Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia

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Abstract

Over the last several decades, L-asparaginase, an important component of therapy for acute lymphoblastic leukemia (ALL), has typically been administered intramuscularly rather than intravenously (IV) in North America because of concerns regarding anaphylaxis. We evaluated the feasibility of giving PEG-asparaginase, the polyethylene glycol conjugate of E. coli L-asparaginase, by IV infusion in children with ALL. Between 2005-2007, 197 patients (age 1-17 years) were enrolled on DFCI ALL Consortium Protocol 05-01 and received a single dose of IV PEG-asparaginase (2,500 IU/m²) over 1 hour during Remission Induction. Serum asparaginase activity >0.1 IU/mL was detected in 95%, 88%, and 7% of patients at 11, 18, and 25 days after dosing, respectively. Toxicities included allergy (1.5%), venous thrombosis (2%), and pancreatitis (4.6%). We conclude that IV administration of PEG-asparaginase is tolerable in children with ALL and potentially therapeutic enzyme activity is maintained for at least two weeks after a single dose in most patients. This study is registered at http://clinicaltrials.gov as NCT00400946.

Introduction

Asparaginase is an important and universal component of therapy for childhood acute lymphoblastic leukemia (ALL). Since 1977, the Dana-Farber Cancer Institute (DFCI) ALL Consortium has included 20-30 consecutive weeks of asparaginase during post-induction consolidation therapy, and has demonstrated that this treatment significantly improves long-term event-free survival.1,2 Asparaginase preparations are bacterially-derived and, therefore, have the potential to be highly immunogenic. Hypersensitivity reactions to asparaginase occur in up to 30% of patients and are frequently associated with the development of neutralizing antibodies.3 Other asparaginase-associated toxicities include pancreatitis (in 5-10% of patients) and thrombosis (in 2-5% of patients).4,5 Patients who receive a truncated course of asparaginase because of intolerable side effects may have an inferior outcome compared with those who receive all intended doses.4

PEG-asparaginase, formed by covalently attaching polyethylene glycol to the native E. coli enzyme, was developed with the objective of reducing the immunogenic potential. When given intramuscularly (IM), PEG-asparaginase has a longer half-life and is associated with a lower rate of antibody formation than the native enzyme.6,7 All asparaginase preparations have typically been administered IM rather than intravenously (IV) in North America because of concerns about the risk of anaphylaxis. Considering that many pediatric patients have indwelling venous catheters, IV administration would be a more convenient and less painful option for dosing than IM injection. Published information pertaining to the clinical experience with IV PEG-asparaginase in pediatric patients is limited. In this report, we describe the toxicity and pharmacokinetics of a single dose of IV PEG-asparaginase given during Induction therapy to 197 children with newly diagnosed ALL.
Patients and Methods

Patients
Between May 2005 and May 2007, 197 evaluable patients between the ages of 1 and 18 years with newly diagnosed ALL were enrolled on DFCI ALL Consortium Protocol 05-01 (National Clinical Trial Reference Number 00400946: Pegasparaginase or Asparaginase and Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia). The Institutional Review Boards at each participating institution approved the protocol prior to patient enrollment. Informed consent was obtained from parents or guardians before starting therapy in accordance with the Declaration of Helsinki.

Treatment
Patients were classified as standard or high risk according to pretreatment criteria, as previously described. For all patients, Remission Induction commenced with 3-days of methylprednisolone followed by 28-days of multiagent therapy including weekly vincristine, daily prednisone (or methylprednisolone), two doses of doxorubicin, and low-dose methotrexate. On day 7, all patients received one dose of PEG-asparaginase (2,500 IU/m²) administered IV over one hour.

Toxicity
Toxicity data were collected prospectively. All toxicities were graded according to the NCI CTCAE version 3.0. All cases of thrombosis were radiographically confirmed. Because Grade 2 pancreatitis (episodes without surgical intervention or life-threatening consequences) can encompass a wide-range of clinical severity, we further classified these cases based on duration of clinical signs/symptoms: Mild/Moderate (<72 hours in duration) or Severe (≥72 hours).

Pharmacokinetic Studies
Serum was harvested from peripheral blood samples obtained prior to IV PEG-asparaginase and 4, 11, 18, and 25 days after its administration. Asparaginase activity was determined by a validated biochemical assay with a 0.025 IU/mL lower limit of quantitation as previously reported. A one-compartment open model with Michaelis-Menten elimination was fit to the mean serum asparaginase activity versus time data by nonlinear regression as previously described.

Statistical Analysis
Asparaginase activity data at the specified timepoints ±1 day were analyzed descriptively. Samples with enzyme activity <0.025 IU/mL were excluded from calculations of the mean and standard deviation. A mixed model for repeated measures adjusted for age, sex and leukocyte count at diagnosis was constructed to test for differences in the log-transformed asparaginase activity. P-values are two-sided with values <0.05 considered statistically significant.
Results and Discussion

Age at diagnosis ranged from 1 to 17 years (median 5 years). Eighty-seven percent had precursor B-cell phenotype and 13% T-ALL. Fifty-eight percent were classified as standard risk and 42% high risk.

Asparaginase activity was determined in serum samples obtained from 186 patients. Measurable serum asparaginase activity was observed in 96% of patients 18-days after a single dose of IV PEG-asparaginase (Table 1). In the adjusted mixed model, there were no statistically significant differences in serum asparaginase activity over time based upon age (p=0.11), sex (p=0.90) or WBC count at diagnosis (p=0.78).

The time course of the mean asparaginase activity is shown in Figure 1. The pronounced negative departure from log-linear decay of the enzymatic activity over time is characteristic of a saturable elimination process. A pharmacokinetic model with Michaelis-Menten elimination yielded an excellent fit of the mean serum asparaginase activity-time data, whereas a model with first-order monoexponential elimination did not describe the data particularly well. This is entirely consistent with the findings described in other pediatric studies of IV PEG-asparaginase.10,12 Moreover, there were no discernable differences between the time course of serum enzymatic activity following IV administration of IV PEG-asparaginase and that reported in other studies in which PEG-asparaginase was given by the IM route.6,7

Many investigators consider that continuously maintaining serum asparaginase activity >0.1-IU/mL is necessary for optimal serum asparagine depletion and therapeutic effectiveness.11 We observed that 88% of patients had serum asparaginase activity >0.1-IU/mL for 18-days after dosing, but only 7% maintained this level of activity after 25 days (Table 1). Other investigators have suggested that continuous exposure to a higher enzyme activity (i.e., >0.2-IU/mL) may be therapeutically beneficial.12 More than 90% of patients had an enzyme activity >0.2-IU/mL for 11 days after dosing and 52% had this level after 18 days. Thus, using either criterion, our findings suggest that a single 2,500 IU/m² dose of IV PEG-asparaginase is likely to provide therapeutically effective serum enzyme activity in most patients for two weeks and for some patients even longer.

The single dose of IV PEG-asparaginase was reasonably well-tolerated. The most common asparaginase-related toxicity was pancreatitis, observed in nine (4.5%) patients (one Grade 1, seven mild/moderate Grade 2 and one severe Grade 2). Pancreatitis developed 0-26 days after dosing (median 13 days). Four patients (2%) developed a thrombotic complication, including two in the CNS (diagnosed 18 and 25 days post-dose) and two non-CNS (14 and 25 days post-dose). There was one case of hypertriglyceridemia (Grade 4, 27 days post-dose) and no asparaginase-related deaths. These toxicity rates are similar to those reported for children with ALL after a single dose of IM PEG during remission induction.7 Asparaginase-related complications occurred in 6% of patients aged 1-10 years and 14% of those 10 years or older at diagnosis (p=0.13).
Hypersensitivity occurred in three patients (1.5%), all during the infusion. One episode was Grade 2 and two were Grade 3. It remains to be determined how IV administration affects antibody formation and allergy rates with re-exposure to asparaginase during subsequent treatment phases. We have previously reported that every 2-week IM PEG-asparaginase was associated with a lower rate of allergy compared with weekly IM E.coli asparaginase during a 30-week Consolidation phase.4

We conclude that the IV administration of PEG-asparaginase is feasible and well-tolerated in children with ALL. A therapeutically effective serum enzyme activity is maintained in nearly all patients for at least two weeks after a single dose of 2,500 IU/m². We are currently comparing the relative toxicity and efficacy of IV PEG-asparaginase (given every 2 weeks) and IM E. coli asparaginase (given weekly) for 30-weeks during the post-induction Consolidation phase of therapy.
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Authorship
Lewis B. Silverman: Designed research, performed research, analyzed and interpreted data, wrote manuscript
Jeffrey G. Supko: Contributed vital analytic tools, performed research, analyzed and interpreted data, wrote manuscript
Kristen E. Stevenson: Analyzed and interpreted data, performed statistical analyses
Christina Woodward: Collected data, edited manuscript
Lynda M. Vrooman, MD: Performed research, edited manuscript
Donna S. Neuberg: Analyzed and interpreted data, performed statistical analyses
Barbara L. Asselin: Performed research, edited manuscript
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Jane E. O’Brien: Collected data, edited manuscript
Harvey J. Cohen: Analyzed and interpreted data, edited manuscript
Stephen E. Sallan: Designed research, edited manuscript

Conflict of Interest Disclosure
Lewis B. Silverman: Received honoraria for speaking engagements from Enzon Pharmaceuticals.
Jeffrey G. Supko: Received research funding from Enzon Pharmaceuticals.
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References


Table 1. Serum asparaginase activity (IU/mL) after a single dose of PEG-asparaginase (2,500 IU/m²) given as a 1 hour IV infusion in children and adolescents with newly diagnosed ALL.

<table>
<thead>
<tr>
<th>Sample time (days)</th>
<th>No. of Patients</th>
<th>Serum asparaginase activity (IU/mL)</th>
<th>Percentage of patients with asparaginase activity (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (range)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>0.66 (&lt;0.025, 2.34)</td>
<td>0.73 ± 0.29</td>
</tr>
<tr>
<td>11</td>
<td>133</td>
<td>0.48 (&lt;0.025, 1.58)</td>
<td>0.49 ± 0.22</td>
</tr>
<tr>
<td>18</td>
<td>112</td>
<td>0.20 (&lt;0.025, 1.24)</td>
<td>0.23 ± 0.14</td>
</tr>
<tr>
<td>25</td>
<td>113</td>
<td>0.04 (&lt;0.025, 0.41)</td>
<td>0.07 ± 0.05</td>
</tr>
</tbody>
</table>
Figure 1. Time course of the mean serum asparaginase activity. Data points depicting the mean of the assayed values for samples collected from all patients at each time point are shown with one standard deviation error bars. The solid curve was generated by fitting the differential equation, $\frac{dA_s}{dt} = (I - CL \cdot A_s) / V$, to the mean serum asparaginase activity ($A_s$) versus time ($t$) data. The value of the drug input function ($I$) was defined as dose / infusion duration during drug administration and as 0 at all other times. $CL$ (total body clearance) = $V_m / (K_m + A_s)$, where $V_m$ and $K_m$ are the maximum metabolic capacity and Michaelis-Menten constant, respectively; $V$ is the apparent volume of distribution. Estimated values of the iterated parameters were: $V_m = 124$ IU/h/m$^2$; $K_m = 0.110$ IU/mL, $V = 2.79$ L/m$^2$. 
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