Bendamustine for the treatment of multiple myeloma in first-line and relapsedrefractory settings: A review of clinical trial data

UNIVERSITÀ DEGLI STUDI DI TORINO

Bendamustine for the treatment of multiple myeloma in first-line and relapsed–refractory settings: a review of clinical trial data

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Abstract

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal growth and/or dysregulation of plasma cells leading to the build-up of malignant plasma cells in the bone marrow and increased production of monoclonal immunoglobulins. Treatment modalities for MM include autologous stem cell transplant (ASCT), chemotherapy with conventional and immunomodulatory agents, radiation therapy and adjunct therapies. Bendamustine is a synthetic chemotherapeutic agent combining the alkylating properties of a mustard group with the activities of a benzimidazole ring, giving it a unique alkylating activity compared with other alkylating agents. Bendamustine has proven activity in both newly diagnosed and relapsed–refractory MM. Bendamustine has also demonstrated activity in MM after relapse from ASCT, and has recently been used successfully as a conditioning regimen for ASCT in combination with melphalan. Bendamustine is generally well tolerated, with the majority of adverse events being due to bone marrow suppression. Extramedullary toxicity is infrequent and usually mild.

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal growth and/or dysregulation of plasma cells that leads to the build-up of malignant plasma cells in the bone marrow and increased production of immunoglobulins [1]. It is the second most common hematological cancer [2]: there were an estimated 22 350 new cases of MM in the USA in 2013, with 10 710 deaths [3]. An estimated 750 000 people worldwide are living with MM [4]. MM is a complex disease to treat, and therapy choices depend on patient age, comorbidity, severity of symptoms and disease. Treatment modalities include autologous stem cell transplant (ASCT), chemotherapy, radiation therapy and adjunct therapies. The alkylating drugs cyclophosphamide and melphalan have been in clinical use for several decades [5,6]. Other agents which have been developed over the last 10 years for the treatment of MM include the proteasome inhibitor bortezomib [7], the immunomodulatory drugs thalidomide and lenalidomide [8,9] and monoclonal antibodies [10]. Dexamethasone and prednisolone are also used in combination with chemotherapies for the treatment of MM [2,11].

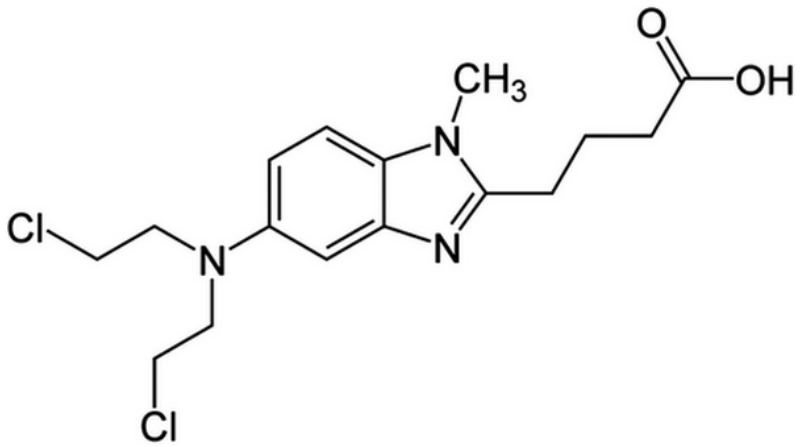
The new proteasome inhibitor carfilzomib was approved in 2012 in the USA for the treatment of patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent [2,11,12]. While significant developments have been made in the treatment of MM over the past 10 years, the disease remains incurable, as multidrug resistance often occurs, leading to relapse and disease progression [13,14]. Current European Society for Medical Oncology (ESMO) treatment guidelines recommend melphalan plus prednisone in combination with either bortezomib or thalidomide for the treatment of elderly patients with advanced-stage or symptomatic MM who are ineligible for high-dose chemotherapy with stem cell support [15]; however, no treatment options have been developed that have been shown to be effective in overcoming melphalan resistance [5].

Bendamustine is a bifunctional alkylating agent derived from 2-chloroethylamine [16,17] which has shown efficacy against a number of tumor types, including hematological malignancies [1,18–20] and solid tumors such as small-cell lung cancer [21], breast cancer [22] and soft tissue sarcomas [23]. It has been approved in the USA and European Union (EU) for chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma refractory to rituximab, as well as for first-line treatment in follicular lymphoma in combination with rituximab in Switzerland [16,17], and in the EU as a first-line MM treatment, in combination with prednisone, in elderly patients with clinical neuropathy who are not eligible for ASCT [16,17]. In MM, the approved dosing is 120–150 mg/m2 bendamustine on days 1 and 2 plus 60 mg/m2 prednisone on days 1–4, every 4 weeks [16].

Pharmacology/pharmacokinetics/mechanism of action

Bendamustine is a butyric acid hydrochloride/benzimidazole ring/alkylator hybrid, with the International Union of Pure and Applied Chemistry (IUPAC) name of 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl] butanoic acid. It contains three structural elements: a 2-chloroethylamine alkylating group and a benzimidazole heterocyclic ring with a butyric acid substituent (Figure 1) [24]. The exact mechanism of action of bendamustine is unknown [17], but it is clear that it is different from that of other 2-chloroethylamine DNA-alkylating agents (e.g. chlorambucil, cyclophosphamide) [24]. The antineoplastic and cytocidal effect of bendamustine is due to a cross-linking of DNA single and double strands by alkylation. As a result, different mitotic checkpoints are inhibited, leading to induction of cell death by mitotic catastrophe. Bendamustine also inhibits the p53-dependent stress pathway and subsequently activates intrinsic apoptosis [24]. Interestingly, the active substance of bendamustine has little or no cross-resistance in human tumor cell lines with different resistance mechanisms, at least in part due to a comparatively persistent DNA interaction [16]. It is for this reason that it is believed to help overcome melphalan resistance [5,24].

Figure 1. Chemical structure of bendamustine: 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid hydrochloride.



Following an injection of bendamustine, the majority (95%) of the substance is bound to serum plasma proteins [16]. Bendamustine has a peak drug concentration of 11.8 µg/mL, and it takes a mean 29.6 min to reach this concentration [16]. The area under the concentration–time curve for bendamustine is 11.7 µg.h/mL. Bendamustine is associated with a mean elimination half-life of 28.2 min, with a central volume of distribution of 19.3 L and a steady-state volume of distribution of 15.8–20.5 L. The relatively short half-life

(t1/2) reflects the rapid metabolism and excretion of bendamustine, primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. Active metabolites – monohydroxybendamustine and dihydroxybendamustine – are formed via a minor metabolic pathway involving cytochrome P450 1A2 (CYP1A2) isoenzyme; the maximum serum concentration (Cmax) and area under the curve (AUC) for these metabolites are approximately 3% of the respective bendamustine values [16]. Conjugation with glutathione is another major route of bendamustine metabolism [16]. Potential interactions between bendamustine and concurrent drugs that strongly inhibit CYP1A2 (e.g. fluvoxamine, ciprofloxacin) may increase plasma concentrations of bendamustine, potentially increasing the risk of toxicity. Conversely, strong inducers of CYP1A2 (e.g. omeprazole, phenobarbital) may decrease plasma concentrations of bendamustine and undermine bendamustine efficacy. Bendamustine does not inhibit other cytochrome P450 isoenzymes, such as CYP1A4, CYP2C9/10, CYP2D6, CYP2E1 and CYP3A4 [16]. Pharmacokinetic parameters are not changed in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/dL). Conversely, a dose reduction of 30% is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2–3.0 mg/dL). Bendamustine is currently contraindicated in patients with severe hepatic impairment (serum bilirubin > 3.0 mg/dL). The pharmacokinetic properties of bendamustine are not influenced by age, or kidney function [16]. There is no evidence that dose adjustments are necessary in elderly patients, or in patients with creatinine clearance > 10 mL/min, although experience in patients with severe renal impairment is limited. Bendamustine is dialyzable.

Efficacy data from clinical multiple myeloma trials

First-line treatment

The approval of bendamustine in the first-line indication was based on a randomized, open-label, multicenter, phase III study conducted by the East German Study Group of Hematology and Oncology (OSHO) [1]. This study compared the efficacy and tolerability of bendamustine 150 mg/m2 and melphalan 15 mg/m2, both in combination with prednisone 60 mg/m2, in 136 adults (131 evaluable) with previously untreated MM aged 38–80 years (median 62 years). Both treatments were infused over 30 min: bendamustine on days 1 and 2 and melphalan on day 1 of a 4-week course. Treatment was continued until a maximum response was observed, and the primary endpoint was time to treatment failure (TTF) [1]. This study showed that in adults with MM, first-line combination therapy with bendamustine was significantly more effective than melphalan at prolonging the TTF (14 months for bendamustine therapy vs. 10 months for melphalan, $p < 0.02$) (Figure 2) [1]. Moreover, the benefits of bendamustine in terms of TTF were maintained beyond 30 months. Bendamustine also significantly improved the complete response (CR) rate ($p = 0.007$; Figure 3) compared with melphalan, with a maximum response achieved significantly faster in patients in the bendamustine treatment group (6.8 vs. 8.7 courses; $p < 0.02$). No significant differences in overall response (OR), stable (SD) and progressive disease (PD) rates (Figure 3) and median overall survival (OS) were observed between treatment groups [1].

Figure 2. Comparison of time to treatment failure following first-line therapy with bendamustine (BP) or melphalan (MP) in patients with multiple myeloma from a randomized, open-label phase III study [1].

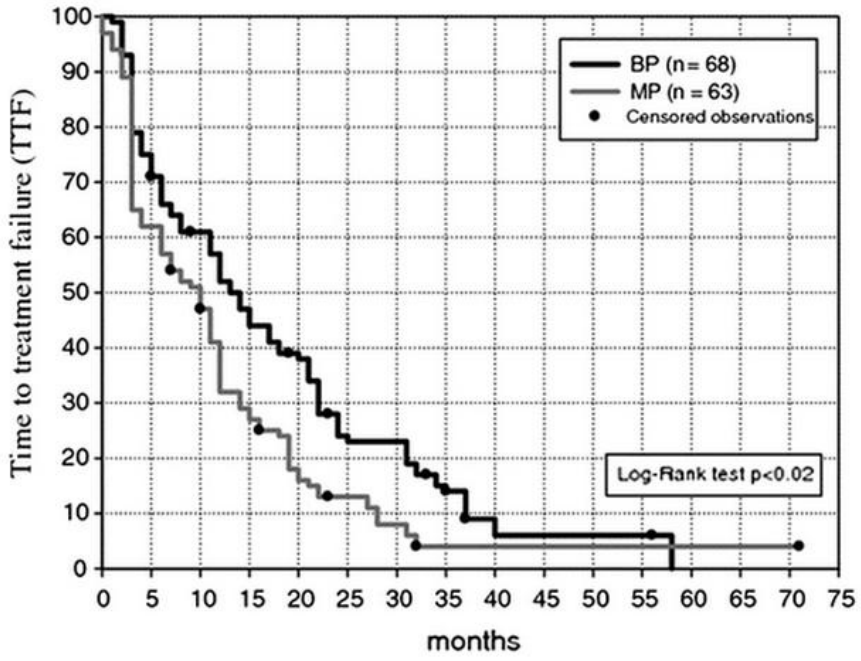
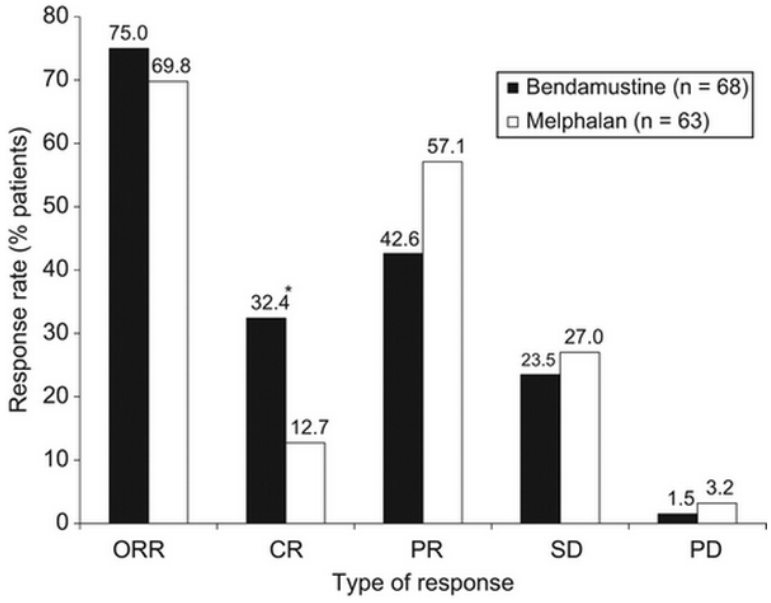


Figure 3. Maximum response following first-line therapy with bendamustine or melphalan in patients with multiple myeloma: data from a randomized, open-label phase III study [1]. CR, complete response rate; ORR, objective response rate (CR + PR); PD, progressive disease rate; PR, partial response rate; SD, stable disease rate. *p = 0.007 vs. melphalan.



Patients with renal failure

The combination of first-line bendamustine/prednisone/bortezomib (BPV) was investigated in 18 patients aged 43–86 years (median 69) with MM and moderate or severe renal failure at diagnosis [25]. Patients received bendamustine 60 mg/m2 as a 30 min infusion on days 1 and 2, oral prednisone 100 mg on days 1, 2, 4, 8 and 11 and intravenous bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11 of a 21-day course. In patients

who were dialysis-dependent, bendamustine and bortezomib were given 30 min after the end of dialysis. Treatment with BPV was continued until a maximum response, dose-limiting toxicity or disease progression was observed [25]. After a median of 17 months, the OS rate was 61% and progression-free survival (PFS) was seen in 57% of patients. The majority of patients (83.3%) responded after the first course of BPV: three patients had a stringent complete response (CR), five patients had a near-CR, five had a very good partial response (VGPR) and two had a partial response (PR) [25]. The first hematological response was observed after a median 14 days, and median time to best response was 42 days. The renal OR rate was 72%, and 50% of dialysis-dependent patients became dialysis-independent [25]. These results suggest that BPV is an effective regimen for the first-line treatment of patients with MM with renal failure.

Relapsed–refractory setting

The value of bendamustine as single agent (in combination with steroids) in patients with MM with relapsed–refractory disease has been investigated in several retrospective observations, with response rates ranging between 30% and 55% [26–28]. Between April 2007 and December 2009 a French compassionate use program enrolled 110 patients with relapsed–refractory MM after prior therapy with alkylators, steroids, immunomodulators (lenalidomide or thalidomide) and bortezomib. Bendamustine was given at 60–150 mg/m2 on days 1 and 2 in combination with prednisone for a median of 4 (range 1–13) 28-day courses. This program reported an OR rate of 30% in patients with relapsed–refractory MM, and after the cut-off day of 10 December 2010, a median duration of response had not yet been reached [26]. Patients had an overall median PFS of 9.3 months and OS was 12.4 months (Table I) [26]. While this was a retrospective study, the authors of the study believe that the 30% response rate observed in these heavily pretreated patients was promising, and they suggest that the results indicate that bendamustine is an interesting supplementary option in the armamentarium of therapeutic options for patients with relapsed–refractory MM [26].

Table I. Studies reporting the use of bendamustine in patients with relapsed-refractory multiple myeloma.

Study	Bendamustine regimen	*n*	Response rate (% patients) OR	CR	PR	MR	SD	PD	Median survival (months) OS	PFS
	Bendamustine alone									
Damaj *et al.* 2012 [26]	60–150 mg/m^2 d1 + 2 q28d	110	30	2	28	NR	20	50	12.4	9.3
Michael *et al.* 2010 [27]	80–150 mg/m^2 d1 + 2 q28d	39	36	0	36	18	26	20	17	7
Knop *et al.* 2005 [28]	60–100 mg/m^2 d1 + 2 q28d	31	55	NR	NR	NR	NR	NR	NR	8
	Bendamustine + lenalidomide									
Lentzsch *et al.* 2012 [32]	75–100 mg/m^2 d1 + 2 q28d + LEN 5–10 mg od d1–21 q28d + DEX 40 mg 1/week	29[‡]	76[§]	0	52	24	16	8	Not reached	6.1
Pönisch *et al.* 2013 [33]	75–100 mg/m^2 d1 + 2 q28d + LEN 10–25 mg od d1–21 q28d + PDN 100 mg d1–4 q28d	21	76	5	71	14	10	NR	64% at 18 months	48% at 18 months
	Bendamustine + thalidomide									
Grey-Davies *et al.* 2012 [29]	60 mg/m^2 d1 + 8 + 15 q28d + THD 50–200 mg/day + DEX 2mg d1, 2, 8, 9, 15, 16, 21, 22 q28d	23	61[¶]	4	22	17	17	39	13	3
Pönisch *et al.* 2008 [30]	60 mg/m^2 d1 + 8 + 15 q28d + THD 50, 100 or 200 mg/day + PDN 100 mg d1, 8, 15, 22 q28d	28	86	14	71	4	7	4	19	11
	Bendamustine + bortezomib									
Berenson *et al.* 2013 [36]	50, 70 or 90 mg/m^2 d1 + 4 q28d + BOR 1.0 mg/m^2 d1, 4, 8, 11 q28d	40	48[§]	3	28	18	43	10	13.3	8.4
Pönisch *et al.* 2013 [37]	60, 80 or 120 mg/m^2 d1 + 2 q21d + BOR 1.3 mg/m^2 d1, 4, 8, 11 q21d + PDN 100 mg d1, 2, 4, 8, 11 q21d	78	69	4	65	12	12	8	50*, 5[†]	11*, 3[†]
Offidani *et al.* 2013 [38]	70 mg/m^2 d1 + 8 q28d + BOR 1.3 mg/m^2 d1, 4, 8, 11 for 2 courses then d1, 8, 15, 22 q28d + DEX 20 mg	75	77	20	57	—	20	3	NR	15.5
Fenk *et al.* 2007 [39]	50–100 mg/m^2 d1 + 8 q28d + BOR 1.3 mg/m^2 d1, 4, 8, 11 q28d + DEX 40 mg d1, 4, 8, 11 q28d	50**	86[§]	0	57	29	NR	NR	NR	NR
Ludwig *et al.* 2014 [40]	70 mg/m^2 d1 + 4 q28d + BOR 1.3 mg/m^2 d1, 4, 8, 11 q28d + DEX 20 mg d1, 4, 8, 11 q28d	79	61	15	46	15	NR	NR	25.6	9.7
Rodon *et al.* 2013 [41]	70 mg/m^2 d1–8 q28d + BOR 1.3 mg/m^2 d1, 8, 15, 22 q28d + DEX 20 mg d1, 8, 15, 22 q28d	73	70	14	56	6	7	17	10.8	23

BEN, bendamustine; BOR, bortezomib; CR, complete response; d, day; DEX, dexamethasone; LEN, lenalidomide; MR, minor response; NR, not reported; od, once daily; OR, overall response; OS, overall survival; PFS, progression-free survival; PDN, prednisone; PD, progressive disease; PR, partial response; q28d, every 28 days; SD, stable disease; THD, thalidomide.
*In patients without severe hematological toxicities due to previous treatments.
[†]In patients with severe hematological toxicities due to previous treatments.
[‡]Efficacy data were available in 25 out of the 29 enrolled patients.
[§]Included minimal response.
[¶]Included stable disease.
**Efficacy results for seven patients who received BEN + BOR + DEX reported.

Another retrospective analysis investigated the use of bendamustine in 39 patients treated for relapsing MM at a single institution in Germany over a 5-year period [27]. Patients had a median of 2 lines of prior therapy. Bendamustine was administered for a median of 3 (1–10) courses. Over the 5-year period, the OR rate to bendamustine was 36% (Table I), the median PFS was 7 months and the median OS was 17 months. There were no differences in remission rates between elderly and younger patients [27]. Although no patients achieved a CR, a PR rate of 36% meets the expected OR rate for an effective anti-myeloma agent, and the authors concluded that bendamustine is an effective salvage therapy option for advanced MM [27].

In 2005 Knop and colleagues [28] presented the results of a small dose-escalation study of bendamustine given in escalating doses (60 mg/m2 up to 100 mg/m2) in 31 patients up to age 70 years with MM progressing after high-dose chemotherapy. Twelve of these patients had previously received high-dose melphalan and six patients had undergone total marrow irradiation, busulfan and cyclophosphamide therapy. Patients in this study had an OR rate of 55%, with the best response rates occurring in the two highest-dose groups (Table I) [28]. These results further highlight the role of bendamustine as an effective salvage therapy option for advanced MM.

Bendamustine in combination with other agents

Multiple studies have investigated the use of bendamustine in combination with other therapies in the relapsed–refractory MM setting; although the majority of these studies were conducted in small patient populations, their results are still generalizable.

Immunomodulatory agents The use of bendamustine in combination with an immunomodulatory drug appears to be a feasible treatment regimen for patients with relapsed–refractory MM. The combination of bendamustine plus thalidomide (alone or with a steroid) in patients with relapsed–refractory MM has been reported in three studies [29–31]. The first of these was a German multicenter trial that assessed the efficacy of bendamustine plus escalating doses of thalidomide plus prednisone in 28 patients who had received a median of 2 (1–4) prior therapies for MM [30]. Patients received bendamustine 60 mg/m2 on days 1, 8 and 15 in combination with oral prednisone 100 mg on days 1, 8, 15 and 22 and a dose escalation of thalidomide 50–200 mg/day in 28-day courses (2–10 courses total). Patients were divided into two groups: A, those who relapsed after standard chemotherapy; and B, those who relapsed after high-dose chemotherapy with stem cell support. The OR rate in these patients was 86% (Table I). No difference in response between groups A and B or between thalidomide dose levels was seen. Patients had an overall median PFS duration of 11 months and an OS duration of 19 months [30]. Between December 2008 and April 2010, the UK compassionate use program enrolled 23 patients with relapsed–refractory MM who received a median of 5 (3–7) prior therapies [29]. Bendamustine was given at 60 mg/m2 on days 1, 8 and 15 in combination with thalidomide 50–200 mg/day and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 21 and 22 for a median of 3 (1–6) 28-day courses. This program reported a clinical response rate (SD or greater response) in 61% of patients; the median PFS was 3 months, with an OS of 13 months (Table I) [29].

Finally, the bendamustine–thalidomide combination was also studied in a retrospective analysis of data from nine patients with newly diagnosed and relapsed myeloma and advanced renal disease, followed for up to 12 months. Findings indicated that bendamustine (120 mg on day 1) with thalidomide (100 mg/day) and dexamethasone (20 mg, days 1, 8, 15, and 22 of a 28-day cycle) was effective; out of nine patients, three achieved a CR, two a PR and two SD, while only two had PD, and the OR rate was 55%. The combination was well tolerated in patients with advanced renal disease due to the limited renal excretion of both drugs [31].

Two studies have reported the use of bendamustine in combination with lenalidomide [32,33]. The first of these studies was an open-label, phase I/II dose-escalation study investigating the efficacy of bendamustine/lenalidomide/dexamethasone (BLD) in patients who had received a median 3 (1–6) prior treatments for MM [32]. Bendamustine 75–100 mg/m2 was administered on days 1 and 2, oral lenalidomide 5–10 mg was administered once daily on days 1–21 and dexamethasone was administered at 40 mg/week during the 28-day courses for a maximum of eight courses. Twenty-five patients were available for response, and a PR or greater occurred in 52% of them (Table I). The median PFS duration was 6.1 months [32]. The second of these studies investigated the efficacy of bendamustine/lenalidomide/prednisolone (BLP) in a single-center, phase I dose-escalation study [33]. Patients with relapsed (first or second relapse only) or refractory MM received bendamustine 60–75 mg/m2 on days 1 and 2, oral prednisolone 100 mg on days 1–4 and oral lenalidomide 10–25 mg once daily on days 1–21 of a 28-day course for a median of 2 (2–8) courses. This study showed that BLP was an effective treatment strategy for relapsed–refractory MM with an OR rate of 76% [33].

Moreover, there is a phase I/II study presented at the American Society of Hematology (ASH) 2013 meeting with the same combination (BLD), in which the dose of bendamustine increased from 40 to 60 mg/m2 on days 1–2 and lenalidomide from 15 to 25 mg for 21 days to find the maximum tolerated dose (MTD) using a 3 + 3 cohort design. MTD was established at bendamustine 40 mg/m2 and lenalidomide 10 mg. Main grade 3/4 adverse events were neutropenia, thrombocytopenia and anemia. With a median follow-up of 10 months, the OR rate in 28 evaluable patients was 50% (three with CR, two with VGPR and nine with PR, and

one with SD). The median PFS was 10 months; median OS was not reached. Phase II of the trial is ongoing [34].

Proteasome inhibitors The proteasome inhibitor bortezomib shows remarkable activity in relapsed–refractory MM as single agent or in combination and, in vitro, was shown to enhance the sensitivity of MM cells to bendamustine [35]. The efficacy of the combination of bendamustine and bortezomib and a corticosteroid has been documented in several studies [36–41]. First, in an open-label, multicenter, non-randomized, dose-escalating, phase I/II study in 40 patients with relapsed–refractory MM, patients received bendamustine plus bortezomib (Table I). This treatment regimen corresponded to an OR rate of 48%, with an additional 43% of patients experiencing SD. Patients had a median PFS of 8.4 months and median OS was 13.3 months [36]. A second study investigating the efficacy of bendamustine plus bortezomib plus prednisone (median 2 [1–7] courses) in 78 patients with relapsed MM and either normal (n = 45) or restricted bone marrow function (n = 33) reported an OR rate of 69%, with no difference between the two patient groups (Table I). However, patients with normal bone marrow function had much better PFS and OS durations than those who did not (Table I) [37].

The activity and toxicity of bendamustine, bortezomib and dexamethasone (BVD) was investigated in a retrospective analysis of 50 patients with MM presenting at a single institution, treated with BVD in a sequential algorithm. Bortezomib was given first, followed by bortezomib plus dexamethasone if there was a < 25% reduction in paraprotein, and then bendamustine was added if the response was still minimal. Overall, seven patients received a median of 5 courses (range 1–8) of BVD. The OR rate in this study (in all treatment groups) was 84%, but higher partial and minimal response rates were seen in patients given BVD compared with the other two treatments. There were no significant differences between treatments in terms of PFS and OS (Table I) [39].

More recently, this combination has been assessed in several phase II studies, including a phase II study enrolling 75 patients with MM previously treated with any new drug (57% thalidomide, 54.5% lenalidomide, 46.5% bortezomib, 40% two new drugs). The response rate ≥ PR was 77% (20% CR, 20% VGPR, 37% PR) [38]. At 12 months of follow-up, median time-to-progression (TTP) was 16.5 months, PFS was 15.5 months and the 1-year OS was 78%. Grade 3–4 adverse events comprised 30.5% thrombocytopenia, 12% anemia, 18.5% neutropenia and 8% infections. Thus, the remarkable anti-myeloma activity of this combination was associated with manageable hematological and non-hematological toxicity (Table I) [38].

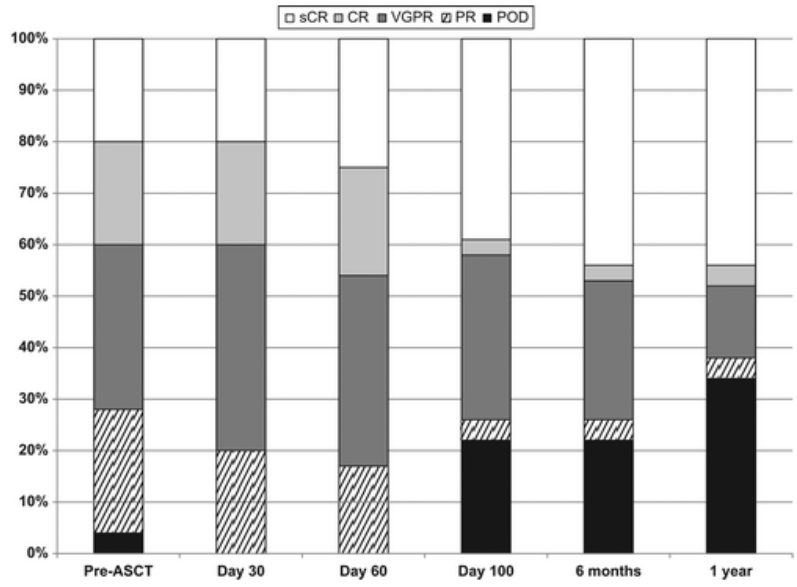
Another phase II study investigated the efficacy of four courses of BVD in 79 patients with MM, and found that the OR rate (CR + PR) was 60.9% (Table I). Twelve patients (15%) had a CR to treatment, 16 (20%) a VGPR, 20 (25.3%) a PR and 12 (15.2%) a minor response. The OR rate in patients previously exposed to bortezomib was 56%, the OR rate being 55% in those pretreated with lenalidomide-based regimens. Median time to response was 31 days (111 to best response). Median PFS and OS were 9.7 and 25.6 months, respectively. Of note in this study, patients who had fluorescence in situ hybridization (FISH)-defined adverse cytogenetics had comparable PFS and OS to patients who did not [40].

Finally, in another phase II study of BVD in 73 elderly patients (median age: 75.8 years), patients were initially given four courses; if they responded, two additional courses were given followed by a maintenance phase with six courses given every 2 months. The overall response rate was 69.8% (Table I) and the median PFS and OS were 10.8 and 23 months [41].

Pre-ASCT setting

One of the mainstays of therapy for MM has been high-dose chemotherapy followed by ASCT [42,43]. Since the establishment of melphalan 200 mg/m2 as the standard of care conditioning regimen [42], several studies have attempted to optimize the conditioning regimen for ASCT in MM; however, as of yet, no regimen has thus far shown clear superiority to this standard without adding to toxicity [44]. A recently published phase I study compared different doses of bendamustine added to melphalan 200 mg/m2 daily in 25 patients with active MM being conditioned for ASCT. The dose-finding phase started from bendamustine 60 mg/m2 and reached 225 mg/m2 subdivided over 2 days without encountering a maximum tolerated dose. Ten patients progressed after a median of 473 days after ASCT and six patients died [44]. Median PFS was 791 days and the median OS was not reached, but the 2-year OS rate was 70% [44]. After ASCT through to 1 year of follow-up, the CR progressively improved: 40% of patients had a CR or better at day 30, 46% at day 60, 42% at day 100, 47% at day 180 and 48% at 1 year (Figure 4). At day 100, the OR rate was 79% [44].

Figure 4. Response rates in patients receiving a pre-autologous stem cell transplant (ASCT) conditioning regimen of bendamustine (30–225 mg/m^2) plus melphalan (100 mg/m^2/day) [44]. ASCT, autologous stem cell transplant; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; POD, progression of disease.



Tolerability

The most frequently reported treatment-emergent adverse events associated with bendamustine monotherapy are fever, allergic reactions, gastrointestinal symptoms and hematological adverse events [16]. Other common adverse events include infection, fatigue and mucositis, whereas extramedullary toxicity is infrequent and usually mild [16].

As first-line therapy, bendamustine was generally well tolerated when administered with prednisone, although more patients in the OSHO study who received bendamustine plus prednisone had severe nausea and vomiting compared with those who received melphalan plus prednisone (12 vs. 0) [1]. In this study, the

tolerability profile of bendamustine was mostly consistent with the known toxicities of the agent, with hematological events (anemia, neutropenia, leukopenia, thrombocytopenia), nausea/vomiting and pyrexia the most frequently reported treatment-emergent adverse events [1]. No treatment-related adverse events led to treatment discontinuation [1]. Hematological adverse events (all grades) were observed in 3–28% of bendamustine plus prednisone recipients; however, no significant differences in the incidence of various hematological adverse events were observed between the bendamustine plus prednisone and melphalan plus prednisone treatment groups (Table II) [1]. Dose reductions because of leukopenia or thrombocytopenia were required in 8.6% and 1.8% of patients who received bendamustine plus prednisone and 4.1% and 0.9% of patients who received melphalan plus prednisone [1].

Table II. Tolerability of intravenous bendamustine in adults with multiple myeloma: incidence of hematological adverse events of grade 3 or 4 severity.

			Incidence, *n* (% patients)			
Study	Treatment	*n*	Anemia	Leukopenia	Neutropenia	Thrombocytopenia
First-line setting						
Pönisch *et al.* 2008 [30]	BEN + PDN	68	24.0	40.0		10.0
	MEL + PDN	63	24.0	31.0		15.0
Pönisch *et al.* 2012 [25]	BEN + BOR + PDN	18	5 (27.8)	6 (33.3)	1 (5.6)	6 (33.3)
Relapsed-refractory setting						
Michael *et al.* 2010 [27]	BEN	39	4 (10.3)		16 (41.0)	10 (25.6)
Lentzsch *et al.* 2012 [32]	BEN + LEN + DEX	29	5 (17.2)	11 (37.9)	18 (62.1)	11 (37.9)
Pönisch *et al.* 2013 [33]	BEN + LEN + PDN	21	4 (19.0)	7 (33.3)	11 (52.4)	4 (19.0)
Grey-Davies *et al.* 2012 [29]	BEN + THD + DEX	23			7 (30.4)	5 (21.7)
Pönisch *et al.* 2008 [30]	BEN + THD + PDN	28	5 (17.9)	10 (35.7)	12 (42.9)	2 (7.1)
Berenson *et al.* 2013 [36]	BEN + BOR	40	8 (20.0)	23 (57.5)	20 (50.0)	12 (30.0)
Pönisch *et al.* 2013 [37]	BEN + BOR + PDN	78	18 (23.1)	31 (39.8)	30 (38.5)	49 (62.8)
Offidani *et al.* 2013 [38]	BEN + BOR + DEX	75	9 (12)		14 (18.5)	23 (30.5)
Fenk *et al.* 2007 [39]	BEN + BOR + DEX	50*	2 (28.6)		1 (14.2)	2 (28.6)
Ludwig *et al.* 2014 [40]	BEN + BOR + DEX	79	14 (18)	14 (18)		30 (38)
Rodon *et al.* 2013 [41]	BEN + BOR + DEX	73			14 (19.1)	8 (10.9)

BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; PDN, prednisone; THD, thalidomide.
*Tolerability results for seven patients who received BEN + BOR + DEX reported.

When administered alone in the refractory setting, the majority of adverse events reported with bendamustine were mild; however, nearly all patients had at least one hematological adverse event after the first course of treatment (Table II), though most were grade 1/2. There was no correlation between dose level and hematologic toxicity [27].

The combinations of bendamustine with thalidomide plus dexamethasone/prednisone [29,31], with lenalidomide plus dexamethasone/prednisone [30], with bortezomib [36] and with bortezomib plus dexamethasone/prednisone (either as first-line therapy [25] or in the relapsed-refractory setting [37,38]) are all feasible treatment regimens with acceptable tolerability profiles. Grade 3/4 hematological adverse events were observed in 7–62% of bendamustine combination recipients (Table II).

In the setting of high-dose treatment, engraftment kinetics observed with escalating bendamustine and melphalan conditioning were similar to those reported previously with the melphalan 200 mg/m2 conditioning regimen. No transplant-related mortality events and no grade 3/4 non-hematological adverse events directly attributable to bendamustine infusion were reported [41]

Current role of bendamustine in the treatment of myeloma

As first-line therapy

Clinical data for bendamustine as monotherapy or in combination with steroids and other agents show that this therapy is effective and well tolerated in patients with newly diagnosed MM, including patients aged over 65 years [1]. Currently it is registered for this indication in many European countries and South Korea, and in Taiwan it is in the pre-registration phase for first-line therapy. However, the role of bendamustine in first-line therapy of MM is not well established.

Since MM affects a large proportion of elderly individuals, the risk/benefit profile of therapy in this population is very important, particularly since many of them will not be eligible for transplant [45]. The benefits of first-line bendamustine are shown in elderly patients; although specific age-stratified analyses were not performed, the population studied by Pönisch et al. was aged up to 80 years (median 62 years) [1]. Although bendamustine has been approved specifically in patients older than 65 years who are not eligible for ASCT, there are other agents also available in this setting. Standard therapies in those who are not candidates for ASCT are melphalan/prednisone/thalidomide, or bortezomib/melphalan/prednisone. In patients not able to receive melphalan due to renal impairment or other comorbidities (common in the elderly population), preferred treatments include thalidomide/dexamethasone, lenalidomide and bortezomib-based dual or triple regimens. If these cannot be used then bendamustine is an option, but its current role in first-line treatment of elderly patients undergoing ASCT is limited at present.

Bendamustine is approved in combination with prednisone for first-line treatment of MM (Durie–Salmon stage II with progress or stage III) for patients older than 65 years who are not eligible for ASCT and who have clinical neuropathy at the time of diagnosis, precluding the use of thalidomide- or bortezomib-containing treatment [16]. Studies are under way to investigate bendamustine with dexamethasone and carfilzomib in patients with newly diagnosed MM (NCT02002598).

In the relapsed–refractory setting

The clinical data for the use of bendamustine as second-line therapy in MM show clear benefits in the relapsed–refractory setting. Ample clinical data show that bendamustine appears to retain efficacy in advanced relapsed–refractory MM as monotherapy and in combination with steroids [27] and immunomodulatory agents, and also as part of triple therapy regimens with dexamethasone or prednisone plus thalidomide [29,30], lenalidomide [32,33] or bortezomib [36–40]. Triple therapy regimens have been shown to be more effective than dual without additional toxicity issues [27,38]. Although much of the evidence is from retrospective analyses and small prospective studies, particularly for monotherapy and dual therapy regimens, three large prospective phase II studies clearly demonstrated that the triple-therapy BVD is effective and well tolerated in patients with relapsed–refractory MM, including elderly patients [38,40,41]. The large phase II study [38] investigating BVD in patients failing up to four previous therapies, discussed in detail earlier in this article, showed that although outcomes were better in those with fewer previous therapies, OR rates of 50–60% and median TTP of 9–10 months were achieved in this difficult to treat population. Interestingly, a regression analysis of factors influencing TTP showed that only prior therapy with bortezomib/lenalidomide (and not number of prior therapies) was identified as significantly affecting TTP [38].

Phase I/II studies are also under way investigating bendamustine as part of quadruple therapy with bortezomib, lenalidomide and dexamethasone (NCT01484626), in triple therapy with dexamethasone and

pomalidomide (NCT01754402) and in combination with bortezomib and pegylated liposomal doxorubicin in patients with relapsed–refractory MM (NCT01177683). Although not currently approved in this indication, bendamustine-based therapies have a role in the treatment of relapsed–refractory pretreated patients with advanced MM, particularly those who are known to be refractory to several available therapies. More data are required to confirm the place of bendamustine in advanced MM as third- or higher-line therapy.

In elderly patients with relapsed–refractory MM, evidence shows efficacy benefits with BVD in patients with first relapse [41], and phase II study data revealed that patients aged over 70 years had the same TTP outcomes as those aged 70 or under [38]. Other studies of BVD in this population are ongoing (e.g. NCT01045681).

Conclusions

Bendamustine is a synthetic chemotherapeutic agent that combines the alkylating properties of a mustard group with the activities of a benzimidazole ring, giving it a unique alkylating activity compared with other alkylating agents. Bendamustine has proven activity in both newly diagnosed and in relapsed–refractory MM. Bendamustine has also demonstrated activity in MM after relapse from ASCT, and has recently been used successfully as a conditioning regimen for ASCT in combination with melphalan. Bendamustine is generally well tolerated, with the majority of adverse events reported with treatment due to bone marrow suppression. Extramedullary toxicity is infrequent and usually mild.

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