Background
- Asparaginase (ASP) is an anticancer drug which is especially important for acute lymphoblastic leukemia (ALL).
- Its mechanism of action is to reduce levels of asparagine (ASN) by hydrolyzing it to aspartic acid and ammonia.
- Since leukemic cells do not synthesize adequate asparaginase, they rely on serum asparaginase for protein synthesis. Therefore, ASP selectively starves leukemia cells.
- There are currently three preparations of ASP available:
  - E. coli (Elspar™); PEG (Oncospar™); and Erwinia (Erwinase™).
- ASP pharmacokinetics are related to outcome:
  - Plasma concentrations > 0.7 IU/ml correlated to CR.
- Asparagine depletion is related to outcome:
  - Patients with >1 μM of CSF asparagine during treatment were more likely to have isolated CNS relapse later.
  - Relapse patients with <3 μM of day 14 asparagine were more likely to achieve 2nd CR.
- There are differences in ASN depletion due to formulation that can be explained by the model parameter VMAX.

Objective
- To assess the pharmacokinetics and pharmacodynamics of asparaginase using both descriptive and mechanistic models.
- To use simulations to compare the effects of asparaginase exposure and pharmacodynamics on asparagine depletion.

Patients and Methods
- Patients and Therapeutic Regimens
  - 38 patients enrolled on the St Jude R16 protocol for relapsed ALL.
  - Patients were randomly assigned during induction therapy to receive either:
    - Elspar (10,000 IU/m² thrice weekly for 12 doses over 26 days)
    - Oncospar (2,500 IU/m² weekly for 4 doses over 26 days)
  - Five patients who had a hypersensitivity reaction to these preparations were switched to Erwinase.

Pharmacokinetic/Pharmacodynamic Sampling
- ASP pharmacokinetic serum samples (4 to 6) were collected on days 8, 22, 29 of induction therapy.
- Serial pharmacodynamic samples of the following were collected on days 8, 22, 29, 37:
  - Plasma asparagine
  - CSF asparagine
  - anti-ASP antibodies
  - Toxicity data (hypersensitivity to ASP)

Results
- Plasma ASP pharmacokinetic serum samples (4 to 6) were collected on days 8, 22, 29, 37:
  - ASP pharmacokinetics
  - CSF asparagine
  - anti-ASP antibodies
  - Toxicity data (hypersensitivity to ASP)

Results (continued…)
- Patients receiving Elspar had a median VMAX comparing to those receiving Oncospar (p=0.02).
- This translated into greater asparagine depletion in patients who received Elspar compared to Oncospar.

Models of Asparaginase and Asparagine Pharmacokinetics and Pharmacodynamics in Pediatric Acute Lymphoblastic Leukemia

Poster #13

John C Panetta¹, Cheng Cheng¹, Wei Liu¹, Amar Gajjar¹, Nobuko Hiija¹, Ching-Hon Pui¹, Mary V Relling¹
¹St. Jude Children’s Research Hospital, Memphis, TN, USA

The Pharmacokinetic/Pharmacodynamic Model

Plasma ASN Model
- Kinetic estimates via NONMEM
- Pharmacokinetics were estimated in ADAPT 6
- (Fixed individual PK estimates)

CSF ASN Model
- Pharmacokinetics were estimated in NONMEM
- Intra-individual estimates via POSTHOC
- Pharmacodynamics were estimated in ADAPT 6

Steady-State Assumption

Results
- Patient Model Fit
- Simulations

Simulations
- Decrease kOUT by half
- Median % Change: -20%
- Two values of Km from literature
- Two values of kOUT from literature
- Increased ASP dose translates to increases in the time the ASN is depleted.

Conclusions
- There are significant pharmacokinetic differences within and between Elspar and PEG asparaginase.
- There are differences in ASN depletion due to formulation that can be explained by the model parameter VMAX.
- Increases in ASP dose translate to increases in the time the ASN is depleted.
- Increased ASP CL (due to AB+) will significantly decrease the time ASN is depleted.
- Model is more sensitive to changes in \(\text{VMAX} \) and \(k_\text{OUT} \).
- Model is less sensitive to changes in \(K_m \).

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E-mail: carl.panetta@stjude.org