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REVIEW

Bendamustine in the Management of Non-Hodgkins Lymphoma

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Abstract: Bendamustine is a unique bifunctional cytotoxic agent that includes a nitrogen mustard group with alkylating properties and a benzimidazole ring with potential antimetabolite properties. It shows only partial cross-resistance with other alkylators *in vitro* and remains highly active in heavily pretreated patients. The history of bendamustine began in the former East German Democratic Republic, where it was developed in the early 1960s. Re-discovered in the 1990s, it demonstrated excellent response rates in several clinical trials with a favorable side-effect profile leading to its approval in 2008 by the U.S. Food and Drug Administration for the treatment of patients with chronic lymphocytic leukemia and for the treatment of patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma. Further studies showed efficacy in the first-line treatment of B-cell NHL and in the treatment of patients with multiple myeloma. We review the data on bendamustine published so far and discuss the future role of this promising agent in the treatment of patients with lymphoproliferative malignancies.

Keywords: bendamustine, alkylating agent, indolent non-Hodgkin lymphoma, chronic lymphocytic leukemia, lymphoproliferative disorders, multiple myeloma

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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogenous group of malignancies that differ in various factors, just like histology, immunophenotype and cytogenetics. An estimated 65.980 new cases of NHL will be diagnosed in the USA in year 2009, and there will be 19.500 NHL-related deaths.[1] Over the last years new agents, especially the monoclonal antibody rituximab, have entered clinical practise, leading to a great advance in the treatment of NHL.[2–4] Although high response rates can usually be achieved with first-line chemotherapy, lymphoproliferative disorders tend to relapse or become refractory over time, going along with the need of a second and further treatment regimens. This highlights the need of substances, which are highly active in patients with relapsed or treatment refractory lymphoma, are able to induce long term remissions and are associated with a low toxicity in the context of pretreated patients.

In recent years the alkylating agent bendamustine has been re-discovered and used in several trials. The history of bendamustine began in the former East German Democratic Republic, where it was developed in the early 1960s by Ozegowski et al.[5] At this time bendamustine showed activity in a variety of malignancies including chronic lymphocytic leukemia (CLL),[6] multiple myeloma,[7] Hodgkin's disease, B-cell lymphoma and lung cancer,[8] but for political reasons it was not widely studied. After the fall of the Berlin Wall a number of well-designed studies have shown promising results of bendamustine in NHL.[9–12] Based on a multicenter European phase III study, bendamustine was approved in 2008 by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL.[13] Shortly afterwards the FDA approved bendamustine for the treatment of patients with indolent B-NHL that progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. This article reviews the presently available data of bendamustine.

Pharmacological Profile

Bendamustine is a white, water soluble microcrystalline powder with amphoteric properties. Its chemical name is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-,monohydrochloride. The aim in the development of bendamustine was to form a bifunctional anticancer agent with alkylating as well as antimetabolite properties. Bendamustine consists of three structural elements: a nitrogen mustard group, a benzimidazole ring and a butyric acid side chain (Fig. 1). The nitrogen mustard group is similar to other alkylators like cyclophosphamide or melphalan and gives the drug its alkylating properties. The benzimidazole ring is similar in structure to some purines, like fludarabine. This compound makes bendamustine unique.

The exact mechanism of action is not completely understood. However, the published data demonstrate that bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases.[14] Notably, bendamustine is associated with more DNA double-strand breaks than melphalan, cyclophosphamide or carmustine.[15] In addition, the DNA double-strand breaks are more durable than those induced by other alkylating agents.[15] Leoni et al could demonstrate that bendamustine does not show cross-resistance with other cytotoxic drugs and displays a distinct pattern of activity unrelated to other DNA-alkylating agents.[16,17] Additional mechanisms of action include activation of DNA-damage stress response and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe.[17] Unlike other alkylators, bendamustine activates a base excision DNA-repair pathway rather than an alkyltransferase DNA-repair mechanism.[17] These characteristics may contribute to its clinical efficacy in lymphoma patients relapsed after or prior refractory to alkalyting agent treatment.

In spite of the fact that bendamustine is in clinical use for over 40 years, only limited data has been published with regard to the pharmacokinetics of bendamustine. It is highly (>95%) protein bound, primary albumin, but only free bendamustine is active.[18] In the study of Matthias et al bendamustine underwent extensive

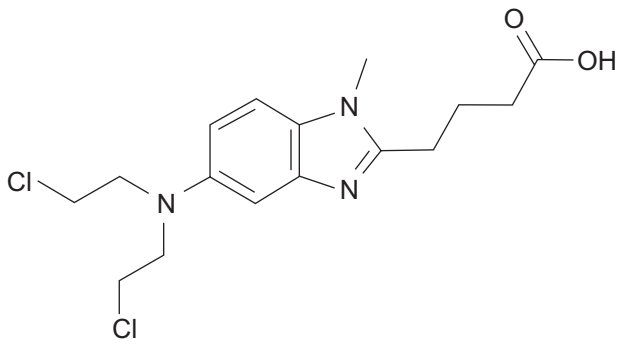

Figure 1. Structure of bendamustine.

first-pass metabolism.[19] After iv administration it was rapidly eliminated with a biphasic half-life of 7 minutes and 32 minutes. The elimination of bendamustine occured predominantly by the renal route. Mean total clearance was 826 mL/min and was independent of dosage over the tested range of 0.5–5 mg/kg. In a phase I study of Rasschaert et al patients with solid tumors received bendamustine on days 1 and 2 every 3 weeks.[20] Mean plasma pharmacokinetic profile values were tmax of 35 minutes with a mean elimination half-life of 49 minutes and a clearance of 265 mL/min/m^2, with no evidence for dose dependency. The mean total amount of bendamustine and its metabolites recovered in the first micturition was 8.3% (range 2.7%–26%). Recently, Owen et al analyzed the pharmacokinetic profile of bendamustine in patients with indolent NHL achieving bendamustine 120 mg/m^2 on days 1 and 2 every 3 weeks.[21] The concentration of bendamustine declined in a triphasic manner, with rapid distribution, intermediate, and slow terminal phases. The intermediate half-life was 40 minutes. Notably, neither moderate renal nor mild liver impairment altered pharmacokinetics. Nevertheless, bendamustine has not been systematically studied in patients with severe renal or hepatic impairment and therefore should be administered with caution to patients with a creatinine clearance <40 mL/min or with an aspartate aminotransferase level or alanine aminotransferase level >2.5 times or bilirubin >3 times the upper limit of normal.[22] Further studies will be required to clarify optimal dosing strategies.

Bendamustine in Chronic Lymphocytic Leukemia

First-line treatment

Monotherapy with the alkylating agent chlorambucil has been the 'gold standard' in front—line therapy of CLL for several decades. Based on early phase II studies in Germany[10–12] an European phase III randomized multicenter trial was undertaken to compare the efficacy and safety of bendamustine with that of chlorambucil in untreated patients with advanced CLL (Table 1).[13] Overall, 319 patients younger than 75 years were randomly assigned to receive bendamustine 100 mg/m^2 on 2 consecutive days or chlorambucil 0.8 mg/kg orally on days 1 and 15 every 4 weeks. Seventy-two percent of patients in the bendamustine group and 71% in the

Table 1. Studies of bendamustine in chronic lymphocytic leukemia.

Study	Phase	No	Status	Dose mg/m^2 (days administered)	ORR (%)	CR (%)
Bergmann[29]	I/II	16	Relapsed, refractory	B 70 (d 1 + 2) every 28 d	56	13
Lissitchkov[30]	I/II	15	Relapsed, refractory	B 100 (d 1 + 2) every 28 d	60	27
Kath[10]	II	23	Pretreated (n = 10) Untreated (n = 13)	B 50–60 (d 1–5) every 28 d	75	36
Avaido[11]	II	21	Relapsed, refractory	B 100 (d 1 + 2) every 28 d	67	29
Bremer[12]	II	15	Relapsed, refractory	B 60 (d 1–5) every 28 d	93	7
Fischer[33]	II	81	Relapsed, refractory	B 70 (d 1 + 2) + Rit 375–500 (d 1) every 28 d	77	15
Fischer[28]	II	117	Untreated	B 90 (d 1 + 2) + Rit 375–500 (d 1) every 28 d	91	33
Knauf[13]	III	319	Untreated	B 100 (d 1 + 2) every 28 d vs.	68	31
				Clb 0.8 mg/kg (1 + 15) every 28 d	31	2

Abbreviations: ORR, overall response rate; CR, complete remission; B, bendamustine; Rit, rituximab; Clb, chlorambucil.

chlorambucil group had Binet stage B disease, while 28% and 29%, respectively, had stage C disease. Overall response rates (ORR) were 68% for bendamustine and 31% for chlorambucil ($P < 0.0001$). Remarkably, 31% of the patients treated with bendamustine showed complete responses, which was significantly higher than 2% with chlorambucil ($P < 0.0001$). The median progression-free survival (PFS) was also prolonged for patients treated with bendamustine with a median of 21.6 months in comparison to 8.3 months in the chlorambucil group ($P < 0.0001$). Furthermore, bendamustine treatment was associated with a longer duration of remission (21.8 versus [vs.] 8.0 months). The incidence of grade 3 to 4 neutropenia according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) was higher in the bendamustine group (23% vs. 11%).[23] Severe grade 3 to 4 infections occurred in 8% of bendamustine-treated patients and 3% of chlorambucil-treated patients. Based on these results bendamustine was approved in 2008 by the FDA for the treatment of patients with CLL. However, the role of bendamustine monotherapy as first-line treatment remains unclear, because alternative treatment options, for example with fludarabine alone or in combination with cyclophosphamide showed high effectiveness in upfront CLL treatment with ORR from 59 to 95%.[24–27] Therefore comparing trials are warranted.

Between March 2007 and September 2008 117 untreated patients were enrolled in a German CLL study group (GCLLSG) protocol consisting of BR (90 mg/m^2 of bendamustine on days 1–2 + rituximab 375 mg/m^2 day 1 cycle 1 and rituximab 500 mg/m^2 day 1 cycle 2–6).[28] Median age was 64 years. ORR was 91% with 33% complete remissions (CR). Treatment related mortality occurred in 2.6%. With grade 3 to 4 anemia in 5%, grade 3 to 4 neutropenia in 7% and grade 3 to 4 thrombocytopenia in 6%, myelosuppression was the most frequent adverse event. Based on this data, the GCLLSG activated a phase III trial (CLL 10 protocol) in October 2008, which compares FCR with BR (90 mg/m^2 of bendamustine on days 1–2 + rituximab 375 mg/m^2 day1 cycle 1 and rituximab 500 mg/m^2 day1 cycle 2–6) in previously untreated CLL patients.

Relapsed or refractory CLL

Early phase II studies conducted in Germany using bendamustine monotherapy in pretreated patients showed promising results (Table 1).[10–12] Response rates ranged between 67 and 93% and a favorable safety profile was documented. The main toxicities were hematological, whereas non-hematologic side effects including reversible reduction of performance status, nausea/vomiting and diarrhea were mild and uncommon. Most important, alopecia did not occur. In these studies patients received 100 mg/m^2 of bendamustine on days 1 and 2 every 3 weeks or 5-day cycles of daily 60 mg/m^2 (50 mg/m^2 for patients older than 70 years) every 4 to 6 weeks.

As a result of a phase I study, the GCLLSG recommended a dose of 70 mg/m^2 of bendamustine on 2 consecutive days every 4 weeks as monotherapy for patients with relapsed disease.[29] On the contrary Lissitchkov et al recommended a dose of 100 mg/m^2 of bendamustine on 2 consecutive days every 4 weeks for relapsed or refractory patients, but this study only contained fludarabine-naive patients.[30] Based on the previous phase I study of the GCLLSG and encouraging *in vitro* data, which demonstrated synergistic effects of bendamustine and rituximab,[31,32] the phase II CLL2 M study was initiated.[33] Eighty-one relapsed patients received 70 mg/m^2 of bendamustine on days 1 and 2 plus 375 mg/m^2 of rituximab on day 1 of the first cycle and 500 mg/m^2 on day 1 of following cycles administered every 4 weeks. ORR was 77%, including 15% CR. Reversible myelosuppression including grade 3 to 4 neutropenia and thrombocytopenia occurred in 12% and 9%, respectively. Similar results with regard to response rates were obtained with a combination of fludarabine, cyclophosphamide and rituximab (FCR) in relapsed or refractory patients,[4] but FCR induced more neutropenias than bendamustine plus rituximab (BR).

Bendamustine in Indolent NHL

Bendamustine monotherapy

Based on an early widespread use of bendamustine in the former German Democratic Republic, Heider and Niederle conducted the first study with bendamustine as a monotherapy in relapsed low-grade NHL (Table 2).[9] Bendamustine was administered to 58 patients with a median age of 63 years at a dose of 120 mg/m^2 on two consecutive days every 3 weeks. All patients had been previously treated with an alkylating agent in their medical history. ORR was 73% with 11% CR. The median duration of remission was 16 months and the median survival time was

Table 2. Studies of bendamustine monotherapy in non-Hodgkin lymphoma.

Study	Phase	No	Status	Dose mg/m² (days administered)	ORR (%)	CR (%)	PFS or TTP months
Heider[9]	II	58	Relapsed, refractory	B 120 (d 1 + 2) every 21 d	73	11	TTP 16
Bremer[12]	II	62	Relapsed, refractory	B 60 (d 1–5) every 4–6 weeks	82	15	–
Friedberg[34]	II	76	Relapsed, refractory	B 120 (d 1 + 2) every 21 d	77	34	PFS 7
Ogura[38]	II	69	Relapsed, refractory	B 120 (d 1 + 2) every 21 d	91	67	–
Kahl[35]	III	100	Relapsed, refractory	B 120 (d 1 + 2) every 21 d	75	17	PFS 9

Abbreviations: ORR, overall response rate; CR, complete remission; PFS, progression-free survival; TTP, time to progression; B, bendamustine.

36 months. The regimen was well tolerated. The second study including 102 pretreated patients with different indolent lymphomas (CLL n = 15, immunocytic NHL n = 46, Multiple Myeloma n = 25, others n = 16) was published by Bremer in 2002.[12] Patients received 5-day cycles of daily 60 mg/m² bendamustine at intervals of 4–6 weeks. Bremer reported an ORR of 77%, a median duration of response of 39 months for patients with NHL and of 17 months for patients with multiple myeloma. Non hematological side effects WHO grade III/IV occurred in less than 5% of the patients. Reversible myelosuppression including grade 3 to 4 neutropenia and thrombocytopenia occurred in 25% and 12% of patients, respectively. No treatment-related mortality was observed.

To confirm the promising results of these German trials, two multicenter single-agent studies were conducted in North America. In the phase II study of Friedberg et al 76 patients with a median age of 38 years with relapsed, refractory or transformed indolent NHL (predominantly indolent 80%, transformed 20%) and a prior refractoriness to rituximab were enrolled in the United States.[34] Refractoriness to rituximab was defined as progressing within 6 months of receiving the first dose of a rituximab-containing regimen. Patients had received a median of two prior unique regimens. Bendamustine 120 mg/m² was administered on days 1 and 2 every 3 weeks for 6–12 cycles. An ORR of 77% was documented with 15% CR, 19% unconfirmed CR, and 43% partial remissions (PR). Of note, the ORR in alkylator-resistant patients was 61% and thus not notably inferior in comparison to alkylator-responding patients. Although remission rates in this heavily pretreated patient group were promising, the achieved remissions did not last long. The median duration of response for all patients was 7 months and 9 months for patients with indolent disease, and 2 months for those with transformed disease. With grade 3 to 4 reversible anemia in 12%, grade 3 to 4 neutropenia in 54% and grade 3 to 4 thrombocytopenia in 25%, myelosuppression was the most frequent adverse event. A multicenter phase III study conducted in the United States and Canada including a more homogenous patient group consisting of 100 patients with rituximab-refractory,[35] indolent B-cell lymphoma confirmed the results of Friedberg et al later on.[34] Histologies included follicular (62%), small lymphocytic (21%) and marginal zone (16%) lymphomas. Patients had received a median of two previous regimens (range, 0–6), whereas 91 of 100 patients had obtained prior alkylant-agent therapy.Thirty-six percent of the patients were refractory to their most recent chemotherapy regimen. In this trial bendamustine was administered in the same dose and schedule as in the study of Friedberg et al[34] and was given for 6 to 8 cycles. An encouraging ORR of 75% with 14% CR, 3% unconfirmed CR, and 58% PR was documented. The efficacy was comparable in the different histologic subtypes: 74% among 62 patients with follicular lymphoma and 71% among 21 patients with small lymphocytic lymphoma. PFS of all patients was 9.3 months and the median duration of response was 9.2 months. Once again, major toxicities of bendamustine were reversible myelosuppression

with grade 3 to 4 neutropenia in 61%, thrombocytopenia in 25%, and anemia in 10%. The results of these two North American studies show the clinical activity and the acceptable toxicity profile of bendamustine in rituximab-refractory patients. Moreover the results are comparable to the response rates achieved with I^{131}-tositumomab in B-cell lymphoma, progressive after rituximab[36] and Y^{90}-ibritumomab in rituximab-refractory follicular NHL.[37] On October 31, 2008, the FDA approved bendamustine for the treatment of patients with indolent B-NHL that progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Recently, Ogura et al presented the data of a multicenter phase II study including 69 patients with relapsed or refractory indolent B-NHL consisting of follicular lymphoma in 75%, and mantle-cell lymphoma in 16% of patients.[38] Bendamustine was administered at a dose of 120 mg/m^2 on days 1 and 2 of each 21-day treatment cycle for up to 6 cycles. Median number of unique prior therapies was 2 with a range of 1–16, whereas 96% of the patients had received rituximab as prior therapy. A formidable ORR of 91% including 67% CR was documented. Median PFS was not reached at a median follow-up duration of 248 days.

In conclusion the remission rates achieved with bendamustine monotherapy in patients with indolent NHL are high, but its duration is relative short. Therefore, bendamustine has been combined with other agents to improve the outcome.

Bendamustine in combination with other cytotoxic substances

Several cytotoxic substances have been combined with bendamustine in the past, but these trials mostly contained a small number of patients. Four studies administered bendamustine in combination with vincristine and prednisone incorporating a total of 157 patients.[39–42] ORR ranged from 66%–90% with a CR rate of 22%–45% and a PR rate of 41%–52%. Heck et al treated 29 patients with a combination of bendamustine and mitoxantrone achieving an ORR of 59% including 7% CR and 52% PR.[43] The combination of mitoxantrone, methotrexate and prednisone with bendamustine was used by Kath et al in 23 patients achieving an ORR of 48% (CR 13%, PR 35%).[44] In another small study bendamustine plus oral etoposide was administered in 38 patients, reporting a high ORR of 97% including 67% CR.[45] In the same year an ORR of 79% (CR 29%, PR 50%) in 18 patients treated with bendamustine plus idarubicine and dexamethasone was published.[46]

Based on *in vitro* data suggesting a synergistic effect of bendamustine plus a purine analoga,[47] a phase I/II study including 29 patients with relapsed or refractory indolent lymphoma was conducted by the East German Study Group Hematology and Oncology (OSHO) combining bendamustine with fludarabine.[48] Bendamustine was given at 30 or 40 mg/m^2/d, fludarabine at 30 mg/m^2/d, each drug on days 1 to 3 every 4 weeks. Analysis of 19 evaluable patients treated with the 40 mg/m^2 dose of bendamustine revealed hematotoxicity NCI-CTC grade III in 47% and grade IV in 26%. One patient with the 40 mg/m^2 dose of bendamustine died of sepsis in neutropenia with persistent thrombocytopenia. As a consequence, 30 mg/m^2/d of both drugs on days 1 to 3 was defined as the recommended dose. ORR was 77%. After a median follow up of 14 months 8 of 15 responders relapsed.

The largest evidence derives from a randomized phase III study from OSHO comparing a BOP regimen (bendamustine 60 mg/m^2 days 1–5, vincristine 2 mg on day 1, prednisone 100 mg/m^2 days 1–5) with a standard COP regimen (cyclophosphamide, vincristine, prednisone).[49] No significant difference was seen in 164 patients with previously untreated advanced follicular lymphoma, immunocytoma or mantle cell lymphoma with regard to response rates between BOP (ORR 66%, CR 22%) and COP (ORR 76%, CR 20%). The projected 5-year survival rate for all patients was 61% with BOP and 46% with COP. In a subgroup analysis of responding patients (CR, PR) the advantage in the projected 5-year survival rate reached significance with BOP (74% vs. 56%; $P = 0.05$). Moreover, the BOP regimen was also less toxic with an incidence of grade 3 to 4 leucopenia of 19% vs. 34% ($P < 0.0001$) in the COP group.

Bendamustine regimens including rituximab

Besides combinations with other cytotoxic agents, combination with rituximab seems most promising due to the tremendous improvement of patients outcome by rituximab in the past.

Based on *in vitro* data showing a synergistic cytotoxic effect of bendamustine plus rituximab in lymphoma cell lines,[31,32] a phase II study including 63 patients with a median age of 63 years and relapsed or refractory lymphoma was conducted by the Study Group Indolent Lymphoma, Germany (StiL) combining bendamustine with rituximab (Table 3).[50] Histologies were 24 follicular, 16 mantle cell, 17 lymphoplasmacytoid, and 6 marginal zone lymphoma. Prior treatment with rituximab was excluded. Bendamustine was administered at a dose of 90 mg/m^2 on days 1 and 2, combined with 375 mg/m^2 rituximab on day 1 every 4 weeks. ORR for all patients was 90% with 60% CR. The remissions were reasonably durable with a median PFS of 24 months. The probability of survival after 4 years was 55%. In mantle cell lymphomas an ORR of 75% including 50% CR was achieved. Of note, the incidence of WHO grade 3 or 4 hematotoxicity was remarkably low in this study with 16% of patients showing neutropenia, 3% thrombocytopenia, and 1% anemia.

The good results of the German study prompted a confirmatory study in North America. Robinson et al administered the same regimen in 66 patients with relapsed, indolent B-cell or mantle cell lymphoma without documented resistance to prior rituximab.[51] Histologies included follicular NHL in 61% of patients, mantle cell lymphoma in 18%, CLL/SLL in 15%, lymphoplasmocytic lymphoma in 3%, and marginal zone lymphoma in 3%. Median age was 60 years and 82% had stage III-IV disease. ORR was 92% (41% CR, 14% unconfirmed CR, and 38% PR) and median PFS was 23 months. Patients with prior rituximab therapy had a lower ORR of 86%, but this difference was not significant. Grade 3 to 4 neutropenia occurred in 36%, and grade 3 to 4 thrombocytopenia in 9% of the patients. In contrast to the StiL study,[50] the toxicity was graded according to the NCI-CTC. Furthermore the toxicity was reported as a function of study participants, whereas the German study reported the toxicity as a function of events per treatment. Therefore the toxicity between these two studies is not easy to compare. Nevertheless, bendamustine was well tolerated and no serious adverse events were detected in both studies. In conclusion, both studies demonstrate an excellent activity of bendamustine plus rituximab in relapsed and/or refractory lymphomas.

Based on these promising results the StiL initiated a multicenter phase III study in October 2003, to compare bendamustine plus rituximab (BR) with the standard of care regimen R-CHOP (rituximab, cyclophosphamide,

Table 3. Studies of bendamustine regimens including rituximab in non-Hodgkin lymphoma.

Study	Phase	No	Status	Dose mg/m^2 (days administered)	ORR (%)	CR (%)	PFS months
Rummel[50]	II	63	Relapsed, refractory	B 90 (d 1 + 2) + Rit 375 (d 1) every 28 d	90	60	24
Robinson[51]	II	66	Relapsed	B 90 (d 1 + 2) + Rit 375 (d 1) every 28 d	92	55	23
Weide[55]	II	57	Relapsed, refractory	B 90 (d 1 + 2) + Mit 10 (d 1) + Rit 375 (d 8) every 28 d	89	35	19
Fowler[58]	II	63	Relapsed, refractory	B 90 (d 1 + 2) + Rit 375 (d 1) + Bor 1.6 (d 1 + 8 + 15 + 22) every 35 d	84	47	–
Friedberg[59]	II	25	Relapsed, refractory	B 90 (d 1 + 4) + Rit 375 (d 1) + Bor 1.3 (d 1 + 4 + 8 + 11) every 28 d	84	52	–
Rummel[52]	III	513	Untreated	B 90 (d 1 + 2) + Rit 375 (d 1) every 28 d vs.	94	40	55
				Rit-CHOP every 21 d	94	31	35

Abbreviations: ORR, overall response rate; CR, complete remission; PFS, progression-free survival; B, bendamustine; Rit, rituximab; Mit, mitoxantrone; Bor, bortezomib.

doxorubicin, vincristine, prednisone) as first-line therapy for patients with follicular, indolent and mantle cell lymphoma.[52] Overall 549 patients with a median age of 64 years were randomized to receive rituximab 375 mg/m^2 on day 1 plus either bendamustine 90 mg/m^2 (day 1 + 2) every 28 days or the standard CHOP regimen every 21 days for a maximum of 6 cycles. Most patients presented with stage IV (BR: 76.9% and CHOP-R: 77.5%) and stage III (BR: 19.2% and CHOP-R: 18.6%) disease. Histologies were distributed equally between BR and CHOP-R and included follicular NHL (55% and 56%), mantle cell lymphoma (18% and 19%), and other indolent lymphomas (27% and 24%). At the time of analysis in August 2009, the median observation time was 32 months. ORR was similar in both arms (93.8% with BR vs. 93.5% with CHOP-R). However, the rate of CR was significantly higher in the BR group (40.1% vs. 30.8%; $P = 0.03$). Furthermore the PFS, event free survival (EFS; an event was defined by a response less than a partial response, disease progression, relapse, or death from any cause) and time to next treatment (TTNT) were significantly longer after BR compared to CHOP-R: PFS 54.8 months vs. 34.8 months ($P = 0.0002$), EFS 54 months vs. 31 months ($P = 0.0002$), and TTNT median not yet reached in the BR group vs. 40.7 months in the CHOP-R group ($P = 0.0002$). Overall survival (OS) did not differ between both arms at this point

Table 4. Studies of bendamustine in multiple myeloma.

Study	Phase	No	Status	Dose mg/m^2 (days administered)	ORR (%)	CR (%)	PFS months
Pönisch[65]	I	28	Relapsed, refractory	B 60 (d 1 + 8 + 15) + Thal 50–200 mg (daily) + Pred 100 mg (weekly) every 28 d	86	14	11
Lentzsch[66]	I	9	Relapsed, refractory	B 75–100 (d 1 + 2) + Len 5–15 mg (d 1–21) + Dex 40 mg (d 1 + 8 + 15 + 22) every 28 d	67	0	–
Michael[62]	I	39	Relapsed, refractory	B 80–150 (d 1 + 2) + Dex 40 mg (d 1 + 2) or Pred 100 mg (d 1–5) every 28 d	36	0	–
Fenk[64]	I	50	Relapsed, refractory	B 50–100 (d 1 + 8) + Bor 1.3 (d 1 + 4 + 8 + 11) + Dex 40 mg (d 1 + 4 + 8 + 11) every 21 d	84	0	8
Knop[61]	I/II	31	Progressive after autolo. stem cell transplant	B 100 (d 1 + 2)* every 28 d	55	6	7
Hrusovsky[63]	II	17	Relapsed	B 60 (d 1 + 8) + Bor 1–1.3 (d 1 + 4 + 8 + 11) + Dex 3 × 8 mg (d 1–3 + 8–10) every 21 d	88	12	–
Pönisch[60]	III	131	Untreated	B 150 (d 1 + 2) + Pred 60 (d 1–4) every 28 d vs.	75	32	–
				M 15 (d 1) + Pred 60 (d 1–4) every 28 days	70	13	–

Note: *Recommended dose for Phase II.
Abbreviations: ORR, overall response rate; CR, complete remission; PFS, progression-free survival; B, bendamustine; Thal, thalidomide; Pred, prednisone; Len, lenalidomide; Dex, dexamethasone; Bor, bortezomib; M, melphalan.

of time. The BR regimen was better tolerated by the patients with a lower rate of alopecia (15% vs. 62%), a significantly lower incidence of peripheral neuropathy (n = 18 vs. n = 73; $P < 0.0001$), a significantly lower number of infectious complications (95 vs. 121; $P = 0.04$) and a significantly lower number of fewer episodes of stomatitis (n = 16 vs. n = 47; $P < 0.0001$). Moreover, the BR regimen induced significantly less neutropenias grade 3 + 4 (BR 10.7% vs. CHOP-R 46.5%; $P < 0.0001$). This formidable results demonstrate that BR does have the potential to become the new standard first-line therapy for patients with follicular, indolent and mantle cell lymphoma. Notably, Zohren et al could demonstrate that quantitative real-time polymerase chain reaction of peripheral blood t(14;18) positive cells predicts treatment response and long-term outcome in patients with follicular lymphoma.[53] In 718 peripheral blood samples of 179 patients with newly diagnosed follicular lymphoma treated within the Stil study the amount of bcl2/IgH positive cells in the peripheral blood at diagnosis ($P = 0.001$) as well as the achievement of a negative minimal residual disease (MRD) status after therapy ($P = 0.0001$) were significant predictors for relapse free survival. After a median follow-up of two years, patients who remained MRD positive in the first measurement after therapy had a significant lower PFS than MRD negative patients ($P = 0.0001$; 9 months vs. not reached).

Several other cytotoxic substances have been combined with bendamustine and rituximab. Kirchner et al combined bendamustine and rituximab with fludarabine including 25 patients with relapsed indolent lymphomas.[54] Patients received bendamustine 50 mg/m^2 (day 1–3), fludarabine 25 mg/m^2 (day 1–3) and rituximab 375 mg/m^2 (day 8, 15, 22, 29). Bendamustine and fludarabine were repeated on day 57 for 4 cycles. ORR was 76% including 28% CR. Despite the good results the study was discontinued because of a high rate of serious infections and hematotoxicity. In a multicenter phase II study of the GLSG (German Low Grade Lymphoma Study Group) 57 patients (median age, 66 years) with stage III/IV relapsed or refractory indolent, and mantle cell lymphomas were treated with a combination of bendamustine (90 mg/m^2 day 1 + 2), mitoxantrone (10 mg/m^2 day 1), and rituximab (375 mg/m^2 day 8) every 29 days for a total of 4 cycles.[55] ORR was 89% with 35% CR. Major toxicity of the regimen was a reversible myelosuppression (grade 3 to 4: leukocytopenia 78%, thrombocytopenia 16%, anemia 10%). In his review article Rudolf Weide reported the sequential use of bendamustine, mitoxantrone and rituximab followed by radio-immunotherapy with ^{90}Y-ibritumomab tiuxetan.[56] In 10 patients with relapsed-refractory indolent lymphoma and mantle cell lymphoma an ORR of 90% was achieved. The main toxicity was a reversible grade 3 or 4 hematotoxicity after ^{90}Y-ibritumomab tiuxetan.

Bendamustine regimens including bortezomib

Moosmann et al recently published the results of a phase II study using the combination of bendamustine and bortezomib in 12 patients with relapsed or refractory NHL.[57]

Histologies included mantle cell lymphoma (n = 5), follicular lymphoma (n = 4), CLL (n = 2) and Waldenstroem's macroglobulinemia (n = 1). Patients received bendamustine (starting dose: 60 mg/m^2) on days 1 + 8 + 15 and bortezomib (1.6 mg/m^2) on days 1 + 8 + 15 + 22 of a 35-day cycle.

In 3 out of 5 patients receiving 80 mg/m^2 of bendamustine (first escalation dose), dose-limiting toxicity was observed, thus defining maximal tolerated dose. The response rates differed between the various histologies. All patients with mantle cell lymphoma responded, whereas only 1 out of 4 patients with follicular lymphoma showed response.

Fowler et al recently presented preliminary phase II data of the VERTICAL study.[58] Patients with relapsed or refractory follicular lymphoma received a combination of bendamustine (90 mg/m^2 day 1 + 2), bortezomib and rituximab. Median age was 58 years and 35% of the patients had high-risk follicular lymphoma. Patients had received a median of 2 prior therapies and 39% were refractory to their last prior rituximab-containing therapy. ORR was 84% including 47% CR. The regimen was generally well tolerated, with manageable toxicities. In a multicenter phase II study Friedberg et al also used a combination of bendamustine (90 mg/m^2 day 1 + 4), bortezomib and rituximab.[59] Patients were heavily pretreated with a median of 4 prior regimens. Histologies were follicular NHL (n = 16), mantle cell lymphoma (n = 7), marginal zone lymphoma (n = 3), SLL (n = 3) and lymphoplasmacytic NHL (n = 2). ORR was 84% with 52% CR. Interestingly, all patients with follicular lymphoma responded to treatment.

Both studies demonstrate that the combination of bendamustine, bortezomib and rituximab is active in patients with relapsed and/or refractory NHL. The furtue will show whether the achieved high response rates correspond to prolonged PFS. A phase II trial of bendamustine, bortezomib and rituximab in patients with previously untreated low grade lymphoma is presently recruiting patients in the US. The study, initiated in January 2010, aims to enroll 55 patients.[60]

Bendamustine in Multiple Myeloma

Bendamustine has also been proven to be active in multiple myeloma. In a phase III study including 131 patients with newly diagnosed multiple myeloma, bendamustine in a dosage of 150 mg/m^2 day 1 + 2 plus prednisone 60 mg/m^2 on days 1–4 revealed to be superior to standard alexanian regimen consisting of melphalan 15 mg/m^2 on day 1 plus prednisone 60 mg/m^2 on days 1–4 in terms of CR rate (32% vs. 13%; $P = 0.007$) and time to treatment failure (14 months vs. 10 months; $P = 0.02$) (Table 4).[61] Furthermore the maximum response was achieved more rapidly with bendamustine (6.8 cycles vs. 8.7 cycles; $P = 0.007$). However, no significant difference was seen in the ORR (75% in the bendamustine arm vs. 70% in the melphalan arm) and the OS between both groups. The toxicities were comparable between the two regimens.

Furthermore, bendamustine has been proven to be effective at the time of first relapse after high dose therapy plus autologous stem cell transplantation.[62] In this dose escalation study including 31 patients, bendamustine 100 mg/m^2 day 1 and 2 per cycle was found to be the maximum tolerated dose. ORR was 55% with a median PFS of 26 weeks. Toxicity was mild and mainly hematologic. In line with this study, Michael et al could demonstrate in a retrospective analysis of 39 patients with relapsed or refractory multiple myeloma the effectiveness of bendamustine.[63] Patients had received a median of 2 prior therapies. Bendamustine dosage was 80–150 mg on days 1 and 2 every 4 weeks, whereas 39% received bendamustine monotherapy and 61% concomitant steroids. Response rates were as follows: 3% very good PR, 33% PR, 18% minimal response, 26% stable disease and 20% progressive disease. The median EFS and OS were 7 and 17 months, respectively. Noteworthy, additive use of steroids resulted in a higher number of infectious complications, whereas no better therapeutic efficacy with regard to response rates, EFS and OS was observed. Bendamustine was associated with relative few and mild side effects. This opens the possibility to combine bendamustine with other agents.

Novel agents like bortezomib, thalidomide and lenalidomide have broadened the treatment options for patients with multiple myeloma. Two trials showed promising results with the combination of bendamustine, bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma.[64,65] Hrusovsky et al[64] used a fixed triple combination, whereas Fenk et al[65] used an escalation algorithm. ORR were 88% in the study of Hrusovsky et al with a median duration of response of 6 months and 84% in the study of Fenk et al with a median PFS of 8 months. In both studies the regimen was well tolerated and toxicity was mild. Further trials comparing a fixed triple combination with a treatment escalation strategy are needed.

In a phase I study the combination of bendamustine (60 mg/m^2 days 1 + 8 + 15) with prednisolone (100 mg weekly), and escalating doses of thalidomide (50–200 mg daily) was administered eyery 28 days to 28 patients with refractory or relapsed multiple myeloma.[66] ORR was 86% with 14% CR. Median PFS and OS were 11 and 19 months, respectively. The maximum tolerated dose of thalidomide was not reached in this study. Lentzsch et al recently presented the first results of a phase I study using the combination of bendamustine, lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma.[67] ORR in 9 patients was 67%. The maximum tolerated dose of thalidomide and bendamustine had not been identified to this point.

In conclusion, bendamustine is an interesting partner for novel agents due to its mild toxicity profile.

Bendamustine in Aggressive NHL

There is very little experience on use of bendamustine in high-grade NHL. In a phase II study 21 patients (median age, 66 years) with relapsed or refractory high-grade NHL were treated with bendamustine at a dose of 120 mg/m^2 on days 1 and 2 every 3 weeks for up to 6 cycles.[68] ORR was 44% including 17% CR. Two complete and two partial responders were

refractory to prior treatment. Response durations were 6, 8+ and 27+ months for the patients achieving a CR and 2, 3 and 10 months for patients with PR. The trial of Friedberg et al included 15 patients with transformed indolent lymphoma.[34] ORR was 66% with 13% CR. After a median follow-up period of 26 months, the median PFS was 4.2 months. Based on a multicenter phase I study showing an ORR of 78% with the combination of bendamustine and rituximab in patients with relapsed or refractory aggressive B-NHL, a phase II study is planned in Japan.[69]

Conclusion

The unique activity of bendamustine in lymphoproliferative disorders, especially in lymphomas resistant to purine analogs or alkylating agents as well as its favorable side-effect profile make it a promising treatment option in patients with NHL or CLL. Bendamustine is approved for CLL and rituximab-refractory indolent lymphoma in the United States and Germany. Moreover it is approved for multiple myeloma in Germany. However, many important questions remain unanswered. The exact mechanism of action is not completely understood, underlining the need of further *in vitro* studies. Over the years, a lot of different dosing strategies have been attempted with bendamustine. The FDA-approved dose for first-line CLL treatment is 100 mg/m^2 administered on days 1 and 2 of a 28-day cycle, whereas the recommended dose for relapsed/refractory NHL is 120 mg/m^2 on days 1 and 2 every 3 weeks. But these regimens might be too intensive for elderly patients or patients with comorbidities. Furthermore bendamustine has not been studied in patients with severe organ dysfunction such as liver or renal dysfunction. Further studies will be required to clarify the optimal dose and schedule of bendamustine for different patients collective. In the meantime, the recommendations for the optimal use of bendamustine recently developed in an international consensus meeting should guarantee the safe and effective use of this drug (Table 5).[70] These recommendations are based on the available clinical data and include the dose and schedule of bendamustine for several clinical indications. The dosage of bendamustine is recommended for initial untreated as well as for relapsed/refractory patients and was adapted whether the drug is being used as a single agent or in combination with other drugs. All regimens as shown in Table 5 should be repeated every 4 weeks, except in patients with aggressive B-cell lymphoma, in whom the regimen should be repeated every 3 weeks.

Table 5. Consensus panel dose recommendations for bendamustine therapy.

Indication	Dose mg/m^2 Days 1, 2*
CLL	
Initial therapy, single agent	100
Initial therapy, with rituximab	90
Relapsed/refractory, single agent (fludarabine naive)	70 (100)
Relapsed/refractory, with rituximab	70**
Follicular/low-grade NHL	
Initial therapy, with rituximab	90
Relapsed/refractory, single agent	120
Relapsed/refractory, with rituximab	90
Aggressive B-NHL	
Relapsed/refractory, single agent	120
Relapsed/refractory, with rituximab	90
Multiple myeloma	
Relapsed/refractory	100

Notes: *All are every 4 weeks except aggressive B-cell, which is every 3 weeks; **Escalate to 90 mg/m^2 if tolerated.
Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

Bendamustine is superior to chlorambucil in upfront CLL treatment,[13] but its exact role in CLL remains unclear. The commonly used first-line therapy for physical fit patients suffering from CLL is a combination of fludarabine, cyclophosphamide and rituximab. A currently ongoing trial of the GCLLSG (CLL10 study) compares FCR with BR in previously untreated CLL patients, but this data is not yet available. However, bendamustine is a reasonable treatment option for patients with comorbidities not considered for fludarabine including regimens as well as for patients not considered for the more immunosuppressive acting alemtuzumab.

Bendamustine has also been proven to be highly active in multiple myeloma.[61–63] The greatest potential of bendamustine in multiple myeloma will likely be as partner with new agents such as lenalidomide or bortezomib, due to the mild toxicity profile of bendamustine.[64–66] There is also some evidence of efficacy in high-grade NHL.[34,68] A currently ongoing phase I/phase II trial investigates the efficacy and safety of the combination of bendamustine plus

lenalidomide and rituximab in patients with relapsed or refractory aggressive B-cell lymphoma who are not eligible for high-dose chemotherapy.[71]

Bendamustine has the capability to play a great role in the treatment of patients with indolent NHL. On the one hand bendamustine has shown clinical activity in rituximab-refractory indolent NHL.[34,35] The results are comparable to the response rates achieved with radioimmunotherapy, what opens up the opportunity to treat patients not eligible for radioimmunotherapy with bendamustine.[36,37] On the other hand a phase III study of the StiL showed a superiority of BR over the standard of care regimen R-CHOP in respect of PFS, CR rate and tolerability as first-line therapy in patients with follicular, indolent and mantle cell lymphoma.[52] This promising results demonstrate that BR does have the potential to become the new standard first-line therapy for this patients collective.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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