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Bendamustine

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Contents

Abstract

▲ Bendamustine is a bifunctional alkylating agent with cytotoxic activity against human ovarian and breast cancers *in vitro*. It shows only partial *in vitro* cross-resistance with cyclophosphamide, melphalan, carmustine and cisplatin.

▲ Bendamustine as monotherapy or as part of combination chemotherapy protocols for first-line or subsequent treatment produced objective response rates of 61 to 97% in patients with Hodgkin's disease or non-Hodgkin's lymphoma (NHL) [41 to 48% in high grade NHL].

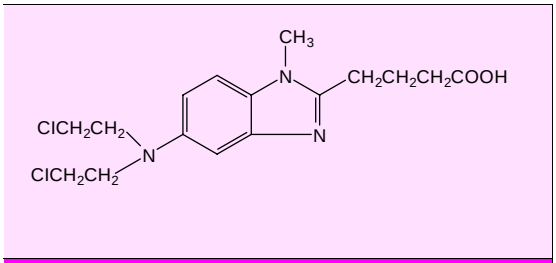
▲ In patients with multiple myeloma, a bendamustine/prednisone regimen produced a higher rate of complete response (32 *vs* 11%) and more durable responses than a melphalan/prednisone regimen.

▲ Substitution of bendamustine for cyclophosphamide in a standard first-line COP regimen (cyclophosphamide, vincristine and prednisolone) yielded similar response rates in patients with advanced low grade NHL.

▲ Substituting bendamustine for cyclophosphamide in the CMF protocol (cyclophosphamide, methotrexate and fluorouracil) prolonged remission from 6.2 to 15.2 months in patients with metastatic breast cancer.

▲ The most common adverse events in patients receiving bendamustine are haematological events and gastrointestinal disturbances. Bendamustine has a relatively low propensity to induce alopecia.

Features and properties of bendamustine	
Indications	
Treatment of Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, chronic lymphocytic leukaemia and breast cancer	
Mechanism of action	
Alkylating agent	Causes crosslinking of DNA single and double strands
Dosage and administration (in clinical trials)	
Haematological	50-60 mg/m^2/day for 3 or 5 days or 100-120 mg/m^2 every 3 to 4 weeks
Solid tumours	120-150 mg/m^2 every 4 weeks
Route of administration	Intravenous (30-60 min infusion)
Frequency of administration	Once daily
Pharmacokinetic profile	
Volume of distribution at steady state	19.80-20.51L
Mean total clearance	31.7-49.6 L/h (mostly renal)
Plasma elimination half-life	32-36 min
Adverse events	
Most frequent	Haematological toxicity and gastrointestinal disturbances



Bendamustine

Bendamustine is a bifunctional alkylating agent consisting of a purine and amino acid antagonist (a benzimidazole ring) and an alkylating nitrogen mustard moiety.[1] The drug has been evaluated as an intravenous infusion mainly in the treatment of lymphomas but also as a therapy for solid tumours, particularly breast cancer.

1. Pharmacodynamic Profile

Alkylating Activity

• The alkylating toxicity of bendamustine is based on crosslinking of DNA single and double strands, leading to disruption of the matrix function of DNA in DNA synthesis.[2] The contribution, if any, of purine and amino acid antagonism to the antitumour effect of bendamustine is yet to be demonstrated.

• Bendamustine demonstrated cytotoxic activity against several human ovarian and breast cancer cell lines *in vitro*. For example, the concentration required to inhibit 50% of cell growth (IC_{50}) was 138 μmol/L against the breast cancer line MCF 7. Cross-resistance between bendamustine and other alkylating agents such as cyclophosphamide, melphalan and carmustine and to cisplatin was only partial.[3]

• Notably, bendamustine also showed good activity against the cisplatin-resistant ovarian cell line A2780-CP2 (IC_{50} 157 μmol/L) and the doxorubicin-resistant breast adenocarcinoma cell line MCF 7 AD [mean IC_{50} 187 μmol/L];[3] indeed, the drug has shown activity against breast cancer in women pretreated with anthracyclines (see section 3.)

• When used in equitoxic concentrations (IC_{50}s), bendamustine consistently induced more DNA double-strand breaks (measured by pulsed field gel electrophoresis) than did melphalan, cyclophosphamide or carmustine. Moreover, bendamustine induced more durable double-strand breaks compared with carmustine or cyclophosphamide.[3]

• Bendamustine induced concentration-dependent apoptosis of B-chronic lymphocytic leukaemia (B-CLL) cells *in vitro*. A synergistic effect was seen with fludarabine in this system. Apoptosis rates for bendamustine plus fludarabine at 48 hours were 1.4-fold higher than the rates expected when the 2 drugs were added together.[4]

Effects on Lymphocyte Subsets

• In a phase I study, bendamustine 60 to 80 mg/m^2 given weekly for up to 8 weeks to patients with refractory solid tumours (n = 12) induced sustained panlymphocytopenia with predominant B-cell cytotoxicity. Peripheral blood B-cells, natural killer cells and T cells were reduced by >90, >70 and >60%, respectively, after 4 weeks. The CD4 : CD8 ratio remained constant throughout treatment.[5]

• However, a ≈50% in the ratio of CD4 : CD8 lymphocytes was noted (from 1.36 to 0.6) after 4 courses of treatment with bendamustine 50 or 60 mg/m^2 (days 1 to 5) in patients with lymphoproliferative disorders (n = 12). Although 2 patients developed opportunistic infections, no correlation was found between infectious episodes and CD4 : CD8 ratio.[6]

2. Pharmacokinetic Profile

• Bendamustine undergoes extensive first-pass metabolism.[7]

• Bendamustine is highly (>95%) protein bound, primarily to albumin, at clinically relevant concentrations. Protein binding is not affected by advanced age (>70 years), low serum albumin levels (31 g/L) or presence of advanced tumours.[8]

• After intravenous administration of bendamustine to >20 patients with tumours, volume of distribution at steady state (Vd_{ss}) was 19.80L. Elimination of bendamustine was rapid and occurred

predominantly by the renal route, with a smaller amount being eliminated by the liver. Mean total clearance was 49.6 L/h and was independent of dosage over the range 0.5 to 5 mg/kg. Plasma elimination half-life ($t_{1/2\beta}$) was 32 minutes.[7]

- Similarly, Vd_{ss} was 20.51L, total clearance was 31.7 L/h and $t_{1/2\beta}$ was 36 minutes in 7 patients who received bendamustine 4.2 to 5.5 mg/kg intravenously. Elimination of the drug was biphasic.[9]

- Unchanged bendamustine accounted for 45% of the total amount of drug recovered in the urine. Metabolites included the major metabolite β-hydroxybendamustine (which is also cytotoxic;[1] 24%), other hydroxy derivatives and *N*-dimethylbendamustine. Biliary elimination occurs mainly as polar metabolites.[7]

- As bendamustine is eliminated primarily by renal mechanisms, it should not be given to patients with glomerular filtration rate <1.8 L/h. The drug also undergoes hepatic metabolism and should not be given to patients with severe hepatic parenchymal damage and jaundice.[1]

- There are at present no published data on placental transfer of bendamustine or excretion in breast milk.

3. Therapeutic Trials

Bendamustine has been evaluated as monotherapy and as part of combination chemotherapy protocols for first-line or subsequent treatment of lymphomas and solid tumours. Most of the studies, including 2 large phase III studies,[10-12] were reported as abstracts and provided few details of methodology and results. In particular, the length of the treatment cycle and response criteria used were frequently not stated.

In this section, objective response (OR) rate refers to the summed total of complete and partial remissions (CR + PR). CR is defined as disappearance of signs and symptoms of disease and PR is generally broadly defined as a >50% reduction of tumour mass. The proportion of patients with no change (NC) and disease progression (PD) are also shown, where stated in the study report.

In a study in patients with multiple myeloma, Southwest Oncology Group (SWOG) response criteria were used. Response to treatment was determined by change in tumour cell mass (TCM), as measured by myeloma protein concentrations. CR was defined as TCM reduction >75% and PR as TCM reduction of 25 to 74%. For either category, additional criteria were no progression of previous osteolytic bone lesions/appearance of new lesions on skeletal x-ray and serum calcium <120 mg/L.[11]

Non-Hodgkin's Lymphoma

Previously Untreated Patients

- Substitution of bendamustine (60 mg/m^2) for cyclophosphamide in a standard first-line COP regimen did not compromise efficacy in previously untreated patients with advanced low grade non-Hodgkin's lymphoma (NHL) randomised to either treatment (n = 162 in total). The COP regimen consisted of cyclophosphamide 400 mg/m^2 day 1 to 5, vincristine 2mg day 1 and prednisolone 100 mg/m^2 day 1 to 5. Objective responses were achieved in 66% of the BOP group (CR 22%, PR 44%) versus 76% of COP recipients (CR 20%, PR 56%) [fig. 1].[10]

- Freedom from treatment failure and overall survival rates were 59 and 73%, respectively, for BOP versus 55 and 84% for COP after a median follow-up of 20 months in this trial.[10]

Previously Treated Patients

- A combination of bendamustine (60 mg/m^2 on day 1 to 5), vincristine and prednisolone achieved a 90% OR (CR 39%, PR 51%; PD 10%) in 31 patients with refractory NHL.[13] A similar combination using bendamustine 50 or 60 mg/m^2 yielded an OR of 86% (CR 45%, PR 41%) in another 22 such patients.[14]

- A combination of bendamustine (25 or 50 mg/m^2) and fludarabine (12.5 or 25 mg/m^2) on days 1 to 3 of a 3- or 4-week cycle achieved a 77% OR in 13 patients (most previously treated) with low grade NHL.[15]

- Among 38 patients (12 pretreated) with NHL (n = 22) or chronic lymphocytic leukaemia (CLL)

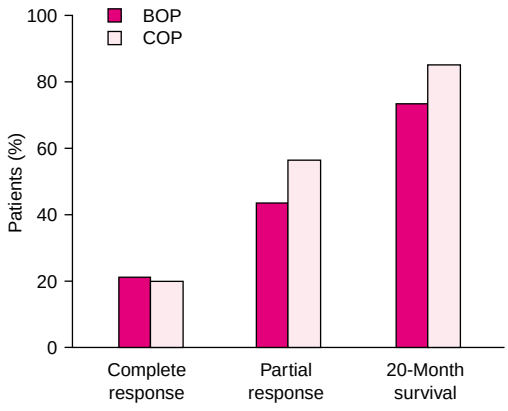


Fig. 1. Substitution of bendamustine for cyclophosphamide in the COP regimen for advanced low grade non-Hodgkin's lymphoma. Outcome of treatment with BOP (bendamustine 60 mg/m^2, vincristine 2mg day 1 and prednisolone 100 mg/m^2 days 1 to 5) versus COP (cyclophosphamide 400 mg/m^2 day 1 to 5, vincristine 2mg day 1 and prednisolone 100 mg/m^2 days 1 to 5) in a randomised study (n = 162).[10]

[n = 16] given bendamustine 100 mg/m^2 on day 1 and etoposide 50mg orally on days 1 to 5 of a 21-day cycle for 8 courses, the OR was 97% (CR 67%, PR 30%). The median duration of remission was about 15 months in patients with CR or PR.[16]

- Bendamustine 70 mg/m^2 days 1 to 3 combined with idarubicin 6 mg/m^2 days 1 and 2 and dexamethasone 4 to 8 mg/m^2 days 1 to 4 in a 21-day cycle produced an OR of 79% (CR 29%, PR 50%) in 14 heavily pretreated patients with NHL (n = 9) or CLL (n = 5). Median duration of remission was 7 months.[17]

- Bendamustine monotherapy (120 mg/m^2 on 2 consecutive days of a 3-week cycle) achieved an OR of 64% (CR 12%, PR 52%) in 33 previously treated patients with relapsed or progressive NHL or multiple myeloma.[18,19]

- An OR of 61% (CR 29%; PR 32%; NC 24%; PD 15%) was achieved in a retrospective analysis of 34 patients with low grade NHL after palliative treatment with bendamustine 100 mg/m^2 on days 1 to 3, alone or in combination with mitoxantrone 6 mg/m^2 on days 1 to 2.[20]

High Grade Non-Hodgkin's Lymphoma

- A combination of bendamustine (50 mg/m^2 on days 1 to 5 or 60 mg/m^2 on days 1 to 3 of a 28-day cycle), methotrexate (30 mg/m^2 on day 3), mitoxantrone (12 mg/m^2 on day 1) and prednisolone (60 mg/m^2 days 1 to 5) was evaluated in 23 patients with resistant or relapsed stage I to IV high grade NHL. Patients (who were mostly aged >60 years) also received granulocyte colony-stimulating factor. OR was 48% (CR 13%, PR 35%, NC 4%, PD 48%).[21]

- Bendamustine as monotherapy (120 mg/m^2/day on days 1 and 2 every 3 weeks) produced an OR of 41% (CR 18%, PR 23%) in 17 outpatients with refractory (n = 8) and/or relapsed high grade NHL, most of whom had been pretreated with ≥2 other therapeutic regimens.[22]

Hodgkin's Disease

Previously Untreated Patients

- A combined modality risk-adapted treatment consisting of CVPP/ABVB hybrid chemotherapy and low dose involved-field radiotherapy (25Gy) was evaluated in previously untreated patients with Hodgkin's disease with elevated risk factors (e.g. mediastinal bulky disease, systemic B symptoms, extranodal lesions, unfavourable histology). CVPP/ABVB consisted of cyclophosphamide, vinblastine, procarbazine, prednisolone, doxorubicin, bleomycin and vincristine with bendamustine 30 mg/m^2 on days 8 to 12 of a 28-day cycle. The OR was 93% in 43 evaluable patients (CR 81%, PR 12%). Three of the partial responders and 1 nonresponder achieved CR after salvage treatment.[23]

- Ten-year follow-up showed that 5- and 10-year relapse-free survival rates were 82 and 70%, respectively. Overall survival at 5 and 10 years was 83 and 73%, respectively. Secondary neoplasms occurred in only 2 patients, both of whom had received intensive retreatment after relapse.[24]

• These results were confirmed in a subsequent comparative multicentre study in 100 nonpretreated patients. CR was achieved in 88% of patients given bendamustine versus 81% of those treated with cyclophosphamide, each in combination with vinblastine, procarbazine, prednisolone, doxorubicin, vincristine and bleomycin with radiotherapy.[25]

Previously Treated Patients

• A bendamustine-containing regimen (DBVB) was as effective as a standard ABVD regimen (doxorubicin, bleomycin, vincristine and dacarbazine) in 73 patients with Hodgkin's disease with primary or secondary resistance to the CVPP regimen (see above). The DBVB regimen consisted of daunorubicin, bleomycin and vincristine with bendamustine 50 mg/m^2 on days 1 to 5 of a 28-day cycle. The OR was 69 versus 83% for ABVD.[1]

Chronic Lymphocytic Leukaemia

• Bendamustine monotherapy (50 or 60 mg/m^2 depending on age, for 5 days of a 28-day cycle) was evaluated in 20 patients with advanced or refractory CLL. The OR was 75% (CR 30%, PR 45%).[6]

• Of 14 elderly pretreated patients with poor prognosis, 4 had a partial and 5 had a complete haematological remission after treatment with bendamustine 100 mg/m^2 days 1 and 2 every 4 weeks.[26]

Multiple Myeloma

• A bendamustine/prednisone regimen produced a 3-fold higher rate of CR (32 *vs* 11%) than a melphalan/prednisone regimen in patients with previously untreated stage II/III multiple myeloma. Patients were randomised to receive bendamustine 150 mg/m^2 day 1 and 2 plus prednisone 60 mg/m^2 days 1 to 4 (n = 68), or melphalan 15 mg/m^2 day 1 plus prednisone 60 mg/m^2 days 1 to 4 (n = 63), of a 4-week cycle. OR were 75% in the bendamustine group versus 68% in the melphalan group (fig. 2).[12]

• Response was also more rapid (after 6.7 *vs* 8.5 cycles) and durable (14 *vs* 10 months, $p < 0.03$) in the bendamustine than the melphalan group. The 30-month probability of progression-free survival was 23 versus 8%. The overall probability of 30-month post-diagnosis survival was the same for the 2 treatment groups (56%). However, the protocol allowed patients who had PD while on therapy or within a 3-month therapy-free interval to be switched to the alternative treatment,[11] and this likely explains the similarity in survival rates.

Breast Cancer and Other Solid Tumours

Bendamustine has also shown promising results in the treatment of solid tumours, particularly breast cancer.[27-30]

• Substituting bendamustine (240 mg/m^2 per cycle) [n = 25] for cyclophosphamide in the CMF protocol (cyclophosphamide, methotrexate and fluorouracil) [n = 24] extended the median duration of remission from 6.2 to 15.2 months in patients with metastatic breast cancer. OR were 52% for the bendamustine and 46% for the cyclophosphamide group.[27]

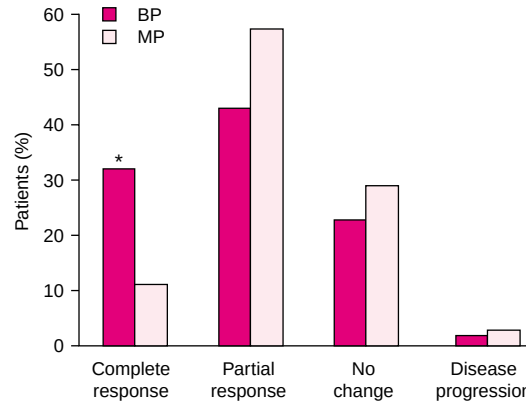


Fig. 2. Comparative efficacy of bendamustine/prednisone in previously untreated stage II/III multiple myeloma. Patients were randomised to receive bendamustine 150 mg/m^2 days 1 and 2 plus prednisone 60 mg/m^2 days 1 to 4 (BP; n = 68), or melphalan 15 mg/m^2 day 1 plus prednisone 60 mg/m^2 days 1 to 4, (MP; n = 63) of a 4-week cycle.[11,12] * $p < 0.003$ *vs* MP.

• Bendamustine (150 mg/m^2 on days 1 and 2 of a 4-week cycle) achieved a 25% OR when used as salvage therapy in 36 patients with advanced breast cancer. The median progression-free interval was 2 months. The efficacy of bendamustine appeared to be independent of previous anthracycline treatment, consistent with the lack of cross-resistance observed in *in vitro* studies (section 1).[28]

• Patients with other tumours who responded to bendamustine-based therapy (n = 15 to 28 per group) included small cell lung cancer (OR 41 to 45%),[31,32] relapsed head and neck cancers (OR 73%)[33] and advanced relapsed gastrointestinal cancers (OR 18%).[34]

• However, bendamustine (120 mg/m^2 on days 1 and 2, repeated every 3 weeks) was not effective in 19 heavily pretreated patients with cisplatin-refractory or relapsed germ cell tumours.[35]

4. Tolerability

• The most common events in patients receiving bendamustine alone or in combination with other agents in phase II or subsequent studies are haematological events (leucopenia, thrombocytopenia, anaemia) and gastrointestinal disturbances (nausea, vomiting and mucositis).[11,20,23]

Haematological

• Leucopenia and thrombocytopenia (all grades) were documented in 58 and 42% (all grades) and 17 and 6% (grades 3/4) of 36 patients receiving bendamustine monotherapy (150 mg/m^2 on 2 days per cycle) for breast cancer.[28]

• Grade 3/4 leucopenia occurred in 38 of 74 courses of bendamustine monotherapy (50 or 60 mg/m^2) in patients with CLL. Three severely immunocompromised patients died from treatment-related causes (leucopenia).[6]

• Bendamustine plus prednisone was associated with a similar incidence of leucopenia and thrombocytopenia to a melphalan/prednisone regimen. Grade 1 to 2 and 3 to 4 leucopenia occurred in 38 and 40% of patients with multiple myeloma, respectively, treated with bendamustine/prednisone and grade 1 to 2 and 3 to 4 thrombocytopenia in 18 and 13% of patients. Respective values for melphalan/prednisone were 39 and 33% for leucopenia, and 27 and 15% for thrombocytopenia.[11]

• A bendamustine-containing regimen (BOP; in which bendamustine 60 mg/m^2 was substituted for cyclophosphamide) was associated with significantly less grade 3/4 leucopenia (19 *vs* 34%; $p < 0.0001$) but significantly more grade 3/4 thrombocytopenia (4.0 *vs* 0.9%; $p < 0.001$) than a standard COP regimen (see section 3) in patients with NHL (n = 162).[10]

• When bendamustine (120 mg/m^2) was substituted for cyclophosphamide in the CMF protocol for breast cancer (section 3), haematological toxicity was more common with the bendamustine-containing regimen. Leucopenia, febrile neutropenia, anaemia and thrombocytopenia occurred in 28 versus 23, 13 versus 2, 11 versus 0 and 11 versus 2 patients, respectively.[36] This interim analysis led to a protocol amendment.

• According to the manufacturer's information, leucocyte and platelet nadirs are reached after 14 to 20 days and bone marrow recovers within 3 to 5 weeks.[1]

Gastrointestinal

• Grade 1 to 3 nausea/vomiting occurred in 50% of 83 patients receiving a bendamustine/prednisone regimen, versus 25% of 75 patients receiving melphalan/prednisone.[11]

• Mucositis was reported in 16 versus 4 patients, respectively, when bendamustine (120 mg/m^2) was substituted for cyclophosphamide in the CMF protocol for breast cancer.[36]

• Grade 2 nausea or emesis developed in 11 of 34 and grade 3 nausea/emesis in 3 of 34 patients with low grade lymphomas treated with bendamustine with or without mitoxantrone in a retrospective analysis.[20]

Allergic/Hypersensitivity

• Allergic and hypersensitivity reactions are less common events. Allergic skin reactions occurred in 25% of 16 patients who received bendamustine 50 or 60 mg/m^2 for 5 days of a 28-day cycle[37] and in 9% of 43 patients treated with bendamustine 120 mg/m^2 on 2 consecutive days of a 3-week cycle.[18]

• Moderate (grade ≤2) allergic skin reactions were more common with the bendamustine- than the cyclophosphamide-containing regimen in the above study in patients with NHL (30 *vs* 14%; p = 0.02).[10]

Alopecia

• Bendamustine has a relatively low propensity to induce alopecia. In several studies, alopecia did not develop[13,15,16,19] or was only mild (maximum WHO grade I).[28-30]

• Grade 3 alopecia was significantly less common with a bendamustine- than a cyclophosphamide-based regimen (3.6 *vs* 48%, p < 0.0001) in patients with NHL.[10]

5. Bendamustine: Current Status

Bendamustine as single-agent or combination therapy is indicated in Germany for the treatment of Hodgkin's disease, NHL, multiple myeloma, CLL and breast cancer.[1]

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