
<td>• White blood count &lt; 50,000/mm³</td>
<td>• White blood count ≥ 50,000/mm³</td>
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<tr>
<td>• LDH &lt; 500 IU/L</td>
<td>• LDH ≥ 500 IU/L</td>
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Allopurinol 300 mg PO daily
Preferably start several days before chemo
IV hydration

Check uric acid, potassium, phosphate, and calcium levels at least every 12-24 hours.

Start ASAP
• Allopurinol 300 mg PO BID x 2-3 days, then 300 mg per day
• Aggressive IV hydration (~2500 mL/m²/day)

When to use rasburicase?
• If patient’s uric acid level elevated:
  • rasburicase 3 mg IV x 1 if uric acid < 15 mg/dL
  • rasburicase 6 mg IV x 1 if uric acid ≥ 15 mg/dL
• May use prophylactically (1.5 - 3 mg) if patient meets all of above criteria without elevated uric acid or patient has Burkitt lymphoma

Check uric acid (ensure sample is placed on ice), potassium, phosphate, and calcium levels at least every 8-12 hours.

• If uric acid level is still elevated, repeat rasburicase dose until uric acid < 9 mg/dL
• If uric acid level is normal, DC rasburicase and continue with allopurinol therapy

Table 3. Pricing

<table>
<thead>
<tr>
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<th>Price/Vial</th>
<th>3 mg Price</th>
<th>6 mg Price</th>
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<tbody>
<tr>
<td>ELITEK 1.5 MG VIAL</td>
<td>$692.92</td>
<td>$1,385.85</td>
<td>$2,771.69</td>
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<tr>
<td>ELITEK 7.5 MG VIAL</td>
<td>$3,464.69</td>
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</tbody>
</table>
References


Trifilio S et al. Reduced dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia. Bone Marrow Transplant 2006; 37: 997-1001.


