Bendamustine: Rebirth of an Old Drug

Bruce D. Cheson and Mathias J. Rummel

ABSTRACT

Bendamustine is a unique cytotoxic agent with structural similarities to alkylating agents and antimetabolites, but which is non-cross-resistant with alkylating agents and other drugs in vitro and in the clinic. Early clinical studies conducted in the German Democratic Republic more than 30 years ago suggested promising activity in indolent non-Hodgkin’s lymphoma (NHL). Two North American trials reported responses in more than 70% of patients with chemotherapy- and rituximab-refractory disease, suggesting that bendamustine may be the most effective drug available for this patient population. Response rates of 90% to 92%, with complete remission in 55% to 60%, have been reported in patients with follicular and mantle-cell lymphoma with the combination of bendamustine and rituximab. Superiority over chlorambucil in previously untreated patients with chronic lymphocytic leukemia (CLL) led to its recent approval for this disease in the United States. Bendamustine is approved in Germany for the treatment of patients with indolent NHL, CLL, and multiple myeloma. Activity has also been noted in patients with breast cancer and small-cell lung cancer. Questions related to the optimization of bendamustine therapy, including dose and schedule, role relative to other available agents, and management of toxicities, are being investigated. However, the availability of bendamustine provides another effective treatment option for patients with lymphoid malignancies.

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INTRODUCTION

Major progress over the past decade in the treatment of lymphoid malignancies has resulted from the availability of safe and effective monoclonal antibodies. Rituximab in combination with chemotherapy has improved response rates and survival of patients with follicular non-Hodgkin’s lymphoma (NHL)1-3 and diffuse large B-cell lymphoma,4-7 and historical comparisons suggest a prolongation of survival in chronic lymphocytic leukemia (CLL) as well.8,9 Immunomodulatory agents thalidomide and lenalidomide have changed the treatment approach for patients with multiple myeloma (MM). Lenalidomide has also demonstrated activity in CLL and various histologies of NHL.10 Other targeted drugs with impressive activity include the proteasome inhibitor bortezomib, which is approved for the treatment of multiple myeloma and mantle-cell lymphoma.11

Nevertheless, patients with indolent lymphoid malignancies, such as follicular lymphoma and CLL/ small lymphocytic lymphoma (SLL), or with MM invariably relapse and require a succession of treatments. Moreover, a substantial proportion of patients with the potentially curable diffuse large B-cell lymphoma are either refractory to or relapse after chemoimmunotherapy. Whereas high-dose chemotherapy with stem-cell transplantation is beneficial for select patients, additional effective salvage approaches are needed.

AN OLD DRUG REDISCOVERED

Bendamustine was first synthesized in the early 1960s at the Institute for Microbiology and Experimental Therapy in Jena, in the former East German Democratic Republic (GDR) by Ozegowski et al.12 The intention was to synthesize a nitrogen-mustard compound that was less toxic than, but at least as effective as, other alkylating agents. By relocating the nitrogen-mustard group to position 5 on a benzimidazole ring, they developed a compound with the chemical name γ-[1-methyl-5-bis(β-chloroethyl)-amino-benzimidazolyl-2]-butyric acid hydrochloride. Bendamustine has structural similarities to both alkylating agents and purine analogs (Fig 1). The benzimidazole ring system may confer nucleoside-like properties and provides stability, allowing for longer-lasting DNA damage.13 Initially, the compound was identified by the code IMET3393, but later it was called bendamustine.12,14 Strumberg et al15 demonstrated incomplete cross-resistance between bendamustine and other
alkylation, and activation of DNA repair mechanisms. The inhibition of mitotic checkpoints is unique to bendamustine compared to other alkylating agents. Bendamustine may also be associated with a slower repair of DNA damage than with other alkylating agents, and may be more stable than other alkylating agents, including cyclophosphamide and chlorambucil.

Bendamustine does not show cross-resistance with other cytotoxic drugs, and is active in primary NHL cells refractory to conventional chemotherapeutic agents such as cyclophosphamide, doxorubicin, and etoposide. Using the National Cancer Institute’s COMPARE analysis, Leoni et al demonstrated that cyclophosphamide, chlorambucil, and melphalan exhibited a high degree of correlation, whereas the sensitivity pattern of bendamustine did not correlate with any other agent tested, suggesting a different mechanistic profile. Leoni et al exposed primary NHL lymphocytes from patients refractory to chemotherapy to various concentrations of bendamustine and a fixed dose of cyclophosphamide. While high concentrations of bendamustine (200 μmol/L) resulted in near 100% growth inhibition, 20 μmol/L still resulted in more than 40% growth inhibition. In contrast to cyclophosphamide, bendamustine demonstrated activity against all samples, including those that were cyclophosphamide resistant. Most recently, bendamustine has been shown to differ from other alkylating agents by activation of DNA damage response pathways and apoptosis, inhibition of mitotic checkpoints, induction of mitotic catastrophe, and activation of a base excision repair pathway rather than an alkyltransferase DNA repair mechanism.

Limited pharmacokinetic data are available for bendamustine. Rasschaert et al delivered the drug once every 3 weeks and found a maximum tolerated dose of 160 mg/m² on day 1 and 8 of an every-4-weeks cycle. Schöffski et al conducted a phase I trial with intravenous bendamustine in patients with solid tumors starting at 80 mg/m² weekly and determined 60 mg/m² to be the phase II dose using this schedule. Schöffski et al identified a maximum tolerated dose of 160 mg/m² on day 1 and 8 of an every-4-weeks cycle. Rasschaert et al escalated bendamustine from 160 mg/m² by increments of 20 mg/m². At 280 mg/m², grade 4 thrombocytopenia, grade 3 fatigue, and grade 2 cardiotoxicity were encountered, the latter considered dose limiting. They recommended 260 mg/m² every 3 weeks for subsequent trials. When delivered on days 1 and 2 every 3 weeks, the maximum tolerated dose was 180 mg/m², and thrombocytopenia was dose limiting.

Limited pharmacokinetic data are available for bendamustine. Rasschaert et al delivered the drug once every 3 weeks and found a maximum serum concentration of 35 minutes with a mean elimination half-life of 49.1 minutes, volume of distribution of 18.31 m² and a clearance of 265 mL min/m², with no evidence for dose dependency. The amount detected in the urine was highly variable. The pharmacokinetic profile (PK) of bendamustine administered on days 1 and 2 every 3 weeks produced virtually identical results, suggesting a lack of schedule dependency. Owen et al conducted a population pharmacokinetic analysis of bendamustine in patients with indolent NHL treated with 120 mg/m² day 1 and 2 every 3 weeks. Plasma concentrations declined in a triphasic manner, with a rapid distribution phase, an intermediate phase, and a terminal decline. They determined the intermediate terminal half-life of 40 minutes to be the most pharmacologically relevant since the initial phases accounted for 99% of the bendamustine area under the curve. Maximum serum concentration was 6 μg/mL. Accumulation was not expected; thus, single-dose PK reflected multidosing schedules. Of interest was that neither mild to moderate renal nor mild liver impairment altered pharmacokinetics.

Synergism between bendamustine and rituximab was demonstrated in severe combined immunodeficiency mice with Daudi xenografts, while adding rituximab reduces the dose of bendamustine required to induce apoptosis in CD20-positive DOHH-2 and WSU-NHL cell lines and ex vivo B-cell CLL cells. These preclinical observations supported clinical studies combining the two agents.

**Phase I and Pharmacokinetics**

Bendamustine is primarily metabolized to mono- and dihydroxy metabolites, with a gamma-OH-bendamustine and N-desmethyl-bendamustine with cytotoxic activity formed by the CYP1A2 oxidative pathway. Bendamustine has been administered in a variety of doses and schedules. In early studies, single doses of 150 mg/m² were delivered on days 1 and 2. Schöffski et al conducted a phase I trial with intravenous bendamustine in patients with solid tumors starting at 80 mg/m² weekly and determined 60 mg/m² to be the phase II dose using this schedule. Schöffski et al identified a maximum tolerated dose of 160 mg/m² on day 1 and 8 of an every-4-weeks cycle. Rasschaert et al escalated bendamustine from 160 mg/m² by increments of 20 mg/m². At 280 mg/m², grade 4 thrombocytopenia, grade 3 fatigue, and grade 2 cardiotoxicity were encountered, the latter considered dose limiting. They recommended 260 mg/m² every 3 weeks for subsequent trials. When delivered on days 1 and 2 every 3 weeks, the maximum tolerated dose was 180 mg/m², and thrombocytopenia was dose limiting.

**Clinical Studies**

For over 30 years, bendamustine was used in the former German Democratic Republic as monotherapy in NHL, CLL, MM, Hodgkin’s lymphoma, and breast cancer. Unfortunately, few validated study results exist from this early period. Following the German reunification, bendamustine was approved for the treatment of patients with indolent NHL, CLL, MM (Table 1), and breast cancer, and study groups began to initiate trials of bendamustine to assess its value in these cancers.

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**Fig 1.** Chemical structure of bendamustine, cyclophosphamide and cladribine. Cl, chlorine; H, hydrogen; N, nitrogen; O, oxygen; P, phosphorus.
<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Overall Response Rate</th>
<th>Duration of Response</th>
<th>PFS or TTP (months)</th>
<th>OS (months)</th>
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<td>Kath (phase II)</td>
<td>Previously treated (n = 10) or untreated (n = 13)</td>
<td>23</td>
<td>Age &lt; 70 years: 60 mg/m² days 1-5, every 28 days; Age ≥ 70 years: 50 mg/m² days 1-5, every 28 days</td>
<td>75 36 7 1-32 Not reported</td>
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<td>Bremer (phase II)</td>
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<td>102 (15 CLL)</td>
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<td>93 7 Not reached</td>
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<td>Relapsed, refractory</td>
<td>54 (21 CLL)</td>
<td>B: 80 mg/m² days 1-3; + Mitox: 10 mg/m² day 1, repeat day 36; + R: 375 mg/m² weeks 2-6, every 28 days</td>
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<td>TTP, 17 1-34+ Not reported</td>
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<td>15</td>
<td>100 mg/m² days 1-2, every 28 days</td>
<td>60 27 22+ (CR) 18+27+ (CR) Not reported</td>
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<td>Kraut (phase III)</td>
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<td>305</td>
<td>100 mg/m² days 1-2, every 28 days versus 0.8 mg/kg days 1, 15, every 28 days</td>
<td>68 30 16 PFS, 21 Not reached</td>
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<td>81</td>
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<td>73 11 16 3-55 TTP; 16 3-55 36 3-67</td>
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<td>Relapsed, refractory, indolent</td>
<td>29</td>
<td>B: 30 (level 1), 40 (level 2) or 50 mg/m² days 1-3 (dose escalation); + F: 30 mg/m² days 1-3, every 28 days</td>
<td>77 45 10.5 2-32 Not reported</td>
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<td>Herold (phase III)</td>
<td>Previously untreated</td>
<td>164 (43 MCI)</td>
<td>B: 60 mg/m² days 1-5; + V: 2 mg day 1; + P: 100 mg/m² days 1-5, every 21 days versus 400 mg/m² days 1-5; + V: 2 mg day 1; + P: 100 mg/m² days 1-5, every 21 days</td>
<td>66 22 27 84+ 76</td>
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Chronic Lymphocytic Leukemia

Phase II studies from East Germany using empiric dosing in relatively small numbers of patients with CLL provided evidence that bendamustine was effective with response rates of 65% to 93%, with a favorable safety profile30-33 (Table 1). In a recent European Intergroup CLL Study, 305 previously untreated CLL patients under 75 years of age and requiring therapy were randomized to bendamustine 100 mg/m² intravenously for 2 consecutive days or oral chlorambucil 0.8 mg/kg on days 1 and 15 of each cycle.34 The median age was 65 years; 70% (34% CR) and 61% (22% CR), respectively, for bendamustine and chlorambucil.

Median duration of remission was 18.9 months for bendamustine and chlorambucil, respectively (P < .0001). Nausea and vomiting were only modest with bendamustine, and there was no alopecia. The incidence of grade 3 to 4 infection was similar (5.8% for bendamustine, 3.5% for chlorambucil). These results led to the recent approval in the United States for bendamustine, and 47% (3% CR) and 22% (0% CR), respectively, for chlorambucil. Median progression-free survival (PFS) was 21.7 months versus 9.3 months for bendamustine and chlorambucil, respectively (P < .0001). Median duration of remission was 18.9 months for bendamustine and 6.1 months for chlorambucil (log-rank, stratified for Binet B/C, P < .0001). Nausea and vomiting were only modest with bendamustine, and there was no alopecia. The incidence of grade 3 to 4 infection was similar (5.8% for bendamustine, 3.5% for chlorambucil). These results led to the recent approval in the United States for bendamustine in CLL.

Encouraged by preclinical data and results with fludarabine and rituximab (F-R) alone or with cyclophosphamide,9,35 the German CLL Study Group (GCLLSG) initiated the CLL2M phase II study to investigate the combination of bendamustine at 70 mg/m² on days 1 and 15 of each cycle.36,37 The median age was 65 years; 70% (30% CR) and 61% (22% CR), respectively, for bendamustine, and 47% (3% CR) and 22% (0% CR), respectively, for chlorambucil. Median progression-free survival (PFS) was 21.7 months versus 9.3 months for bendamustine and chlorambucil, respectively (P < .0001). Median duration of remission was 18.9 months for bendamustine and 6.1 months for chlorambucil (log-rank, stratified for Binet B/C, P < .0001). Nausea and vomiting were only modest with bendamustine, and there was no alopecia. The incidence of grade 3 to 4 infection was similar (5.8% for bendamustine, 3.5% for chlorambucil). These results led to the recent approval in the United States for bendamustine in CLL.

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However, the GCLLSG has recommended 70 mg/m² administered on days 1 and 2 every 4 weeks.34

Median duration of remission was 16 months. Bremer31 administered indolent lymphomas. The ORR was 73%, including 6 CRs (11%).

One possible reason for the lower dose in the latter series was that some patients had previously received fludarabine and, therefore, may have had more compromised bone marrow reserves.37 The recommended dose of bendamustine for previously untreated patients with CLL is 100 mg/m² on days 1 and 2 every 4 weeks.34

**Indolent Non-Hodgkin’s Lymphomas**

Initial studies from the German Democratic Republic stimulated further interest in pursuing bendamustine in indolent NHL (Table 1). Heider and Niederle38 administered bendamustine at 120 mg/m² on 2 successive days every 3 weeks to 52 patients with relapsed or refractory indolent lymphomas. The ORR was 73%, including 6 CRs (11%). Median duration of remission was 16 months. Bremer31 administered 60 mg/m²/d for 5 consecutive days to 102 patients with a variety of lymphoid malignancies, including 46 with lymphoplasmacytic lymphoma, and reported a response rate of 82%, with 15% CRs.

Based on the encouraging German studies, two single-agent phase II trials were conducted in the United States. Friedberg et al39 reported 76 patients with relapsed or refractory indolent and transformed NHL who were refractory to rituximab, defined as progressing within 6 months of the first dose of rituximab, rituximab maintenance, or chemotherapy plus rituximab. Bendamustine 120 mg/m² was administered on days 1 and 2 every 21 days for six to eight cycles. The median age was 63 years, 61% had follicular lymphoma, 19% had transformed to an aggressive histology, and 88% had stage III or IV disease. Patients had received a median of two prior regimens (range, one to five priors). The Follicular Lymphoma International Prognostic Index categories for the 46 patients with follicular NHL were low- (26%), intermediate- (30%), and high-risk (33%), with 11% unknown. Of 74 evaluable patients, the ORR was 77%, including 34% CR and unconfirmed CR (CRu). Non-cross-resistance to alkylating agents was supported by the ORR of 61% (including 13% CR) in alkylator-refractory patients. PFS was 7.1 months; 8.3 months for the indolent histologies and 4.2 months for the transformed NHL. The median duration of response for all patients was 6.7 months, 9 months for those with an indolent histology and 2.3 months for those with transformed disease; 33% of the patients with indolent disease remained disease-free at 2 years (Fig 2).

These data were confirmed in the pivotal trial reported by Kahl et al,40 conducted in the United States and Canada in 100 patients with rituximab-refractory, indolent NHL. Bendamustine was administered at 120 mg/m² on days 1 and 2 every 21 days for six to eight cycles. Histologies included follicular NHL (62%), CLL/SLL (26%), and marginal-zone NHL (21%); 76% had stage III-IV disease. Patients received a median of three prior regimens, including two prior rituximab-containing regimens; 37% had received prior nucleoside analog therapy; 24% prior radioimmunotherapy; and 36% were refractory to the last prior chemotherapy. The ORR of 84% including 32% CR and CRu confirmed the prior phase II trial.39 The median response duration was 9.3 months and the median PFS was 9.7 months.

These studies demonstrate that bendamustine is highly active in rituximab-refractory patients. Response rates are at least comparable with ibrutinib, tositumomab or Y90, ibritumomab in relapsed or refractory follicular and low-grade NHL, the only agents currently approved for this indication.41,42

Several combinations incorporating bendamustine have been evaluated. Herold et al43 compared a more intensive bendamustine schedule (60 mg/m² daily for 5 days) with vincristine and prednisone (BOP) with cyclophosphamide (400 mg/m²/d for 5 days), vincristine and prednisone (COP); a second randomization between interferon maintenance therapy and observation complicates interpretation of the study. In 164 previously untreated patients with stages III and IV follicular lymphoma, immunocytoma, or mantle-cell lymphoma, response rates were similar with BOP (ORR 66%; CR 22%) and COP (ORR 76%; CR 20%). The projected 5-year survival rate was 61% with BOP and 46% with COP, and the median overall survival was 76 months for BOP and 54 months for COP (P = .2). However, a projected 5-year survival advantage for BOP was observed for responding patients, 74% versus 56% (P = .05). The 5-year event-free survival rate among responding patients who did not receive interferon maintenance was 69.7% and 47% in BOP- and COP-treated patients, respectively (P = .03). BOP was better tolerated with a lower incidence of grade 3 to 4 leukopenia (19% v 34%, P < .0001).

Weide et al44 treated 57 patients with relapsed or refractory indolent (n = 39) and mantle-cell lymphomas (n = 18) using bendamustine, mitoxantrone, and rituximab. An ORR of 89% was achieved, with 35% CRs. The estimated median PFS was 19 months. Mitoxantrone did not appear to add to the expected efficacy of the combination of B-R,26 but increased hematotoxicity with WHO grade 3 and
4 leukopenia in 78% of cases. Similarly, the combination of fludara- 
bine with bendamustine was not superior to what would have been 
expected with bendamustine alone.

**Bendamustine in Combination With Rituximab**

Bendamustine (90 mg/m² on days 1 and 2) plus rituximab (375 
mg/m²) was first studied by the Study Group indolent Lymphomas 
(SGiL) in 63 patients with relapsed or refractory lymphomas (median 
age, 63 years). Histologies included follicular lymphoma (n = 24), 
mantle-cell lymphoma (n = 16), immunocytoma (n = 17), and 
marginal-zone lymphoma (n = 6). One third of patients were refrac-
tory to their last treatment, mainly a regimen of cyclophosphamide, 
doxorubicin, vincristine, and prednisone (CHOP). Prior treatment 
with rituximab was excluded. B-R was administered every 4 weeks for 
up to four cycles. Additional doses of rituximab were administered 
1 week before the first cycle and 4 weeks after the last cycle. Forty-three, 
12, and eight patients had received one, two, or three prior treatments, 
respectively. ORR was 90%, including 60% CRs. Among the 16 pa-
tients with mantle-cell lymphoma, of whom seven were resistant to 
their last treatment, remission was achieved in 75%, with 50% CRs. All 
17 patients with lymphoplasmacytic lymphoma responded. The me-
dian PFS for all patients was 24 months (5 to ≥ 44 months). The 
probability of survival after 4 years was 55%. Hematological toxic-
ity included grade 3 or 4 leukopenia (16% of cycles), thrombocy-
topenia (3% of cycles), and anemia (1% of cycles). No organ 
toxicity was reported.

These data have been confirmed by a US multicenter trial re-
ported by Robinson et al in patients with follicular, low-grade, and 
mantle-cell NHL relapsing after chemotherapy with or without ritux-
imab, but not rituximab-refractory NHL. The regimen included ben-
damustine 90 mg/m² on days 2 and 3 every 28 days, with rituximab 
375 mg/m² on day 1 of each cycle to replicate the regimen of Rummel 
et al. Median age was 60 years, and 82% had stage III or IV disease. Most patients had an indolent histology (82%) including 61% follic-
ular NHL, 15% CLL/SLL, 3% lymphoplasmacytic lymphoma, 3% 
marginal-zone NHL, and 18% mantle-cell lymphoma. The Follic-
ular Lymphoma International Prognostic Index score for the 40 patients 
with a follicular histology was evenly distributed between 
risk groups. Prior therapies included rituximab in 56% of patients. 
ORR was 92% including 55% CR and CRu with no difference between 
patients with indolent and mantle-cell histologies or by the number of 
prior regimens (one ν > one). The ORR was lower in patients who 
received prior rituximab (86%, with 35% CRs), but the difference was 
not significant. The PFS was similar between mantle-cell and indolent 
histologies, number of prior regimens, or prior rituximab therapy 
(Fig 3).

On the basis of these results, the SGiL initiated two prospective, 
randomized, phase III studies comparing B-R with two standard ther-
apapeutic regimens. In the first, B-R was compared with a regimen of 
rituximab plus cyclophosphamide, doxorubicin, vincristine, and 
prednisone (R-CHOP) as first-line therapy in patients with indolent 
and mantle-cell NHL. In a preliminary analysis of 315 evaluable 
patients, ORR were 93% for both arms, with CRs in 47% and 42% for 
B-R and R-CHOP, respectively. At a median follow-up of 18 months, 
PFS was comparable (not yet reached for B-R ν 39 months for 
R-CHOP [P = .11]), and overall survival was similar. Toxicity favored 
B-R, with 0% versus 94% alopecia and 16% versus 41% grade 3 or 4 
leukopenia. A comparison of B-R with F-R in relapsed/refractory 
patients with indolent NHL is ongoing. Combinations of bendamus-
tine and rituximab with other drugs are being studied.

**Aggressive Non-Hodgkin’s Lymphomas**

Limited data suggest activity for bendamustine against aggressive 
lymphomas (Table 1). Weidmann et al administered bendamustine 120 
mg/m² on days 1 and 2 every 3 weeks to 18 patients (median age, 66 
years) who had relapsed or were resistant to their previous treatment 
and not considered candidates for autologous stem-cell transplanta-
tion. Eight patients (44%) responded with three CRs (17%). The CRs 
lasted 6, 8+, and 27+ months, compared with only 2, 3, and 10 
months for the partial remissions.

Friedberg et al reported 15 patients with indolent NHL that had 
transformed to an aggressive NHL. The ORR (66%) was lower than 
with follicular lymphoma (81%), and the median PFSs were 4.2 
months and 8.3, respectively.

**Multiple Myeloma**

Bendamustine is also active in patients with MM (Table 1). Pó-
nisch et al randomly assigned 131 patients to bendamustine (150 
mg/m² days 1 and 2) or melphalan (15 mg/m² day 1) every 4 weeks; 
both arms received prednisolone (60 mg/m² daily on day 1 through 4). 
Cross-over was permitted within 3 months for progression. The ORR 
was 75% for the bendamustine-prednisolone arm and 70% for 
melphalan-prednisolone. However, bendamustine achieved CRs in 
32% compared with 13% with melphalan (P = .007), with a shorter 
time to maximum response with bendamustine: 6.8 cycles for 
bendamustine-prednisolone, but 8.6 cycles with melphalan-
prednisolone (P < .02). Time-to-treatment failure was longer for 
bendamustine at 14 months compared with 10 months for melphalan 
(P < .02), with no difference in overall survival. The toxicities of the 
two arms were comparable. Further evaluation of bendamustine in 
MM appears warranted and it is currently being tested in combination 
with new, active agents, such as bortezomib.

**Bendamustine in Other Malignancies**

Based on a single study, bendamustine does not appear to be effective 
in acute myelogenous leukemia or myelodysplastic syndrome. 
Activity has been reported in breast and small-cell lung cancer and 
sarcoma, but not melanoma, germ cell tumors, hepatocellular or bile 
duct cancers, or head and neck cancer (Table 2).
In general, bendamustine is well-tolerated. Friedberg et al. reported that 47% of patients experienced grade 3 to 4 neutropenia, but only 7% had febrile neutropenia. Grade 3 to 4 thrombocytopenia and grade 3 anemia were reported in 24% and 9% of patients, respectively. The most common nonhematologic toxicities included nausea, fatigue, vomiting, fever, diarrhea, and constipation, almost all mild to moderate in severity. An infusion reaction syndrome in seven patients was characterized by fevers, hypotension, back and muscle pain, chills, and rash. Table 2 shows the efficacy of bendamustine in solid tumors.

### Table 2. Efficacy of Bendamustine in Solid Tumors

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>Tumor</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Response Rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schöffski</td>
<td>I</td>
<td>Mixed, refractory</td>
<td>12</td>
<td>B: (starting dose, 80 mg/m²) IV weekly × 8 weeks</td>
<td>Overall CR PR</td>
<td>Recommended dose for phase II study: 60 mg/m² weekly</td>
</tr>
<tr>
<td>Rasschaert</td>
<td>I</td>
<td>Mixed, refractory</td>
<td>26 (18 evaluable)</td>
<td>B: (starting dose, 160 mg/m²) IV day 1; 21-day cycles</td>
<td>0 0</td>
<td>Recommended dose for phase II study: 280 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Rasschaert</td>
<td>I</td>
<td>Mixed, refractory</td>
<td>15</td>
<td>B: (starting dose, 120 mg/m²) IV days 1 &amp; 2; 21-day cycles</td>
<td>0 0</td>
<td>4 SD; grade 4 thrombocytopenia was DLT at 180 mg/m²; recommended dose for phase II study: 160 mg/m²</td>
</tr>
<tr>
<td>Bottke</td>
<td>I</td>
<td>Head &amp; neck</td>
<td>13 (relapsed following primary therapy)</td>
<td>B: (80, 100, 120 mg/m²) IV day 1; followed by radiotherapy; 28-day cycles; maximum, 6 cycles</td>
<td>62 0 62</td>
<td>Recommended dose for phase II study: 120 mg/m² every 4 weeks</td>
</tr>
<tr>
<td>Kollmansberger</td>
<td>II</td>
<td>Germ cell</td>
<td>19 (cisplatin-refractory, or relapsed following high-dose chemotherapy and autologous stem-cell support)</td>
<td>B: 120 mg/m² IV days 1 &amp; 2; 21-day cycles</td>
<td>5 0 5</td>
<td>Duration of PR 6 wk</td>
</tr>
<tr>
<td>Köster</td>
<td>II</td>
<td>SCLC, extensive stage</td>
<td>56 (previously untreated)</td>
<td>Carboplatin: AUC 5 day 1; B: 80 mg/m² IV days 1 &amp; 2; 21-day cycles</td>
<td>73 2 71</td>
<td>Median OS 8.3 months (95% CI, 6.6 to 9.6 months)</td>
</tr>
<tr>
<td>Schmittel</td>
<td>II</td>
<td>SCLC</td>
<td>21 (19, extensive stage; first relapse)</td>
<td>B: 120 mg/m² IV days 1 &amp; 2; 21-day cycles; maximum, 6 cycles</td>
<td>29 0 29</td>
<td>Median OS 7 months (95% CI 5.8 to 8.2 months)</td>
</tr>
<tr>
<td>Eichbaum</td>
<td>II</td>
<td>MBC</td>
<td>34 (relapsed following anthracycline-and/or taxane-based therapy)</td>
<td>B: 60 mg/m² days 1, 8, &amp; 15; T: 2 mg/kg IV weekly (only in HER-2/neu-positive pts; n = 10); 28-day cycles; 6 cycles</td>
<td>18 0 18</td>
<td>Clinical benefit (CR/PR/SD &gt; 6 months): B, 41%; BT, 60%</td>
</tr>
<tr>
<td>Reichmann</td>
<td>II</td>
<td>MBC</td>
<td>51 (relapsed, median two prior therapies)</td>
<td>B: 120 mg/m² IV days 1 &amp; 2; 28-day cycles</td>
<td>20 0 20</td>
<td>Clinical benefit (CR/PR/SD &gt; 6 months): 48%</td>
</tr>
<tr>
<td>Hartmann</td>
<td>II</td>
<td>Soft tissue sarcoma</td>
<td>36 (relapsed, refractory)</td>
<td>B: 100 mg/m² IV days 1 &amp; 2; 28-day cycles</td>
<td>3 0 3</td>
<td>Stable disease 31%</td>
</tr>
<tr>
<td>Schoppmeyer</td>
<td>II</td>
<td>Hilar bile duct</td>
<td>6 (impaired liver function)</td>
<td>B: 140 mg/m² cycle 1, 100 mg/m² cycles 2-4, IV days 1 &amp; 21-day cycles; maximum, 4 cycles</td>
<td>0 0 0</td>
<td>Transaminase and bilirubin levels remained stable throughout study treatment</td>
</tr>
<tr>
<td>Schmidt-Hieber</td>
<td>II</td>
<td>Uveal melanoma, with metastases</td>
<td>11</td>
<td>B: 120 mg/m² IV days 1 &amp; 2; 21-day cycles</td>
<td>0 0 0</td>
<td></td>
</tr>
<tr>
<td>von Minckwitz</td>
<td>III</td>
<td>MBC, first-line</td>
<td>364</td>
<td>BMF v CMF: B: 120 mg/m²; C: 500 mg/m²; M: 40 mg/m²; F: 600 mg/m²; IV days 1 &amp; 8; 28-day cycles</td>
<td>TTP (primary endpoint): 8.2 months (BMF) v 6.7 months (CMF); P = .007</td>
<td></td>
</tr>
<tr>
<td>Zulkowski</td>
<td>Case report</td>
<td>Breast</td>
<td>1 age 38 years, invasive ductal breast cancer with brain, liver metastases</td>
<td>B: 150 mg/m² IV days 1 &amp; 2; 28-day cycles</td>
<td>NA NA NA</td>
<td>Regression of brain and liver metastases observed</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PR, partial remission; IV, intravenous; SD, stable disease; SCLC, small-cell lung cancer; AUC, area under the curve; OS, overall survival; MBC, metastatic breast cancer; HER-2, human epidermal growth factor 2; B, bendamustine; T, trastuzumab; C, cyclophosphamide; M, methotrexate; F, fluorouracil; TTP, time to progression.
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and rigos within 24 hours of administration of the drug, up to the third creatinine. The syndrome resolved with discontinuation of the drug or with the introduction of corticosteroids.

Kahl et al 40 reported that 24% of patients had dose reductions due to adverse events, primarily neutropenia and thrombocytopenia, although the relative dose intensity was 88%. Grade 3 to 4 neutropenia occurred in 61% of patients, leading to filgrastim use in 38% of patients. Grade 3 to 4 thrombocytopenia in 25% of patients was the most common reason for premature treatment discontinuation (9%). Infections of any grade were recorded in 69 patients. Seven fatal adverse events were thought to be possibly drug-related, including cytomegalovirus pneumonia and three other pneumonias with respiratory failure or sepsis. Infusion reactions were mild and uncommon.

Because bendamustine is an alkylating agent, secondary malignancies are a potential concern. Friedberg et al 39 noted two patients with myelodysplastic syndrome and one with chronic myelomonocytic leukemia, all heavily pretreated. Kahl et al 40 reported a patient who developed myelodysplastic syndrome and another with a squamous cell carcinoma. Future studies should monitor patients closely for these complications.

CONCLUSION

Recently completed trials in the United States and Europe have confirmed the efficacy and safety of bendamustine as a single agent or in combination with rituximab in follicular, low-grade, and mantle-cell lymphoma. This drug was approved for CLL and rituximab-refractory indolent lymphoma in the United States and for CLL, NHL, and MM in Germany. The relative tolerability of bendamustine provides a favorable treatment option for patients with CLL and NHL in general, and may be a preferred option for elderly patients, those with comorbidities, and patients with CLL who are not considered suitable candidates for more immunosuppressive agents such as alemtuzumab. Because of the possibility of nausea and vomiting, prophylactic antiemetics should be routinely used. The risk of infection with bendamustine does not appear to be increased over other chemotherapy regimens, thus prophylactic antimicrobials are not indicated. Whether bendamustine is immunosuppressive has not been determined, and the depth and duration of myelosuppression needs to be better characterized. As bendamustine is more widely used, less common toxicities may be encountered and should be reported.

Despite the lengthy history of this agent, a number of important questions remain unanswered. The precise mechanism of action and of resistance needs to be clarified. The optimal dose and schedule have yet to be determined. In various studies in CLL or NHL, doses have ranged from 100 mg/m² to 120 mg/m² as a single agent, and 70 mg/m² to 90 mg/m² when combined with rituximab, varying from every 3 weeks to every 4 weeks. It has also been given weekly to women with advanced breast cancer. 54 However, phase I studies in solid tumors have recommended doses ranging from 60 mg/m² weekly to 150 mg/m² on 2 consecutive days every 3 weeks. 28 Pharmacokinetic data on which to base scheduling strategies are lacking.

Different doses may be required for different patient populations, and the optimal dose has not yet been defined. For example, the dose supporting the US Food and Drug Administration approval for NHL is 120 mg/m² on days 1 and 2 every 3 weeks, which may be too intensive for elderly or heavily pretreated patients. The current recommendation is to use the drug with caution in patients with mild to moderate renal or hepatic impairment, but not with a creatinine clearance less than 40 mL/min or with an AST or ALT more than 2.5 times or bilirubin more than three times the upper limit of normal. 66 Patients with more severe dysfunction have not been studied and optimal dosing strategies are needed.

Bendamustine is superior to chlorambucil in CLL, 34 and therefore is a reasonable initial treatment option, especially for patients not considered candidates for fludarabine-based regimens, such as the elderly or those with comorbidities. Results of ongoing studies comparing bendamustine with fludarabine may alter current treatment patterns. The activity of bendamustine will likely be enhanced by the addition of rituximab. Bendamustine provides an option for patients with CLL not suitable for alemtuzumab because of bulky lymph nodes or a history of recurrent infections. Clinical trials are needed to define the efficacy of this agent compared with more effective, standard regimens such as F-R alone or with cyclophosphamide, and its role in patients who have failed these regimens needs to be determined.

Bendamustine has the potential to play an important role in patients with indolent NHL due to reported response rates of over 70% in rituximab-refractory patients, 39,40 which are comparable to radioimmunotherapy 41,42; thus, bendamustine would be a suitable alternative for patients not candidates for radioimmunotherapy because of bone marrow involvement or other contraindications. With the favorable results of B-R compared with R-CHOP in first-line therapy, 46 the former could be a reasonable alternative in older patients, or those with cardiac impairment; longer follow-up is needed before B-R can replace R-CHOP in younger patients. Based on its response rates, bendamustine could be considered an effective alternative to a regimen of rituximab plus cyclophosphamide, vincristine, and prednisone.

Bendamustine may also play a role in aggressive histologies. The reported 92% ORR with 59% CRs and a median duration of response of 19 months in patients with relapsed or refractory mantle-cell lymphoma 21 compares favorably to the 33% ORR with 8% complete remissions and a median time to progression of 6.2 months with bortezomib, the only drug approved for this indication. 11 Weidmann et al 48 reported 44% responses for bendamustine in relapsed aggressive NHL. Given the lack of effective options for this group of patients, bendamustine-based regimens should be studied. In addition, the role of bendamustine in T-cell NHL and Hodgkin’s lymphoma remains to be evaluated.

Sequencing issues also need to be considered. Bendamustine is active in patients for whom alkylating agents or fludarabine have failed (Kahl et al, manuscript submitted for publication). 39 However, whether these drugs will be effective and tolerated following bendamustine has not been evaluated.

The greatest potential for bendamustine will likely be in combination with other agents such as monoclonal antibodies, lenalidomide, and bortezomib. A phase I trial of bendamustine, lenalidomide, and rituximab in CLL and NHL currently underway will provide the doses for future phase II and III trials (B. Cheson, personal communication, January 2009). A multicenter phase I/II trial of bendamustine with bortezomib and rituximab is accruing patients with relapsed and refractory follicular and transformed NHL. Ongoing phase III trials of the StiL in Germany of B-R versus R-CHOP and B-R versus rituximab or with the introduction of corticosteroids.
F-R will further define the role of bendamustine in indolent and mantle-cell lymphomas relative to current standard practices.

In summary, bendamustine is a novel agent with significant activity, especially in patients with lymphoid malignancies. Rational development of bendamustine-based combinations will likely improve the outcome of patients with lymphomas and CLL.

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Manuscript writing: Bruce D. Cheson, Mathias J. Rummel
Final approval of manuscript: Bruce D. Cheson, Mathias J. Rummel

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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