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 methotrexate (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 result in potential serious toxicity
- Increased use of HDMTX resulted in recognizable toxicities
  - Myelosuppression
  - Nephrotoxicity
  - Acute hepatitis
  - Fatal toxicity → secondary to renal failure or sepsis

Prevention of Methotrexate Toxicity
- Hydration
- Alkalization 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
  - Sodium bicarbonate administration for urine pH ≥ 7
- Fatal toxicity
  - Mucositis
  - Precipitation of drug occurs in the renal tubules
- Fatal toxicity → secondary to renal failure or sepsis

METHODS

- 56-year-old female with Non-Hodgkin’s Lymphoma received HDMTX (1200 mg/m² bolus followed by 5520 mg/m² 24-hr infusion) on September 16, 2011
  - Treatment resulted in delayed MTX elimination despite stable renal function

RESULTS

- Concomitantly received intravenous leucovorin 150 mg q 3 hours
- Obtained medication from manufacturer; administered a single bolus dose of glucarpidase 3,000 units (50 units/kg) intravenously
- Obtained informed consent from patient
- Urgent approval obtained from the investigational review board
- 56-year-old female with Non-Hodgkin’s Lymphoma received HDMTX (1200 mg/m² bolus followed by 5520 mg/m² 24-hr infusion) on September 16, 2011
  - Treatment resulted in delayed MTX elimination despite stable renal function

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

REFERENCES
http://www.accessmedicine.com/content.aspx?bookid=74&chapterid=2551615

METHODS

- Glucarpidase (Voraxaze®) is an enzyme produced in Escherichia Coli that hydrolyzes the carbonyl 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.

RESULTS

- 56-year-old female with Non-Hodgkin’s Lymphoma received HDMTX (1200 mg/m² bolus followed by 5520 mg/m² 24-hr infusion) on September 16, 2011

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