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REVIEW

Bendamustine: Safety and Efficacy in the Management of Indolent Non-Hodgkins Lymphoma

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Abstract: Bendamustine (Treanda, Ribomustin) was recently approved by the US Food and Drug Administration (FDA) for treatment of patients with rituximab refractory indolent lymphoma and is expected to turn into a frontline therapy option for indolent lymphoma. This compound with amphoteric properties was designed in the former Germany Democratic Republic in 1960s and re-discovered in 1990s with multiple successive well-designed studies. Bendamustine possesses a unique mechanism of action with potential anti-metabolite properties, and only partial cross-resistance with other alkylators. Used in combination with rituximab in vitro, bendamustine shows synergistic effects against various leukemia and lymphoma cell lines. In clinical studies, 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. The optimal dosing and schedule of bendamustine administration is largely undecided and varies among studies. Results of ongoing trials and dose-finding studies will help to further help ascertain the optimal place of bendamustine in the management of indolent NHL.

Keywords: bendamustine, indolent non-Hodgkin's lymphoma, follicular lymphoma, novel therapy, lympho-proliferative disorders

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Introduction

Non-Hodgkin's lymphoma (NHL) belongs to a diverse group of hematologic malignancies originating in B or T lymphocytes. Approximately 85% of NHLs are of B-cell origin, with the remainder mostly of T-cell origin. Non-Hodgkin's Lymphoma (NHL) is the second-fastest growing cancer in terms of mortality with 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. NHL is the seventh most common cancer in the United States, contributes to approximately 4% to 5% of all cancer cases in the United States, and causes approximately 3% of all cancer-related deaths.[1] Currently, nearly 500,000 people are living with the disease or are in remission. More than 65000 new cases of NHL are diagnosed in the United States each year and there are approximately 20000 NHL-related deaths.[1] Similar estimates for the year 2004 in the European Union (EU) indicate 62300 new cases of NHL and 31500 deaths associated with the disease.[2]

With an incidence of two out of 100 000, Follicular Lymphoma (FL) is the most frequent lymphoma in the western world after diffuse large B-cell lymphoma (DLBCL) and is by far the most frequent indolent lymphoma,[3] hence often used as a treatment model for all other indolent lymphomas. FL represents a heterogenous group of lymphoproliferative neoplasms that contain mainly centrocytes and a variable component of centroblasts, the frequency of which yields the grade (1, 2 or 3, depending on the percentage of centroblasts). The disease follows an unpredictable clinical course with some patients have waxing and waning disease for five years or more without the need for therapy, while others present with more aggressive, symptomatic disease and high tumour burden requiring immediate treatment.

Historically, the median overall survival (OS) for patients with FL was 8–10 years, but outcomes have improved, largely attributable to the incorporation of rituximab into treatment regimens.[4,5] Management of FL has, therefore, been traditionally approached either by watch and wait or with single-agent treatments with the principle of offering a good quality of life for a prolonged time.[6] The appearance 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,[10,11] have driven many clinicians to abandon this minimalist strategy while trying to obtain a prolongation of survival or even cure by giving more rigorous regimen at diagnosis or as soon as treatment was necessary. The use of rituximab with upfront chemotherapy is now considered standard. While a watch-and-wait approach may still be considered in selected patients, the majority (81%) of FL patients in the US receive therapy.[12] In addition, more successful frontline approaches have made assessment of newer agents as apart of initial therapy a more difficult and long-term process.

However, a cure of FL is still elusive. The survival curve of FL patients is a continuously descending straight line never reaching a plateau. Patients invariably become refractory to rituximab over time and require a succession of treatments. Demonstration of efficacy in this patient population is tricky. Preclinical data suggests that the biologic basis of rituximab resistance may vary as a function of the prior therapies received.[13] In addition, the optimal chemotherapy backbone of rituximab remains unsettled. Data from the US Lymphocare Project indicates the most commonly used regimens in the US are R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone] (55%), R-CVP [rituximab, cyclophosphamide, vincristine, and prednisone] (23%), rituximab-fludarabine-based (16%) and other (6%).[12] Randomized data has shown that, while fludarabine yields higher response rates compared with regimens such as CVP and CHOP, it also causes higher toxicity, including increased bone marrow damage, myelosuppression and potential infection risk.[14] The lack of randomized data to show improved progression-free survival (PFS) or overall survival (OS) with fludarabine, in light of this increased toxicity, probably explains the general preference in the USA for R-CHOP and R-CVP.

While novel anti-CD20 molecules do offer the prospect of enhanced activity relative to rituximab, clinical data is not very compelling. Yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab have confirmed activity in patients refractory to single-agent rituximab,[15] but their use has been constrained by strict eligibility criteria and other factors. In consequence, nearly all patients with FL receive rituximab at multiple

times over their treatment. It is, thus, imperative that we establish benchmarks of activity in this unique and growing patient population for which there are no published trials evaluating other agents or regimens.

Bendamustine is one such agent that may offer answers to the questions raised in the discussion so far and forms the basis of the present review. 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 extensively used, but not systematically studied until the 1990s. 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, multiple myeloma (MM), and chronic lymphocytic leukemia (CLL).

Several well-designed and well-supervised studies in recent years have provided exciting results that has enthused great interest in the potential role of bendamustine for treatment of lymphoproliferative disorders. Clinical trials appear to also indicate some activity of bendamustine in breast cancer, small-cell lung cancer, and leiomyosarcomas. The agent 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] It is currently indicated in Germany, Singapore and Hong Kong, and has been recommended for approval in the EU, for the treatment of various haematological malignancies. A new drug application has also recently been filed in Japan for the treatment of refractory and relapsed low-grade NHL and mantle cell lymphoma (MCL).

The following review provides an overview of the pharmacological properties of bendamustine and attempts to assemble and assimilate the presently available clinical trial data for the practicing clinician contemplating this chemotherapy option in the management of indolent NHL.

Chemistry, Pharmacology and Pre-Clinical Data

Chemically, the bendamustine molecule is gamma-[1-methyl-5-bis(β-chloroethyl)-amino-benzimidazolyl-2]-butyric acid hydrochloride.[16] The molecule has three structural elements: a mechlorethamine (nitrogen mustard) group, a benzimidazole ring and a butyric acid side chain. The nitrogen mustard group is structurally similar to cyclophosphamide and chlorambucil and gives the drug its alkylating properties, while the butyric acid group confers water solubility.[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 there has been speculation that bendamustine may have purine analog activity as well, no definite evidence has been published.

While other alkylating agents, such as chlorambucil, cyclophosphamide, and melphalan have very analogous mechanisms of action to each other, that of bendamustine appears to differ.[20,21] 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. The removal of DNA double-strand breaks induced by bendamustine hydrochloride in breast carcinoma cell lines is comparatively slow with the majority of DNA double-strand breaks still being detectable after 24 h.[22] This widespread DNA damage delays timely DNA repair, culminating in inhibition of mitotic checkpoints.

Bendamustine has recently been shown to simultaneously trigger several distinct apoptotic pathways and has been linked to a stronger activation of intrinsic apoptosis, as well as an alternative cell death pathway. This unique mechanism differs from other alkylating agents by activation of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints and induction of mitotic catastrophe.[20,23] Bendamustine has been shown to down-regulate several mitosis-related genes, including *polo-like kinase*

1 (*PLK-1*), *Aurora Kinase A*, and *cyclin B*1 and activate the primary DNA-damage signalling kinases, ataxia telangiectasia mutated protein and checkpoint kinase 2, leading to G2 arrest, and also activate p53 mediated apoptosis. Evidence also suggests that bendamustine activates a base-excision DNA-repair pathway. While other alkylators induce an alkyltransferase mechanism of DNA repair, Bendamustine does not; drug resistance based on alkylguanyl transferase expression may, as a result, not affect the efficacy of bendamustine.

The regulation of apoptotic pathways by bendamustine has many unique facets as well.[20] The DNA damage caused by alkylating agents genes *Noxa* (p53-induced proapoptotic Bcl-2 family member) and *p21*(Cip1/Waf1/cyclin-dependent kinase inhibitor 1A; p53-induced cell division kinase inhibitor) were induced to a numerically greater extent with bendamustine than with chlorambucil or phosphoramide. 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 was the only agent to cause an appreciable increase in the protein expression of Bax in SU-DHL-1 cells leading to p53 mediated apoptosis.

In pre-clinical studies, bendamustine demonstrated exceptional activity in tumor cells resistant to other alkylating agents.[19] Earlier studies noted that the relative degree of resistance to bendamustine hydrochloride was lower in all cell lines compared with cyclophosphamide, melphalan and BCNU,[22] suggesting only incomplete cross-resistance. When investigated 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, bendamustine and cladribine exhibited in vitro synergy, while antagonism was observed with mitoxantrone and doxorubicin.[24] Pre-clinical research also supported the use of bendamustine in conjunction with rituximab,[25] fludarabine or gemcitabine.

Kanekal et al[26] demonstrated synergism between bendamustine and rituximab using Daudi human lymphoma tumor xenografts in severe combined immunodeficiency (SCID) mice. After 20 days of treatment with bendamustine, rituximab or a combination of both treatments (a control group received no treatment), mice in treated groups had significantly (*P*-value not stated) smaller tumours than those in the control group, and the combination group had significantly ($P < 0.02$) smaller tumours than the rituximab group. 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]

Pharmacokinetics and Phase 1 Studies

After an intravenous single-dose administration (100 mg/m^2) of bendamustine, peak plasma concentration of the drug (Cmax) is typically reached near the end of the infusion period.[17,18,29] The mean steady state volume of distribution is 25 L.[17,30] The drug is 94%–96% bound to serum plasma proteins, primarily albumin, but only free bendamustine is pharmacologically active.[17] Bendamustine is unlikely to be displaced by or to displace highly protein-bound drugs. In human blood, it appears to distribute freely in red blood cells, with a blood : plasma concentration ratio of 0.84–0.86 over a concentration range of 10–100 mg/mL. 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 BM phase I metabolism producing two metabolites less or similarly toxic than the parent compound.[31] Nevertheless, active metabolites such as gamma-hydroxybendamustine (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. Nonmetabolized particles have been found to constitute 45% of the excreted portion of the drug in urine.[32] Phase II conjugation with glutathione may be another major route of bendamustine metabolism in humans.

Preliminary research shows that pharmacokinetics of bendamustine are not affected by age or mild hepatic or renal sufficiency.[17] The effects of more severe hepatic or renal impairment have not been investigated 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] Older age and sex do not appear to affect the pharmacokinetics of bendamustine in patients with NHL.

Also, the drug-drug interactions involving bendamustine have not been formally studied. CYP1A2 inhibitors or inducers may affect bendamustine pharmacokinetics, as bendamustine is metabolized via this pathway; caution is recommended. 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 iso-enzymes, including CYP1A2.[17,30] 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.

In wake of sub-optimal drug development strategies in its formative years, 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 weeks schedule[34] produced a MTD of 140 mg/m^2, with fatigue and dry mouth as DLTs. A high incidence of lymphocytopenia was also seen, but with no opportunistic infections. The use of weekly bendamustine[35] reported a 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. The third phase I trial using a single dose of bendamustine every 3 weeks[28] determined the MTD at 280 mg/m^2. Grade 4 thrombocytopenia, grade 3 fatigue, and grade 2 cardiotoxicity were encountered, the latter considered 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 mlmin^1 m^2, with no evidence of dose-dependency.

The most recent phase I study[29] used a 30 min intravenous infusion of bendamustine 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, suggest a lack of schedule dependency. A recent phase 1 study from Japan used bendamustine 90 or 120 mg/m^2 (dose escalation) administered intravenously over 60 min on days 1 and 2 every 3 weeks for up to three cycles.[36] Nine patients (eight indolent B-NHL and one MCL) received per-protocol treatment, three at 90 mg/m^2 and six at 120 mg/m^2. No dose-limiting toxicities were observed; thus, the maximum-tolerated dose was not reached.

Owen et al[37] 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. Plasma concentrations declined in a triphasic manner, with a rapid biphasic phase ($t1/2\alpha$ = 17 minutes, $t1/2\beta$ = 42 minutes) and a slow terminal phase (t1/2c = 110 hours). The terminal phase contributed less than 1% of the total AUC, and therefore, the half-life of the β-phase was determined to be bendamustine's mean half-life, which is approximately 40 minutes.

Bendamustine Monotherapy

In a single institution trial from 2001,[38] 58 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 were given; 52 patients were evaluable for response and toxicity. The overall response rate was 73% (11% CR, 62% PR). SD was seen in 10% with progressive disease (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). A subsequent European study[39] enrolled 102 patients with relapsed indolent lymphomas (CLL 15, MM 25, immunocytic 46 and others 16) and treated them with bendamustine, 60 mg/m^2, days 1–5 every 4–6 weeks. A median of 4 cycles (1–11) were given; no TRM was seen. The ORR was 77% with SD 20% and PD in 4%.

These results stirred healthy interest in the US and consequently, a phase 2 multi-center study was designed to appraise the efficacy and toxicity of bendamustine in patients with B-cell non-Hodgkin's lymphoma (NHL) refractory to rituximab.[40] 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. Unlike the larger noncomparative study described below, patients who were intolerant of continued rituximab therapy were also included in this phase II study. 76 patients 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 (range, one to five) 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%). Patients with relative thrombocytopenia at baseline (inclusion criteria allowed patients with platelet counts of at least 100,000/mm^3) were often incapable of tolerating the full dose of bendamustine and dosage reductions were requisite. Non-hematologic toxicities were common, but generally mild. 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 (DOR) was 6.7 months (95% CI, 5.1 to 9.9 months); 36 percent 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.

Durable responses were seen in a similarly designed multicentre phase II trial of 102 patients with rituximab-refractory indolent and transformed NHL.[41] 76% patients had advanced-stage disease at enrolment; histologies included FL (n = 63), SLL (n = 21), lymphoplasmacytoid lymphoma (n = 1), and MZL (n = 16). The ORR was 75% (a 14% CR, a 3% unconfirmed CR, and a 58% PR). Among alkylator-refractory subjects (n = 30), the ORR was 60%. The median PFS for the overall study population was 9.3 months at a median follow-up of 11.8 months. Efficacy of bendamustine was comparable in different indolent histological subtypes; ORR was 74% among the 62 patients who had FL and 71% among the 21 patients who had SLL. These results highlighted 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. Most recently, a Japanese phase 2 study[42] enrolled 58 patients with indolent B-NHL and 11 with MCL; using 120 mg/m^2 on days 1–2 of a 21-day cycle for up to six cycles, bendamustine produced an ORR of 91%; 90% and 100% in patients with indolent B-NHL and MCL, respectively), with a CR rate of 67% (95% CI, 54%–78%). After a median follow-up of 12.6 months, median PFS had not been reached. Estimated PFS rates at 1 year were 70% and 90% among indolent B-NHL and MCL patients, respectively. Bendamustine was generally well tolerated. In general, the remission rates induced by bendamustine mono-therapy are high, but the duration of remission is rather short (Table 1) suggesting that bendamustine monotherapy may be inadequate for this patient sub-group.

Bendamustine in Combination Chemotherapy

In the early years, studies using bendamustine in combination chemotherapy regimens were crippled by inconsistent response assessments. The combination with vincristine and prednisone was evaluated in 4 small trials with a total of 157 patients.[43–46] 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).[47] The BMMP regimen (bendamustine/mitoxantrone/methotrexate/prednisone) reported an ORR of 48% (13%CR, 35% PR) in 23 patients.[48] An ORR of 79% (29% CR, 50% PR) was seen in 14 patients treated with

Table 1. Studies using bendamustine monotherapy in indolent NHL.

Study (reference)	Number	ORR (%)	CR (%)	PR (%)	DOR (months)	PFS (months)	OS (months)
Heider et al[38]	58	73	11	62	16		36
Bremer et al[39]	102	77	11	66	39		29
Kahl et al[41]	38	84	29	53	9.3	9.7	
Friedberg et al[40]	76	77	15	43	6.7	7.1	
Ohmachi et al[42]	69	91	39	53			

bendamustine was combined with idarubicin and dexamethsone.[49] Another small study comprising 38 patients used bendamustine/etoposide and reported an ORR of 97% (67% CR, 30% PR).[50]

The Eastern German Study Group for Hematology and Oncology (OSHO) compared the efficacy and toxicity of bendamustine, vincristine and prednisone (BOP) with a standard regimen of cyclophosphamide, vincristine and prednisone (COP) in a phase 3 trial comprising patients with previously untreated advanced indolent non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma.[51] No significant differences were seen in the ORR, DOR and overall survival, although BOP caused less toxicity. A clear survival advantage was, however, pragmatic 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 tumour 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 using bendamustine and fludarabine[52] reported an ORR of 77%; 8 out of 15 responders relapsed after a median of 14 months.

Bendamustine in Combination with Rituximab

In 1999, a small pilot study provided the preliminary evidence of the efficacy of bendamustine/ rituximab combination in patients with relapsed-refractory lymphoma. Weide and colleagues used a combination of bendamustine, mitoxantrone and rituximab (BMR) in alkylator resistant indolent B-cell malignancies.[53] The dose of bendamustine was 90 mg/m^2 on day 1–2, with 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,[54] reported an ORR of 96% (52/54) with CR 41% (22/54) and PR 55% (30/54). No TRM or hospitalizations were reported. Of note, 46% patients received only one cycle of BMR, suggesting outstanding potency.[55] Treatment responses were durable, with majority of subjects in CR 9 years after the completion of treatment.

This promise culminated in a multi-center phase 2 trial that firmly established the efficacy of BMR regimen in rituximab pre-treated, relapsed/refractory FL, MCL and other indolent lymphomas.[56] Treatment consisted of bendamustine 90 mg/m^2 days 1 + 2, mitoxantrone 10 mg/m^2 day 1, rituximab 375 mg/m^2 day 8 and was repeated on day 29 for a total of four cycles. Overall response rate (ORR) was 89% (CR 35%, PR 54%). ORR in R-chemo pre-treated patients was 76% (38% CR, 38% PR). After a median observation time of 27 months,[1–13] the estimated median progression free survival was 19 months. The 2 year overall survival was 60% for patients with FL and MCL.

Analogous to this study, a multicenter trial evaluated 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.[57] 63 patients were accrued (FL 24, MCL 16, LPL [lymphoplasmacytic lymphoma] 17 and MZL [marginal zone lymphoma] 6). Bendamustine was administered at a dose of 90 mg/m^2 as a 30-minute 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 needed. Leukopenia was the most common side effect (16% grade 3–4 events); no evidence of cumulative myelosuppression was found. There was no TRM. 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); 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). In an American study that followed, 66 patients were treated with the BR regimen.[58] 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 both indolent and mantle cell histologies. Myelosuppression was the primary toxicity (grade 3 or 4 neutropenia, 36%; grade 3 or 4 thrombocytopenia, 9%).

Taking a step further to see if this combination would benefit patients if used upfront, a multicenter randomized phase-III study was initiated in October 2003 to compare efficacy and safety of B-R versus CHOP plus rituximab (CHOP-R) as first-line therapy for patients with follicular (FL), indolent and mantle cell lymphomas (MCL).[59] 549 patients in need of treatment 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. 513 randomized patients were evaluable for the final analysis (B-R: n = 260; CHOP-R: n = 253). A median number of 6 cycles was given in both treatment arms each. 82% of B-R and 86% of CHOP-R group received 6 cycles. While the ORR for patients treated with B-R was similar to the CHOP-R group (93,8% vs. 93,5%, respectively), the CR rate was significantly higher with 40,1% for B-R compared to 30,8% for CHOP-R. The median PFS, event-free survival (EFS) and time to next treatment (TTNT) were significantly longer after B-R compared to after CHOP-R. CHOP-R treatment was more frequently associated with serious adverse events (SAE) (n = 49 in B-R 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 leukocytopenia grade 3+4 (BR 12,1% vs. CHOP-R 38,2%; $P < 0.0001$). G-CSF was more often used in CHOP-R treated pts (20,0% of all cycles) than it was used in the B-R group (4,0%) ($P < 0.0001$).

When combined with fludarabine and rituximab (BFR) in the treatment of relapsed indolent lymphomas,[60] the regimen, given over 4 cycles, appeared 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 (Table 2). BR elicits responses that are durable, with a low incidence of severe and life-threatening events. Also, excellent activity is seen against low-grade lymphomas across multiple histological subtypes.

Table 2. Selected studies using bendamustine combination therapies in NHL.

Study (reference)	Bendamustine plus	No.	ORR (%)	CR (%)	PR (%)
Ruffert et al[43]	Vincristine + prednisone	31	90	38	52
Blumenstengel et al[44]	Vincristine + prednisone	22	86	45	41
Herold et al[45]	Vincristine + prednisone	82	66	22	44
Kath et al[46]	Vincristine + prednisone	22	86	45	41
Heck et al[47]	Mitoxantrone	29	59	7	52
Kahl et al[48]	Mitoxantrone + MTX + prednisone	23	48	13	35
König et al[49]	Dexamethasone + idarubicine	14	79	29	50
Ruffert[50]	Etoposide	38	97	67	30
Kirchner et al[60]	Fludarabine + rituximab	25	76	28	48
Weide et al[55]	Mitoxantrone + rituximab	54	96	41	55
Königsmann et al[52]	Fludarabine	29	77	45	32
Rummel et al[57]	Rituximab	63	90	60	30
Robinson et al[58]	Rituximab	54	84	21	63
Weide et al[56]	Mitoxantrone + rituximab	57	89	35	54

Recent Updates

In a freshly published single-center phase 2 trial,[61] the combination of weekly bendamustine and bortezomib was evaluated in patients with relapsed or refractory Indolent NHL or B-CLL. 12 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-minute 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.

Friedberg and colleagues[62] recently published the results of a phase 2 study that included patients with relapsed or refractory indolent and mantle cell lymphoma and adequate organ function. Therapy included bendamustine 90 mg/m^2 days 1 and 4; rituximab 375 mg/m^2 day 1, and bortezomib 1.3 mg/m^2 days 1, 4, 8, 11. Six 28-day cycles were planned. Thirty patients (7 with mantle cell lymphoma) were treated. Eight patients experienced serious adverse events, including one event of grade 5 sepsis. Non-hematologic adverse events were generally grade 1 or grade 2 and included nausea (50%), neuropathy (47%), fatigue (47%), constipation (40%), and fever (40%). Of 29 patients evaluable, 24 (83%) achieved an objective response (including 15 with complete response). With median follow-up of 24 months, 2-year progression-free survival is 47% (95% confidence interval, 25%–69%).

Addressing a similar combination, the phase 1 portion of the VERTICAL trial reported at ASCO identified 90 mg/m^2 on days 1 and 2 as the dose of bendamustine for phase 2 studies.[63] At ASH 2009, Fowler and colleagues presented phase 2 data[64] on the VBR combination in 49 patients with relapsed and refractory FL. The 5 cycles of VBR combination were delivered at 5-week intervals as follows: bendamustine 90 mg/m^2 on days 1 and 2; rituximab 375 mg/m^2 on day 1, 8, 15, and 22 of the first cycle and day 1 of each subsequent cycle; and bortezomib 1.6 mg/m^2 weekly for 4 weeks. The ORR was 80% with 47% CR.

Sequential use of chemo-immunotherapy with bendamustine followed by radio-immunotherapy has also been reported.[65] 10 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%). 5 out of 6 patients in CR achieved a durable response. Reversible grade 3–4 hematotoxicity after Zevalin TM was the only major adverse event.

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[66] with the intention of evaluating overall safety profile, plasma pharmacokinetics and preliminary antitumor activity. A similar study across the Atlantic[67] will investigate the use of BLR regimen in in patients with relapsed or refractory aggressive B-cell lymphoma who are not eligible for High Dose Chemotherapy (HDC).

Researchers at MD Andersen Cancer Center (MDACC) are evaluating the safety and efficacy of Fludarabine, Bendamustine and Rituximab conditioning in an open label trial[68] with the primary aim of reporting the MTD of Bendamustine when given with a stem cell transplant and chemotherapy (fludarabine and rituximab). Another non-randomized study at MDACC is making use of the Bendamustine, Mitoxantrone, and Rituximab (BMR) combination for patients with previously untreated FL.[69] 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.

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.[70] With the primary aim of comparing the CR rates, the study will enrol 296 participants and report preliminary results in 2011.

Further studies may use bendamustine in combination with immuno-modulators such as thalidomide and lenalidomide or newer anti-B cell antibodies, such as Ofatutumab, a humanized anti-CD20 molecule recently approved for treatment of refractory CLL.

Current Place of Bendamustine in the Treatment of Indolent Lymphoma

The approved dosage regimen of bendamustine for indolent NHL in the US is 120 mg/m^2 infused intravenously over 60 minutes on days 1 and 2 of each 21-day cycle for up to eight cycles[17,18] with some patients requiring a dose-reduction to 90 or 60 mg/m^2. However, most experts recommend a dose of 90 mg/m^2 on days 1 and 2 when bendamustine is used in combination with rituximab, based on data in relapsed setting; however, this regimen is not yet FDA approved.[71,72] Outside of a clinical trial, bendamustine should not be combined empirically with any other myelosuppressive chemotherapy agent. As for the duration of treatment, a panel of international experts recently recommended that six cycles is likely to be adequate for previously untreated patients while for relapsed/refractory cases, 4–6 cycles are be intended based on tolerance and co-morbidities.[72] Patients who experience grade 3 or worse myelosuppression may be considered for myeloid growth factor support with future drug exposure; dose delay and/or reduction may be unavoidable in some situations.

Conclusions

The future is full of exciting possibilities for those seeking a cure for indolent lymphomas. Multiple small molecules and novel compounds have shown promising activity in broad-based pre-clinical and clinical studies in B-cell malignancies. However, the challenge lies in determining which patient subsets may gain the most from these newer agents and which combinations may be of most benefit for patients with FL.

The promise of Bendamustine lies in its efficacy, favorable tolerability profile, ease of administration, and lack of cross-resistance with commonly used chemotherapeutic agents. However, many questions remain unanswered. The precise mechanism of action and of resistance is largely debatable; the optimal dose and schedule is not firmly established yet. BM has not been evaluated in patients with moderate-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, the relationship between bendamustine and secondary myelodysplastic syndromes needs to be carefully studied.

Ongoing and future studies will help to better define the place of bendamustine in the management of indolent NHL. Bendamustine may be a very reasonable substitute to R-CHOP in elderly patients with multiple co-morbidities, including cardiac dysfunction. It will be of interest to look out for the results of studies evaluating the use of bendamustine in untreated patients, as the underlying disease may be somewhat more uniform in its characteristics and the variables of prior therapy can be eliminated.

Disclosures

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

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