Pediatric Dose Determinations for the Phase I Study of the DOT1L Inhibitor, EPZ-5676, in MLL-r Acute Leukemia: Leveraging Early Clinical Data in Adults through Physiologically-Based Pharmacokinetic Modeling

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Abstract

Relapsed/refractory (R/R) MLL-r acute leukemia in children has a poor prognosis, with a reported 5 year overall survival for children less than one year of age with recurrent MLL-r leukemia being 4-20%. The MLL gene, on chromosome 11q23, codes for a histone methyltransferase (HMT) that is responsible for methylation of H3K4, a modification associated with active transcription. Translocations of MLL result in the loss of the SET or catalytic domain of the protein with the most common translocation partners, AF4, AF9, and ENL, recruiting another HMT, DSS1. The aberrant recruitment of DOT1L to MLL fusion target genes results in ectopic H3K79 methylation and increased expression of genes including HOMA and MEIS2, which are involved in leukemogenesis of MLL-rearranged leukemias. EPZ-5676 is a small molecule inhibitor of MLL with sub-nanomolar affinity and >100 fold selectivity over other HMTs. Preclinically, EPZ-5676 selectively inhibits intracellular histone H3K79 methylation, downstream target gene expression and demonstrated complete tumor regressions in an MLL rearranged leukemia xenograft model. The first in human phase I open label study in adult patients with R/R leukemia is ongoing (CT.gov: NCT01684150). Due to the unmet need of R/R leukemia in children, we leveraged early clinical data in adult patients to successfully guide dose selection and trial design for a companion pediatric study. Pediatric starting dose selection was informed using a physiologically-based PK (PBPK) modeling and simulation approach (Simcyp, [2]), such that the maturation and developmental aspects of various physiological and biochemical processes important in drug disposition were accounted for e.g. tissue blood flows, organ size, and drug metabolizing enzyme expression. In addition to pharmacokinetic data from adult patients across the dose range of 12–20 mg/m2/day administered as a continuous IV infusion (CIV), various in vitro data including physicochemical properties, plasma protein binding, blood partitioning, in vitro metabolic stability and P450 phenotyping were incorporated into the model. Dose proportional pharmacokinetics was observed in adult patients, with rapid attainment of steady-state plasma concentrations on Day 1 of CIV (ASH abstract, 2014). A successful model fit of the adult clinical exposures (n = 16) was achieved that adequately described the time-concentration profiles and PK parameters in terms of population mean and variability. The median clearance observed in adults was 6.00 L/h, and was well predicted using a permeability-limited liver model. System variables related to the pediatric population (organ size, blood flows, enzyme expression) were appropriately adjusted and simulations were performed at a fixed dose across various age groups from 0-18 years. The median clearance predicted in pediatric patients was 0.54, 0.80, 1.09, 1.90, and 4.21 L/h in 1-3 months, 3-6 months, 6 months-2 years, 2-6 years and 6 years-18 years, respectively. Based on simulations of the predicted steady-state systemic exposure of EPZ-5676 using these pediatric models, dose adjustments of 55%, 65%, 73%, 83% and 100% of the adult dose would be needed to achieve equivalent exposures in the respective age bands. For practical and safety purposes, this was further simplified in a conservative manner to derive a pediatric starting dose of 80% and 50% of the highest adult dose (90 mg/m2/day) in >12 month olds and <12 month olds respectively. This study demonstrates that prospective application of modeling and simulation tools, such as PBPK, can support clinical trial design in rare populations early in clinical development, as recently highlighted in FDA’s ‘Strategic Plan for Accelerating the Development of Therapies for Pediatric Rare Diseases.’ These modeling results provided dosing recommendations for the ongoing trial of EPZ-5676 in pediatric MLL-r R/R leukemia which is currently open and enrolling children ages 3 months to 18 years. (CT.gov: NCT02141828).

Results

Figure 2: Predicted mean total plasma concentration-time profiles of EPZ-5676 administered as a 24 mg/m2/d IV infusion across the age ranges

Table 3: Summary of the predicted clearance (CL) and dose across the age ranges with a targetCss of 300 ng/mL equivalent to that observed in adult at 20 mg/m2/day

<table>
<thead>
<tr>
<th>Age</th>
<th>Median CL (L/h/m2)</th>
<th>Adult CL (L/h)</th>
<th>% Adult CL</th>
<th>Median dose (mg/m2/d)</th>
<th>% Adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mo</td>
<td>1.54</td>
<td>6.00</td>
<td>25%</td>
<td>6.00</td>
<td>50%</td>
</tr>
<tr>
<td>3-6 y</td>
<td>2.03</td>
<td>6.00</td>
<td>34%</td>
<td>4.10</td>
<td>33%</td>
</tr>
<tr>
<td>6 mo - 2 y</td>
<td>2.03</td>
<td>6.00</td>
<td>34%</td>
<td>4.10</td>
<td>33%</td>
</tr>
<tr>
<td>2-6 y</td>
<td>2.46</td>
<td>6.00</td>
<td>41%</td>
<td>4.95</td>
<td>49%</td>
</tr>
<tr>
<td>6-12 y</td>
<td>2.46</td>
<td>6.00</td>
<td>41%</td>
<td>4.95</td>
<td>49%</td>
</tr>
</tbody>
</table>

Conclusions

- The time-concentration profiles of EPZ-5676 administered as an i.v. infusion at doses of 12–20 mg/m2/day in adult leukemia patients were well predicted by a permeability-limited liver uptake PBPK model, incorporating various drug-specific parameters related to the physicochemistry, in vitro ADME and cytochrome P450 isoforms involved in the clearance of EPZ-5676.
- This adult model was transformed to the pediatric setting based on age-dependent system-specific parameters such that the ontogeny of organ size, blood flows, P450 expression, plasma protein binding, molecular weight, hydrogen bond donors and acceptors, polar surface area and logP were appropriately adjusted.
- Simulations of the predicted steady-state systemic exposure of EPZ-5676 using these pediatric models demonstrated that dose adjustments of 55%, 65%, 73%, 83% and 100% of the adult dose would be needed to achieve equivalent exposures in the respective age bands. For practical and safety purposes, this was further simplified to derive a pediatric starting dose of 80% and 50% of the highest adult dose (90 mg/m2/day) in >12 month olds and <12 month olds respectively.
- This study demonstrates that prospective application of modeling and simulation tools, such as PBPK, can support clinical trial design in rare populations early in clinical development, and provided dosing recommendations for the ongoing trial of EPZ-5676 in pediatric MLL-r R/R leukemia which is currently open and enrolling children ages 3 months to 18 years (CT.gov: NCT02141828).

References