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PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTITHYMOCYTE GLOBULIN IN PEDIATRIC HEMATOPOIETIC STEM-CELL TRANSPLANT RECIPIENTS: PRELIMINARY ANALYSIS

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Introduction: Antithymocyte globulin (ATG) is increasingly being used in allogeneic hematopoietic stem-cell transplantation (HSCT) to prevent graft rejection mainly in the context of non-myeloablative regimens and post-engraftment therapy, and to prevent acute graft-versus-host disease (GVHD). Data on the pharmacokinetics and pharmacodynamics of ATG in pediatric HSCT are limited. The aim of this study was to describe ATG disposition in children undergoing HSCT and to explore associations between pharmacokinetic parameters and certain HSCT outcomes.

Methods: Rabbit ATG (Thymoglobulin®; Genzyme) was given at a dose of 2.5 mg/kg/day as a single daily dose for 3 days on day -3 to day -1. Blood samples for ATG concentration determination were obtained at 0, +1, +4, +7, +14, +28, +60, +75 and +100 days post-HSCT. ATG serum concentrations were analyzed using a validated immunoassay.

ATG pharmacokinetic parameters were estimated using a non-compartmental model (Phoenx WinNonlin 6.0.0.1648). The relationship between HSCT outcomes (acute GVHD, chronic GVHD, graft failure, EBV viremia, viral infection or viremia, post-transplant lymphoproliferative disease (PTLD) and overall survival) and pharmacokinetic parameters was explored.

Results: 17 patients (median age: 6.2 yr; range: 0.5-13 yr) participated. On average, 8 samples were obtained from each patient. Median time of follow-up was 13 months (range: 4 to 22 months). 2/15 children developed acute GVHD; 3/17 had engraftment failure; 4/13 had a viral infection or viremia and 3/17 developed PTLD. 14 were alive at the time of last follow-up. Large inter-patient variability was observed in pharmacokinetic parameters. (Table 1) Mean Cmax was significantly lower in children with acute GVHD (mean Cmax: 4.12 ± 0.968 vs 8.82 ± 2.645 mg/L; p = 0.0086). A trend toward a higher Cmax in children with viral infection/reactivation of any type was observed (8.79 ± 2.680 vs 5.62 ± 2.617 mg/L; p = 0.0546)

Conclusion: Large inter-patient variability in ATG pharmacokinetic disposition was observed in pediatric HSCT patients. The maximum ATG concentration after the third dose (Cmax) is inversely associated with acute GVHD. Data in a larger sample should be obtained to correlate ATG pharmacokinetic disposition with HSCT outcomes.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Elimination rate constant (hr⁻¹)</td>
<td>0.0039 ± 0.00141</td>
<td>0.0015 to 0.0068</td>
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<tr>
<td>Elimination half-life (hr)</td>
<td>204.9 ± 93.30</td>
<td>101.9 to 470.2</td>
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<tr>
<td>Maximum concentration (mg/L)</td>
<td>7.86 ± 2.979</td>
<td>3.43 to 13.62</td>
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<tr>
<td>Area under the curve (hr*mg/L)</td>
<td>1434 ± 740.8</td>
<td>419 to 2539</td>
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<tr>
<td>Clearance (L/hr)</td>
<td>0.044 ± 0.0254</td>
<td>0.011 to 0.103</td>
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<tr>
<td>Time to thymoglobulin concentration &lt; 0.01 mg/L (days)</td>
<td>96.2 ± 27.93</td>
<td>48.6 to 135.6</td>
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</table>

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OUTCOME USING NON-TBI CONDITIONING FOR 127 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTS IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBlastic LEUKEMIA

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Introduction: Total body irradiation (TBI) has been considered as the cornerstone of conditioning for hematopoietic stem cell transplantation (HSCT) in pediatric patients diagnosed with acute lymphoblastic leukemia (ALL). However, it involves important late effects such as growth delay, gonadal and thyroid dysfunction, cataracts and secondary cancers.

Material and Methods: We present our results of 127 transplants performed in 105 children with ALL in our unit with chemotherapy-based conditioning from 1996 to 2011. Median age was 7 years (range, 4 months-17 years). There were 91 male and 36 female. Disease status was 1st CR in 41, 2nd CR in 33 in 1st CR and 32 in 2nd CR. Stem cell source was mainly peripheral blood in 91 patients, 26 cord blood and in 10 patients was bone marrow. Donor was an identical sibling in 41, matched and mismatched unrelated donor in 54 and haploidentical in 32 cases. It was the second hematopoietic transplant for 32 patients. All conditioning regimens integrated oral or iv busulfan combined with cyclophosphamide from 1996 to 2003 and iv fludarabine/thiotepa since 2004 to 2011. Graft-versus-host disease prophylaxis consisted on cyclosporine ± methotrexate.

Results: With a median follow-up of 4 years, disease-free-survival (DFS) was 51.5%. The incidence of relapse was 18% and transplant-related mortality was 34%. Primary or secondary graft failure was 10%. In multivariate analysis of DFS the only prognostic factor was disease status at transplant (p<0.002). DFS according disease status was 72% ± 7% in 1st CR, 47% ± 7% in 2nd CR, 33% ± 8% in 3rd CR. Conclusion: Chemotherapy-based conditioning can be used in children with ALL, with similar outcome than using TBI and reducing long-term toxicity.