Rescue Therapies for AKI in Onco-Nephrology
Rasburicase and Glucarpidase

Sheron Latcha, MD FASN
Clinical Member and Attending, Memorial Sloan Kettering Cancer Center
Associate Professor of Clinical Medicine, Weill Cornell Medical College
Program Director, Onco-Nephrology Fellowship
latchas@mskcc.org
Bio Slide
Sheron Latcha, MD

SUNY Stony Brook Medical School
Medicine Residency @North Shore University Hospital
Memorial Sloan Kettering Cancer Center
Nephrology Fellowship @ North Shore University Hospital
Clinical Member, Memorial Sloan Kettering Cancer Center
Attending Physician, Memorial Hospital for Cancer and Allied Diseases
  • Clinical focus: Onco-Nephrology
Disclosures

• I have no financial disclosures
Objectives:

- Rasburicase (TLS)
- Glucarpidase (HD MTX ≥500mg/m²)

- Case based discussion
  - Etiopathogenesis of TLS and HD MTX toxicity
  - Are these “antidotes” targeting the appropriate pathogenetic moiety
  - Quality of evidence forming the basis of these guidelines
Case 1:

- 55YOF, newly diagnosed NK T-cell lymphoma
  - Transfer OSH
  - ICU septic/hypovolemic shock, intubated, pressor requiring, bacterial and fungal PNA, EF 40% (1 month)

- MTX 3gm/m2 (Total: 5gm over 3H)

<table>
<thead>
<tr>
<th>Time (hours from MTX)</th>
<th>Serum Cr (mg/dl)</th>
<th>Serum MTx (µM/L)</th>
<th>WBC (K/mcl)</th>
<th>Leucovorin dose (mg)</th>
<th>Urine output ml/24H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.8</td>
<td>2.1</td>
<td>25 IV Q6H</td>
<td>2800</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.2</td>
<td>208</td>
<td>0.4</td>
<td>250 IV Q8H</td>
<td>1560</td>
</tr>
<tr>
<td>48</td>
<td>1.5</td>
<td>81</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Question 1:

Based on the current guideline for the treatment of HD MTX toxicity, the ICU team is requesting that you prescribe glucarpidase? Which of the following is supported by current data on glucarpidase?

- A) It will rapidly lower intracellular MTX levels
- B) It will rapidly lower serum MTX levels
- C) It lowers mortality from MTX toxicity
- D) It decreases the duration and severity of AKI

<table>
<thead>
<tr>
<th>Time (hours after HD MTx)</th>
<th>Serum level (µM/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 H</td>
<td>208</td>
</tr>
<tr>
<td>48 H</td>
<td>81</td>
</tr>
</tbody>
</table>

Adapted from Ramsey L et al, Oncologist 2017
MTX: Methotrexate
CH2THF: 5,10-Methylenetetrahydrofolate
DHFR: Dihydrofolate reductase
FPGS: Folylpolyglutamate synthase
SHMT1: Serine hydroxymethyltransferase 1
THF: Tetrahydrofolate
TYMS: Thymidylate synthase
Methotrexate Toxicity

- Intracellular toxicity
  - Bone marrow $\rightarrow$ prolonged neutropenia
  - GI epithelium: Mucositis/stomatitis $\rightarrow$ dehydration

- Renal toxicity $\rightarrow$ 70-90% of MTx clearance
  - Tubules
  - Afferent arteriolar constriction
  - Mesangial cell constriction
  - Liver $\rightarrow$ 5-10% of MTX elimination

Jacob SA et al JCI 1976
Garneau AP et al NEJM 2015
Widemann BC et al The Oncologist 2006
Skarby T et al Can Chemother Pharm 2003
Leucovorin Rescue

Mortality rate 6% → <1%

Von Hodd DD Cancer Treat Rep 1977
Cerminara Z Journal of Oncol Pharm Pract 2017
May J et al Leuk Lymphoma 2014
Wicer T et al J Oncol Pharm Practice 2016

Adapted from Ramsey L et al, Oncologist 2017
Glucarpidase

97% reduction in 15 minutes

Adapted from Ramsey L et al, Oncologist 2017
Glucarpidase: Cost

- $43,977.60 for 1000 unit vial
- 50 units/kg
- 70kg → 4 vials → $175,910.40
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients studied (#courses)</td>
<td>8</td>
<td>65</td>
<td>43</td>
<td>100</td>
<td>20</td>
<td>26</td>
<td>13</td>
<td>88 (100)</td>
</tr>
<tr>
<td>Median age yrs (range)</td>
<td>55 (27-61)</td>
<td>15 (1-72)</td>
<td>54 (18-78)</td>
<td>17 (1-82)</td>
<td>12 (4-20)</td>
<td>12 (4-20)</td>
<td>18 (8-80)</td>
<td>51 (9-90)</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective</td>
<td>Prospective, Nonrandomized</td>
<td>Prospective, Nonrandomized</td>
<td>Prospective, Glucarpidase + Leucovorin +/- thymidine for AKI</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Entry criteria MTx (µmol/L)</td>
<td>MTX 36H≥10 or 42H ≥5 or 48H≥3 or Cr ≥1.5 or oliguria</td>
<td>MTX 36H≥10 or 42H ≥5 or 48H≥3 and Cr ≥1.5 or oliguria</td>
<td>MTX 42H ≥5 or Cr ≥1.5 or and/oliguria at 42H and MTX ≥1 at 42H or 48H&gt;0.4</td>
<td>MTX 42H ≥10 or Cr ≥1.5 orCrCl ≤60 and/oliguria and MTX at 12H ≥2 SD above mean</td>
<td>MTX 24H≥50 or 42H ≥10 and Cr ≥1.5</td>
<td>MTX 24H≥50 and 42H ≥10 and Cr ≥1.5</td>
<td>MTX 24H≥10; 48H ≥10 and 72H ≥1</td>
<td>MTX 48H≥10 and/or 72H≥1</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>&gt;1 dose glucarpidase (%)</td>
<td>12 (0.5-901)</td>
<td>5.1 (0.4-166)</td>
<td>17 (0.4-849)</td>
<td>20 (1.3-591)</td>
<td>39 (1.3-591)</td>
<td>24H:164 (102-940); 48H 16 (10.5-190); 72H 6 (1.4-39)</td>
<td>24H 69 (2.2-40); 48H 6.9 (1.3-64); 72H 2 (0.05-26)</td>
</tr>
<tr>
<td>Median MTX serum level µmol/L (range)</td>
<td>11.8 (6.4-138)</td>
<td>12 (0.5-901)</td>
<td>5.1 (0.4-166)</td>
<td>17 (0.4-849)</td>
<td>20 (1.3-591)</td>
<td>39 (1.3-591)</td>
<td>24H:164 (102-940); 48H 16 (10.5-190); 72H 6 (1.4-39)</td>
<td>24H 69 (2.2-40); 48H 6.9 (1.3-64); 72H 2 (0.05-26)</td>
</tr>
<tr>
<td>AKI number (%)</td>
<td>7 (88%)</td>
<td>34 (82%)</td>
<td>43 (98%)</td>
<td>Not reported</td>
<td>20 (100%)</td>
<td>12 (92%)</td>
<td>Cr ≥ 2x 50 (50%)</td>
<td></td>
</tr>
<tr>
<td>Median time to renal recovery (D)</td>
<td>(12-36)</td>
<td>22 (5-77)</td>
<td>21 (7-56)</td>
<td>18 (2.54)</td>
<td>(0-25)</td>
<td>Number of days SCr ≥1.5: 7 (0-43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (myelosuppression/sepsis)</td>
<td>0</td>
<td>5 (6%)</td>
<td>10 (23%)</td>
<td>6 (6%)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Flombaum C et al, Pharmacotherapy 2019
Glucarpidase and the Kidney

Figure 4. Concentrations of MTX and SCr in a patient enrolled on the Nordic Society of Paediatric Haematology and Oncology acute lymphoblastic leukemia 2008 protocol treated with glucarpidase following a 5 g/m² dose of MTX over 24 hours.

Adapted from Ramsey et al, The Oncologist 2017
Glucarpidase and the Kidney

- FPIA (Fluorescence polarization immunoassay)
  - MTX + DAMPA + other metabolites
- HPLC: MTX
  - Need to coordinate with laboratory
- LV is a substrate for glucarpidase
  - Wait 2H after glucarpidase
  - Administer for at least 48H after glucarpidase (MTx rebound)

Adapted from Ramsey et al, The Oncologist 2017
Repeated Glucarpidase doses: Antibodies, Rebound and AKI

• Glucarpidase prophylaxis study
  • Phase 1, 8 patients
  • HD MTX
    • Q2W, up to 8 cycles
    • Glucarpidase 24H later

• 4/8 developed antibodies

• 24H MTx reduction percent
  • Ab+ 77%; Ab- 95%
  • In 3 of 4 with Abs → rebound increase in serum MTX ≥50%

• 2 AKIs due to rebound MTX

Schaff L et al, BMC Cancer 2022
Glucarpidase – cutting costs:

- $43,977.60 per 1000unit vial
- 8 patients, CNS lymphoma
- Flat dose 2000U
  - → 95% reduction within 15 minutes in 33/34 doses (97.1%)
- Flat dose 1000U
  - → 95% reduction in 15/20 doses (75%)
Extracorporeal Treatment for Methotrexate Poisoning
Systematic Review and Recommendations from the EXTRIP Workgroup

Marc Channountie,1,2 Darren M. Roberts,3 David S. Goldfarb,4 Jesper Heldrup,5 Kurt Anseeuw,6 Tais F. Galvao,7 Thomas D. Nolfi,8 Robert S. Hoffman,9 Valery Lavergne,10 Paul Meyers,10 Sophie Gosselin,11 Tudor Botnaru,12 Karine Mardini,13 and David M. Wood14 for the EXTRIP workgroup*

Box 1. General recommendations of extracorporeal treatments in methotrexate poisoning

In patients with severe methotrexate poisoning receiving standard care treatments including folinic acid rescue therapy:

1) We suggest AGAINST performing extracorporeal treatments when glucarpidase is not administered (weak recommendation; very low–quality evidence) (median: 2; upper quartile: 5.25; disagreement index: 0.61)

2) We recommend AGAINST performing extracorporeal treatments when glucarpidase is administered (strong recommendation; very low–quality evidence) (median: 1; upper quartile: 3; disagreement index: 0.13)

3) We recommend AGAINST performing extracorporeal treatments instead of administering glucarpidase (strong recommendation; very low–quality evidence) (median: 1; upper quartile: 3; disagreement index: 0.29)
Case 2

• 78YOM
• Recent bx: DLBCL
• AKI – Ibuprofen for 4D PTA
• PE: 98% RA, BL LE edema

<table>
<thead>
<tr>
<th>Lab</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>9.1 mg/dL</td>
</tr>
<tr>
<td>Potassium</td>
<td>6.1 mEq/L</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>15.7 mg/dL</td>
</tr>
<tr>
<td>Phosphate</td>
<td>6.7 mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.5 mg/dL</td>
</tr>
<tr>
<td>Laboratory TLS (≥2 present)</td>
<td>Clinical TLS (≥1 present)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Uric acid ≥8 mg/dL, or 25% increase from baseline</td>
<td>Creatinine &gt;1.5 times the upper limit of normal</td>
</tr>
<tr>
<td>Potassium ≥6 mmol/L, or 25% increase from baseline</td>
<td>Cardiac arrhythmia/sudden death</td>
</tr>
<tr>
<td>Phosphorus ≥4.5 mg/dL (adults), or 25% increase from baseline</td>
<td>Seizure</td>
</tr>
<tr>
<td>Calcium &lt;7 mg/dL, or 25% decrease from baseline</td>
<td></td>
</tr>
</tbody>
</table>

TLS indicates tumor lysis syndrome.

Case 2:

- The oncology team diagnoses the patient with clinical TLS.
- Rasburicase 7.5mg, IV NS 200cc/hr
- UO 100 cc/hr. Cr unchanged. UA 3.4mg/dl
- Team requests dialysis
- What is your assessment and recommendation?
  - A) AKI is due to TLS but there is no indication for dialysis
  - B) AKI is due to TLS. You begin dialysis
  - C) AKI may be due to TLS. You recommend placement of a R PCN
Pathogenesis: Uric Acid Dependent Pathways

Cellular breakdown
- Hyperphosphataemia
- Purine metabolism
- Increased Ca-P product
- Hyperuricaemia

Release of inflammatory mediators
- Crystal-independent pathway
  - Vasocostriction
  - Impaired autoregulation
  - Decreased renal blood flow
  - Prooxidative
  - Proinflammatory

Crystal-dependent pathway
- Intratubular precipitation

Cossey L et al Sem Diag Path 2020
Shimada, M et al NDT 2009
Conger J et al J Clin Invest 1976
TLS and Uric Acid

PURINE CATABOLISM

HYPOXANTHINE

XANTHINE

Xanthine Oxidase

URIC ACID
(urinary excretion)*

ALOPURINOL

Urate Oxidase

ALLANTOIN
(urinary excretion)

Goldman S et al Blood 2001
In CHILDREN: When compared to standard therapy, urate oxidase:

Randomized Controlled Trial (1) → no difference in all-cause or TLS mortality or renal failure

Pooled results (3) Case Control Trials
→ significantly lower mortality due to TLS
→ no difference in all cause mortality

Pooled results (5) Case Control Trials
→ significant lower incidence of renal failure

Pooled results (3) Case Controlled Trials
→ higher frequency AE with urate oxidase
Uric Oxidase: AKI, Mortality

• Lopez-Olivio, M et al AKJD 2013
• Systemic review and meta-analysis – 1,261 adults
• 4 Randomized Controlled Trials
  • Primary outcome: normalization or change in UA levels
  • Secondary outcome: only 1 of 4 evaluated Cr
  • None evaluated mortality
  • 3 of 4 sponsored by pharmaceutical manufacturer of rasburicase
  • High level of bias (Cochrane Collaboration Risk of Bias tool)
  • No statically significant differences in cTLS in rasburicase vs. allopurinol groups
• 17 Observational studies
  • After rasburicase: UA ,TLS, Cr (few)
  • After rasburicase: 7.4% developed TLS; 4.4% AKI; 2.6% died
  • Most did not show any significant difference in Cr level before and after rasburicase
Rasburicase: Cost

- 0.2mg/kg/d for 5 days
- 1.5mg vial $1215.16; 7.5mg $6,075.82
- 70kg → $60,758.20
## Rasburicase: Single dosing regimens

### Efficacy and Cost

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Number Patients</th>
<th>Rasburicase Dose</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nauffal et al 2019</td>
<td>Retrospective cohort</td>
<td>92</td>
<td>6mg</td>
<td>95% $\rightarrow$ &lt;7.5mg/dl Non-responders had higher median baseline UA</td>
</tr>
<tr>
<td>Vines et al 2010</td>
<td>Retrospective cohort</td>
<td>34</td>
<td>6mg</td>
<td>Median UA 9.2 $\rightarrow$ 1.8 mg/dl by day 3 2 required repeat dosing before day 3</td>
</tr>
<tr>
<td>McDonnell et al 2006</td>
<td>Retrospective cohort</td>
<td>11</td>
<td>6mg</td>
<td>Median UA 11.7 mg/dl $\rightarrow$ 2 mg/dl by day 1</td>
</tr>
<tr>
<td>Kraus et al 2015</td>
<td>Retrospective cohort</td>
<td>108</td>
<td>6mg vs 3mg</td>
<td>No difference in % with UA &lt;8mg/dl after 24 and 48H</td>
</tr>
<tr>
<td>McBride et al 2013</td>
<td>Retrospective cohort</td>
<td>373</td>
<td>7.5mg vs 6mg vs 3mg vs 0.16mg/kg</td>
<td>No difference at 24H</td>
</tr>
<tr>
<td>Trifilio et al 2011</td>
<td>Retrospective cohort</td>
<td>247</td>
<td>3mg</td>
<td>Baseline UA predicted UA lowering 84% failure for baseline UA &gt;12mg/dl; 18% &lt;12mg/dl</td>
</tr>
<tr>
<td>Vadhan-Raj et al 2012</td>
<td>Randomized</td>
<td>80</td>
<td>0.15mg/kg (10.5mg)</td>
<td>Only small subset required second dose for UA &gt;7.5mg/dl</td>
</tr>
</tbody>
</table>
TLS and Uric Acid Independent Pathways of Injury

- Release of intranuclear histone
- Alterations in peritubular capillary shape and permeability, disruption of renal blood flow
Concluding remarks: Rasburicase and Glucarpidase

• Expensive/Financial toxicity
• No well-designed clinical trials powered to evaluate AKI, mortality
• More investigations into the pathogenesis of organ toxicity with TLS and HD MTX toxicity → targeted therapy