

# 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),<sup>1-3</sup> 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%.<sup>4</sup> 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 al<sup>5</sup> reported that a patient diagnosed with refractory adult Philadelphia chromosome-positive (Ph<sup>+</sup>) ALL was treated successfully with a bortezomib-containing chemotherapy regimen. In addition, Hu et al<sup>6</sup> 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<sup>+</sup> 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

Patients	Disease Age/sex Cytogenetics	Disease status at entry	Prior therapy	Bortezomib-based therapy	Number of cycles to get CR	HSCT	Relapse/progression	Status at last follow-up
1	B-ALL 37/male Der 14q32,t(1;19)	2nd relapse	GRAALL 2003 CR Hyper-CVAD PR	Bortezomib + Hyper-CVAD	1	Allo/MUD	Yes	Dead
2	B-ALL 29/female t(9;22)	Refractory	Clofarabine + cytarabine CR GRAAPH 2005 NR Hyper-CVAD PR	Bortezomib + Hyper-CVAD + Imatinib	1	Allo/Sib	No	Alive in CR1
3*	B-ALL 40/male t(8;14)	Refractory	GRAALL 2003 NR	Bortezomib + Hyper-CVAD				Dead
4	T-ALL 31/female t(9;22)	Refractory	GRAAPH 2005 NR Hyper-CVAD + imatinib PR	Bortezomib + Hyper-CVAD + Imatinib	1	Allo/MUD	Yes	Dead
5	B-ALL 35/male t(4;11)	2nd relapse	GRAALL 2003 CR MA PR	Bortezomib + MA	1	Allo/MUD	No	Alive in CR3
6	T-ALL 40/male Complex	Refractory	GRAALL 2003 NR Hyper-CVAD PR	Bortezomib + Hyper-CVAD	2	Allo/Sib	No	Alive in CR3
7	B-ALL 21/female Normal	2nd relapse	GRAALL 2003 CR Hyper-CVAD CR MA PR	Bortezomib + MA	1	Allo/Sib	Yes	Dead
8	T-ALL 27/male t(1;14)	2nd relapse	GRAALL 2003 CR Hyper-CVAD PR	Bortezomib + Hyper-CVAD	2	Allo/MUD	No	Alive in CR3
9	B-ALL 33/male Normal	Refractory	Clofarabine + ara-C CR GRAALL 2003 NR Hyper-CVAD PR	Bortezomib + Hyper-CVAD	1	Allo/Sib	No	Alive in CR3

**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;<sup>17</sup> GRAAPH 2005, Chalandon et al;<sup>12</sup> Hyper-CVAD, MA, Kantarjian et al.<sup>13</sup>  
**Abbreviations:** ALL, acute lymphoblastic leukemia; Allo, myeloablative allogeneic 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.

Henan Tumor Hospital. Other eligibility criteria included a performance status of 2 or lower according to the Eastern Cooperative Oncology Group (ECOG), adequate hepatic and renal function, and adequate cardiac status.

As a salvage reinduction regimen, all patients received a bortezomib-based therapy at a median time of 6 months (range 1.9–13.5 months) after ALL diagnosis. Five patients received the bortezomib (1.3 mg/m<sup>2</sup>/day on days 1, 4, 8, and 11) + fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) regimen and two patients received the bortezomib (1.3 mg/m<sup>2</sup>/day on days 1, 4, 8, and 11) + (high-dose methotrexate and ara-C) regimen. The other two patients with refractory Ph<sup>+</sup> ALL were treated with bortezomib (1.3 mg/m<sup>2</sup>/day on days 1, 4, 8, and 11) + imatinib (400 mg/day) + Hyper-CVAD regimen. CR was defined as ≤5% lymphoblasts in a normocellular or hypercellular marrow with no evidence of circulating blasts or extramedullary disease, and with absolute neutrophil count  $1 \times 10^9$ /L and platelet count  $\geq 100 \times 10^9$ /L. Treatment-related toxicities were assessed and graded according to the National Cancer Institute Expanded Common Toxicity Criteria (version 3.0). After a salvage reinduction regimen, patients getting CR could receive one or more first consolidation courses, followed by allo-HSCT as soon as possible. After allo-HSCT, patients with refractory/relapsed Ph<sup>+</sup> ALL were maintained on dasatinib (70 mg twice a day). Patients who failed to obtain CR after two courses were taken off the study. A third-line regimen called FLAG-IDA was suggested for patients who failed to obtain CR after the salvage treatment and for those who relapsed after the salvage treatment and before allo-HSCT.<sup>7</sup> Overall survival (OS) was calculated from the beginning of salvage therapy to the date of the last follow-up or death for survivors, whatever the cause, while disease-free survival (DFS) was calculated from CR until relapse, death from any cause, or the last contact for survivors. Probability of OS rate was estimated according to the Kaplan–Meier method.

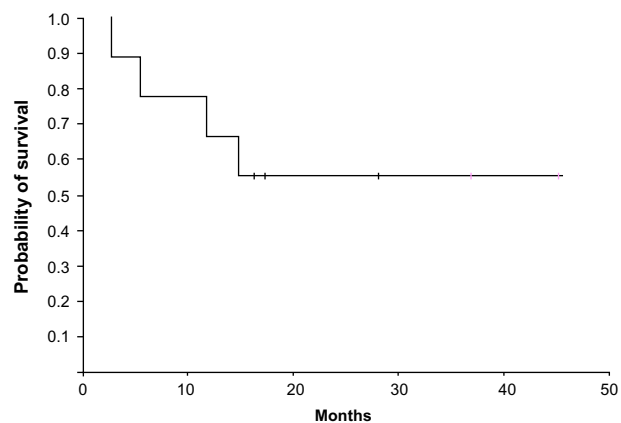
Table 1 shows the responses and outcome details of therapy. Patient 3, who failed to respond to the first course of salvage treatment, gave up therapy and died 1.7 months after stopping treatment. The other eight patients achieved CR after 1–2 courses of bortezomib-containing chemotherapy. Then, after receiving one or more first consolidation courses, all underwent an allo-HSCT. At the time of the last follow-up, three of eight eligible patients who had achieved CR died of leukemia relapse (at 4.2, 10.6, and 13.8 months, respectively), while the other five patients were still alive and in CR at 15.1, 16.3, 35.8, and 44.3 months, respectively. The median DFS was 15.7 months (range 8.1–44.3 months) and the median OS was 16.4 months

(range 2.7–45.4 months). Two-year OS rate was 56.4 months (95% CI 8.9–30.7 months) (Figure 1). The combination of bortezomib plus chemotherapy was well tolerated. No patient discontinued therapy because of toxicity and there was no treatment-related mortality. All patients experienced grade 3–4 anemia, neutropenia, and thrombocytopenia. The median time to reach absolute neutrophil count  $>0.5 \times 10^9$ /L was 19 days (range 15–24 days) from the start of chemotherapy. Platelet count  $>20 \times 10^9$ /L was achieved in a median time of 21 days (range 18–26 days). The most common grade 1–2 nonhematologic toxicities in the study included constipation (50%), vomiting (100%), fatigue (100%), diarrhea (37.5%), and skin rashes (12.5%). In addition, Grade 1–2 peripheral neuropathy and grade 3 pulmonary infections occurred in one (12.5%) and four (50%) patients, respectively.

## Discussion

Treatment of refractory/relapsed adult ALL, including Ph<sup>+</sup> ALL, represents a considerable clinical challenge. These patients are often refractory to currently available treatment options, and the alternative salvage therapeutic approaches remain elusive.

Single-agent bortezomib was studied in adults with refractory/relapsed acute leukemia and found to be ineffective in controlling disease progression,<sup>8</sup> but the results from a combination trial have suggested bortezomib is a rational strategy to overcome chemoresistance and induce chemosensitization. Attar et al<sup>9</sup> reported that the treatment of bortezomib plus cytarabine and idarubicin in patients with relapsed acute myeloid leukemia showed encouraging activity, and that the regimen had also been well tolerated. In addition, in patients with fludarabine-refractory chronic lymphocytic leukemia, single-agent bortezomib demonstrated biologic



**Figure 1** Overall survival in nine patients with refractory/relapsed adult acute lymphoblastic leukemia treated with bortezomib-based therapy.

activity.<sup>10</sup> Recently, Hu et al<sup>6</sup> 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.

## Acknowledgments

The authors would like to thank all patients for their cooperation. This study was supported by grants from the

National Natural Science Foundation of China (Number 30900637) and the National Natural Science Foundation of China (Number 81370661).

## Disclosure

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

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