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Novel Approaches in the Treatment of Hematologic Malignancies Utilizing Bendamustine

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Novel Approaches in the Treatment of Hematologic Malignancies Utilizing Bendamustine

This is the fourth article in a 4-part series on bendamustine. While the previous articles discussed the efficacy and safety of bendamustine for patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) in the registration studies cited in the US product labeling, this article discusses ongoing clinical investigations of the agent in a wide range of therapeutic areas.

Lymphoid Malignancies

At the 54th Annual Meeting of the American Society of Hematology (ASH 2012), 29 abstracts were presented describing the use of bendamustine as a treatment for a number of lymphoid malignancies. Bendamustine, both alone and in combination with rituximab or other chemotherapeutic agents, has demonstrated substantial efficacy in a number of lymphoid malignancies, and ongoing studies are examining bendamustine with bortezomib, lenalidomide, ofatumumab, and other novel agents.[1]

CLL

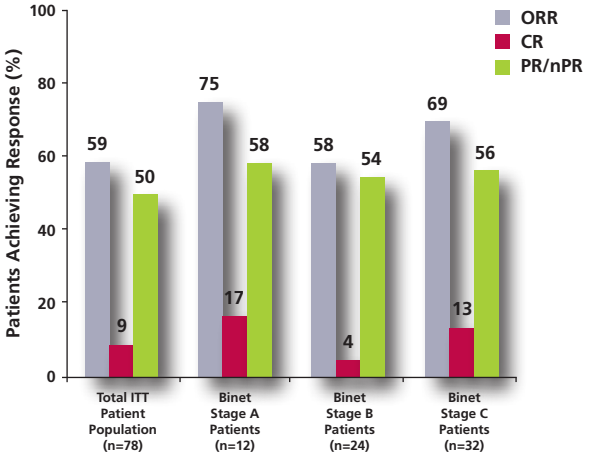
Bendamustine Plus Rituximab

The results of a German multicenter phase 2 study to evaluate the efficacy and safety of bendamustine in combination with rituximab in patients with relapsed/refractory CLL have been published.[2] The primary end point of this study was overall response rate (ORR). Secondary end points included toxicity, quality and duration of response, event-free survival (EFS), minimal residual disease levels, and ORR in biologically defined risk groups. Eighty-three patients with relapsed/refractory B-cell CLL were initially enrolled in the study between March 2006 and June 2007. Seventy-eight patients (male, n=51) with a median age of 66.5 years (range, 42-86 years) received at least 1 dose of treatment and established the intent-to-treat (ITT) population for analysis. Twenty-nine of these 78 patients (37%) were ≥70 years of age. Five patients were excluded from the study due to missing informed consents (n=3) or diagnosis other than CLL (n=2). Patients had to be ≥18 years to enroll in the study, and inclusion criteria consisted of at least 1 but not more than 3 previous treatments for CLL, WHO performance status of 0 to 2, life expectancy of at least 12 weeks, and adequate renal and liver function. The median number of prior treatments was 2, which included 2 protocol violators (4 previous treatments, n=1; 5 previous treatments, n=1). Twenty-two of the 78 ITT patients (28%) were refractory to fludarabine. Sixty-three patients (81%) had received prior fludarabine monotherapy and/or a fludarabine-containing regimen. Seven patients (9%) had received previous rituximab-containing therapies, and 5 patients (6%) were previously administered alemtuzumab-containing regimens. Patient response rates for the ITT population (n=78) are presented in **Figure 1**.

For the ITT population, median EFS (after a median follow-up of 24 months) was 14.7 months (95% CI, 14.1-20.1 months). The median overall survival (OS) was 33.9 months (95% CI, 25.5-42.1 months), and the median progression-free survival (PFS) was 15.2 months (95% CI, 12.5-17.9 months). Median EFS for the subsets of Binet stages A, B, and C patients was reached at 27.5, 20.5, and 13.8 months, respectively. Overall, of 46 responders, the median duration of response was 15.2 months (95% CI, 12.1-18.3 months).

Additional analyses were done for the subgroup of patients previously treated with fludarabine (n=72). In those patients who were fludarabine naive (n=12), the ORR was 100%, with a complete response (CR) achieved in 33%. In those

Figure 1. Responses to Bendamustine in Combination With Rituximab in Patients With Relapsed/Refractory CLL[2]



CR indicates complete response; ITT, intent-to-treat; nPR, nodular partial response; ORR, overall response rate; PR, partial response.

patients who were fludarabine sensitive (n=38), the ORR was 61%, with 8% CR. Finally, in those patients who were fludarabine refractory (n=22), the ORR was 46% with no CRs reported. Five of the 7 patients (71%) who had received previous rituximab therapy achieved a partial response (PR). Six of 10 patients (60%) who had received prior therapy with an antibody-containing regimen were observed to have a PR.

Toxicities were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. In the ITT population (n=78), 46 patients (59%) had at least 1 reported adverse event (AE) grade ≥3, most commonly myelosuppression, which occurred in 39 patients (50%); neutropenia in 18 patients (23%); thrombocytopenia in 22 patients (28%); and anemia in 13 patients (17%). The most common nonhematologic toxicity reported was grade 3 infection, which occurred in 10 patients (13%); no grade 4 infections were reported. Dose reductions of >10% of the study dose in either of the 2 drugs were applied in 29 patients (37%) mainly due to the onset of treatment-related neutropenia. Other dose modifications included 19 patients (24%) with a dose reduction of rituximab alone; 18 patients (23%) with a dose reduction of bendamustine alone; and 5 patients (6%) with a dose reduction of both rituximab and bendamustine. A total of 34 patients (44%) discontinued treatment early due to withdrawal of consent (n=9), toxicity (n=15), progressive disease (n=8), or other (n=2). After the median follow-up time of 24 months, 28 deaths had occurred, 21 of which were deemed unrelated to treatment with study drug. Three of 7 patient deaths (4%) were considered related to study drug therapy, including 1 patient with preexisting Richter's transformation. All 3 deaths were the result of infections during the first 2 courses of therapy (septicemia [n=2]; pneumonia [n=1]).

Bendamustine and bendamustine-containing regimens are currently being investigated in 21 clinical studies in patients with CLL.

Bendamustine Plus Rituximab and Fludarabine

Preliminary results were presented at ASH 2012 from a phase 1/2 dose escalation study using bendamustine concomitantly with fludarabine and rituximab for the treatment of 35 evaluable patients (median age 62 years; median 3 prior therapies [range, 1-6]) with active CLL.[3] Patients received escalating doses of bendamustine at 20, 30, 40, or 50 mg/m^2 IV on days 1, 2, and 3 with fludarabine 20 mg/m^2 IV administered 2 hours prior to bendamustine on days 2 and 3. Rituximab 375 to 500 mg/m^2 IV was given on day 3. Courses were repeated every 28 days. Among the 35 evaluable patients, 71% achieved an objective response, including 26% who achieved a CR or a CR with incomplete recovery of cytopenias. Myelosuppression was the most common treatment-related toxicity considering all courses given (n=106). Grade 3 neutropenia occurred in 26% of courses and grade 4 in 29%. Grade 3 thrombocytopenia occurred in 14% of courses and grade 4 in 9%. Grade 3 anemia occurred in 15% of courses and grade 4 in 2%. There were no treatment-related deaths.

Bendamustine Plus Alemtuzumab

The results of an Italian multicenter, single-arm, open-label, dose-escalation study of bendamustine combined with alemtuzumab in 43 evaluable patients with relapsed/refractory CLL were also presented at ASH 2012.[4] Median age was 67 years; 64% were male; all had Binet stage B or C; median number of prior therapies was 2 (range, 1-4); 84% had previously received fludarabine-based treatment, and 70% had received monoclonal antibodies as monotherapy or in combination. Results showed a 70% ORR, including 26% CR and 44% PR. Median time to progression in responders was reached after a median follow-up of 15.5 months. Grade 3/4 neutropenia occurred in 33% of courses, thrombocytopenia and anemia in 7% and 4%, respectively. Febrile neutropenia developed in 15% of courses.

Bendamustine and bendamustine-containing regimens are currently being investigated in 21 clinical studies in patients with CLL (**Table 1**).[5]

Indolent NHL

Bendamustine-Rituximab

Results of a prospective, multicenter, randomized, phase 3 study (German Study Group for Indolent Lymphomas [StiL]) that compared 6 cycles of bendamustine-rituximab (BR; n=261) with 6 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=253) as first-line treatment in 514 patients with indolent lymphomas, including a subset of patients (18% of enrolled patients) with mantle cell lymphoma (MCL), showed that patients treated with BR had significantly higher PFS as well as improved tolerability compared with those who received R-CHOP.[6] At ASH 2012, Rummel and colleagues presented results of a subanalysis of the StiL study that examined the impact of response quality on PFS and OS.[7] The ORR for patients receiving BR was 92.7%, and for R-CHOP, 91.3%. CRs were achieved by 39.8% of patients in the BR arm and by 30% of those in the R-CHOP arm (P=.021). The achievement of CR was associated with a significantly prolonged PFS and OS (**Table 2**). Patients in CR following first-line treatment had a significantly longer PFS and OS compared with those achieving a PR.

Table 1. Ongoing Clinical Trials of Bendamustine in Patients With CLL[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 4	Bendamustine	Adult Filipino patients with CLL	NCT01739491
Phase 4	Bendamustine + rituximab vs rituximab + chlorambucil	CLL	NCT01056510
Phase 3	Bendamustine	Previously untreated CLL	NCT01657955
Phase 1/2	Bendamustine + TRU-016 vs bendamustine alone	Relapsed CLL	NCT01188681
Phase 1	Bendamustine + alemtuzumab	Refractory CLL	NCT00947388
Phase 2	Bendamustine + rituximab	Relapsed B-cell CLL	NCT00274989
Phase 1/2	Bendamustine + rituximab + fludarabine	CLL	NCT01096992
Phase 2	Bendamustine + rituximab vs bendamustine + MEDI-551	Relapsed or refractory CLL patients ineligible for transplant	NCT01466153
Phase 2	Bendamustine + rituximab + NOX-A12	Relapsed CLL	NCT01486797
Phase 1/2	Bendamustine + rituximab + MK2206	Relapsed CLL or SLL	NCT01369849
Phase 2	Bendamustine + rituximab induction chemotherapy + lenalidomide maintenance	Relapsed/refractory CLL or SLL	NCT00974233
Phase 2	Bendamustine + rituximab induction followed by maintenance rituximab + lenalidomide	Previously untreated CLL or SLL	NCT01754857
Phase 2	Bendamustine + rituximab induction followed by maintenance rituximab + lenalidomide	Relapsed and refractory CLL or SLL	NCT01754870
Phase 1/2	Bendamustine + rituximab + lenalidomide	CLL	NCT01558167
Phase 1	Bendamustine + rituximab + lenalidomide	Untreated CLL or SLL	NCT01400685
Phase 3	Bendamustine + rituximab + idelalisib (GS-1101)	Previously treated CLL	NCT01569295
Phase 3	Bendamustine + rituximab + ibrutinib	Relapsed or refractory CLL or SLL	NCT01611090
Phase 3	Bendamustine + ofatumumab vs chlorambucil + ofatumumab	Patients with CLL who are considered not fit enough for rituximab + fludarabine + cyclophosphamide	NCT01678430
Phase 2	Bendamustine + ofatumumab + methylprednisolone	Relapsed B-cell CLL	NCT01612988
Phase 1	Bendamustine + ofatumumab + pentostatin	CLL and lymphoma	NCT01352312
Phase 1	Bendamustine and/or rituximab + SAR245409	Indolent lymphoma, MCL, or CLL	NCT01410513

CLL indicates chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

Bendamustine-Rituximab Versus R-CHOP/R-CVP

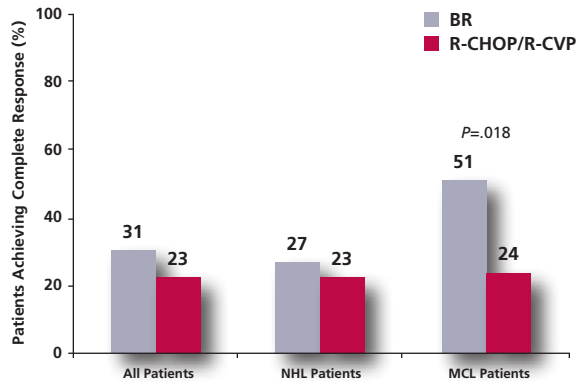
Also at ASH 2012, Flinn and colleagues presented results of an open-label, randomized phase 3 study (BRIGHT) of BR compared with R-CHOP or rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) in the first-line treatment of 447 patients with advanced indolent NHL or MCL.[8] Of 447 randomized patients, 436 received treatment (BR, n=221; R-CHOP/R-CVP, n=215 [R-CHOP, n=99; R-CVP, n=116]) and were evaluable for safety. Dose delays were more common for BR-treated patients (35% vs 19%), and dose reductions were more common for patients receiving R-CHOP/R-CVP (29% vs 22%). The AE profile of BR was distinct from that of R-CHOP/R-CVP. The most common AEs reported in patients receiving BR and R-CHOP/R-CVP, respectively, were nausea (139 vs 102 patients), fatigue (113 vs 107), neutropenia (76 vs 85), constipation (65 vs 90), and

Table 2. Impact of Response Quality on PFS and OS in the StiL Trial[7]

		All Patients	R-CHOP Arm	BR Arm
PR	Median PFS	43.5 months	30.9 months	57.2 months
	5-year OS rate	77.5%	75.4%	80.1%
CR	Median PFS	57.5 months	53.7 months	Not reached
	5-year OS rate	90.3%	89.6%	91.0%

BR indicates bendamustine-rituximab; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Figure 2. Responses to Bendamustine in Combination With Rituximab in Patients With Relapsed/Refractory CLL[2]



BR indicates bendamustine-rituximab; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone.

alopecia (8 vs 74). Grade 3/4 hematologic toxicities for BR and R-CHOP/R-CVP were lymphopenia (137 vs 64), neutropenia (98 vs 151), leukopenia (84 vs 116), thrombocytopenia (16 vs 15), and anemia (6 vs 9), respectively. The most frequent investigator-reported nonhematologic grade 3/4 AEs for BR and R-CHOP/R-CVP were infusion-related reactions (13 vs 8 patients). Six deaths occurred among patients receiving BR (causes of death were pneumonia, respiratory failure, and sepsis; acute respiratory failure; cardiac arrest; pneumonia; chronic obstructive pulmonary disease; lung cancer), and 1 patient receiving R-CHOP/R-CVP died due to sepsis. A total of 419 patients (BR, n=213, 61% men, median 60 years of age; R-CHOP/R-CVP, n=206 [R-CHOP, n=97; R-CVP, n=109], 59% men, median 58 years of age) were evaluable for efficacy. In both groups, 64% of patients were classified as ECOG performance status 0, 83% of patients had indolent NHL, and 62% of patients had stage IV disease. Assessment by an independent review committee showed that in patients with advanced indolent NHL and MCL, high ORRs were attained in both treatment groups: 94% for BR and 84% for R-CHOP/R-CVP. BR produced a CR rate that was noninferior to that of R-CHOP/R-CVP (**Figure 2**). In the subgroup of patients with MCL, BR produces a significantly higher CR rate (51% vs 24%; *P*=.018).

> In patients with advanced indolent NHL and MCL, high ORRs were attained: 94% for BR and 84% for R-CHOP/R-CVP.

Bendamustine-Rituximab

At ASH 2012, Knauf and colleagues presented results (obtained from a large prospective registry that collects data on the treatment of patients with lymphoid B-cell neoplasms as administered in hematology outpatient centers in Germany) from 645 patients who received systemic first-line treatment for indolent NHL.[9] Results showed that rituximab was part of the first-line treatment in 94% (n=606) of patients with indolent NHL, while bendamustine was part of the first-line treatment in 71% (n=455) of patients with indolent NHL. In 66% (n=428) of patients, the combination of bendamustine and rituximab (BR) was used. Only 2% (n=10) of patients received bendamustine as monotherapy. The use of BR increased from 62% in 2009 to 68% in 2011, while the rate of R-CHOP decreased from 19% in 2009 to 15% in 2011. BR was used more often than R-CHOP in elderly patients (mean age 67.3 years vs 60.9 years). In patients <66 years, BR was also the preferred treatment (BR 60% vs R-CHOP 23%). Among the 121 patients in the registry who received second-line treatment for indolent NHL, rituximab was part of the treatment in 84% (n=102) of patients, and bendamustine was part of the second-line treatment in 68% (n=82) of patients. In 60% (n=72) of patients, the combination of BR was used. Only 7% (n=9) of patients received bendamustine as monotherapy. R-CHOP was used as second-line therapy in 7% (n=9) of patients with indolent NHL. These results indicate that in Germany, R-CHOP can no longer be considered as "standard of care" for patients with indolent NHL. The authors also point out that these data also show that results from clinical trials are quickly implemented into daily practice.

Bendamustine, Rituximab, and Bortezomib

The combination of bendamustine, rituximab, and bortez-

Table 3. Patients With Grade ≥3 AEs: IBR vs IB vs IR[11]

Parameter	Regimen		
	IBR n=13	IB n=33	IR n=30
Neutropenia (%)	46	52	43
Rash (%)	23	6	10
Diarrhea (%)	15	3	10
Anemia (%)	8	15	10
Thrombocytopenia (%)	8	15	7
Infections (%)	8	15	7
Febrile neutropenia (%)	0	12	0
Pneumonia/pneumonitis (%)	0	33	7
Hepatic transaminase elevation (%)	0	24	13

AEs indicates adverse events; IB, idelalisib-bendamustine; IBR, idelalisib-bendamustine-rituximab; IR, idelalisib-rituximab.

omib (BRB) was assessed in a phase 2 study in 55 patients with previously untreated low-grade lymphoma (follicular center cell lymphoma, 69%; marginal zone lymphoma, 15%; small lymphocytic lymphoma [SLL], 9%; or lymphoplasmacytic lymphoma, 7%).[10] After a median follow-up of 13 months (range, 6-26 months), 78% of patients had completed 6 cycles of BRB, and 56% had continued to receive maintenance rituximab. Five patients (9%) discontinued treatment due to toxicity (1 due to grade 2 neuropathy, 1 due to grade 2 atrial fibrillation, 1 due to grade 3 pancreatitis, 1 due to grade 3 diarrhea, and 1 due to grade 3 rash). The remaining 5 patients discontinued prematurely (1 patient died due to stroke, 1 discontinued due to wound complication, 1 was lost to follow-up, 2 discontinued due to request). Treatment-related grade 3/4 hematologic toxicities were neutropenia (25%), febrile neutropenia (2%), thrombocytopenia (5%), and anemia (4%). The most common grade 3 treatment-related nonhematologic AEs were neuropathy (9%), diarrhea (7%), fatigue (7%), constipation (5%), and rash (5%). At the time of the data cutoff, 3 patients (5.5%) had progressed or relapsed and 3 patients (5.5%) had died. An objective response was achieved in 89% of patients, including CR 47% and PR 42%.

Idelalisib (GS-1101) Plus Rituximab and/or Bendamustine

Fowler and colleagues presented results of a phase 1 study of combinations of the phosphatidylinositol 3-kinase-delta inhibitor idelalisib with rituximab (IR; n=30), bendamustine (IB; n=33), or bendamustine plus rituximab (IBR; n=13) in 76 patients with previously treated (median 3 prior therapies) indolent NHL (follicular lymphoma, 74%; SLL, 20%; or marginal zone lymphoma, 6%).[11] Grade ≥3 AEs and laboratory abnormalities were generally consistent with those expected with each of the single agents (**Table 3**).

Table 4. Reductions in Lymphadenopathy: IBR vs IB vs IR[11]

Parameter	Regimen		
	IBR n=11	IB n=32	IR n=30
Patients with decrease in adenopathy (%)	100	97	97
Maximum adenopathy change, median (%) (range)	-88 (-97 to -21)	-79 (-100 to 58)	-74 (-100 to 0)

IB indicates idelalisib-bendamustine; IBR, idelalisib-bendamustine-rituximab; IR, idelalisib-rituximab.

Lymph node shrinkage was rapid, and all evaluable patients had reductions in lymphadenopathy (**Table 4**), resulting in ORRs of 77%, 85%, and 77% for the IR, IB, and IBR regimens, respectively, including CRs in 13%, 16%, and 30% of patients, respectively. With median follow-up duration ranging from 28 to 48 weeks, 1-year PFS rates were 82%, 90%, and 78% for the 3 groups, respectively.

The authors concluded that idelalisib-based combination therapy with rituximab and/or bendamustine offers major and rapid reductions in lymphadenopathy, and that all 3 regimens provide durable tumor control. They recommended that phase 3 combination trials of idelalisib with rituximab- and/or bendamustine-containing regimens be conducted in patients with indolent NHL.

Idelalisib-based combination therapy with rituximab and/or bendamustine offers reductions in lymphadenopathy.

Bendamustine Plus Ofatumumab

When combined with bendamustine in NHL, ofatumumab may have comparable efficacy to rituximab. Initial results of a phase 2 study of bendamustine plus ofatumumab in 45 evaluable patients with untreated indolent B-cell NHL (follicular lymphoma, n=36; marginal zone lymphoma, n=13; lymphoplasmacytic lymphoma, n=13) showed an ORR of 98%, including 60% CR.[12] Seven patients withdrew from the study due to AEs. At the time of this analysis, the most commonly observed grade 3/4 AEs were neutropenia and fatigue. Serious AEs were reported in 13 patients (27%).

Bendamustine and bendamustine-containing regimens are currently being investigated in 17 clinical studies in patients with indolent NHLs (**Table 5**).[5]

Table 5. Ongoing Clinical Trials of Bendamustine in Patients With Indolent NHLs[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 3	Bendamustine	Rituximab-refractory or relapsed B-cell indolent lymphoma	NCT01570049
Phase 3	Bendamustine	Chinese patients with indolent NHL refractory to rituximab treatment	NCT01596621
Phase 3	Bendamustine vs treatment of physician's choice	Indolent B-cell NHL	NCT01289223
Phase 2	Bendamustine + rituximab	Relapsed or refractory CD20-positive B-cell NHL	NCT00385125
Phase 2	Bendamustine + rituximab	Untreated, low-grade B-cell NHL and MCL	NCT01718691
Phase 1	Conditioning with bendamustine + rituximab + fludarabine	Lymphoid malignancies	NCT00880815
Phase 2	Bendamustine + rituximab ± bortezomib followed by rituximab ± lenalidomide	High-risk stage II, stage III, or stage IV follicular lymphoma	NCT01216683
Phase 1/2	Bendamustine + rituximab + etoposide + carboplatin	Relapsed or refractory lymphoid malignancies or select untreated lymphomas	NCT01165112
Phase 3	Bendamustine + rituximab + idelalisib (GS-1101)	Previously treated indolent NHL	NCT01732926
Phase 2	Bendamustine + rituximab + ibritumomab tiuxetan + fludarabine followed by allogeneic stem cell transplant	CD20-positive lymphoid malignancies	NCT01490723
Phase 1/2	Bendamustine + rituximab + temsirolimus	Relapsed follicular lymphoma or MCL	NCT01078142
Phase 1	Bendamustine + ofatumumab	Indolent B-cell NHL	NCT01691807
Phase 2	Bendamustine + ofatumumab ± bortezomib	Untreated follicular NHL	NCT01286272
Phase 1/2	Inotuzumab ozogamicin (CMC-544) + fludarabine + bendamustine ± rituximab, followed by stem cell transplant	CD22-positive lymphoid malignancies	NCT01664910
Phase 1/2	Bendamustine + rituximab + veliparib	Advanced lymphoma, multiple myeloma, or solid tumors	NCT01326702
Phase 1	Bendamustine and/or rituximab + SAR245409	Indolent lymphoma, MCL, or CLL	NCT01410513
Phase 1	Bendamustine + rituximab + PCI-32765	Relapsed DLBCL, MCL, or indolent NHL	NCT01479842

CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NHLs, non-Hodgkin lymphomas.

Mantle Cell Lymphoma

Bendamustine, Rituximab, and Cytarabine

The safety and efficacy of bendamustine in combination with rituximab and cytarabine have been evaluated in a recently published prospective, phase 2 study in 40 patients (median age 70 years) with previously untreated (50%), relapsed (15%), or refractory (35%) MCL.[13] Among the previously untreated patients, the ORR was 100%, including 95% CR. Among the relapsed/refractory patients, the ORR was 80%, including 70% CR. The 2-year PFS rate was 95% in the previously untreated group and 70% in the relapsed/refractory group. Transient grade 3/4 thrombocytopenia occurred in 87% of patients and febrile neutropenia occurred in 12% of patients.

Bendamustine-containing regimens are currently being investigated in 17 clinical studies in patients with MCL (**Table 6**).[5]

Aggressive NHLs

Bendamustine Plus Rituximab

At the 2010 American Society of Clinical Oncology Annual Meeting, Vacirca and colleagues presented initial results of their open-label, single-arm phase 2 study examining BR in CD20-positive patients with relapsed/refractory diffuse large B-cell lymphoma who were ineligible for autologous stem cell transplant (ASCT).[14] At the time of that presentation, the ORR for 26 evaluable patients was 58%, including 19% CR. Grade 3/4 AEs are shown in **Table 7**.

Table 6. Ongoing Clinical Trials of Bendamustine in Patients With MCL[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 2	Bendamustine/rituximab (first 3 cycles) + rituximab/cytarabine (second 3 cycles)	MCL	NCT01661881
Phase 2	Bendamustine + rituximab + cytarabine	Patients ≥65 years of age with MCL	NCT01662050
Phase 2	Bendamustine + rituximab	Untreated, low-grade B-cell NHL and MCL	NCT01718691
Phase 1	Conditioning with bendamustine + rituximab + fludarabine	Lymphoid malignancies	NCT00880815
Phase 2	Bendamustine + rituximab + lenalidomide	Second-line therapy for first relapsed/ refractory MCL	NCT01737177
Phase 1/2	Bendamustine + rituximab + lenalidomide	First-line therapy for patients >65 years of age with MCL	NCT00963534
Phase 2	Bendamustine + rituximab + bortezomib followed by rituximab + lenalidomide	Older patients with previously untreated MCL	NCT01415752
Phase 2	Bendamustine + rituximab + bortezomib + dexamethasone	First-line treatment for MCL	NCT01457144
Phase 3	Bendamustine + rituximab + ibrutinib	Newly diagnosed MCL	NCT01776840
Phase 2	Bendamustine + rituximab or combination chemotherapy + rituximab followed by consolidation chemotherapy + stem cell transplantation	Older patients with previously untreated MCL	NCT01412879
Phase 1/2	Bendamustine + rituximab + temsirolimus	Relapsed follicular lymphoma or MCL	NCT01078142
Phase 2	Bendamustine + ofatumumab vs ofatumumab alone	Patients with MCL who are ineligible for autologous stem cell transplant	NCT01437709
Phase 1/2	Bendamustine + ofatumumab + dexamethasone	First-line treatment for MCL	NCT01221103
Phase 1	Bendamustine + ofatumumab + pentostatin	CLL or lymphoma	NCT01352312
Phase 1/2	Bendamustine + rituximab + veliparib	Advanced lymphoma, multiple myeloma, or solid tumors	NCT01326702
Phase 1	Bendamustine and/or rituximab + SAR245409	Indolent lymphoma, MCL, or CLL	NCT01410513
Phase 1	Bendamustine + rituximab + PCI-32765	Relapsed DLBCL, MCL, or indolent NHL	NCT01479842

CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

Bendamustine and bendamustine-containing regimens are currently being investigated in 8 clinical studies in patients with aggressive NHL (**Table 8**).[5]

Hodgkin Lymphoma

Mian and colleagues from Italy recently published a report on 2 patients with Hodgkin lymphoma in whom bendamustine was successfully used as salvage treatment for relapse after allogeneic bone marrow transplantation.[15] Corazzelli and colleagues, also from Italy, reported on 41 patients with Hodgkin lymphoma that recurred after stem cell transplantation who were treated with bendamustine.[16] At first assessment (after 2-4 cycles), the ORR was 78%, including 12 CRs (29%) and 20 PRs (49%). Upon treatment prolongation to 6 to 8 courses, 40% of PRs progressed, yielding a final ORR of 58% with 31% CR. Eight patients (2 with CRs and 6 with PRs) subsequently underwent ASCT. The median PFS exceeded 11 months and the median OS exceeded 21 months. Among the group that had reached a CR, the median disease-free survival time was more than 9 months, with a relapse rate of only 30%. No life-threatening or unexpected AEs occurred.

A retrospective study evaluated the efficacy and toxicity of bendamustine in 28 patients (median 5 prior therapies) with refractory/relapsed Hodgkin lymphoma after ASCT used as part of a French compassionate use program.[17] The ORR was 50%, including 29% CR. The median PFS for all patients was 5.7 months; for patients who achieved a CR, the median PFS

Table 7. Grade 3/4 AEs in Relapsed/Refractory DLBCL Patients After Treatment With Bendamustine Plus Rituximab[14]

AE	Grade 3	Grade 4
Neutropenia	9	3
Anemia	4	0
Thrombocytopenia	3	1
Leukopenia	3	0
Lymphocytopenia	1	0

AEs indicates adverse events; DLBCL, diffuse large B-cell lymphoma.

was 10.2 months. During the first 6 cycles, 2 patients experienced febrile neutropenia and 4 patients had grade 3/4 thrombocytopenia.

In the United States, Moskowitz and colleagues recently published the results of a phase 2 study that evaluated the efficacy of bendamustine in 34 evaluable patients (median 4 prior therapies) with relapsed/refractory Hodgkin lymphoma who were ineligible for ASCT (25%) or for whom this treatment failed (75%).[18] The ORR was 56%, including 12 CRs. The median response duration was 5 months. Five patients (20% of those eligible) proceeded to ASCT after treatment with bendamustine. The most commonly reported grade ≥3 AEs were thrombocytopenia (20%), anemia (14%), and infection (14%).

Bendamustine-containing regimens are currently being investigated in 3 clinical studies in patients with Hodgkin lymphoma (**Table 9**).[5]

Solid Tumors

Phase 2 studies have demonstrated the efficacy of bendamustine in the treatment of various types of solid tumors, including small cell lung cancer,[19,20] refractory soft tissue sarcoma,[21] and relapsed or refractory germ cell cancer.[22]

Bendamustine was recently investigated in a phase 2 study in 10 women with platinum- and taxane-resistant epithelial ovarian cancer who had been treated with a median of 5 prior therapies.[23] Results showed no objective tumor response; 2 patients achieved stable disease. Overall, the regimen was associated with fatigue and gastrointestinal side effects and was not well tolerated. However, the authors noted that the patients in this study experienced less bone marrow suppression than did patients in other studies. They suggested that the lack of tolerability could reflect the degree of tumor burden within the peritoneal cavity as well as the high number of prior regimens received by the patients participating in this study.

In 2005, von Minckwitz and colleagues published the results of a large study (N=364) comparing the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) with the combination of bendamustine, methotrexate, and fluorouracil (BMF) as first-line treatment for patients with metastatic breast cancer. The study showed a significant im-

Table 8. Ongoing Clinical Trials of Bendamustine in Patients With Aggressive NHL[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 2	Bendamustine + cytarabine + etoposide + melphalan	Conditioning for autologous stem cell transplant in aggressive NHL	NCT01296256
Phase 2	Bendamustine + rituximab	Patients ≥61 years of age with aggressive B-cell lymphoma or elderly patients with aggressive B-cell lymphoma ineligible for a CHOP-like treatment	NCT01686321
Phase 2	Bendamustine + rituximab	Relapsed/refractory DLBCL	NCT01118845
Phase 2	Bendamustine + rituximab	Patients ≥65 years of age with previously untreated DLBCL	NCT01234467
Phase 1/2	Bendamustine + rituximab + lenalidomide	Aggressive B-cell lymphoma	NCT00987493
Phase 2	Bendamustine + ofatumumab	Elderly patients with newly diagnosed DLBCL who are poor candidates for R-CHOP chemotherapy	NCT01626352
Phase 1/2	Bendamustine + ofatumumab + carboplatin + etoposide	Refractory or relapsed aggressive B-cell lymphomas	NCT01458366
Phase 1	Bendamustine + rituximab + PCI-32765	Relapsed DLBCL, MCL, or indolent NHL	NCT01479842

CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab plus CHOP.

Table 9. Ongoing Clinical Trials of Bendamustine in Patients With Hodgkin Lymphoma[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 1/2	Bendamustine + lenalidomide	Relapsed or primary refractory Hodgkin lymphoma	NCT01412307
Phase 1/2	Bendamustine + gemcitabine	Relapsed or refractory Hodgkin lymphoma	NCT01535924
Phase 1/2	Bendamustine + brentuximab vedotin	Hodgkin lymphoma or anaplastic large cell lymphoma	NCT01657331

provement in time to progression – from 6.7 months with CMF to 8.2 months with BMF (P=.0071).[24] ORRs did not significantly differ between the 2 regimens. More mucositis and leukopenias were seen in the BMF group than in the CMF group.

Phase 2 studies have been conducted in Germany of single-agent bendamustine as salvage therapy for metastatic breast cancer.[25-27] In 1998, Höffken and colleagues reported the results of a phase 2 pilot study of bendamustine monotherapy as salvage treatment in 37 patients with advanced breast cancer.[25] Treatment consisted of 150 mg/m^2 bendamustine on days 1 and 2 of a 4-week treatment course. Among the 33 patients evaluable for response, an ORR of 27% was seen. However, the toxicity profile of this regimen was high; grade 3 AEs occurred in 5 patients and grade 4 AEs occurred in 3 patients. The median time to tumor progression was 2 months (range, 1-14 months). In 2007, Reichmann and colleagues reported the results of a similar phase 2 study (N=51), in which bendamustine was administered at a lower dose (120 mg/m^2).[26] Of 50 evaluable patients, 10 achieved a PR. Comparison of efficacy between the 2 trials must be done with caution because of potential differences in the study populations, the size of the studies, and improvements in response assessment over time.[28] Also in 2007, Eichbaum and colleagues conducted a study of weekly administration of bendamustine as salvage treatment in 34 patients with metastatic breast cancer.[27] Patients received 60 mg/m^2 bendamustine on days 1, 8, and 15 every 28 days for 6 cycles. Five patients (19%) achieved PRs. No grade 3 or 4 hematologic toxicities occurred. Only 3 patients experienced grade 3 nonhematologic toxicities. Steinbild and colleagues conducted a phase 2 study of bendamustine given as a flat dose of 200 mg on days 1 and 2 every 4 weeks in 22 patients with metastatic breast cancer who had been pretreated with 2 to 3 different chemotherapy regimens.[29] Among 18 patients evaluable for efficacy, 3 patients (17%) achieved a PR. The main toxicities reported were nausea, weight loss, and fatigue.

Bendamustine has also been studied in combination with paclitaxel, and results show that both drugs can be given together without dose compromises. In a phase 1 study (RiTa I), the weekly doses were established at 70 mg/m^2 for bendamustine and 90 mg/m^2 for paclitaxel.[30] A phase 2 study (RiTa II) was conducted using these recommended doses of bendamustine and paclitaxel.[31] A total of 26 patients with breast cancer (27% of whom had triple-negative breast cancer) received the combination of bendamustine and paclitaxel (15 received it as first-line therapy; 11 as beyond first-line therapy). The median PFS was 7.3 months, and the median OS, 14.9 months. The 1-year PFS rate was 20.3%, and the 1-year OS rate, 71.2%. The ORR was 42.3%, including 4 CRs and 7 PRs. Among the subset of patients with triple-negative breast cancer, the ORR was 71.4%. The subset of patients who had been pretreated with anthracyclines achieved an ORR of 43.8%.

An ongoing phase 1/2 study (NCT00834678), conducted by a group from the Ohio State University Comprehensive Cancer Center, is currently investigating the combination of bendamustine with erlotinib in treating patients with stage IIIB, stage IIIC, or stage IV breast cancer.[5]

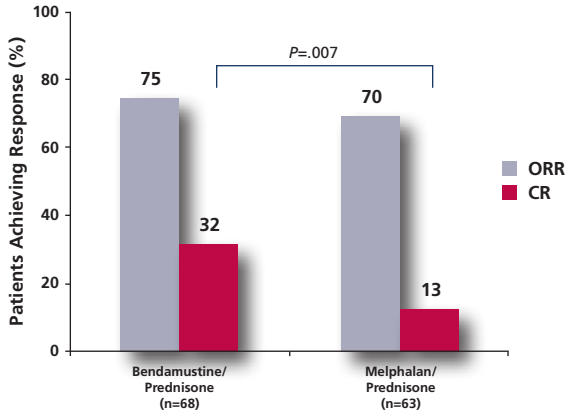
A phase 1/2 study is investigating the combination of bendamustine with erlotinib in treating patients with advanced breast cancer.

Multiple Myeloma

The efficacy of bendamustine as a first-line therapy in multiple myeloma (MM) patients not eligible for transplantation has been demonstrated in a phase 3 trial in Europe in which patients newly diagnosed were randomized to receive either a bendamustine/prednisone regimen (n=68) or standard melphalan/prednisone (n=63).[32] Results showed similar ORR with the 2 regimens, but the treatment with bendamustine led to an increased CR rate (**Figure 3**). In addition, the maximum response was achieved more rapidly in patients treated with bendamustine (6.8 vs 8.7 cycles; P<.02).

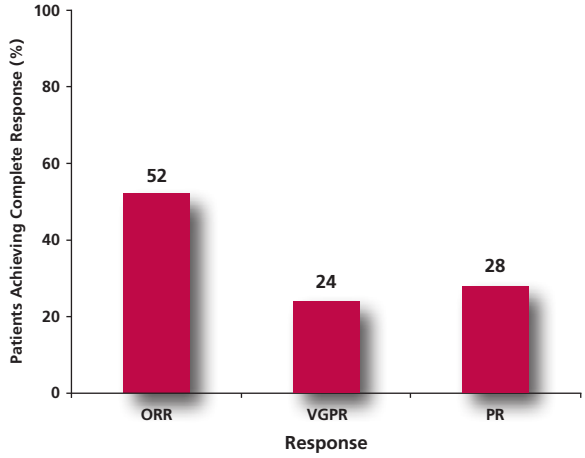
More recently, a small (N=18) study of bendamustine in combination with bortezomib and prednisone was conducted in patients with newly diagnosed MM who had severe renal

Figure 3. Response Rates in Patients Newly Diagnosed With Multiple Myeloma: Bendamustine/Prednisone vs Melphalan/Prednisone[32]



CR indicates complete response; ORR, overall response rate.

Figure 4. Response Rates in Patients With Relapsed/Refractory Multiple Myeloma: Bendamustine, Lenalidomide, and Dexamethasone[38]



ORR indicates overall response rate; PR, partial response; VGPR, very good PR.

failure (glomerular filtration rate <35 mL/min) at diagnosis.[33] Results showed an ORR of 83% (including 3 stringent CRs [sCR], 5 near CRs [nCR], and 5 very good PRs [VGPRs]) after at least 1 cycle of chemotherapy. Thirteen patients (72%) improved their renal function after treatment.

A recent phase 2 study investigated the addition of bendamustine to melphalan conditioning for ASCT.[34] At day 100 after ASCT, 79% of patients achieved an ORR, including 9 sCRs, 1 CR, and 7 VGPRs. Six patients (24%) with preexisting high-risk disease died of progressive myeloma during study follow-up, all at or beyond 100 days after ASCT. The authors concluded that bendamustine up to a dose of 225 mg/m^2 added to ASCT conditioning with high-dose melphalan did not exacerbate expected toxicities.

The NCCN Guidelines for MM recommends bendamustine as salvage therapy for patients with relapsed/refractory disease.

The latest version of the National Comprehensive Cancer Network Guidelines for MM recommends bendamustine as salvage therapy, both as monotherapy and in combination with lenalidomide and dexamethasone, for patients with relapsed/refractory disease.[35] In a trial by Knop and colleagues, 31 patients who had experienced relapse after high-dose chemotherapy and ASCT were enrolled to receive increasing doses of bendamustine.[36] The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90-100 mg/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients showed that bendamustine is effective and tolerable in patients with advanced progressive myeloma, with an ORR of 36%.[37] A multicenter phase 1/2 study (N=29) investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients with relapsed/refractory MM.[38] Results showed that 52% (n=13) of the 25 evaluable patients achieved an objective response, including 24% (n=6) who reached a VGPR and 28% (n=7) who reached a PR (**Figure 4**). The median PFS was 6.1 months (95% CI, 3.7-9.4 months), and the 1-year PFS rate was 20% (95% CI, 6%-41%).

Bendamustine has also been studied in combination with prednisolone and thalidomide. In a phase 1 study in 28 patients with refractory or relapsed MM after ASCT or conventional chemotherapy, bendamustine in combination with prednisolone and thalidomide resulted in an ORR of 86%.[39] Median PFS was 11 months and median OS was 19 months.

In addition, bendamustine has been studied in combination with bortezomib. In a recent open-label phase 1/2 study, the combination of bendamustine and bortezomib was assessed in 40 heavily pretreated patients with relapsed/refractory MM. The ORR was 48% (including 1 CR and 2 VGPRs).[40] In another study, patients not responding to a bortezomib/dexamethasone regimen received a triple therapy

Table 10. Ongoing Clinical Trials of Bendamustine in Patients With MM[5]

Stage of Development	Regimen	Study Population	Clinical Trial Registry Number
Phase 2	Bendamustine	MM	NCT01179490
Phase 2	Bendamustine + bortezomib	Relapsed/refractory myeloma	NCT01315873
Phase 2	Bendamustine + bortezomib + prednisone	Newly diagnosed MM	NCT01376401
Phase 2	Bendamustine + bortezomib + dexamethasone	First-line treatment of patients with MM who are not candidates for high-dose chemotherapy	NCT01056276
Phase 1/2	Bendamustine + bortezomib + pegylated liposomal doxorubicin	MM	NCT01177683
Phase 2	Bendamustine + bortezomib + simvastatin + zoledronic acid + high-dose methylprednisolone	Relapsed/refractory MM	NCT01332617
Phase 1/2	Bendamustine + weekly bortezomib + lenalidomide + dexamethasone	MM	NCT01484626
Phase 2	Bendamustine + lenalidomide + dexamethasone	Second-line therapy for relapsed or refractory MM	NCT01701076
Phase 1/2	Bendamustine + lenalidomide + prednisone	Relapsed or refractory MM	NCT01002703
Phase 1/2	Bendamustine + lenalidomide + dexamethasone	Relapsed MM	NCT01049945
Phase 1/2	Bendamustine + lenalidomide + low-dose dexamethasone	Relapsed MM	NCT01686386
Phase 2	Bendamustine + thalidomide + dexamethasone	Patients with MM refractory to treatment with lenalidomide and bortezomib or who are ineligible to receive one of these drugs	NCT01526694
Phase 2	Bendamustine + etoposide + dexamethasone + filgrastim	Peripheral blood stem cell mobilization in treating patients with refractory or recurrent lymphoma or MM	NCT01110135
Phase 1/2	Bendamustine + rituximab + veliparib	Advanced lymphoma, MM, or solid tumors	NCT01326702
Phase 1/2	Bendamustine + pomalidomide + dexamethasone	Relapsed/refractory MM	NCT01754402
Phase 1	Conditioning with bendamustine + melphalan followed by transplant	MM	NCT00916058

MM indicates multiple myeloma.

consisting of bendamustine, bortezomib, and dexamethasone, which resulted in a 57% ORR.[41]

A recently published retrospective study assessed hematology/oncology department medical records of 78 patients with relapsed or refractory MM treated between 2005 and 2011 who received the combination of bendamustine, bortezomib, and prednisone.[42] Results showed that 69% (n=54) of patients achieved an objective response (including 3 CRs, 10 nCRs, and 10 VGPRs) after at least 1 cycle of chemotherapy. Among the 45 patients without severe hematologic toxicities due to previous treatments, the median PFS was 11 months and the median OS was 50 months. However, among the 33 patients with grade 3/4 hematologic toxicities, the median PFS was 3 months and the median OS was 5 months.

Bendamustine and bendamustine-containing regimens are currently being investigated in 16 clinical studies in patients with MM (**Table 10**).[5]

Conclusion

As evidenced by the large number of ongoing clinical investigations of bendamustine and bendamustine-containing regimens, the oncology and hematology/oncology communities are very interested in exploring the potential of this chemotherapy drug – especially in combination with novel

agents that are emerging. Therefore, a large number of studies are currently being conducted using regimens with a bendamustine backbone, and experts predict that more of these studies will be initiated in the future.[43] ■

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Advances in Bendamustine Clinical Trials

Colleen Ross, RN, MSN, MHA, OCN

Bendamustine is currently approved for the treatment of chronic lymphocytic leukemia (CLL), and many ongoing studies are investigating its efficacy in drug combinations. Data in the relapsed/refractory setting are promising regarding improved overall survival and manageable toxicities, such as reversible myelosuppression, nausea, and fatigue – nursing implications mandate careful patient monitoring and management of these adverse effects. To this end, knowledge of the toxicity profile of bendamustine and combination therapy will improve patient outcomes.

Lymphoid Malignances

Therapy with bendamustine and rituximab in CLL has demonstrated efficacy in the relapsed/refractory setting. The most common adverse effect was myelosuppression, in the form of neutropenia, anemia, and thrombocytopenia.[1] Twenty-one clinical trials are currently ongoing for patients with CLL. Other trials include combinations such as bendamustine, rituximab, and fludarabine. Using the combination of alemtuzumab and bendamustine for a patient population in which 84% were previously treated with fludarabine, an overall response rate (ORR) of 70% was reported, including a 26% complete response (CR) and 44% partial response (PR) rate.[2]

Indolent and Mantle Cell NHLs

Seventeen ongoing clinical trials are investigating the use of combination therapy in indolent non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL). Bendamustine plus rituximab is approved for use in the first-line setting for the treatment of MCL. Compared with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), bendamustine and rituximab resulted in longer progression-free survival (57.2 vs 30.9 months in patients achieving PR).[3] Another study presented at the 2012 American Society of Hematology Annual Meeting investigated bendamustine versus R-CHOP/R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone).[4] Again, the ORR was impressive: 94% for bendamustine and rituximab versus 84% for R-CHOP/R-CVP. In the MCL group, bendamustine and rituximab resulted in a significantly higher CR rate than did R-CHOP/R-CVP (51% vs 24%; *P*=.018). Other combinations under investigation include bendamustine, rituximab, and bortezomib; idelalisib (GS-1101) plus rituximab and/or bendamustine; and bendamustine plus ofatumumab. A bendamustine, rituximab, and cytarabine combination has been studied in patients in the first-line setting, relapsed and refractory. These patients did not qualify for an autologous stem cell transplant (ASCT). Promising results were shown with an ORR of 100% in treatment-naive patients, including a 95% CR rate. In patients with relapsed/refractory disease, ORR was 80%, with a 70% CR rate.[5]

Aggressive NHL

Eight trials are ongoing trials for aggressive NHL. At the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, bendamustine plus rituximab presented efficacy in relapsed/refractory diffuse large B-cell lymphoma. These patients were ineligible for ASCT. During the 2010 ASCO Annual Meeting presentation, ORR reported was 58%, including a 19% CR rate.[6]

> Data in the relapsed/refractory setting are promising regarding improved overall survival and manageable toxicities.

Other Malignancies

Combination therapies with bendamustine are in clinical trials for other disease sites as well. Current trials for Hodgkin lymphoma are investigating bendamustine coupled with drugs such as lenalidomide, gemcitabine, and brentuximab vedotin. Sixteen clinical trials are ongoing for multiple myeloma (MM). For newly diagnosed patients with MM receiving either bendamustine/prednisone or melphalan/prednisone, ORR was 75% versus 70%, respectively, and a significantly higher number achieved CR with bendamustine (32% vs 13%; *P*=.007).[7] In addition, maximum response was noted to be faster in the bendamustine arm. Other studies include bendamustine/bortezomib/prednisone in patients who are compromised renally, and a conditioning trial of bendamustine and melphalan for patients undergoing bone marrow transplant. Solid tumor ongoing treatment studies include non–small cell lung cancer, metastatic breast cancer, and sarcoma.

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The Developing Treatment Role of Bendamustine

Susanne Liewer, PharmD, BCOP

Bendamustine has demonstrated activity as monotherapy and in combination for patients with lymphoid and hematologic as well as solid tumors. In the United States, bendamustine has been approved by the FDA for the treatment of patients with indolent B-cell non-Hodgkin lymphoma (NHL) who have progressed during or within 6 months of receiving rituximab or a rituximab-containing regimen and in patients with chronic lymphocytic leukemia (CLL). However, the efficacy of bendamustine in CLL relative to first-line therapies other than chlorambucil has not been established.

While bendamustine has already received FDA approval for its use in the CLL population, its role in the treatment of patients with CLL continues to evolve. Initial studies of bendamustine in CLL were generally single-agent trials in relapsed/refractory patients. Based on the activity of bendamustine and its favorable side effect profile, it is often tested in combination with other therapies to optimize outcomes.

> The role of bendamustine in the treatment of patients with chronic lymphocytic leukemia continues to evolve.

Phase 1 and 2 trials combining bendamustine with rituximab, alemtuzumab, or fludarabine and rituximab have reported response rates of 50% to 70% in previously treated patients.[1-3] These trials conveyed toxicities such as myelosuppression, nausea, and fatigue. While the activity of bendamustine in the relapsed and refractory populations has been reported, the role of bendamustine in therapy-naive patients continues to be refined. The CLL10 trial, sponsored by the German CLL Study Group, is a phase 3 randomized study comparing fludarabine, cyclophosphamide, and rituximab (FCR) with bendamustine and rituximab in previously untreated patients with CLL. This trial has completed enrollment, and the forthcoming outcomes will provide much needed information regarding the use of bendamustine as frontline therapy.

Bendamustine is also an effective agent in the treatment of indolent NHL and mantle cell lymphoma (MCL). Studies report activity among patients refractory to rituximab.[4] As with CLL, the role of bendamustine in frontline therapy continues to develop. The results of 2 phase 3 trials comparing bendamustine plus rituximab (BR) with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were recently published. The German Study Group for Indolent Lymphoma trial included over 500 therapy-naive patients, including a subset of patients with MCL. Both regimens had response rates over 90%, with the BR group reporting complete responses (CRs) in 39.8% compared with 30% in the R-CHOP group (P=.021). Patients who achieved a CR were associated with a prolonged progression-free and overall survival.[5] Investigators from the BRIGHT trial, another phase 3 trial, also reported their experience comparing BR and R-CHOP/rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) as frontline therapy in indolent NHL. They reported response rates similar to the aforementioned study (94% vs 84%). The CR rates for the regimens were similar; however, the subset of patients with MCL had a higher CR rate in the BR group compared with the R-CHOP/R-CVP arm. The BRIGHT trial also highlighted the difference between the toxicity profiles of the regimens. The R-CHOP/R-CVP group was more likely to have dose reductions, and fewer patients in the BR group reported neutropenia, suggesting that the BR combination is less myelosuppressive.[6]

Bendamustine is a versatile agent that has activity in a variety of malignancies such as Hodgkin lymphoma, multiple myeloma, and even solid tumors. In several European countries, bendamustine has an indication for the treatment of multiple myeloma. Several clinical trials have reported efficacy with bendamustine either as monotherapy or in combination with other agents for patients not eligible for an autologous transplant or for those with relapsed or refractory disease. For patients with Hodgkin lymphoma, bendamustine has demonstrated activity in case studies and in small trials in patients with relapsed disease after stem cell transplantation. Monotherapy with bendamustine was able to produce durable responses in order to bridge patients to allogeneic stem cell transplant.[7] Finally, bendamustine has also been studied in a variety of patients with relapsed or refractory solid tumors, including small cell lung cancer, soft tissue sarcomas, germ cell tumors, and ovarian and breast cancer. While ben-

damustine has some activity in all of these tumor types, a considerable amount of data has been published on its use with metastatic breast cancer both as initial therapy and in the salvage setting.

Cancer treatments have made tremendous progress in the past 20 years. Patients are surviving the diagnosis of cancer and living longer with their disease. However, many patients still succumb to their disease. Clinicians remain actively engaged in improving existing therapies and providing more options to cancer patients. Bendamustine is an effective agent with a toxicity profile that provides clinicians with the ability to use it as monotherapy or in combination in a variety of malignancies in the battle against cancer. ■

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Advances in Bendamustine Clinical Trials

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Summary

Bendamustine, either alone or in combination therapy, has proven to have efficacy in lymphoma and CLL. As clinical trials continue, we hope in the near future to see treatment protocols that are effective, minimize toxicities, and help improve patient outcomes and quality of life. Clinical trial information is an important part of educating our patients, empowering them to choose among treatment options. Clinical Web sites, such as www.clinicaltrials.gov, are a good resource for patients to access information on current trials and locations. ■

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Bendamustine: Progress in Clinical Investigations

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At the 54th Annual Meeting of the American Society of Hematology, a number of abstracts were presented demonstrating the efficacy and toxicities of bendamustine either alone or in combination with other agents for the treatment of several lymphoid malignancies such as chronic lymphocytic leukemia (CLL) and indolent as well as aggressive non-Hodgkin lymphoma (NHL). In most of these trials, bendamustine was combined with a monoclonal antibody such as rituximab, ofatumumab, or alemtuzumab. In addition, a third agent has now been combined in many of the more recent trials, such as fludarabine in CLL or bortezomib, idelalisib (GS-1101), or cytarabine for NHL. All of these trials demonstrated toxicity that was acceptable and expected, such as mild to moderate neutropenia, anemia, and thrombocytopenia. The response rates are high in the patients on these trials; however, further follow-up will be needed for the long-term outcomes. Bendamustine is also being evaluated for other uses such as treatment of Hodgkin lymphoma. A few trials in Hodgkin lymphoma are currently available that combine bendamustine with several agents, including lenalidomide, gemcitabine, and brentuximab vedotin. Results from these interesting trials are pending.

> The clinical usefulness of bendamustine may be much broader than the current indication.

More recently, bendamustine has also been evaluated for the treatment of several solid tumors, including small cell lung cancer, ovarian cancer, and metastatic breast cancer. Additional small studies have been performed in patients with soft tissue sarcoma and refractory germ cell neoplasms. The results from these trials are outlined in the article. Bendamustine has also been used as a first-line therapy in patients with multiple myeloma. The patients in this trial had an overall response rate similar to that achieved with standard therapy. Combination therapy with bortezomib or lenalidomide in patients with multiple myeloma has also shown promise. A phase 2 dose-escalation study of bendamustine plus standard high-dose melphalan as a conditioning regimen for autologous stem cell transplantation has also been performed. In this study, bendamustine could be dose escalated to 225 mg/m^2 without any added toxicities.

With the demonstrated activity and versatility of bendamustine as well as the ability to combine it with many other active agents, the clinical usefulness of bendamustine may be much broader than the current indication. Future clinical trials will be needed to confirm the reported effectiveness. ■

Bendamustine: Ongoing Clinical Investigations

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