The Use of Glucarpidase in an Open-Label Treatment Protocol as Adjunctive Treatment for a Patient with Delayed Methotrexate Elimination

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BACKGROUND

Methotrexate (MTX)

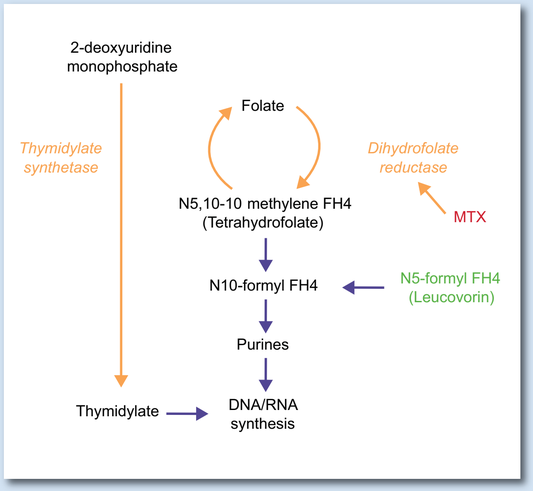
- Cytotoxic agent that competitively inhibits dihydrofolate reductase (DHFR), the intracellular enzyme responsible for converting folic acid to reduced folate inhibitors, necessary for DNA synthesis
- Used since 1948 in the treatment of various malignancies and as a disease-modifying agent in rheumatoid arthritis and psoriasis
- High-dose mexthotrexate (HDMTX) began in 1960s solely or in combination with other chemotherapeutic agents

Methotrexate Toxicity

- Almost exclusively cleared through the kidneys
  - Precipitation of drug occurs in the renal tubules
  - Prolonged elevations of systemic MTX concentrations results in potential serious toxicity
- Increased use of HDMTX resulted in recognizable toxicities
  - Myelosuppression
  - Mucositis
  - Nephrotoxicity
  - Acute hepatitis
  - Fatal toxicity → secondary to renal failure or sepsis

Prevention of Methotrexate Toxicity

- Hydration
- Alkalinization of urine
  - Sodium bicarbonate administration for urine pH ≥ 7
- Leucovorin
  - Counteracts cellular damage caused by MTX as it is converted to tetrahydrofolate, a precursor of DNA synthesis
  - Does NOT reduce the amount of circulating MTX



Glucarpidase (Voraxaze®)

- An enzyme produced in *Escherichia Coli* that hydrolyzes the carboxyl terminal glutamate from folic acid and its analogues, including MTX, resulting in inactive metabolites
- Offers an alternative to rapidly reducing the amount of MTX in systemic circulation
- Evaluated in 3 clinical studies → produced a clinically important reduction (CIR) in MTX concentrations in majority of patients (72/116, 62%)
  - Most frequently reported adverse events: allergic reaction and non-allergic paraesthesia

METHODS

- 56-year-old female with Non-Hodgkin's Lymphoma received HDMTX (1200 mg/m^2 bolus followed by 5520 mg/m^2 24-hr infusion) on September 16, 2011
  - Treatment resulted in delayed MTX elimination despite stable renal function

	METHOTREXATE LEVELS (microM/L)	
Hours	**Reference Range**	**Patient's Level***
24-hours	Up to 5	9.10
48-hours	Up to 0.5	1.70
72-hours	Up to 0.05	0.94

*Patient's levels correspond to approximate times (hours)

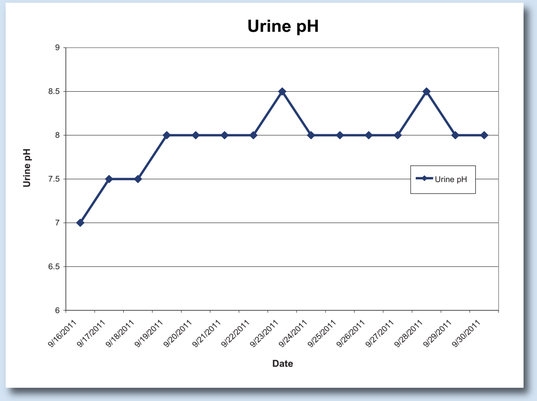
  - Maintained elevated serum MTX levels post 72-hours of drug administration

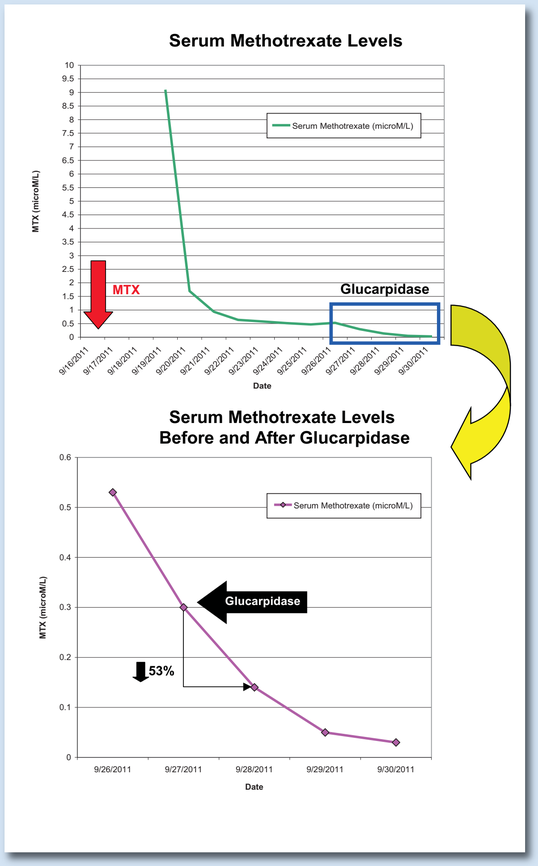
Compassionate Use of Glucarpidase

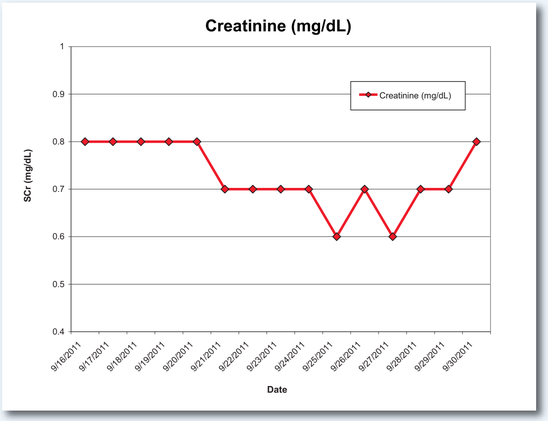
- Urgent approval obtained from the investigational review board under the drug manufacturer's open-label treatment protocol
  - Study protocol exemption request approved by drug manufacturer
- Obtained informed consent from patient
- Obtained medication from manufacturer; administered a single bolus dose of glucarpidase 3,000 units (50 units/kg) intravenously
- Concomitantly received intravenous leucovorin 150 mg q 3 hours and urinary alkalinization with oral and intravenous sodium bicarbonate
- Blood samples obtained, as required by manufacturer, for analysis of anti-glucarpidase antibodies

RESULTS

- Glucarpidase administered day-11 post MTX on September 27, 2011
- MTX levels decreased by 53% 24-hours following glucarpidase administration
  - Decreased from 0.30 microM/L to 0.14 microM/L
- 48-hour and 72-hour MTX levels following glucarpidase: 0.05 microM/L and 0.03 microM/L, respectively
- Intravenous leucovorin continued following glucarpidase
  - Dose decreased to 25 mg q 6 hours
- Patient denied any adverse events previously reported with glucarpidase







FDA Approval

- Glucarpidase (Voraxaze®) was FDA approved in January 2012 for the treatment of toxic plasma MTX concentrations (>1 microM/L) in patients with delayed MTX clearance secondary to impaired renal function
  - Use not indicated for patients with expected MTX elimination or those with normal/mildly impaired renal function

CONCLUSION

- Glucarpidase served as a safe and effective adjunctive treatment for this patient at risk of MTX toxicity
  - Rapidly reduced MTX serum concentrations, thereby preventing potential toxicity
- Despite patient's normal renal function, the use of glucarpidase may be a viable option for those with delayed MTX elimination
  - Further clinical evaluation in a larger population is required to determine efficacy in patients with a similar drug profile

Disclosures

- Cheryl A. Abbas: Nothing to disclose
- Anne Marie Valorie-Oberle: Nothing to disclose

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