Treatment of refractory/relapsed adult acute lymphoblastic leukemia with bortezomib-based chemotherapy

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Abstract: Nine pretreated patients aged >19 years with relapsed/refractory acute lymphoblastic leukemia (ALL) were treated with a combination of bortezomib plus chemotherapy before allogeneic hematopoietic stem cell transplantation (allo-HSCT). Eight (88.9%) patients, including two Philadelphia chromosome-positive ALL patients, achieved a complete remission. Furthermore, the evaluable patients have benefited from allo-HSCT after response to this reinduction treatment. We conclude that bortezomib-based chemotherapy was highly effective for adults with refractory/relapsed ALL before allo-HSCT. Therefore, this regimen deserves a larger series within prospective trials to confirm these results.

Keywords: acute lymphoblastic leukemia, refractory, relapsed, bortezomib

Introduction
The prognosis in patients with refractory/relapsed adult acute lymphoblastic leukemia (ALL) is dismal. Currently, there is no standard salvage therapy for such patients and the only realistic strategy resides in getting another complete remission (CR) followed by a successful allogeneic hematopoietic stem cell transplantation (allo-HSCT),1–3 provided that the toxicity of the salvage regimen is acceptable. In the reinduction setting, the use of chemotherapeutic agents similar to those administered during initial induction chemotherapy may get CR, but the possibility of achieving a second CR is less than 50%.4 In addition, this regimen is limited, particularly in adults with refractory ALL. Treatment strategies to further improve the efficacy of antileukemic therapy are often based on the introduction of novel agents. Recently, Dewar et al5 reported that a patient diagnosed with refractory adult Philadelphia chromosome-positive (Ph+) ALL was treated successfully with a bortezomib-containing chemotherapy regimen. In addition, Hu et al6 obtained encouraging results in a relapsed adult T-cell acute lymphoblastic leukemia (T-ALL) by administration of bortezomib combined with chemotherapy. Thus far, no series has reported the use of bortezomib for the treatment of relapsed/refractory adult ALL. We report here the outcomes of nine such patients treated by a combination of bortezomib plus chemotherapy as part of a pilot study. Favorable responses were observed.

Case report
Between March 2008 and November 2010, a total of nine consecutive patients with refractory/relapsed adult ALL, including Ph+ ALL, were enrolled in this study at the Henan Institute of Haematology (Table 1). Informed consent was obtained from all patients and the study was approved by the Institutional Review Board at

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### Table 1: Characteristics of patients and outcomes after bortezomib-based therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Disease status at entry</th>
<th>Prior therapy</th>
<th>Bortezomib-based therapy</th>
<th>Number of cycles to get CR</th>
<th>HSCT</th>
<th>Relapse/progression</th>
<th>Status at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2nd relapse</td>
<td>GRAALL 2003 CR Hyper-CVAD PR</td>
<td>Bortezomib + Hyper-CVAD</td>
<td>1</td>
<td>Allo/MUD</td>
<td>Yes</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>Refractory</td>
<td>GRAAPH 2005 NR Hyper-CVAD PR</td>
<td>Bortezomib + Hyper-CVAD + Imatinib</td>
<td>1</td>
<td>Allo/Sib</td>
<td>No</td>
<td>Alive in CR1</td>
</tr>
<tr>
<td>3</td>
<td>Refractory</td>
<td>GRAALL 2003 NR</td>
<td>Bortezomib + Hyper-CVAD</td>
<td>1</td>
<td>Allo/MUD</td>
<td>Yes</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>Refractory</td>
<td>GRAAPH 2005 NR Hyper-CVAD + imatinib PR</td>
<td>Bortezomib + Hyper-CVAD + Imatinib</td>
<td>1</td>
<td>Allo/MUD</td>
<td>Yes</td>
<td>Dead</td>
</tr>
<tr>
<td>5</td>
<td>2nd relapse</td>
<td>GRAALL 2003 CR MA PR Hyper-CVAD CR</td>
<td>Bortezomib + MA</td>
<td>1</td>
<td>Allo/MUD</td>
<td>No</td>
<td>Alive in CR3</td>
</tr>
<tr>
<td>6</td>
<td>Refractory</td>
<td>GRAALL 2003 NR Hyper-CVAD PR</td>
<td>Bortezomib + Hyper-CVAD</td>
<td>2</td>
<td>Allo/Sib</td>
<td>No</td>
<td>Alive in CR3</td>
</tr>
<tr>
<td>7</td>
<td>2nd relapse</td>
<td>GRAALL 2003 CR Hyper-CVAD CR MA PR</td>
<td>Bortezomib + MA</td>
<td>1</td>
<td>Allo/Sib</td>
<td>Yes</td>
<td>Dead</td>
</tr>
<tr>
<td>8</td>
<td>2nd relapse</td>
<td>GRAALL 2003 CR Hyper-CVAD PR Clofarabine + ara-C CR</td>
<td>Bortezomib + Hyper-CVAD</td>
<td>2</td>
<td>Allo/MUD</td>
<td>No</td>
<td>Alive in CR3</td>
</tr>
<tr>
<td>9</td>
<td>Refractory</td>
<td>GRAALL 2003 NR Hyper-CVAD PR</td>
<td>Bortezomib + Hyper-CVAD</td>
<td>1</td>
<td>Allo/Sib</td>
<td>No</td>
<td>Alive in CR3</td>
</tr>
</tbody>
</table>

**Notes:** *This patient who failed to respond to the first course of salvage treatment gave up therapy and died later. Protocols: GRAALL 2003, Huguet et al.11 GRAAPH 2005, Chalandon et al.12 Hyper-CVAD, MA, Kantarjian et al.13 Abbreviations: ALL, acute lymphoblastic leukemia; Allo, myeloablative allogenic hematopoietic stem cell transplantation; B-ALL, B-cell acute lymphoblastic leukemia; CR, complete response; Der, derivation; GRAALL or GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia; HSCT, hematopoietic stem cell transplantation; Hyper-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MA, high-dose methotrexate and ara-C; MUD, matched unrelated donor; NR, no response; PR, poor response; t, translocation T-ALL, T-cell acute lymphoblastic leukemia.*
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activity. Recently, Hu et al reported that administration of bortezomib plus dexamethasone and liposomal doxorubicin to a heavily pretreated adult with relapsed ALL achieved another CR.

Our results suggest that the addition of bortezomib to conventional chemotherapy programs in adults with refractory/relapsed ALL is feasible and that the salvage treatment was generally well tolerated. Indeed, we can confidently conclude that CR achievement was due to the addition of bortezomib. All eight evaluable patients had refractory disease after receiving Hyper-CVAD-based or imatinib-based induction regimens, but they were all in CR after receiving the bortezomib + Hyper-CVAD, or bortezomib + Hyper-CVAD + imatinib, respectively, indicating the efficacy of bortezomib and a synergistic effect of the combination. Thus, the combined bortezomib-based reinduction therapy may be a promising salvage alternative for this population with a very poor prognosis as a springboard to allo-HSCT, the only potential curative intervention.

Furthermore, all eight eligible patients have benefited from allo-HSCT as consolidation after CR was assessed. However, the idea that bortezomib could overcome or reverse chemoresistance and increase sensitivity to conventional or targeted agents was not evaluated in this study. This could be a pivotal factor in selecting optimal patients who might respond to the combination of bortezomib plus conventional chemotherapy, and this should be addressed in future studies.

Conclusion
Reinduction with the bortezomib-based regimen followed by allo-HSCT may be a feasible approach for adults with refractory/relapsed ALL. Larger series within prospective trials are needed to evaluate this concept.

Author contributions
All authors designed the research, enrolled the study patients, supervised the study, collected clinical data, analyzed the data, and drafted and revised the manuscript.

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Disclosure
The authors declare no potential conflicts of interest in this work.

References