Published in final edited form as:
Clin Lymphoma Myeloma Leuk. 2012 June ; 12(3): 197–200. doi:10.1016/j.clml.2012.03.004.

Phase I-II Study of Bendamustine in Patients With Acute Leukemia and High Risk Myelodysplastic Syndrome

Christelle Chacar, **Elias Jabbour**, **Farhad Ravandi**, **Gautam Borthakur**, **Tapan Kadia**, **Zeev Estrov**, **Mary Beth Rios**, **Jorge Cortes**, and **Hagop Kantarjian**
The Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

A phase I-II study of bendamustine fractionated twice daily schedule for 4 days identified 75 mg/m^2 intravenously (IV) twice daily for 4 days as a phase II study schedule.

Background—Alkylating agents have shown activity in leukemia. Bendamustine, an active alkylating agent in lymphoma and chronic lymphocytic leukemia, was given in a fractionated twice daily schedule for 4 days to patients with acute leukemia and myelodysplastic syndrome (MDS) to define the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD).

Patients and Methods—Adults with refractory acute leukemia or high-risk MDS were treated with bendamustine at a starting dose of 50 mg/m^2 IV over 1-2 hours twice daily for 4 days. Dose escalations were by 25 mg/m^2 in the 1st 3 levels. The study used the 3 + 3 design.

Results—A total of 25 patients were treated. Their median age was 57 years; the median salvage number was 3. Grade 2 creatinine elevations were observed in 1 of 6 patients at the 50 mg/m^2 dose, in 2 of 13 patients at the 75 mg/m^2 dose, and in 3 of 6 patients at the 100 mg/m^2 dose. This was considered significant, even though DLT was not reached. One patient achieved marrow complete remission. Significant reductions of marrow blasts (50% or more) were observed in 6 of 25 patients (24%).

Conclusion—Bendamustine fractionated dose level of 100 mg/m^2 IV twice daily for 4 days (800 mg/m^2 per course) was associated with Grade 2 renal toxicity. The proposed phase II schedule is 75 mg/m^2 IV twice daily for 4 days. Future studies should evaluate this schedule in less heavily treated patients.

Keywords

Fractionated dose schedule

Address for correspondence: Hagop Kantarjian, MD, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Leukemia Department, Unit 428, Houston, TX 77030 Fax: 713-792-2031; hkantarj@mdanderson.org.

Introduction

With current modern intensive chemotherapy regimens, the complete response (CR) rate in adults with acute myeloid leukemia (AML) is 60%-70%, and the cure rate is approximately 20%-30%.[1] In adult acute lymphocytic leukemia (ALL), the CR rate is 90% and the cure rate 30%-50%.[2] In myelodysplastic syndrome (MDS), hypomethylating agents have improved survival, which however remains modest.[3] This indicates the need to develop and discover new treatments and strategies to improve the prognosis in acute leukemia and MDS.

Alkylating agents and nucleoside analogs are 2 classes of drugs that have provided us with many active agents in leukemia. Alkylating agents have included cyclophosphamide, chlorambucil, melphalan, busulfan, lomustine, and others.[4] Nucleoside analogs have included fludarabine, 2-chlordeoxyadenosine, clofarabine, nelarabine, cytarabine, decitabine, azacitidine, and others.[5-7]

Bendamustine is a rationally designed drug that incorporates properties of alkylating agents and a purine-like benzimidazole ring structure. Bendamustine has shown activity in preclinical model. Several clinical trials, initially in Germany, and later throughout the world, have demonstrated its efficacy in lymphoid malignancies including chronic lymphocytic leukemia (CLL) and lymphoma. Bendamustine is currently approved in the United States for the treatment of patients with CLL and for patients with indolent B-cell non-Hodgkin lymphoma whose disease has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[8-15] Bendamustine has been used at doses of 70-100 mg/m^2 daily for 2 days in CLL and lymphoma. Bendamustine was investigated in a small pilot trial in AML and high risk MDS using the dose schedule of 100 mg/m^2 daily for 2 days. Among 15 patients treated, no objective responses were observed. However, in 11 of 12 patients with initial leukocytosis, a significant reduction of blast counts was observed.[16] In the lymphoma studies, the maximum tolerated dose (MTD) was dose-limited by myelosuppression. In acute leukemia, many agents can be dose escalated up to 3-20 times the solid tumor dose before extramedullary toxicities (eg, organ dysfunctions) become dose-limiting toxicities (DLT). In acute leukemia, fractionation of the alkylating agent doses has resulted at times in improved treatment results, as was noted in the Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen in adult ALL.[17,18] Fractionating the bendamustine dose may improve the antileukemic efficacy. The purpose of this phase I-II study is to establish the MTD of bendamustine in a fractionated dose schedule in patients with acute leukemia and high risk MDS.

Patients and Methods

Adults aged 16 years or older with a diagnosis of refractory or relapsed leukemia were eligible for the study after confirmation of the diagnosis and after a consent form was obtained according to institutional guidelines. Patients with poor risk MDS (with excess blasts) and patients with chronic myeloid leukemia in blastic phase were also eligible. Older patients (age 70 or older) with a newly diagnosed AML who were not eligible for front-line

standard therapy or who refused intensive chemotherapy were also considered. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0-3, and normal organ functions including serum creatinine ≤2.0 mg/dL, total bilirubin ≤1.5 times the upper limit of normal (ULN), and alanine aminotransferase or aspartate amino-transferase ≤3 times ULN, unless considered due to organ leukemic infiltration. Patients with active central nervous system leukemia were eligible and would be treated concurrently with intrathecal chemotherapy. Women of childbearing potential were required to have negative pregnancy tests prior to beginning therapy. Exclusion criteria included uncontrolled intercurrent illness including uncontrolled infections, congestive heart failure, arrhythmias, myocardial infarction in the previous 3 months, unstable angina, or New York Heart Association (NYHA) Class 3 or 4.

Therapy

The starting dose level of bendamustine was 50 mg/m^2 intravenously (IV) over 1-2 hours twice daily for 4 days (total dose 400 mg/m^2 per course). Dose escalations considered were 75, 100, 150, and 200 mg/m^2 twice daily for 4 days (total 600, 800, 1200, and 1600 mg/m^2 per course). Patients were observed for 6 weeks at a dose level before accrual at the new dose level.

The phase I portion followed the classic 3 + 3 design. Three patients were treated at a particular dose level. If none experienced grade 3-4 DLT in the first cycle, the dose was escalated. If 1 of 3 experienced drug related grade 3-4 DLT, 3 more patients were added at the particular dose level. If 2 or more patients out of 6 experienced DLT, the dose level was considered to be above the MTD, and lower dose levels were further explored. The MTD was defined as the dose level at which 1 out of 6 patients experienced DLT.

In the phase II portion of the study, consideration for expanding the study in particular disease subsets was entertained if interesting antitumor activity was noted.

Statistical Considerations

The phase I portion of the study was designed to define the DLT and MTD of the new schedule of bendamustine. The phase II portion was to be considered only if interesting activity was noted in the phase I portion. This would be defined as an objective response rate of more than 10% for a particular disease.

Toxicity criteria were based on the National Cancer Institute Common Terminology Criteria (NCI-CTC) for adverse events, version 3.0. Pertinent to this analysis, Grade 1 creatinine elevation was defined as >1 and up to 1.5 times ULN, Grade 2 elevation was defined as >1.5 and up to 3 times ULN, Grade 3 elevation was defined as >3 and up to 6 times ULN, and Grade 4 elevation as >6 times ULN.

A CR was defined as normalization of the bone marrow and peripheral blood counts with ≤5% marrow blasts in a normo-or hypercellular marrow, with a granulocyte count of ≥10^9/L and a platelet count of ≥100 × 10^9/L. A partial response (PR) was defined as for CR, but with only ≥50% reduction of marrow blasts and to a range of 6%-25%. A marrow complete

response was defined as a reduction of marrow blasts to ≤5% but without recovery of peripheral counts.

Results

A total of 27 patients were registered on study; 2 patients were found to be ineligible and did not receive therapy on protocol. A total of 25 patients were treated on study. Their median age was 57 years (range 22-88 years); 12 patients (48%) were 60 years or older. Nine patients (36%) were female. The diagnosis was AML: 22 patients; ALL: 2 patients; and MDS: 1 patient. Most patients had refractory disease with a median salvage number of 3. The characteristics of the study group are detailed in Table 1.

The number of patients treated at each dose level is shown in Table 2. At the dose level of 100 mg/m^2 twice daily for 4 days (dose level 2; bendamustine total dose 800 mg/m^2 per course), toxicities included renal dysfunction and prolonged myelosuppression. Among 6 patients treated at this dose level, no DLTs were identified. However, 3 patients experienced Grade 1 elevation of creatinine and 3 patients experienced Grade 2 elevations of creatinine. The highest creatinine levels in the latter 3 patients were 1.7, 2.6, and 3.2 mg/dL, occurring on Days 6 and 7, and being reversible. This consistent pattern of renal dysfunction suggested that bendamustine may not be explored at such dose levels, which could result in high rates of renal dysfunction which, though reversible and not severe, limit the practical use of the drug. Based on these findings, the lower dose schedule of 75 mg/m^2 IV twice daily for 4 days (total dose of 600 mg/m^2 per course) was further explored. Patients entered subsequently were selected based on a creatinine level <1.3 mg/dL and a creatinine clearance >50 mL per minute. At the bendamustine dose of 75 mg/m^2 (a total of 13 patients), 1 patient had Grade 1 creatinine elevation and 2 patients had Grade 2 creatinine elevations (highest creatinine levels 2 and 3.3 mg/dL, respectively). Thus, overall, Grade 2 creatinine elevations occurred in 1 of 6 patients (17%) at the 1st dose level (50 mg/m^2 twice daily for 4 days), in 2 of 13 patients (15%) at the 2nd dose level (75 mg/m^2), and in 3 of 6 patients (50%) at the 3rd dose level (100 mg/m^2). Based on the results (Table 2), a dose of bendamustine 75 mg/m^2 IV twice daily for 4 days was proposed for phase II studies.

Considering the refractory nature of the study group, 1 patient with AML in salvage 1 with translocation (9; 11) achieved a brief marrow CR (reduction of marrow blasts from 27% to 4% lasting 4 weeks). Overall, 6 of 23 patients (26%) with peripheral blasts more than 10% had disappearance of peripheral blasts. Six of 25 patients (24%) had >50% reduction in marrow blasts. One patient died within 2 weeks of the start of therapy with active leukemia; 4 patients died within 4 weeks. The median survival was 9 weeks; the 1-year survival rate was 4%.

Discussion

In this phase I-II study, we evaluated a fractionated dose schedule of bendamustine twice daily doses for 4 days. While no Grade 3-4 DLTs were identified, we noted a consistent pattern of Grade 1-2 reversible renal dysfunction which would not be clinically acceptable at doses of 100 mg/m^2 twice daily for 4 days. The proposed phase II dose of bendamustine was

suggested to be 75 mg/m^2 twice daily for 4 days. Of interest, this dose schedule of bendamustine resulted in significant reductions of leukemic burden in 25% of patients, considering the heavily treated condition of this study group (median salvage number 3). These findings are similar to those reported by Strupp et al who also observed significant reduction in AML blasts with bendamustine 100 mg/m^2 daily for 2 days: 11 of 12 patients with high blast counts had significant reductions of AML disease burden.[16] The antileukemic activity of bendamustine should be further explored in better prognosis patients. Lomustine, another alkylating agent, was added to standard AML therapy (idarubicin and cytarabine) as a single induction dose of 20 mg/m^2 orally on Day 1.[4] Compared with historical data of idarubicin and cytarabine, the addition of lomustine significantly improved the CR rate (68% vs. 58%; $P = .002$), and median survival (12.7 vs. 8.7 months; $P = .004$). Bendamustine should be further explored in such settings of high-risk AML, either in front-line combination study, or as consolidation therapy to eradicate residual resistant stem cell leukemia.

The usual schedule of bendamustine is 80 mg/m^2 IV over 1 hour daily for 2 days; the DLT is myelosuppression. This is generally a favorable feature in considering such agents for further exploration in acute leukemia, where the extramedullary DLT is often found to be at dosages 3-20 times higher than the doses in solid tumors. Examples include cytarabine, topotecan, clofarabine, anthracyclines, and others. Studies with alkylating agents (eg, cyclophosphamide and other nucleoside analogs) have shown that fractionated schedules (eg, twice daily with Hyper-CVAD in ALL) and longer exposures (eg, 3-7 days) may be at times more effective than shorter exposures.[17,18] Bendamustine has been used as a continuous infusion daily for 4 days. The MTD was 85 mg/m^2 daily for 4 days (340 mg/m^2 per course); the DLT was myelosuppression. The MTD for a single high dose exposure of bendamustine was 215 mg/m^2, the DLT being cardiac arrhythmias and neurotoxicity. In our study of fractionated longer exposure schedule of bendamustine, we identified renal dysfunction as clinically relevant and which limited explorations beyond 75 mg/m^2 twice daily for 4 days, although no severe toxicities (Grade 3-4 renal toxicity by NCI-CTC criteria) were observed. We recommend the schedule to be further explored in phase II studies. These could include studies in high risk AML in first remission with a high risk for relapse (bendamustine consolidation to eradicate resistant minimal residual disease), in older patients with newly diagnosed AML not fit for intensive chemotherapy, and perhaps in AML salvage 1 comparing standard high dose cytarabine versus high dose cytarabine plus bendamustine. Finally, studies of bendamustine in ALL are also indicated.

Conclusion

In summary, this study has defined a phase II schedule of fractionated bendamustine in acute leukemia and high risk MDS. Exploring bendamustine in patients having received less pretreatment with AML and ALL is warranted.

References

1. Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol. 2011; 29:487–94. [PubMed: 21220605]

2. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011; 29:532–43. [PubMed: 21220592]
3. Garcia-Manero G, Fenaux P. Hypomethylating agents and other novel strategies in myelodysplastic syndromes. J Clin Oncol. 2011; 29:516–23. [PubMed: 21220589]
4. Pigneux A, Harousseau JL, Witz F, et al. Addition of lomustine to idarubicin and cytarabine improves the outcome of elderly patients with de novo acute myeloid leukemia: a report from the GOELAMS. J Clin Oncol. 2010; 28:3028–34. [PubMed: 20479424]
5. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006; 106:1794–803. [PubMed: 16532500]
6. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2007; 109:52–7. [PubMed: 16882708]
7. Wierda WG, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol. 2006; 23:4070–8. [PubMed: 15767647]
8. Rummel MJ, Al-Batran SE, Kim S, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol. 2005; 23:3383–9. [PubMed: 15908650]
9. Cheson B, Rummel M. Bendamustine: rebirth of an old drug. J Clin Oncol. 2009; 27:1492–501. [PubMed: 19224851]
10. Knauf W, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009; 27:4378–84. [PubMed: 19652068]
11. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multi-center phase II trial of the German chronic lymphocytic leukemia study group. J Clin Oncol. 2011; 29:3559–66. [PubMed: 21844497]
12. Kalaycio M. Bendamustine. A new look at an old drug. Cancer. 2008; 115:473–9. [PubMed: 19117340]
13. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer. 2010; 116:106–14. [PubMed: 19890959]
14. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol. 2008; 26:204–10. [PubMed: 18182663]
15. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008; 26:4473–9. [PubMed: 18626004]
16. Strupp C, Knipp S, Hartmann J, et al. A pilot study of bendamustine in elderly patients with high-risk MDS and AML. Leuk Lymphoma. 2007; 48:1161–6. [PubMed: 17577779]
17. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004; 101:2788–801. [PubMed: 15481055]
18. Thomas D, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor b-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010; 28:3880–8. [PubMed: 20660823]

Clinical Practice Points

- Patients with refractory-relapsed acute leukemia have a poor prognosis.
- Discovering new agents with activity in acute leukemia is a critical need.
- Bendamustine is active in lymphoma and chronic lymphocytic leukemia.
- This study evaluated a new schedule of fractionated bendamustine, twice daily for four days in a phase 1 study.
- A phase 2 schedule was defined which can be tested in acute leukemia.
- If significant activity is shown, bendamustine may be incorporated into salvage and frontline acute leukemia regimens.

Table 1

Study Group (N = 25)

Characteristic	N (%)
Age ≥60 Years	12 (48)
Median (range)	57 (22-88)
Female Sex	9 (36)
Diagnosis	
Acute myeloid leukemia	22 (88)
Acute lymphocytic leukemia	2 (8)
Myelodysplastic syndrome	1 (4)
Karyotype Acute Myeloid Leukemia	
Diploid	6 (24)
Chromosome 5 or 7 abnormal	2 (1)
Complex ≥3 abnormality	5 (20)
Trisomy 8	3 (12)
Other/insufficient metaphases	8/1 (36)
Salvage	
First	4 (16)
Second	4 (16)
Third	7 (28)
Fourth or more	9 (36)
Newly diagnosed	1 (4)
Dose Levels (mg/m2 Twice Daily for 4 Days)	
50	6 (24)
75	13 (52)
100	6 (24)

Table 2

Drug-Related Side Effects

	Bendamustine Dose Level in mg/m^2 Twice Daily for 4 Days		
Number With Toxicity Grade 1/2	50	75	100
Number Treated	6	13	6
Creatinine Elevation	1/1	1/2	3/3
Nausea and Vomiting	3/1	2/2	2/1
Diarrhea	3/0	0/1	1/2
Mucositis	1/0	0/0	0/0
Liver Function Abnormality	1/0	2/1	1/0
Other	1 Headache grade 1	1 Rash grade 2	—

Two patients had Grade 3-4 liver function abnormalities at 75 mg/m^2; these were attributed to events unrelated to bendamustine (combination of infections and medications).