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REVIEW

The role of bendamustine in the treatment of indolent non-Hodgkin lymphoma

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Abstract: There is no consensus on recommendations for the treatment of relapsed and refractory indolent non-Hodgkin lymphoma (NHL). Bendamustine hydrochloride (bendamustine) has recently been approved for treatment of these patients. Bendamustine is a uniquely structured alkylating agent that lacks cross-resistance with other alkylators. This agent has a high degree of activity against a variety of tumor cell lines. Clinically, bendamustine has demonstrated activity against indolent NHL, chronic lymphocytic lymphoma, multiple myeloma and mantle cell lymphoma. Moreover, studies have validated its activity in patients with indolent NHL who are resistant to purine analogs and rituximab. The cytotoxic activity of bendamustine has been shown to be synergistic with rituximab in hematological malignancies. The incidence of alopecia is significantly less than with other alkylating agents. Myelosuppression is the major toxicity associated with bendamustine.

Keywords: bendamustine, Treanda, indolent non-Hodgkin lymphoma, alkylating agent, chronic lymphocytic lymphoma

Introduction to management issues in the treatment of indolent non-Hodgkin lymphoma

The clinical behavior of non-Hodgkin lymphomas (NHL) is widely variable. For example, Burkitt lymphoma may be rapidly fatal in the absence of urgent therapy, whereas patients with follicular lymphoma (FL) may live for many years without any treatment. NHL accounts for approximately 5% of newly diagnosed cancers in men and 4% of newly diagnosed cancers in women.[1] In 2009 it is estimated that there will be 65,980 new case of NHL diagnosed in the US, and that 19,500 people will die with this diagnosis. Indolent (low-grade) lymphomas comprise approximately 40% of NHLs in the US. Follicular lymphoma is the most common type of indolent lymphoma accounting for approximately 20% to 25% of all lymphomas in the US. Although patients with indolent NHL usually have advanced-stage disease at the time of diagnosis, they are often asymptomatic. Long-term progression-free survival (PFS) can be observed following treatment for indolent NHL, but these patients are usually considered incurable with standard therapy.

Management of patients with indolent NHL has historically relied on a watch-and-wait approach until evidence of symptomatic disease is present. It is still unknown whether overall survival (OS) is modified when treatment is initiated early for patients with nonbulky asymptomatic disease. Early studies prior to the introduction of rituximab failed to establish a survival benefit when treatment with chemotherapy was compared to a watch-and-wait approach.[2–4] The survival of patients with

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follicular lymphoma has improved over the last 30 years.[5] This improvement is undoubtedly related in part to the use of rituximab combined with chemotherapy in primary treatment regimens.[6–9] The use of rituximab with upfront chemotherapy is now considered standard. Although a watch-and-wait approach may still be indicated for selected patients, studies have shown that the majority (81%) of FL patients received therapy in the US.[10]

Therapy is indicated for patients with symptomatic or bulky disease. Several management options have been recommended including single agent chemotherapy or immunotherapy with rituximab, combination therapy, and high-dose chemotherapy followed by hematopoietic stem cell transplantation. The optimal chemotherapy regimen has not been defined. Alkylating agents (chlorambucil, cyclophosphamide) or purine analog (fludarabine)-based regimens are used most commonly.

Although the initial therapy for indolent NHL is associated with high response rates, the majority of patients will eventually relapse, with successive reductions in the length of response to each salvage regimen. Treatment of patients with relapsed or refractory indolent NHL must be individualized. One evolving exciting area is the introduction of the radioimmunoconjugates (^{131}I-tositumomab, ^{90}Y-ibritumomab-tiuxetan), which have demonstrated significant activity for patients with pre-treated and previously untreated indolent NHL.[11–15] Autologous and allogeneic hematopoietic stem cell transplantation may be considered for some patients with relapsed and refractory indolent lymphomas.[16,17]

New chemotherapy options are warranted for patients with indolent lymphomas. Bendamustine is an alkylating agent, which has been recently approved for use in the US. It has been associated with excellent response rates when used as monotherapy or in combination with monoclonal antibodies in patients with refractory NHL.

Review of bendamustine pharmacology

Bendamustine was initially manufactured in the former East German Democratic Republic in the early 1960s by Ozegowski et al in an attempt to create an antineoplastic agent exhibiting dual antitumor activity with a favorable toxicity profile.[18] Until 1990, the use of bendamustine was primarily limited to East Germany. Following the German reunification, the use of bendamustine for a wide variety of hematologic malignancies and solid tumors has been investigated throughout the world.

Bendamustine structure

Bendamustine hydrochloride (Treanda®; Cephalon, Inc.) is a bifunctional alkylating agent with antimetabolite effects. Bendamustine has been recognized as a novel agent with exceptional function in different tumor cell lines.[19–22] The distinctive activity of bendamustine is related to its unique structure (Figure 1). It consists of a nitrogen mustard (mechlorethamine) group, a characteristic element of alkylators such as chlorambucil and cyclophosphamide, simultaneously with a benzimidazole ring that substitutes for the benzene ring seen in chlorambucil. The benzimidazole ring is seen in purine-analogs, and may be responsible for the potential antimetabolic activity, although this has not been confirmed *in vivo*. In addition, the structure contains a butyric acid chain that makes bendamustine water-soluble.[23,24] Chemically, bendamustine is identified as 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride.

Mode of action

Although the bendamustine molecule has characteristics in common with alkylators and purine-analogs, the antineoplastic activity is primarily related to the former. Bendamustine induces DNA damage through intra- and inter-strand cross-linking of DNA base pairs, which subsequently leads to cell apoptosis. In addition, it causes stimulation of DNA damage stress response and apoptosis, down-regulation of mitotic checkpoints, and induction of mitotic catastrophe, which interrupts cell division.[23,25] In contrast to other alkylating agents, the impact of bendamustine on DNA damage was verified to be more extensive, long-lasting and more resistant to repair, which might be attributed to the potency and lack of complete cross-resistance that distinguishes bendamustine from other alkylators.[26,27]

Bendamustine pharmacokinetics

Following the intravenous infusion of bendamustine, the mean peak plasma concentration (C_{max}) occurs at the end of the infusion, and C_{max} and the area under the plasma

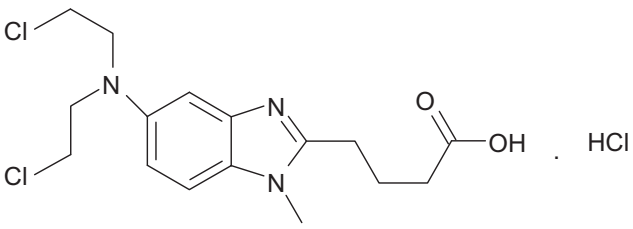

Figure 1 Structure of bendamustine.

concentration curve (AUC) shows independent relationship to the administered dose.[28,29] At steady state, bendamustine has a volume of distribution (V_d) of 20 to 25 L.[28–32]

Bendamustine metabolism predominantly occurs through hydrolysis, and phase I metabolite formation seems to be mediated via hepatic cytochrome P450 1A2.[33] Hydrolysis generates active and inactive metabolites. Nevertheless, active metabolites such as gamma-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4) occur in negligible concentrations compared to the parent component, and this verified that the cytotoxic activity of bendamustine is mainly generated by the original compound. Nonmetabolized particles have been found to constitute 45% of the excreted portion of the drug in urine.[33]

Following a 60-minute intravenous administration in patients with NHL, serum bendamustine declined in a rapid biphasic manner ($t½\alpha$ = 17 minutes, $t½\beta$ = 42 minutes) and a slow terminal phase ($t½c$ = 110 hours), but the terminal phase composed less than 1% of the total AUC, and therefore, the half-life of the β-phase represents bendamustine mean half-life, which is approximately 40 minutes.[34]

The drug is eliminated mainly via feces and to a lesser extent in the urine. A preclinical study illustrated that approximately 90% of administered bendamustine was recovered in feces.30 Bendamustine is highly bound to serum protein (>95%), primarily to albumin.

The experience with bendamustine has demonstrated insignificant variation in its pharmacokinetics based on age, gender, and existence of mild to moderate renal dysfunction or mild hepatic dysfunction.[34] Nevertheless, bendamustine should be used with caution in patients with mild hepatic dysfunction and mild to moderate renal impairment, bendamustine should be avoided with more profound failure (CrCL < 40 mL/min, AST or ALT > 2.5 upper limit of normal (ULN), or total bilirubin >1.3 ULN) as limited studies have been executed in these sittings.[30]

Drug-drug interactions with bendamustine have not been well-studied, but due to the role hepatic cytochrome P450 1A2 enzyme plays in bendamustine biotransformation,[33] CYP P450 1A2 inhibitors as well as inducers may lead to altered serum levels, and dosage adjustment of bendamustine may be needed in these situations.

Bendamustine administration and recommended dosage

Bendamustine is a water soluble white powder. It is infused intravenously over 30 to 60 minutes once daily. Prior to bendamustine administration, the powder must be reconstituted with sterile water and diluted in normal saline. The product is available in single-use 100 mg vials.[30]

Several doses of bendamustine have been investigated in phase I, II and III trials. Significant toxicity was encountered in a phase I study in patients with solid tumors when bendamustine doses were escalated up to 280 mg/m^2.[28] Therefore, a dose of 260 mg/m^2 every 21 days was recommended for further studies. When bendamustine was delivered on days 1 and 2 every 21 days, the maximum tolerated dose (MTD) was 180 mg/m^2.[29] In a phase I/II study conducted to evaluate bendamustine dosage in 15 pre-treated patients with chronic lymphocytic lymphoma (CLL), a dose of 110 mg/m^2 was identified as MTD, and 100 mg/m^2 on days 1 and 2 of 21-day cycles was recommended for future studies.[35] In a phase I/II study conducted to evaluate the toxicity and efficacy of bendamustine combined with mitoxantrone in 22 patients with CLL, the bendamustine dose was escalated from 80 mg/m^2 to a maximum of 240 mg/m^2 and divided into 2 or 3 doses with mitoxantrone (8–10 mg/m^2).[36] Four of 6 patients who received 240 mg/m^2 dose developed grade III infections and myelosuppression. A dose of 150 mg/m^2 in combination with 10 mg/m^2 mitoxantrone was recommended for further investigations.

The recommended dosage for bendamustine in patients with CLL is 100 mg/m^2 on days 1 and 2 of a 28-day cycle for up to 6 cycles. For NHLs, bendamustine is administered at 120 mg/m^2 on days 1 and 2 of a 21-day cycle for up to 8 cycles.[30]

It is recommended that subsequent cycles of bendamustine be delayed if grade IV hematological toxicity is experienced, and therapy should be held until recovery of blood counts. The recommendations should also be applied if significant grade II or higher nonhematological toxicity is faced. Subsequent cycles can be reinitiated at reduced doses (50 mg/m^2 for CLL, and 90 mg/m^2 for NHL on days 1 and 2) when toxicity is resolved. If recurrent toxicity is seen subsequently, further dosage reduction can be applied (25 mg/m^2 for CLL, 60 mg/m^2 for NHL on days 1 and 2) for the next cycles. Doses can be re-escalated as tolerated in subsequent cycles if toxicity subsides.[30]

Efficacy studies for bendamustine

Although bendamustine is not a new antineoplastic agent, it has been recently attained considerable attention in the US and is now FDA approved for use in the treatment of CLL and indolent NHL. In addition, studies have shown encouraging activity in various other malignancies including multiple myeloma (MM),[37] mantle cell lymphoma (MCL), and breast cancer.[38] The use of bendamustine is currently being

investigated in solid malignancies such as nonsmall cell lung cancer and breast cancer. In a recent report, bendamustine has been acknowledged as one of the major advances that have been made in cancer treatment in 2008.[39] On October 31, 2008, bendamustine was approved for the treatment of patients with relapsed/refractory indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen, in addition to the earlier approval of bendamustine for treating patients with CLL on March 20, 2008.[40]

Bendamustine in preclinical studies

Preclinical studies demonstrated a distinct apoptotic effect of bendamustine on cell lines of B-CLL, MM, and NHL.[19–22] Moreover, bendamustine demonstrated exceptional activity toward cancer cells resistant to conventional alkylating agents.[26,41] Animal and *in vitro* studies, in NHL and CLL models, showed synergistic effect of bendamustine in combination with rituximab on tumor inhibition.[42,43]

Bendamustine as a single agent

Bendamustine was investigated in two studies as a single agent in chemotherapy-refractory NHL/CLL patients with or without prior exposure to purine-analogs. An overall response rate (ORR) of 73% and 77% in various histologic subtypes was reported.[44,45] Bendamustine toxicity was tolerable, and no alopecia was observed in either study. The major reported adverse effect was myelosuppression.

The first study enrolled 58 patients with relapsed indolent NHL and CLL (CLL 27, centroblastic/-cytic 22, centrocytic 6, immunocytic 3).[44] The majorities of patients had advanced disease and were heavily pretreated with prior cytotoxic regimens, except for purine-analogs or high dose chemotherapy. Bendamustine was administered as a single agent at 120 mg/m² on days 1 and 2 every 21 days, and a median of 6 cycles were given. The study demonstrated an objective ORR of 73% (complete response [CR] 11%, partial response [PR] 62%) and stable disease (SD) in 10% of 52 patients assessable for response and toxicity. The median duration of remission and survival time was 16 and 36 months, respectively. Toxicity was acceptable and no treatment-related mortality was observed. Reported adverse effects included reversible grade I/II hematological and gastrointestinal toxicities. Three patients with grade III leukopenia, and 3 patients with grade II allergic reactions required treatment interruption. No alopecia or grade IV toxicity was seen in the study. Bendamustine was reported as a safe and active therapy in treating relapsed indolent NHL.

In the second phase II study, 5-day cycles of daily bendamustine 60 mg/m^2 every 4–6 weeks, for a median of 4 cycles, were administered to 102 pretreated patients with indolent NHL (CLL 15, immunocytic 46, MM 25, MCL 5, others 11).[45] Patients had received a median of 2 prior cytotoxic regimens. Bendamustine achieved a 76.5% ORR (CR 10.8%, PR 65.7%). Furthermore, histological sub-analysis yielded an ORR of 93% in CLL, 82% in NHL, and 52% in MM. The median duration of response and median survival for all patients was 39 and 29 months, respectively. The median duration of response was significantly longer in patients with CLL and NHL (39 months for NHL, and not reached with CLL), compared to MM (17 months). Treatment was associated with grade III/IV hematological toxicity (anemia 6.9%, thrombocytopenia 11.8% and leukopenia 24.5%) and moderate nonhematological toxicities. Less than 5% of patients experienced grade III/IV toxicities including reversible impairment of performance status and gastrointestinal toxicities. No alopecia was seen. The study demonstrated a high response rate for bendamustine in pre-treated indolent NHL and absence of cross-resistance with other alkylating agents.

The promising results bendamustine achieved in chemotherapy-refractory NHL has led to evaluation of its efficacy as a single agent in rituximab-refractory NHL and CLL in phase II trials.[46,47] Inclusion criteria in these studies were absence of response or disease progression within 6 months of completing treatment with rituximab alone, rituximab and chemotherapy, or radioimmunotherapy. Studies reported an ORR of 77% and 84% with acceptable adverse effects.

In a multicenter phase II trial, the efficacy of bendamustine was evaluated in 100 patients with rituximab-refractory NHL. Preliminary results in 38 patients (FL 53%, CLL/small lymphocyte lymphoma (SLL) 26%, extranodal marginal zone 21%) was presented at the American Society of Hematology (ASH) meeting in 2007.[46] The majority of the patients had advanced disease, and had received a median of 2 prior rituximab-containing regimens in addition to a median of 3 other treatments including chemotherapy and radioimmunotherapy. Bendamustine was given at a dose of 120 mg/m^2 on days 1 and 2 every 21 days for 6 to 8 cycles. ORR was 84% (CR 29%, unconfirmed complete response (CRu) 3%, PR 53%), with a median response duration (RD) and PFS of 9.3 and 9.7 months, respectively. Toxicity was predominantly hematological, including grade III/IV leukopenia, thrombocytopenia and anemia in 60%, 24% and 5%, respectively. Other observed toxicities included moderate gastrointestinal toxicity and fatigue.

In a similar multicenter phase II study, 76 patients with rituximab-refractory indolent and transformed NHL (FL 46, SLL 12, transformed 15, others 3) were treated with single-agent bendamustine at 120 mg/m² on days 1 and 2 every 21 days.[47] The majority of enrolled patients had advanced disease. Of 74 patients evaluable for response, ORR was 77% (CR 15%, CRu 19%, PR 43%), and the median duration of response was 6.7 months (9 months for patients with indolent disease and 2.3 months for patients with transformed disease). The median PFS was 7.1 months in all patients (8.3 months in patients with indolent disease and 4.2 months for patients with transformed disease), and 36% of responses exceeded one year. Toxicity included cytopenias (grade III/IV neutropenia, thrombocytopenia and anemia in 54%, 25% and 12%, respectively), gastrointestinal complaints and fatigue.

Single-agent bendamustine was compared to other therapies for CLL in 2 randomized trials as first- and second-line treatment.[48,49] Both studies demonstrated superior outcomes with bendamustine as compared with standard therapies.

In a phase III study, 319 chemotherapy-naive patients with advanced B-cell CLL were randomized to receive bendamustine 100 mg/m² on days 1 and 2 or chlorambucil 0.8 mg/kg on days 1 and 15 every 4 weeks.[48] The primary end-points of the study were ORR and PFS. Both values showed superiority in the bendamustine arm compared to chlorambucil (68% vs 31%) and (21.6 vs 8.3 months), respectively. OS was a secondary end-point and no significant difference was identified between the two arms of the study. Of 312 patients assessable for safety, bendamustine was associated with a higher incidence of grade III/IV neutropenia (40% vs 19%) as well as infectious complications (8% vs 3%) compared to chlorambucil.

In the second study, 96 pre-treated patients with relapsed or refractory CLL were randomized to receive bendamustine 100 mg/m² on days 1 and 2 in a 28-day cycle, or fludarabine 25 mg/m² on days 1 to 5 every 28 days.[49] Both regimens were administered until best response was reached or to a maximum of 8 cycles. The primary end-point of the study was PFS. Ninety-five percent of the patients had been previously treated with chlorambucil-based regimens. Patients who received fludarabine or bendamustine therapy had been excluded from the study. The bendamustine arm yielded a favorable ORR compared to the fludarabine arm (78% vs 65%) with CR of 29% vs 10%, and a superior PFS (83 vs 64 weeks) after 2 years median follow up. Although a higher incidence of hematologic toxicity occurred in the bendamustine arm, grade III/IV infectious complications were similar in both groups (15%).

These studies have demonstrated significant activity with single agent bendamustine in patients with indolent NHL and CLL. Bendamustine has shown significant activity in previously treated patients with relapsed or refractory NHL/CLL.[44,45] Notably, it yielded a response rate approaching 80% in rituximab-refractory disease.[46,47] Furthermore, bendamustine has demonstrated efficacy in chemotherapy-naïve CLL patients and demonstrated superior outcomes in comparison to standard therapy such as chlorambucil.[48] Finally, bendamustine exhibited a favorable ORR and PFS when compared with fludarabine when it was administered as a second-line therapy in patients with advanced CLL.[49] These results have led to additional studies exploring the merit of using bendamustine in combination with other antineoplastic agents and monoclonal antibodies.

Bendamustine in combination with chemotherapy

Bendamustine has been investigated in combination with other antineoplastic agents in treating NHL and CLL. A regimen consisting of bendamustine, vincristine and prednisone (BOP) was associated with overall response rates of 66% to 90% in patients with indolent NHL.[50] Bendamustine has also been tested in combination with other agents such as such as mitoxantrone, mitoxantrone/methotrexate/prednisone, and idarubicin/dexamethasone, with overall response rates of 48 to 79%.[51–53] A phase II study of oral etoposide and bendamustine was conducted in thirty-eight pretreated (n = 12) and previously untreated patients with indolent NHL and CLL.[54] Bendamustine was given at 100 mg/m² on day 1 and etoposide was given at a dose of 50 mg on days 1 to 5. Treatment was administered in 21-day cycles. The study reported an ORR of 97% (CR 67%, PR 30%). The regimen was tolerable and only minor hematological and gastrointestinal toxicity was observed.

In advanced CLL, bendamustine combined with mitoxantrone achieved an ORR of 86% (CR 27%, PR 59%) in 22 previously treated patients.[36] The majority of the patients (20/22) experienced a median time to progression and median survival of 10 and 39 months, respectively. Bendamustine was administered in escalating doses from 80 mg/m² to 240 mg/m² (divided on days 1–3) every 29 days. Significant toxicities occurred at the 240 mg/m² dose level and predominantly consisted of infections and hematologic toxicities, and therefore, a dose of 150 mg/m² was recommended for further studies.

The encouraging results achieved with the BOP regimen for indolent NHL led to a phase III trial designed to compare

its efficacy to standard combination therapy as first-line treatment.[55] The study recruited 164 untreated patients with advanced NHL (FL, MCL and lymphoplasmacytic lymphoma) and randomized them to either BOP (bendamustine 60 mg/m² days 1–5, vincristine 2 mg on day 1, and prednisone 100 mg/m² on days 1–5) or COP (cyclophosphamide 400 mg/m² on days 1–5 instead of bendamustine). Treatment was given in 21-day cycles up to a maximum of 8 cycles. The ORR was 66% (CR 22%, PR 44%) in the BOP arm and 76% (CR 20%, PR 56%) in the COP arm. There was no significant statistical difference between these values. However, in responding patients, BOP treatment resulted in a longer median time to progression, as compared to COP (84+ months vs 28 months, $P = 0.037$). Furthermore, the 5-year projected survival rate was significantly longer for those who had responded to BOP, as compared to COP (74% vs 56%; $P = 0.05$). The study exhibited variation in survival based on histological subtypes in the BOP group. The 5-year OS was 66%, 74%, and 43% ($P = 0.03$) in FL, lymphoplasmacytic, and MCL, respectively. Treatment with the COP regimen was associated with a higher incidence of grade III/IV leukopenia (34% vs 19%) and anemia (13% vs 10%) as compared to BOP, although, thrombocytopenia was slightly more common in the BOP arm. Grade III/IV alopecia occurred more frequently in the COP arm, as compared to the BOP group (48% vs 4%). The study concluded that BOP is an appealing alternative to COP in managing patients with advanced indolent NHL, and the regimen has an acceptable toxicity profile.[55]

In vitro studies using mononuclear cells obtained from patients with a leukemic phase of indolent NHL have demonstrated a synergistic effect of bendamustine and purine-analog combinations on leukemic cells,[44] and this justified investigating bendamustine in combination with fludarabine in a phase I/II study.[56] Bendamustine was administered in 2 dose levels (level I was 30 mg/m², and level II was 40 mg/m²), with fludarabine 30 mg/m² on days 1 to 3 every 28 days. Twenty-nine patients with relapsed or refractory NHL (FL 14, MCL 11, lymphoplasmacytic 2, and marginal zone 2), with advanced disease were included. One death from febrile neutropenia was reported in the level II dose group. Of 19 patients treated at the level I dose and assessable for response, an ORR of 77% (CR 45%, PR 32%) was observed. However, 53% of the responders relapsed after a median of 14 months. Hematologic toxicity was the most prominent adverse effect of the combination regimen with grade III/IV toxicity seen in 73% of cases.[56]

Despite the high response rate associated with combinations of bendamustine with other agents, toxicities were prominent and intractable. Therefore, the search for safer combinations has been initiated. Rituximab is a chimeric monoclonal antibody against CD20. The combination of rituximab with bendamustine is discussed in the next section.

Bendamustine in combination with rituximab

The experience of the bendamustine, rituximab, and mitoxantrone (BMR) combination has yielded a response rate approaching 90%.[57–59] This outpatient regimen was tested initially in a phase I/II prospective study in 20 pre-treated patients with advanced NHL/CLL (FL 9, CLL 4, lymphoplasmacytic 3, secondary high grade 4).[57] Patients were given bendamustine 90 mg/m² (80 mg/m² for CLL) on days 1 to 3, mitoxantrone 10 mg/m² on day 1, and rituximab 375 mg/m² weekly in weeks 2 to 5. Cycles were administered every 36 days or sooner after blood counts recovered, for a maximum of 5 cycles. The regimen achieved an ORR of 95% (CR 35%, PR 60%), and only one patient with secondary high grade lymphoma had progressive disease. At seven months follow-up, 75% of patients continued to respond to treatment.

An updated analysis including 54 patients with symptomatic relapsed or refractory NHL/CLL (B-CLL 21, B-cell prolymphocytic leukemia 1, FL 14, lymphoplasmacytic 8, MCL 2, marginal 2, secondary high grade 6) treated with the BMR regimen has been published.[58] The ORR in the study was 96% (CR 41%, PR 55%). The ORR varied with histological types and was reported as 100%, 95%, and 83% in indolent NHL, CLL, and secondary high grade lymphomas, respectively. The median time to progression was 17 months for CLL and had not been reached for indolent NHL after 27 months median follow-up. No treatment associated deaths or hospitalizations were observed. Myelosuppression was the main toxicity, with grade III/IV symptomatic and asymptomatic hematologic toxicity in 19% and 43% of patients, respectively. No grade III/IV nonhematological toxicity was reported.

The promising outcomes BMR obtained from the single center reports has led to a phase II multicenter study which enrolled 57 patients with advanced relapsed or refractory indolent lymphomas or MCL (FL 29, MCL 18, other indolent lymphomas 10).[59] Thirty-nine percent of patients had received prior treatment with rituximab-containing regimens. The ORR was 89% (CR 35%, PR 54%) in all patients, and 76% in patients who had received a rituximab-containing regimen. The estimated PFS during 27 months follow-up was 19 months. Sub-group analysis revealed an ORR of 92%

for FL versus 78% for MCL. The 2-year OS was similar in both groups. Grade III/IV toxicities were predominantly myelosuppression (leukopenia 78%, anemia 10%, and thrombocytopenia 16%). Other observed grade III/IV toxicities include gastrointestinal toxicity, alopecia (5%), and cardiac toxicity (7%). Unexpected hospitalization occurred in 4% of patients.

The combination of bendamustine and rituximab (BR) has also been associated with durable responses and a favorable toxicity profile. In a phase II multicenter trial in patients with relapsed or refractory NHL or MCL (FL 24, MCL 16, lymphoplasmacytoid, marginal zone 6), the BR combination was administered for a maximum of 4 cycles every 28 days.[60] Bendamustine 90 mg/m² was administered on days 1 and 2 of each cycle. The combination was associated with a 90% ORR (CR 60%, PR 30%). The median PFS was 24 months. Sub-group analysis revealed an ORR of 75% in MCL and 96% in FL. The treatment was well tolerated, and toxicity was mainly myelosuppression. Grade III/IV leukopenia, thrombocytopenia and anemia was seen in 19%, 4% and 1% of patients, respectively.

In a similar phase II trial the BR regimen was used in 67 patients with relapsed indolent NHL or MCL, in the absence of prior documented rituximab resistance.[61] The regimen consisted of bendamustine (90 mg/m² on days 2 and 3 every 28 days) in combination with rituximab on day 1. Sixty-six patients (FL 40, small lymphocytic 10, MCL 12, other indolent 4) received at least one treatment. The ORR was 92% (CR 41%, CRu 14%, PR 38%). Sub-group analysis revealed an ORR of 86% in patients with prior rituximab exposure (37 patients) versus 100% in patients without prior rituximab exposure (29 patients). The median duration of response and PFS was 21 and 23 months, respectively. No significant difference in response rate was observed between patients with indolent NHL or MCL. Myelosuppression was the major toxicity. Grade III/IV neutropenia and thrombocytopenia occurred in 36% and 95%, respectively.

The most interesting data was derived from a phase III multicenter trial including 546 patients randomized to BR (bendamustine at 90 mg/m² on days 1 and 2 every 28 days) or CHOP-R (up to 6 cycles) as first-line therapy for indolent NHL or MCL.[62] The histologic subtypes were equally distributed in both arms of the study (FL 52%, MCL 20%, other indolent lymphomas 28%). The ORR was 94% (CR 41%) in patients who received BR as compared to 93% (CR 33%) in patients who received CHOP-R. The primary end-point of the study (event-free survival [EFS]) was not reached in the BR group, compared to 39 months in CHOP-R group. Relapse or progression was noted in 58 and 75 patients treated with BR and CHOP-R, respectively. The mortality rate was similar in each group, although less toxicity was seen in the bendamustine arm (alopecia 0% vs 89%, infectious complications 25% vs 37%, and grade III/IV leukopenia 19% vs 36%).

Since elderly patients are less able to tolerate aggressive therapy, a phase II trial targeting patients older than 75 years was conducted to assess the efficacy and safety of the BR combination (bendamustine at dose of 90 mg/m² on days 1 and 2 every 28 days) in patients with indolent NHL and MCL.[63] The median age of patients was 79 years. The ORR was 88% (CR 35%) in 26 patients assessable for response. Major toxicities of the regimen were due to myelosuppression.

Preclinical studies have documented that the addition of rituximab can reduce the bendamustine dose that is required to induce apoptosis in *ex vivo* B-CLL cells.[42,43] Therefore, a phase II trial was conducted in 81 pre-treated patients with refractory or relapsed CLL using the BR regimen.[64] Bendamustine (70 mg/m² on days 1 and 2 every 28 days) was administered in combination with rituximab (375 mg/m² on the first cycle, then 500 mg/m² for subsequent cycles) for up to 6 cycles. The ORR was 77.4% (CR 14.5, PR 62.9) in 62 patients assessable for response. Disease progressed in 4.8% of cases. Sub-groups analysis revealed variable outcomes based on molecular cytogenetic profile of the tumor. Three treatment-related deaths occurred secondary to infectious complications. Other adverse effects were grade III/IV leukopenia, thrombocytopenia, and anemia occurring in 11.9%, 9.1%, and 6.1% of patients, respectively.

These studies demonstrate the activity of the BR regimen in treating relapsed or refractory indolent NHL and CLL. This combination has shown high response rates with efficacy equivalent to standard therapies in addition to a favorable toxicity profile in groups such as the elderly (Table 1).

Safety and tolerability of bendamustine

The most common toxicity of bendamustine is hematological secondary to bone marrow suppression. However, an *in vitro* study showed less stem cell toxicity associated with bendamustine as compared to fludarabine.[65] Blood counts should be monitored closely during the course of therapy, and schedule delays have been advocated for patients who experience significant myelosuppression. Treatment can be reinitiated at reduced doses after hematopoietic recovery (ANC $> 1 \times 10^9$/L and platelet count $>75 \times 10^9$/L).[30]

Table 1 Efficacy studies for bendamustine in NHL and CLL

Study	Phase	Line of therapy	Therapy	Doses (mg/m^2)	Malignancy	No. pts	ORR% (CR, PR)	RD (m)	PFS (m)	OS (m)	Toxicities
Heider et al[44]	II?	≥2	B	120 d 1,2 q21d	CR-NHL/CLL	58	73 (11, 62)	16		36	MS, GI, AR
Bremer et al[45]	II	≥2	B	60 d 1–5 q4–6w	CR-NHL/CLL	102	76.5 (11, 66)	39		29	MS, GI, impair PS
Kahl et al[46]	IIB	≥2	B	120 d 1,2 q3w	RR-NHL/CLL	38 of 100	84 (29, 53)	9.3	9.7		MS, GI, fatigue
Friedberg et al[47]	II	≥2	B	120 d 1,2 q3w	RR/transformed-NHL	76	77 (15, 43)	6.7	7.1		MS, GI, fatigue
Knauf et al[48]	III	1st	B vs C	100 d 1,2 q4w	Untreated advanced CLL	162	68 (31, –)	21.8	21.6		MS, IC
Niederle et al[49]	III	2nd	B vs F	100 d 1,2 q4w	CR-CLL	46	78 (29, –)		20.7		MS, IC
Ruffert et al[54]	II	≥1	BE	100 d 1 q3w	Untreated/previously treated NHL/CLL	38	97 (67, 30)				MS, GI
Herold et al[55]	III	1st	BOP vs COP	60 d 1–5 q3w	Untreated advanced NHL	82	66 (22, 44)		84+		MS, GI
Koenigsmann et al[56]	I/II	≥2	BF	30 d 1–3 q4w	Advanced refractory NHL	19	77 (45, 32)				MS, FN
Weide et al[57]	I/II	≥2	BMR	90 d 1–3 q5w	Advanced refractory NHL/CLL	20	95 (35, 60)				MS
Weide et al[58]	II	≥2	BMR	90 d 1,2 q4w	Advanced/refractory (RR) NHL/CLL	54	96 (41, 55)				MS
Weide et al[59]	II	≥2	BMR	90 d 1,2 q4w	Relapsed/refractory (RR) NHL	57	89 (35, 54)		19	33	MS, GI, cardiac
Rummel et al[60]	II	≥2	BR	90 d 1,2 q4w	Relapsed/refractory NHL	63	90 (60, 30)		24		MS
Robinson et al[61]	II	≥2	BR	90 d 2,3 q4w	Relapsed NHL	66	92 (41, 38)	21	23		MS, GI, AR
Rummel et al[62]	III	1st	BR vs CHOP-R	90 d 1,2 q4w	Advanced NHL	221	94 (41, –)				MS, IC
Fischer et al[64]	II	≥2	BR	70 d 1,2 q4w	Relapsed/refractory CLL	62 of 81	77 (14.5, 63)				MS, IC

Abbreviations: AR, allergic reaction; B, bendamustine; BE, bendamustine and etoposide; BF, bendamustine and fludarabine; BMP, bendamustine, mitoxantrone, and rituximab; BOP, bendamustine, vincristine, and prednisone; BR, bendamustine and rituximab; C, chlorambucil; CHOP-R, cyclophosphamide, adriamycin, vincristine, prednisone and rituximab; COP, cyclophosphamide, vincristine, and prednisone; CR, chemotherapy-refractory; CR, complete response; F, fludarabine; FN, febrile neutropenia; GI, gastrointestinal; m, months; IC, infectious complications; MS, myelosuppression; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; Pts, patients; RD, median duration of response; PS, performance status; RR, rituximab-refractory; w, week.

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Infectious complications including pneumonia and sepsis have been reported during bendamustine use, and certain cases have been complicated by septic shock and even death. Therefore, patients on bendamustine therapy should report early signs of infection to prevent advanced complications.

Aside from hematological toxicities, bendamustine is associated gastrointestinal toxicities (including nausea, vomiting, constipation, and diarrhea), fatigue, pyrexia, asthenia, weight and appetite loss, dehydration, and cardiac complications. Most nonhematological toxicities occur in mild to moderate severity. Skin reactions have been reported during bendamustine therapy.

Infusion reaction and anaphylaxis is a potential risk after the initial cycle bendamustine therapy.[30,47] Bendamustine should be discontinued if severe reaction occurs. For mild reactions, patients need to be pretreated with antihistamines, antipyretics and corticosteroids. Tumor lysis syndrome is a serious risk when bendamustine therapy is initiated and prophylactic measures should be taken in high risk patients.

In comparison to other alkylating agents, bendamustine use has been associated with substantially less alopecia when compared with other alkylating agents.

Bendamustine is classified as a Pregnancy Category D medication. Bendamustine injection during organogenesis in rodents resulted in decreased body weights and increased fetal malformations. Therefore, women of childbearing age should avoid pregnancy with adequate birth control methods.[30]

Conclusion

Bendamustine has emerged as a unique alkylating agent for the treatment of indolent lymphomas, with only partial cross-resistance to other alkylating agents. Use of bendamustine either as a single agent or in combination with other cytotoxic agents or rituximab has yielded promising outcomes, especially when it has been applied in the context of rituximab-refractory indolent lymphomas. Single agent bendamustine has shown superiority as a first- and second-line therapy for indolent NHL over standard therapies such as chlorambucil and fludarabine. Furthermore, in combination with rituximab, bendamustine achieved equivalent efficacy to the CHOP-R regimen in treating indolent NHL, and the combination had been employed safely and effectively in managing elderly patients. Studies have shown a favorable toxicity profile for bendamustine limited primarily to myelosuppression.

Although bendamustine has exhibited significant activity toward lymphoid malignancies, additional studies are warranted to define the optimal doses and schedules, subgroups that benefit the most from the agent, and novel combinations.

Disclosures

The authors disclose no conflicts of interest.

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