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

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Poster #13

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 asparagine, they rely on serum asparagine 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 (Abshire et al., Blood 2000; Hawkins et al., Clin.Cancer Res. 2004)
- Asparagine depletion is related to outcome:
  - Patients with > 1 μmol/L of CSF asparagine during treatment were more likely to have isolated CNS relapse later (Avramis et al., Blood 2002: CCG-1962)
  - Relapse patients with <3 μmol/L day 14 asparagine were more likely to achieve 2nd CR (Hawkins et al., Clin.Cancer Res. 2004; Jarrar et al., Pediatr. Blood Cancer 2006: CCG-1941)

Objectives

- 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

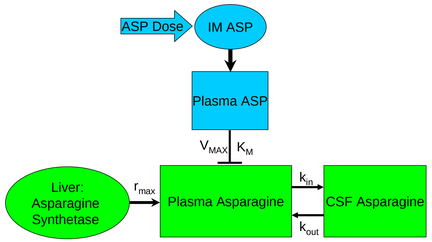
Patients and therapeutic regimens

- 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/m^2 thrice weekly for 12 doses over 26 days)
  - Oncospar (2,500 IU/m^2 weekly for 4 doses over 21 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 and 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)

The Pharmacokinetic/Pharmacodynamic Model



Plasma ASN Model

$$\frac{dASN}{dt} = r_{max}\left(1 - \frac{ASN}{ASN_0}\right) - \frac{k_{in}\,ASN}{K_{mCSF} \quad ASN} + k_{out}\,ASN_{CSF} - \frac{V_{max}\,ASP\,ASN^n}{K_m^n \quad ASN^n}$$

CSF ASN Model

$$\frac{dASN_{CSF}}{dt} = \frac{k_{in}\,ASN}{K_{mCSF} + ASN} - k_{out}\,ASN_{CSF}$$

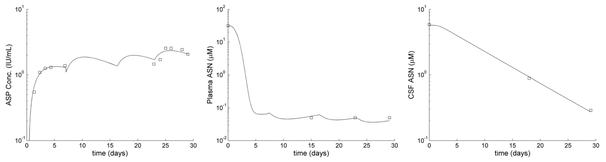
Steady-State Assumption

$$k_{out} = k_{in}\,\frac{ASN_0}{ASN_{CSF0}\,(K_{mCSF} + ASN_0)}$$

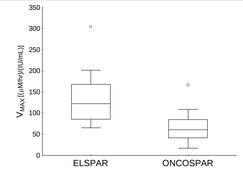
- Pharmacokinetics were estimated in NONMEM
  - Individual estimates via POSTHOC
- Pharmacodynamics were estimated in ADAPT II
  - (Fixed individual PK estimates)
- Simulations were performed using Matlab.
- Varied: ASP Dose; ASP Clearance; r_{max}; V_{MAX}; K_M; k_{in}
- Determined the time < 1μM CSF ASN

Results

Sample Model Fit

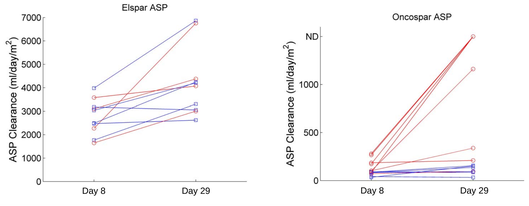


- Patients receiving Elspar had a higher V_{MAX} compared to those receiving Oncospar (p<0.02).
- This translated into greater asparagine depletion in patients who received Elspar compared to Oncospar (Avramis et al., Blood 2002; Appel et al., Leukemia 2003; Hak et al. Leukemia 2004)

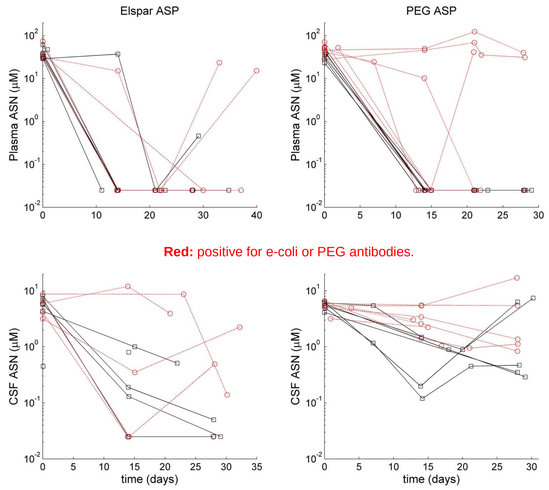


Results (continued…)

- Asparaginase Clearance is significantly higher for Elspar vs Oncospar (p=0.001)
- Asparaginase Clearance is significantly increased from Day 8 to Day 29 (p=0.002)
- Oncospar Clearance is significantly higher in patients with positive antibodies (red lines) for Oncospar (p=0.004)



- Patients who were positive for antibodies (at any point during therapy) had attenuated depletion of plasma and CSF asparagine compared to those who were negative for antibodies (p=0.01 and p=0.04 respectively)



Red: positive for e-coli or PEG antibodies.

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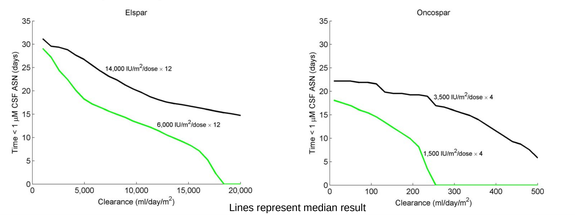
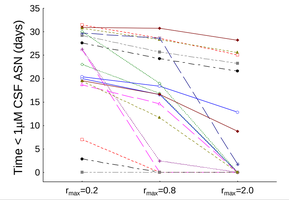
Simulations

- Effects of ASP exposure on CSF ASN
- Increased dose yields longer times above threshold
- Increased ASP CL (due to Ab+) yields shorter times above threshold

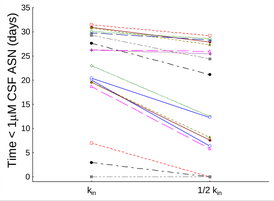


Lines represent median result

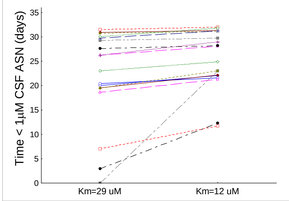
- Vary endogenous asparagine production: r_{max} (μM/hr)
- Range from Literature
  - ~ 0.06 to 6.0 μM/hr
- Median % Change from r_{max}=0.2 to:
  - r_{max}=0.8: -16%
  - r_{max}=2.0: -97%



- Decrease k_{in} by half
- Median % Change: -20%



- Two values of K_M from literature
- Median % Change: 7%



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 V_{MAX}.
- Increases in ASP dose translate to increases in the time ASN is depleted.
- Increased ASP CL (due to Ab+) can significantly decrease the time ASN is depleted.
- Model is more sensitive to changes in r_{max}, V_{MAX}, and k_{in}.
- Model is less sensitive to changes in K_M.

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