The Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibitor, OT–82, Exhibits In Vitro and In Vivo Efficacy Against Patient-Derived Xenograft Models of High-Risk Acute Lymphoblastic Leukemia

A Report from the Pediatric Preclinical Testing Consortium

Kathryn Evans1, Tara Pitchard1, Michelle J. Henderson1, Klaartje Somers1, Mawar Karsa1, Leanna Cheung1, Raymond Ying1, Stephen W Erickson2, Liubov Korotchkina3, Olga Chernova4, Andrei Gudkov2,4, Malcolm A. Smith5, and Richard B. Lons6

1Children’s Cancer Institute, Low Cancer Research Centre, UNSW Australia, Sydney, NSW, Australia; 2RTI International, Research Triangle Park, NC; 3Cemotaxis, Inc., Buffalo, NY, USA; 4Rosewell Park Cancer Institute, Buffalo, NY, USA; 5Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA

Abstract

#1942

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and although almost all children with ALL are cured, certain subgroups have significant clinical and biological heterogeneity. Alternatively, fractionation in the treatment of ALL has been shown to be associated with the development of drug resistance in patients with ALL. Therefore, the identification of novel therapeutic approaches to overcome the drug resistance in ALL is of significant clinical importance.

METHODS

In vitro drug sensitivity studies

Cell viability of all drug treatments was determined using the MTS proliferation assay evolution incubations with OT–82 (0-200 nM) in combination with AraC (0-200 nM) and the calculated GI50 values were analyzed. Cell viability was defined as the percentage of cell survival relative to the control.

RESULTS

OT–82 demonstrated in vitro efficacy against a diverse panel of pediatric ALL PDx

Figure 1. Survival of ALL PDx ALL-7, ALL-19, ALL-55, and ALL-56 after exposure to OT–82 and AraC. The PDx data are representative of 5 independent experiments. Data represent mean +/- SEM. *p < 0.05, **p < 0.01, ***p < 0.001.

Table 1. Survival of ALL PDx after exposure to OT–82 and AraC.

<table>
<thead>
<tr>
<th>PDx</th>
<th>OT–82 (nM)</th>
<th>AraC (nM)</th>
<th>AraC+OT–82 (nM)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-7</td>
<td>0</td>
<td>200</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>ALL-19</td>
<td>0</td>
<td>200</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>ALL-55</td>
<td>0</td>
<td>200</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>ALL-56</td>
<td>0</td>
<td>200</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>

SUMMARY OF FINDINGS

OT–82: a single agent demonstrated low nanomolar IC50 values in vitro with leukemia cell lines and significant anti-leukemia activity as a single agent against a diverse panel of pediatric ALL PDx, in vivo OT–82 treatment elicited objective responses in 2/5 (40%) of ALL PDx with pretreated hematopoiesis in 4/5 (80%).

REFERENCES


ACKNOWLEDGEMENTS

This research was supported by the National Cancer Institute (Grant No. CA204903). OT–82 was provided for testing by Decipheron, Children’s Cancer Institute is affiliated with the University of New South Wales and Sydney Children’s Hospital Network.

 mortar text