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MINI REVIEW

Bendamustine: something old, something new

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Abstract
Background Bendamustine (Treanda, Ribomustin) is a water-soluble, bifunctional chemotherapeutic agent that also has potential antimetabolite properties and only partial cross-resistance with other alkylators. Designed in 1963 and re-discovered in 1990s, this drug's unique mechanism of action and favorable side-effect profile promise a major role in the management of lymphoproliferative disorders. Bendamustine has been designated as an orphan drug in the United States, conferring prolonged market exclusivity.
Objective This article provides a comprehensive review of the data on efficacy and toxicity from trials investigating the use of bendamustine for the treatment of lymphoproliferative neoplasms. The pharmacology, pharmacokinetics, and pre-clinical studies with bendamustine are also reviewed.
Methods MEDLINE and Pubmed databases (1970–2010) were searched using the terms bendamustine, bendamustin, Treanda, Ribomustin, SDX-105, IMET-3393, and Cytostasan. All relevant articles were reviewed and references screened for additional articles. The databases of the American Society of Hematology (2004–2009) and the American Society of Clinical Oncology (1995–2009) were also searched for relevant abstracts.
Results Bendamustine induces a remission in more than three-fourths of patients with rituximab-refractory indolent B cell non-Hodgkin lymphoma (NHL). Combined with rituximab in vitro, bendamustine shows synergistic effects against various leukemia and lymphoma cell lines. Clinical trials supporting these results show that bendamustine plus rituximab is highly effective in patients with relapsed-refractory indolent lymphoma, inducing remissions in 90% or more and a median progression-free survival of 23–24 months. Bendamustine has been reasonably well tolerated in clinical trials with low propensity to induce alopecia.
Conclusions Combination of bendamustine and rituximab has the potential to become a new standard first-line treatment option for patients with FL, MCL, and indolent lymphomas. Results of ongoing trials will help to further elucidate the optimal role of bendamustine in indolent NHL.

Keywords Bendamustine · Indolent non-Hodgkin's lymphoma · Novel therapy · Lymphoproliferative disorders

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Introduction

Lymphomas/Leukemias are an ideal model of the progress that has been achieved in the diagnosis, classification, and management of malignant neoplasms. While the first attempts to explore drugs effective against malignant diseases are accredited to Paul Ehlrich, the beginnings of modern chemotherapy may be ascribed to the remarkable tumor response of a patient who was treated with nitrogen mustard (HN3) at Yale-New Haven Hospital in 1942 [1]. This observation, after authenticated by others, inspired extensive research on alkylating agents as anti-cancer therapy. Subsequent decades saw the beginnings of combination therapy in non-Hodgkin's lymphomas, with phase

2 trials studying the usefulness of three new agents (cyclophosphamide, prednisone, and vincristine) [2]. However, tumor cell resistance remained a problem and this, in combination with treatment toxicity, stirred further research that led to the emergence of monoclonal antibodies as a targeted therapy for cancer. Amidst the continued search for newer targets and small-molecule inhibitors, investigators have re-discovered older agents that have proved extremely valuable in cancer treatment; bendamustine is one such alkylating agent and forms the basis of the present review.

Non-Hodgkin's lymphoma (NHL) is the second-fastest growing cancer in terms of mortality, and an incidence rate that has nearly doubled in the last four decades with an annual increase of 4%, due to reasons that are not entirely clear. 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 [3]. Similar estimates for the year 2004 in the EU indicate 62,300 new cases of NHL and 31,500 deaths associated with the disease [4].

Indolent B cell lymphomas, including follicular lymphoma (FL), represent a heterogenous group of lymphoproliferative disorders with a median survival that may be as long as 10 years. With an incidence in the western world of two out of 100,000, follicular lymphoma (FL) is the second most frequent non-Hodgkin lymphoma (NHL) after diffuse large B cell lymphoma. Compared with Asia and developing countries, the incidence is much higher in Western Europe and North America and has increased in the period 1978–1995 by 16–22% for White Americans and by 77% for Afro-Americans. The disease follows an erratic clinical course with some patients have waxing and waning disease for 5 years or more without the need for therapy, while others present with more disseminated disease at diagnosis, with involvement of multiple lymph nodes, liver, and spleen.

The disease, however, is not curable with available treatment, and most patients tend to relapse after treatment with shorter intervals of remission in between. It has, therefore, been traditionally approached either by watch and wait or with single-agent treatments with the purpose of maintaining a good quality of life for a prolonged time [5, 6]. The emergence of more aggressive regimens, including combination chemotherapy, radio-immunotherapy [7, 8], high-dose chemotherapy with stem-cell rescue [9], and the positive effect of the addition of rituximab to the latter have prompted many clinicians to abandon this minimalist strategy while trying to obtain a prolongation of survival or even cure by giving more intensive regimen at diagnosis or as soon as treatment was necessary. 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 (82.3%) of patients with FL received therapy in the United States [10].

In the pivotal trial of patients with relapsed FL, single-agent rituximab demonstrated a moderate efficacy of <50% [11]. While the advantage of adding rituximab is established for several regimens including CVP and CHOP [12, 13], a cure is still elusive. Patients invariably become refractory to rituximab over time and require a succession of treatments. Pre-clinical data suggests that the biologic basis of rituximab resistance may vary as a function of the prior therapies received [14]. Although yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab have confirmed activity in patients who are refractory to single-agent rituximab [15], their use has been restricted by strict eligibility criteria and other factors. Also patients with indolent B cell lymphoma are more likely to be treated with rituximab–chemotherapy combinations than with single-agent rituximab. Thus, it is important to establish benchmarks of activity in this unique and growing patient population for which there are no published trials evaluating other agents or regimens Table 1.

Bendamustine (Treanda; Cephalon, Inc., Frazer, Pa) was synthesized in 1963 by Ozegowski and Krebs at the Institute for Microbiology and Experimental Therapy in Jena, in what was then the German Democratic Republic (East Germany) [16]. It was widely used but never studied systematically in patients until the 1990s. East German investigators demonstrated its clinical activity in a number of malignancies, including chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), non-Hodgkin's lymphoma, multiple myeloma (MM), and lung cancer.

Table 1 Studies using Bendamustine monotherapy in indolent NHL

Study (reference)	Number	ORR (%)	CR (%)	PR (%)	DOR (in months)	PFS (in months)	OS (in months)
Heider et al. [37]	58	73	11	62	16		36
Bremer et al. [38]	102	77	11	66	39		29
Kahl et al. [40]	38	84	29	53	9.3	9.7	
Friedberg et al. [39]	76	77	15	43	6.7	7.1	

ORR overall response rate, *CR* complete response, *PR* partial response, *DOR* duration of response, *PFS* progression-free survival, *OS* overall survival

Table 2 Selected studies using Bendamustine combination therapies in NHL

Study (Reference)	Bendamustine plus	Number	ORR (%)	CR (%)	PR (%)
Ruffert et al. [41]	Vincristine + prednisone	31	90	38	52
Blumenstengel et al. [42]	Vincristine + prednisone	22	86	45	41
Herold et al. [43]	Vincristine + prednisone	82	66	22	44
Kath et al. [44]	Vincristine + prednisone	22	86	45	41
Heck et al. [45]	Mitoxantrone	29	59	7	52
Kahl et al. [46]	Mitoxantrone + MTX + prednisone	23	48	13	35
König et al. [47]	Dexamethasone + idarubicine	14	79	29	50
Ruffert [48]	Etoposide	38	97	67	30
Kirchner et al. [58]	Fludarabine + rituximab	25	76	28	48
Weide et al. [53]	Mitoxantrone + rituximab	54	96	41	55
Königsmann et al. [50]	Fludarabine	29	77	45	32
Rummel et al. [55]	Rituximab	63	90	60	30
Robinson et al. [56]	Rituximab	54	84	21	63
Van der Jagt et al. [67]	Rituximab	66	94	41	53
Weide et al. [54]	Mitoxantrone + rituximab	57	89	35	54

ORR overall response rate, *CR* complete response, *PR* partial response

Bendamustine received its first marketing approval in Germany, under the trade name Ribomustin (Mundipharma International Corporation Limited), for use as a single-agent or in combination-chemotherapy regimens for indolent NHL, MM, and CLL Table 2.

More recently, several well-designed and well-supervised trials, conducted outside Germany, have provided exciting results that have stirred considerable interest in the potential role of bendamustine for the treatment of lymphoproliferative disorders. Bendamustine was granted orphan drug status in 2007 and, subsequently, approved by the FDA for the treatment of CLL on March 20, 2008 [17]. On October 31, 2008, the FDA approved bendamustine for treating patients with indolent B cell NHL whose disease has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen [18]. This review assembles and assimilates the presently available data for the practicing clinician contemplating this chemotherapy option.

Chemistry and pharmacology

Bendamustine is a white, water-soluble microcrystalline powder with amphoteric properties due to a nitrogen mustard group and a butyric acid side chain. Chemically, the bendamustine molecule is gamma-[1-methyl-5-bis(β-chloroethyl)-amino-benzimidazolyl-2]-butyric acid hydrochloride [16]. It has three structural elements: a mechlorethamine (nitrogen mustard) group, a benzimidazole ring, and a butyric acid side chain (Fig. 1). The nitrogen mustard group is structurally similar to cyclophosphamide and

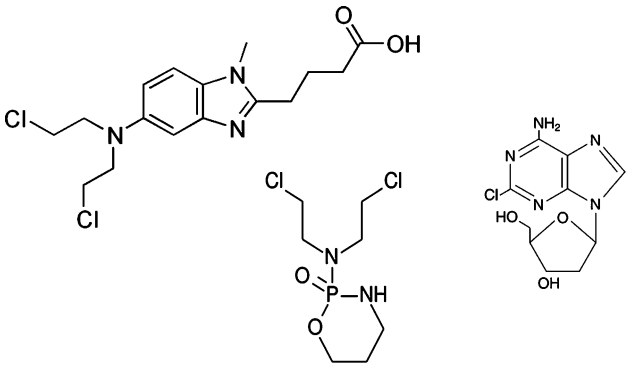

Fig. 1 Chemical structure of Bendamustine, Cyclophosphamide and Cladribine

chlorambucil and gives the drug its alkylating properties [17, 19]. The benzimidazole ring, which replaces the benzene ring in chlorambucil, is similar in configuration to some purine analogs such as 2-chlorodeoxyadenosine and represents a unique facet of the molecule. The intent of adding this structure to the nitrogen mustard was to include the antimetabolite properties shown for benzimidazole. While this has led some to suggest that bendamustine may have purine analog activity as well, no definite evidence has been confirmed.

The exact mechanism of action of bendamustine has not yet been fully elucidated. Like other alkylating agents, it causes intra-strand and inter-strand cross-links between DNA bases [20, 21]. However, the DNA breaks induced by Bendamustine are more extensive than those produced by cyclophosphamide or carmustine and more durable than those associated with melphalan, cyclophosphamide, or

carmustine. Bendamustine may also be associated with a relatively slower repair of DNA damage than with other alkylating agents. Strumberg et al. [22], using breast carcinoma cell lines, showed that removal of DNA double-strand breaks induced by bendamustine hydrochloride was relatively slow with the majority of DNA double-strand breaks still being detectable after 24 h. The widespread DNA damage prevents timely DNA repair, culminating in inhibition of mitotic checkpoints.

Bendamustine has recently been shown to have a unique mechanism that differs from other alkylating agents by the activation of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe [20, 23]. Evidence suggests that bendamustine activates a base-excision DNA-repair pathway. While other alkylators induce an alkyltransferase mechanism of DNA repair, bendamustine does not. This suggests that bendamustine may be less susceptible to drug resistance based on alkylguanyl transferase expression.

The mechanism by which bendamustine-regulated apoptotic pathways was also found to be different from that of other alkylating agents [20]. Compared with equitoxic concentrations of phosphoramide mustard and chlorambucil, the genes p21 (Cip1/Waf1/cyclin-dependent kinase inhibitor 1A; p53-induced cell division kinase inhibitor) and *NOXA* (p53-induced proapoptotic Bcl-2 family member) are induced much more strongly and more rapidly by bendamustine. Bendamustine also leads to a striking up-regulation of Ser^{15}, which is one of the key initial events known to trigger apoptosis through p53. P53 levels were increased to a numerically greater extent by bendamustine than by phosphoramide and did not change at all following exposure to chlorambucil. Also bendamustine, but not phosphoramide or chlorambucil, caused an appreciable increase in the protein expression of Bax in SU-DHL-1 cells leading to p53-mediated apoptosis.

Bendamustine causes a significantly greater increase in the proportion of cells in the S-phase of the cell cycle, which along with the down-regulation of several mitosis-related genes, including *polo-like kinase 1* (*PLK-1*), *Aurora Kinase A*, and *cyclin B1,* suggesting that, in addition to inducing apoptosis, bendamustine may also cause the inhibition of mitotic checkpoints and initiation of mitotic catastrophe [20].

Bendamustine in pre-clinical studies

Pre-clinical studies demonstrated exceptional activity of bendamustine in tumor cells resistant to other alkylating agents [19]. Strumberg et al. [22] noted that the relative degree of resistance to bendamustine hydrochloride was lower in all cell lines compared with cyclophosphamide, melphalan, and BCNU, suggesting only incomplete cross-resistance. Thereafter, Chow et al. [24] investigated the activity of bendamustine in combination with other established cytotoxic drugs, using lymphoma cell lines in vitro and in ex vivo cells from patients with leukemic progression of lymphoma. While bendamustine and cladribine exhibited in vitro synergy, antagonism was observed with mitoxantrone and doxorubicin.

Pre-clinical research also supports the use of bendamustine in conjunction with rituximab [25]. Using Daudi human lymphoma tumor xenografts in SCID mice, Kanekal et al. [26] demonstrated a synergism between bendamustine and rituximab. Tumors in treated groups were significantly smaller than tumors in the control group, and the tumors in the combination group were significantly smaller than tumors in the rituximab group ($P < 0.02$). This was further substantiated by a study showing that addition of rituximab reduces the dose of bendamustine required to induce apoptosis in CD20-positive DOHH-2 and WSU-NHL cell lines and ex vivo B cell CLL cells [27].

Administration of bendamustine during organogenesis in rodents resulted in decreased body weights and increased fetal malformations. Bendamustine has been classified as a Pregnancy Category D medication [17]. Therefore, women of childbearing age should avoid pregnancy with adequate birth control methods.

Pharmacokinetics and phase 1 studies

After an intravenous single-dose administration (100 mg/m^2) of bendamustine, peak plasma concentration of the drug (C_{max}) is achieved at the end of a 1-h infusion (17, 28, and 29). The mean steady-state volume of distribution is 25 l [17, 30], and the drug is 94–96% bound to serum plasma proteins, primarily albumin, but only free bendamustine is pharmacologically active [17]. The drug is eliminated mainly via feces (90%) and to a lesser extent in the urine [17].

CYP1A2-catalyzed N-dealkylation and gamma hydroxylation are the major routes for bendamustine phase I metabolism producing two metabolites less or similarly toxic than the parent compound [31]. Nevertheless, active metabolites such as gamma-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4) occur in only negligible concentrations when compared to the parent component, and this implies that the cytotoxic activity of bendamustine is mainly generated by the original compound. Non-metabolized particles have been found to constitute 45% of the excreted portion of the drug in urine [32].

Preliminary research shows that pharmacokinetics of bendamustine are not affected by age or mild hepatic or renal sufficiency [17]. However, our experience with this

drug is limited, and hence, caution must still be used in patients with hepatic or renal insufficiency. The effect of race on bendamustine pharmacokinetics has not yet been established; however, a study of 6 Japanese subjects did indicate that their bendamustine exposure was 40% higher than the non-Japanese subjects [17].

Also, the drug–drug interactions involving bendamustine have not been well studied and require further attention. In an evaluation of a wide range of CYP isoenzymes using human hepatic microsomal preparations or primary cultures of human hepatocytes, bendamustine did not induce/inhibit any isoenzymes, including CYP1A2 [17, 30]. However, pharmacokinetics may be affected if the drug is used concomitantly with CYP1A2 inducers/inhibitors; caution is warranted.

The use of Bendamustine has been tried using a variety of doses and schedules. Early studies used single doses of 150 mg/m^2 bendamustine on days 1 and 2 of a 4-week treatment course [33]. Using a day 1 and 8 of an every 3-week schedule, Schöffski et al. [34] determined an MTD at 140 mg/m^2 and reported fatigue and dry mouth as DLTs. They also observed a high incidence of lymphocytopenia without opportunistic infections. Later, the same investigators conducted a phase I study of weekly bendamustine [35] and reported an MTD of 80 mg/m^2, with cholinergic events, fatigue, and fever as DLTs. Again a near absolute lymphocytopenia was noted (11 out of 12 patients). Flow cytometric studies demonstrated that bendamustine had a deleterious effect on all lymphocyte subsets, but most prominently on B cells.

In a third phase I trial in which a single dose of bendamustine every 3 weeks was studied [28], the MTD was determined at 280 mg/m^2. Grade 4 thrombocytopenia, grade 3 fatigue, and grade 2 cardiotoxicity were encountered, the latter considered as dose limiting. The pharmacokinetic evaluation revealed a mean elimination half-life of bendamustine in plasma of 49.1 min with the volume of distribution being 18.3 lm^{-2} and the clearance 265 ml/min/m^2, with no evidence of dose dependency.

In the most recent phase I study by the same investigators [29], bendamustine hydrochloride was given by a 30-min intravenous infusion for two consecutive days every 3 weeks. Thrombocytopenia grade 4 was the DLT at 180 mg/m^2 per day. Other important toxicities were long-lasting lymphocytopenia, observed from the first cycle onwards and present in every patient irrespective of the given dose, and some non-hematologic toxicity, that is, fatigue, loss of appetite, nausea, and vomiting. The recommended dose for further phase II testing is 160 mg/m^2 per day. The pharmacokinetic profile (PK) of bendamustine produced virtually identical results, which when compared to previous results, suggests a lack of schedule dependency.

Owen et al. [36] conducted a population pharmacokinetic analysis of bendamustine in patients with indolent NHL treated with 120 mg/m^2 day 1 and 2 every 3 weeks. Following a 60-min intravenous administration, plasma concentrations declined in a rapid biphasic manner ($t½\alpha = 17$ min, $t½\beta = 42$ min) and a slow terminal phase ($t½c = 110$ h), 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 min.

Bendamustine monotherapy

In a study published in 2001 [37], Heider and Niederle investigated the efficacy and toxicity of bendamustine in the treatment of relapsed low-grade NHL in a single institution trial. Fifty-eight patients with relapsed low-grade NHL (CLL 27, centroblastic/-cytic 22, centrocytic 6, immunocytic 3) were enrolled and treated with bendamustine 120 mg/m^2 as a 1-h infusion on 2 consecutive days of 3-week cycle. The treatment was repeated until complete remission (CR), partial remission (PR), or stable disease (SD) was confirmed on two consecutive cycles. A median of 6 cycles was given; 52 patients were evaluated for response and toxicity. The overall response rate was 73% (11% CR, 62% PR). SD was seen in 10% with PD in 17% patients. The median duration of remission and survival was 16 and 36 months, respectively. The regimen was surprisingly well tolerated, and no treatment-related mortality was noted. Only 3 patients experienced grade 3 or 4 toxicity (grade 3 leukopenia).

Subsequently, another European study [38] was published in 2002 that enrolled 102 patients with relapsed indolent lymphomas (CLL 15, MM 25, immunocytic 46, and others 16). The dose of bendamustine used was 60 mg/m^2, days 1–5 every 4–6 weeks. A median of 4 cycles [1–11] was administered; no TRM was seen. The ORR was 77% with SD 20% and PD in only 4% patients. Grade 3–4 hematotoxicity constituted the majority of adverse events with anemia in 7%, thrombocytopenia in 12%, and leukopenia in 25% patients.

To authenticate these observations, a North American phase 2 multi-center study was designed to evaluate the efficacy and toxicity of bendamustine in patients with B cell non-Hodgkin's lymphoma (NHL) refractory to rituximab [39]. Patients enrolled on this study were defined as rituximab-refractory if they failed to respond or progressed within 6 months of previous treatment with rituximab. Seventy-six patients (age 38 to 84 years), with predominantly stage III/IV indolent (80%) or transformed (20%) disease, were treated using bendamustine 120 mg/m(2) intravenously on days 1 and 2 of each 21-day cycle; 74

were assessable for response. Patients received a median of two prior unique regimens; twenty-four (32%) were refractory to chemotherapy. Grade 3 or 4 reversible hematologic toxicities included neutropenia (54%), thrombocytopenia (25%), and anemia (12%). Non-hematologic toxicities were common, but generally mild with grade 1–2 nausea in 68% and grade 1–2 fatigue in 42%. An ORR of 77% (15% CR, 19% unconfirmed CR, and 43% PR) was observed. Among patients with fludarabine-refractory disease ($n = 8$), the ORR was 62%. The median duration of response was 6.7 months (95% CI, 5.1 to 9.9 months); 36% of these responses exceeded 1 year. The median DOR was only 2.3 months in the transformed population, but limiting the analysis to the patients who had indolent histology resulted in a median DOR of 9 months.

In the most recent study evaluating single-agent bendamustine in rituximab-refractory NHL, Kahl et al. [40] enrolled 102 patients at 28 institutions [39]. Seventy-six percentage of patients had advanced-stage disease at enrollment; Histologies included FL ($n = 63$), SLL ($n = 21$), lymphoplasmacytoid lymphoma ($n = 1$), and MZL ($n = 16$). The ORR was 75% (a 14% complete response rate, a 3% unconfirmed complete response rate, and a 58% partial response rate). Among alkylator-refractory patients ($n = 30$), the ORR was 60%. On the basis of a median follow-up of 11.8 months, the median PFS for the overall study population was 9.3 months. Also the efficacy of bendamustine appears to be comparable in the different indolent histological subtypes. The ORR was 74% among the 62 patients who had follicular lymphoma and 71% among the 21 patients who had small lymphocytic lymphoma.

These results established the promising clinical activity of bendamustine in patients with rituximab-refractory, indolent B cell lymphoma and formed the basis for approval by the United States Food and Drug Administration in October 2008. The remission rates induced by bendamustine mono-therapy are high; however, the duration of remission is rather short. This suggests that bendamustine, if combined with other agents, could improve the present results.

Bendamustine in combination chemotherapy

Early studies using bendamustine in combination-chemotherapy regimens suffered from inconsistent response assessment. The combination with vincristine and prednisone was evaluated in 4 small trials with a total of 157 patients [41–44]. The ORR ranged from 66–90% (CR 22–45%, PR 41–52%). Mitoxantrone used in conjunction with bendamustine produced rewarding results, with an ORR of 59% (7% CR, 52% PR) [45]. Another trial using the BMMP regimen (bendamustine/mitoxantrone/methotrexate/prednisone) enrolled 23 patients and reported an ORR of 48% (13%CR, 35% PR) [46]. Bendamustine was combined with idarubicin and dexamethasone in 14 patients with an ORR of 79% (29% CR, 50% PR) [47]. In another small study, 38 patients were treated with bendamustine/etoposide with an ORR of 97% (67% CR, 30% PR) [48].

A randomized phase 3 trial by the OSHO group compared the efficacy and toxicity of bendamustine, vincristine, and prednisone (BOP) with a standard regimen of cyclophosphamide, vincristine, and prednisone (COP) in patients with previously untreated advanced indolent non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma [49]. No significant differences were seen in the ORR, DOR, and overall survival, although BOP caused less toxicity. A clear survival advantage was, however, observed in patients who responded (PR or CR) to BOP relative to those who responded to COP (5-year projected survival rate of 74 and 56%, respectively; $P = 0.05$). When the available data was sub-divided based on tumor histopathology, BOP recipients with FL or LPL had a significantly superior 5-year survival rate than those with mantle cell lymphoma (66 and 74% versus 43%; $P = 0.03$). Patients with MCL had an OS of 34 months, compared with 76 months and 64 months, respectively, for those with FL or LPL.

Another study by the OSHO group treated 29 patients with bendamustine and fludarabine [50]. The reported ORR was 77%; 8 out of 15 responders relapsed after a median of 14 months. one patient died from febrile neutropenia; significant grade 3–4 hematotoxicity was observed.

Bendamustine in combination with rituximab

As early as 1999, Weide et al. reported the first clinical data using combination of bendamustine, mitoxantrone, and rituximab (BMR) in alkylating agent–resistant indolent B cell malignancies [51]. This small pilot study provided preliminary evidence of the efficacy of BMR regimen in this poor prognostic cohort. Patients received bendamustine dose was 90 mg/m^2 on day 1–2, mitoxantrone (M) 10 mg/m^2 on day 1, and rituximab (R) 375 mg/m^2 on day 8,15,22 and 29. Bendamustine was repeated on day 36 for 3–5 more cycles every 28 days. Final results of this pilot study, published in 2002 [52], reported an ORR of 96% (52/54) with CR 41% (22/54) and PR 55% (30/54). No TRM or hospitalization occurred within the study period. Furthermore, 46% patients received only one cycle of BMR, suggesting outstanding potency [53]. Also the treatment responses were durable, with a significant proportion of the subjects in CR 9 years after BMR.

These promising results led to a multi-center phase 2 trial that established the efficacy of BMR regimen in rituximab pre-treated, relapsed/refractory FL, MCL, and other indolent

lymphomas [54]. Therapy consisted of bendamustine 90 mg/m(2) days 1 + 2, mitoxantrone 10 mg/m(2) day 1, rituximab 375 mg/m(2) day 8. Treatment was repeated on day 29 for a total of four cycles. The overall response rate (ORR) was 89% (CR 35%, PR 54%). ORR in R-chemo pretreated patients was 76% (38% CR, 38% PR). After a median observation time of 27 months [1–43], the estimated median progression-free survival was 19 months. The 2-year overall survival was 60% for patients with FL and MCL. The foremost grade 3/4 toxicity was reversible myelosuppression (10% anemia, 78% leukocytopenia, 46% granulocytopenia, 16% thrombocytopenia).

Parallel to this study, a multicenter trial sought to evaluate the progression-free survival, response rate and toxicity of the combination of bendamustine and rituximab (BR) in patients with mantle cell or low-grade lymphomas [55]. Sixty-three patients were accrued (FL 24, MCL 16, LPL 17, and MZL 6). Bendamustine was given at a dose of 90 mg/m^2 as a 30-min infusion on days 1 and 2, combined with 375 mg/m^2 rituximab on day 1, for a maximum of four cycles every 4 weeks. All but four patients received all four cycles of treatment; no dose reductions were required. Leukopenia was the most common side-effect (16% grade 3–4 events); no evidence of cumulative myelosuppression was found. Non-hematologic toxicity was generally mild and mainly consisted of WHO grade 1 and 2 events. There was no TRM. Also none of the patients suffered from alopecia, a toxicity that is severe with other alkylator- or anthracycline-containing regimens, and of exacting importance, no organ toxicity was seen. The ORR in all 63 patients was 90% (CR 60%, PR 30%). The ORR in patients with relapsed MCL was 75% ($n = 12/16$), and 50% achieved CR. The responses were fairly durable, with median PFS for all patients being 24 months (range, 5 to 44+ months) and 41 patients still in remission (at the time of publication).

The outstanding results of this study drove researchers to design a similar study in the United States. Sixty-six patients were treated with the BR regimen [56]. The ORR was 92% (41% CR, 14% uCR, and 38% PR). The median DOR and PFS were 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies. The primary toxicity was myelosuppression (grade 3 or 4 neutropenia, 36%; grade 3 or 4 thrombocytopenia, 9%).

Even though the therapeutic efficacy of BR as demonstrated by both studies is similar, the same conclusion cannot be drawn regarding the treatment toxicities. While the German study used WHO guidelines for grading toxicities, the US trial utilized National cancer Institute's Common Terminology Criteria. Also the German study reported toxicity as a function of events per treatment cycle, while the US study reported it as a function of study participants. However, no serious adverse events were noted in either of the two trials.

In order to further investigate the role of the combination BR, a multicenter randomized phase-III study was initiated in October 2003 to compare efficacy and safety of BR versus CHOP plus rituximab (CHOP-R) as first-line therapy for patients with follicular (FL), indolent, and mantle cell lymphomas (MCL) [57]. A total of 549 patients (patients) in need of treatment for their disease were randomized to receive rituximab 375 mg/m^2 (day 1) plus either bendamustine 90 mg/m^2 (days 1 + 2) every 28 days or the standard CHOP regimen every 21 days for a maximum of 6 cycles. Five hundred and thirteen randomized patients are evaluated for the final analysis (BR: $n = 260$; CHOP-R: $n = 253$). A median number of 6 cycles was given in both treatment arms each. Eighty-two of BR patients and 86% of CHOP-R patients received 6 cycles. While the ORR for patients treated with BR was similar to the CHOP-R group (93.8 vs 93.5%, respectively), the CR rate was significantly higher with 40.1% for BR compared to 30.8% for CHOP-R. The median PFS, EFS, and TTNT were significantly longer after BR compared to those after CHOP-R. CHOP-R treatment was more frequently associated with serious adverse events (SAE) ($n = 49$ in BR vs $n = 74$ in CHOP-R). Significant differences in hematologic toxicities were observed for neutropenia grade 3 + 4 (BR 10.7% vs CHOP-R 46.5%; $P < 0.0001$) and for leukopenia grade 3 + 4 (BR 12.1% vs CHOP-R 38.2%; $P < 0.0001$). G-CSF was more often used in CHOP-R treated patients (20.0% of all cycles) than it was used in the BR group (4.0%) ($P < 0.0001$). Only drug-associated erythematous skin reaction (urticaria, rash) was more often seen with BR ($n = 42$) than with CHOP-R ($n = 23$).

Bendamustine has also been combined with fludarabine and rituximab (BFR) in the treatment of relapsed indolent lymphomas [58]. In this study, bendamustine was applied at a dose of 50 mg/m^2 on days 1–3, fludarabine at a dose of 25 mg/m^2 days 1–3, and rituximab (375 mg/m^2) was given on days 8, 15, 22, 29. The chemotherapy part (bendamustine plus fludarabine) was repeated on day 57 for 4 cycles. BFR proved to be effective with an ORR of 76% (28% CR, 48% PR). Unfortunately, the study could not be continued due to a significant hematotoxicity and a high rate of serious infections.

Results of the above-mentioned studies clearly demonstrate the efficacy of combined bendamustine and rituximab for patients with relapsed indolent and mantle cell NHL. BR elicits responses that are durable, with a low incidence of severe and life-threatening events. Excellent activity has been seen against low-grade lymphomas across multiple histological subtypes, suggesting that the combination of BM and rituximab may have the potential to

become a new standard first-line treatment option for patients with FL, MCL, and indolent lymphomas.

Future directions

In a recent review article, Rudolf Weide [59] reported the sequential use of chemo-immunotherapy with bendamustine followed by radio-immunotherapy. Ten patients with relapsed-refractory indolent lymphoma and MCL were treated using 3 cycles of BMR followed by 90Y-ibritumomab tiuxetan (Zevalin TM). The ORR was 90% (CR 60%, PR 30%, PD 10%). Five out of 6 patients in CR achieved a durable response. The major treatment-related adverse event was reversible grade 3–4 hematotoxicity after Zevalin TM.

In a freshly published single-center phase 2 trial [60], weekly bendamustine and bortezomib combination therapy has been evaluated in relapsed or refractory Indolent NHL or B-CLL. Twelve patients were enrolled (MCL 5, FL 4, CLL 2, and WM 1). All patients had received a median of three prior treatment lines (range 1–8). On Days 1, 8, 15, and 22 of a 35-day cycle, patients received intravenous bolus bortezomib 1.6 mg/m^2 for a maximum of three cycles. Bendamustine was administered as 30-min intravenous infusion on Days 1, 8, and 15 before bortezomib. Dose escalation was started at 60 mg/m^2 bendamustine (level 0) with 80 mg/m^2 as the first escalation step (level 1). Four patients were treated per dose level. Without dose-limiting toxicity (DLT), the bendamustine dosage was escalated. The four patients entering dose level 0 showed no DLT. In three out of five patients on level 1, DLT was eventually observed, thus defining MTD. Adverse events with an overall incidence of =20% were diarrhea, nausea, vomiting, anemia, leukopenia, neutropenia, thrombocytopenia, and fatigue. The combination worked particularly well in MCL; all patients responded. Results, however, were not that encouraging in FL; all cases of PD were observed in FL.

A similar single-arm, multi-center study in the United States [61] seeks to evaluate the efficacy and safety of bortezomib (Velcade), bendamustine, and rituximab (VBR) in patients with relapsed/refractory FL (the VERTICAL study). The data on safety of dose escalation of bendamustine in combination with VR were recently presented. Sixteen patients (4 at B 50 mg/m^2, 6 each at B 70 and 90 mg/m^2) with a median of 3 prior therapies were enrolled. One DLT at bendamustine 70 mg/m^2 (severe rash requiring treatment discontinuation) and one DLT at 90 mg/m^2 (grade 3 thrombocytopenia requiring treatment delay) were observed. Hematologic toxicities were manageable and included 4 (25%) $\geq$ G3 neutropenia and 1 (6%) G4 thrombocytopenia. Grade 3–4 Non-hematologic toxicities in >1 patient were diarrhea (31%), fatigue (25%), vomiting (13%), and nausea (13%). Peripheral neuropathy was reported in 6 patients (38%; 1 G3). The trial is presently enrolling patients in the phase 2 portion of the study.

A phase 1 trial of bendamustine, lenalidomide, and rituximab in CLL and NHL (Phase I BLR) is presently enrolling patients at the Georgetown University Hospital/Lombardi Cancer Center, USA [62]. The study, initiated in February 2009, aims to enroll 96 patients. The study will be conducted in 2 parts. In part I of the study, the maximum tolerated dose of bendamustine and lenalidomide will be determined independently for the CLL and NHL groups. In part II of the study, CLL and NHL subjects will be enrolled at the MTD of BL determined in Part I for CLL and NHL and all subjects will receive rituximab. At this point, the regimen will be evaluated for overall safety profile, plasma pharmacokinetics, and preliminary antitumor activity. A study with similar study design was recently initiated in Switzerland [63]; this phase 1/phase 2 trial will investigate the use of BLR regimen in patients with relapsed or refractory aggressive B cell lymphoma who are not eligible for high-dose chemotherapy (HDC).

An open-label intervention study at MD Andersen Cancer Center is evaluating the safety and efficacy of fludarabine, bendamustine and rituximab conditioning for patients with lymphoid malignancies [64]. The study aims to report the MTD of bendamustine when given with a stem-cell transplant and chemotherapy (fludarabine and rituximab). The study, initiated in April 2009, plans to enroll 46 patients.

Another non-randomized study at MD Andersen Cancer Center is using bendamustine, mitoxantrone, and rituximab (BMR) in combination for patients with previously untreated follicular B cell non-Hodgkin's lymphoma [65]. This study, in addition to confirming the results of European trials, will aim to determine the correlation between molecular complete response and response to therapy and examine the immediate and prolonged effects of BMR on immune effector cell number and function. With an estimated enrollment of 37 patients, the study is expected to close by May 2012.

Challenging the current standard of care for patients with FL, an open-label, randomized, multi-center study of the BR regimen compared with R-CVP or R-CHOP in the first-fine treatment of patients with advanced Indolent NHL or MCL (The Bright Study) is presently recruiting participants [66]. With the primary aim of comparing the CR rates, the study will enroll 296 participants and report preliminary results in 2011.

Further studies may use bendamustine in combination with immuno-modulators such as thalidomide and lenalidomide or anti-angiogenesis agents like bevacizumab. Combination with newer anti-B cell antibodies, such as the

recently approved Ofatutumab, may provide interesting results.

Conclusions

Incurability of indolent B cell lymphomas with the current treatment, which includes the upfront use of monoclonal antibody, rituximab, leaves a wide scope for the development of newer treatment strategies that are highly active against relapsed/refractory disease and can provide durable complete remissions (CR) and/or extended quality of life. Given the long-term survival of patients with FL, drugs with favorable side-effect profile and minimal long-term risks are desirable.

The presently available clinical data, combined with the emerging worldwide experience for bendamustine, strongly suggest that bendamustine is a valuable addition to our treatment armamentarium for patients with indolent lymphomas resistant to alkylating agents, purine analogs and rituximab. However, many questions remain unanswered. The precise mechanism of action and of resistance as well as the optimal dose and schedule has not been determined yet. Bendamustine has not been evaluated in patients with moderate to severe liver or renal dysfunction; hence, more precise dosing strategies are required. The influence of prior bendamustine therapy on stem-cell mobilization and harvest is principally unknown. Also any relationship between BM and secondary myelodysplastic syndromes has not been explored.

Trials to help clarify the optimal role of bendamustine in lymphoproliferative disorders are ongoing. BM may be a reasonable substitute to R-CHOP in elderly patients with multiple co-morbidities, including cardiac dysfunction. There is evidence of effectiveness in aggressive NHL, T cell lymphoma, MM, and Hodgkins lymphoma where further investigation is indicated.

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