



United Kingdom Myeloma Forum (UKMF) position statement on the use of bendamustine in myeloma

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SUMMARY

Bendamustine is a unique bifunctional alkylating agent with promising activity in myeloma. Despite the increasing number of studies demonstrating its efficacy in both the upfront and relapse settings, including patients with renal insufficiency, the optimal use of bendamustine, in terms of dosage, schedule and combination with other agents, has yet to be defined. It is currently licensed for use as frontline treatment with prednisolone for patients with myeloma who are unsuitable for transplantation and who are contraindicated for thalidomide and bortezomib. Studies in relapsed/refractory patients are currently ongoing with other combinations. Given the increasing data to date, the UK Myeloma Forum believes that bendamustine with steroids alone or in combination with a novel agent could be considered for patients with multiply relapsed myeloma. This document provides guidance for the use of bendamustine for patients with myeloma until the results of definitive studies are available.

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Recommendations are based on the systematic review of published English language literature up to December 2012.

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INTRODUCTION

Myeloma is a haematological malignancy characterized by a monoclonal expansion of abnormal plasma cells in the bone marrow.

In the UK, the incidence of myeloma is approximately seven cases per 100 000 of the population with around 4500 newly diagnosed patients each year [1], equivalent to 1.7% of all cancers. The incidence increases with age; 71% of cases occur in the over 65-year age group, but very few cases involve patients younger than 40 [1].

Clinical manifestations are varied, but the most common include bone pain as a result of bone destruction, anaemia, recurrent or persistent infection due to immunosuppression, hypercalcaemia and renal impairment [2].

The clinical course is typically one of the episodes of clinical remission in response to treatment and subsequent relapse. The period of remission though is unpredictable, and relapse is inevitable with further treatment required. However, patients progressively acquire resistance to treatments and eventually become refractory to them.

Myeloma therefore remains an incurable cancer, but treatment can prolong survival and improve quality of life by reducing the burden of symptoms. Approximately 10% of patients die within the first 3 months after diagnosis, but the majority have a life

expectancy of several years and a minority of patients survive greater than 10 years [3].

Prior to the introduction of alkylating agents, the outlook for patients with myeloma was poor with a 1-year survival rate <30%. The use of melphalan in the 1960s, its combination with other chemotherapy agents [4] and the establishment of high-dose therapy and stem cell transplantation [5, 6] markedly improved survival: from 1971 to 2001 1-year survival rates rose from 35–66% [7].

The addition of the novel agents thalidomide, lenalidomide and bortezomib in the last decade not only expanded treatment options but, importantly, improved survival outcomes much further for patients with myeloma [8]. Nevertheless, defining the best use of these agents, in terms of the sequence, combination and setting, continues to be a challenge.

STANDARD TREATMENT

At present, the standard of care in the UK for newly diagnosed patients younger than 70 years with good performance status and without severe comorbidities is a period of induction treatment followed by high-dose therapy and autologous stem cell transplantation (HDT-ASCT).

In the wake of the Myeloma IX trial, cyclophosphamide, thalidomide and dexamethasone (CTD) is one of the favoured induction treatments [9] over the

previous standard combination of vincristine adriamycin and dexamethasone (VAD). Other induction regimens involving novel agents are favoured in some countries and increasingly in the UK, but there is a lack of randomized trials to guide us currently as to optimal induction treatments.

For patients not eligible for HDT-ASCT, attenuated CTD that showed superior response rates to melphalan and prednisolone (MP) in the nonintensive arm of Myeloma IX [10], or thalidomide added to melphalan and prednisolone (MPT) [11, 12] are most widely used.

A direct comparison of cyclophosphamide, lenalidomide, dexamethasone with CTD as initial treatment is being made in the current Myeloma XI study. The results of this study may lead to future changes in the preferred first-line treatment.

Maintenance treatment has been explored with thalidomide, bortezomib and more recently with lenalidomide. Lenalidomide maintenance has been shown to significantly improve progression-free survival [13–15] and is being explored in the Myeloma XI study.

In the relapse setting, treatment is currently restricted by National Institute for Health and Clinical Excellence (NICE) guidance in the UK. Treatment may incorporate various combinations of bortezomib (generally used at first relapse as per NICE guidance) or lenalidomide (generally used at second relapse as per NICE guidance) with steroids and/or alkylating agents [16–20].

However, the options for relapsed patients become increasingly limited once resistance to the novel agents develop. Consequently, there is a significant unmet need for the treatment for relapsed myeloma that is no longer responsive to thalidomide, bortezomib or lenalidomide, and the need to improve treatment options for relapsed/refractory patients continues to be a pressing priority.

Although a range of newer agents are currently under investigation (including next generation proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors and monoclonal antibodies) – and early indications suggest these are promising – they will not offer a cure and their place in treatment remains unclear. Significant opportunities are also available with existing agents used for other indications, and some of these could be exploited further, in

particular, to fulfil the unmet need in the relapsed/refractory setting.

BENDAMUSTINE

Bendamustine is an antitumour agent with a novel mechanism of action. Originally developed in the 1960s, it was used successfully to treat various B-cell malignancies, breast cancer and small-cell lung cancer in the former East German Democratic Republic. Bendamustine has since been ‘rediscovered’ by the wider haematology community [21] and is currently an option for indolent non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and myeloma.

Bendamustine has similarities to both alkylating agents and purine analogues and is comprised of three structural elements consisting of a 2-chloroethylamine group, a butyric acid side-chain and a benzimidazole central ring system.

Its primary antitumour effect is based on the production of both single and double strand breaks resulting in impairment of DNA matrix function, DNA synthesis and repair [22, 23].

What distinguishes bendamustine from other agents is its ability to cause more extensive and significantly more durable strand breaks [24]. Caspase 3 activation is seen in myeloma cell lines treated with bendamustine, this would enhance synergy with other agents such as dexamethasone and thalidomide used in myeloma. Cell cycle arrest in G2 phase is through inhibition of ATM and Chk2 and not ATR and Chk1 which markedly contrasts the mechanism of action in comparison with traditional alkylating agents [25]. Microarray studies also show that it possesses a unique pattern of gene activity which includes induction of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints and activation of a base excision DNA repair pathway rather than an alkyltransferase DNA repair mechanism [22]. As a consequence, bendamustine only exhibits partial cross-resistance with other alkylating agents.

Bendamustine is administered via intravenous infusion over a 30–60-min period. There are little data regarding its pharmacokinetics in patients with myeloma. However, it is known that the primary route of metabolism is hydrolysis to inactive mono- and dihydroxy metabolites implying that the parent compound is the main cytoactive agent [26]. Over

95% of a single dose of bendamustine is excreted in the bile, while urinary excretion accounts for the remainder.

Although bendamustine has been used for over 50 years, the number of studies reporting its efficacy in patients with myeloma has, until recently, been remarkably scarce [21]. However, more evidence of the safety and efficacy of bendamustine in different settings and in combination with other agents is beginning to emerge following its renewed interest in myeloma.

Upfront setting

In the upfront setting, a randomized phase III study comparing bendamustine and prednisolone (BP) to MP established bendamustine as a viable first-line treatment option [27].

All patients in the study received prednisone on days 1–4 in combination with bendamustine (150 mg/m²) on days 1 and 2 or melphalan (15 mg/m²) on day 1 of a 28-day cycle. The overall response rates [complete response (CR) + partial response (PR)] were 75% and 70% in the BP and MP groups, respectively, but treatment with bendamustine led to a significantly higher CR (32 vs. 13%, $P < 0.01$) with a shorter time to maximum response (6.8 vs. 8.6 cycles, $P < 0.02$). Similarly, the duration of remission in patients with CR or PR (18 months vs. 12 months, $P < 0.02$) and time-to-treatment failure (TTF; 14 months vs. 10 months, $P < 0.02$) were significantly longer although median overall survival was not significantly different (32 vs. 33 months, NS).

BP was well tolerated with comparable toxicities to MP. However, the percentage of patients receiving BP who required dose reduction for leukopenia (8.6 vs. 4.1%) and thrombocytopenia (1.8 vs. 0.9%) was twice that of patients receiving MP. On the other hand, 4 months into treatment, patients on BP reported pain less frequently and an overall better quality of life than those receiving MP.

Bendamustine is a therapeutic option for myeloma patients with renal impairment. Bendamustine is predominantly metabolized to hydroxyl derivatives with rapid elimination mainly by hepatic excretion. Pharmacokinetic data available in myeloma patients with renal impairment show no accumulation of the drug in patients with end-stage renal disease with only 5%

of the administered dose detected in the urine and metabolites present in the dialysate [28].

Bendamustine (60 mg/m²) was an effective initial treatment option for patients with stage 4/5 renal insufficiency [29]. When given on days 1 and 2 of a 21-day cycle and combined with bortezomib and prednisone, the majority of patients ($n = 15$; 83%) responded rapidly with three stringent CRs, five near CRs, five VGPR and two PR over a median of two cycles (range 1–5). Progression-free survival (PFS) at 18 months was 57% and overall survival (OS) was 61%. Of note, a high renal response rate (72%) was observed including four patients who became dialysis independent.

Relapse setting

Early evidence for the efficacy of bendamustine monotherapy in the relapse setting came from a phase I dose-escalation study involving patients progressing after high-dose therapy and autologous stem cell transplantation (HDT-ASCT) [30].

The maximum tolerated dose (MTD) was 100 mg/m² on days 1 and 2 of each 28-day cycle. An overall response rate of 55% was achieved, and the median progression-free survival was 26 weeks. Toxicity was generally mild, and one patient on bendamustine (100 mg/m²) developed dose-limiting febrile neutropenia, while three patients had grade 2 nausea and vomiting.

A recent retrospective study identified 39 relapsed patients (median of two previous lines of treatment, range 1–5) receiving bendamustine at doses ranging between 80 and 150 mg/m² with or without steroids, achieving an overall response rate of 36% [31]. Subgroup analysis showed no significant differences in outcome in relation to the dose of bendamustine received.

In another retrospective study involving a more heavily pretreated population (median of four previous lines of treatment, range 1–9), bendamustine at doses between 60 and 150 mg/m² in combination with prednisolone produced an overall response rate amongst 110 patients of 30% including 2% with CR [32]. This compared favourably with that previously described for thalidomide, bortezomib or lenalidomide [33] and for agents in development. For example, pomalidomide and low-dose dexamethasone produced

an overall response rate of 32% in patients ($n = 34$) refractory to lenalidomide [34].

However, response rates notably improved when bendamustine was combined with a corticosteroid and a novel agent.

In a phase I study of fixed-dose bendamustine (60 mg/m^2) and prednisolone (100 mg) with escalating doses of thalidomide (50–200 mg), an overall response rate of 86% was observed in relapsed/refractory patients. The combination, even at 200 mg of thalidomide, was well tolerated [35].

The outcome of 23 patients involved in a compassionate use programme in the UK between December 2008 and April 2010 demonstrated the effectiveness of bendamustine, thalidomide and dexamethasone (BTD) [36]. Patients involved in the programme had previously received a median of five previous lines of treatment (range, 3–7), and the majority had already received thalidomide, bortezomib and lenalidomide.

Thalidomide was escalated, depending on tolerance, to a maximum of 200 mg with fixed-dose bendamustine (60 mg/m^2) and dexamethasone (20 mg). Clinical benefit (\geq stable disease) was observed in 61% of patients. Compared with nonresponders, those achieving at least SD had an improved OS of 15 vs. 3 months ($P < 0.001$).

While the evidence points to the effectiveness of the BTD, the optimal dose of bendamustine in this combination has yet to be defined. The current randomized phase II Myeloma UK MUK *one* trial is hoping to shed light on the best dosing strategy by comparing 60 mg/m^2 vs. 100 mg/m^2 bendamustine with fixed-dose thalidomide (100 mg) and dexamethasone (20 mg).

The combination of bendamustine with lenalidomide and dexamethasone (BLD) has recently been reported in a phase I/II dose-escalation study of 29 relapsed/refractory patients [37]. The median number of prior treatments was 3 (range, 1–6) of which 97% of patients had already received lenalidomide, thalidomide or both; 66% had received bortezomib and 69% had previously undergone HDT-ASCT.

The MTD was 75 mg/m^2 (days 1 and 2 of a 28-day cycle) and the overall response rate including MR was 76% with 52% achieving PR or better. Notably, 69% of the patients who had already received lenalidomide and/or thalidomide responded to BLD. Median PFS was 6.1 months with a 1-year

PFS of 20%. Grade 3 or 4 adverse events included neutropenia, thrombocytopenia, anaemia, hyperglycaemia and fatigue.

Following on from promising early data [38, 39], bendamustine in combination with bortezomib and dexamethasone has emerged as a well-tolerated regimen with promising efficacy in relapsed or refractory disease [40–43] as well as in renal failure [28].

Bendamustine was used in a treatment algorithm with bortezomib and dexamethasone and given in the second escalation step to patients nonresponsive to bortezomib monotherapy or bortezomib and dexamethasone treatment [40]. Of the 38 patients, seven received bendamustine, bortezomib and dexamethasone which produced a response rate of 57% PR and 29% MR. Compared with the other groups, patients receiving the bendamustine combination had a significantly higher rate of cytopenia and subsequently higher transfusion requirement.

Ludwig *et al.* [41] reported a response rate of 52% and a PFS of 9.6 months in 33 heavily pretreated myeloma patients receiving bendamustine (70 mg/m^2 , days 1 and 4 of a 28-day cycle), bortezomib and dexamethasone with promising response rates observed in patients pre-exposed to bortezomib (33.3%) and lenalidomide (36.4%).

Berenson *et al.* [42] reported a phase I/II trial in relapsed or refractory disease using intravenous bendamustine 50, 70 or 90 mg/m^2 (days 1 and 4) plus bortezomib 1.0 mg/m^2 (days 1, 4, 8 and 11) for up to eight 28-day cycles and identified bendamustine 90 mg/m^2 plus bortezomib 1.0 mg/m^2 as the MTD with the commonest grade 3/4 toxicity being neutropenia (50%) and thrombocytopenia (30%). The overall response rate was 48% (one CR, two VGPR, nine PR and seven MR) for all 40 enrolled patients, 52% (16/31) at the MTD (90 mg/m^2) and 42% and 46% for prior use of bortezomib ($n = 31$) or alkylators ($n = 28$) respectively.

Ponisch *et al.* [43] reported a phase II trial in relapsed or refractory disease using bendamustine 60 (-120) mg/m^2 on days 1 and 2, bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 and prednisone 100 mg on days 1, 2, 4, 8 and 11 as a 21 day cycle. In 12/78 patients, the dose of bendamustine was escalated in subsequent courses.

Patients received a median number of two (range 1–7) BPV treatment cycles with the majority ($n = 54$;

69%) responding after at least one cycle of chemotherapy with 3 CR, 10 nCR, 10 VGPR and 31 PR. Median PFS and OS for patients without severe haematological toxicities due to previous treatments ($n = 45$) were 11 and 50 months, respectively, but for the 33 patients with pre-existing grade 3–4 haematological toxicities, the PFS and OS were only 3 months ($P = 0.05$) and 5 months ($P = 0.001$), respectively.

Taken together, the evidence to date indicates a number of potential advantages in using bendamustine for patients with myeloma. These include the following:

- Unique mechanism of action including its ability to activate apoptosis and inhibit mitotic checkpoints, making it potentially more effective than other alkylating agents,
- Partial cross-resistance with other alkylating agents,
- Suitability for patients with renal impairment,
- Favourable toxicity profile, the most common adverse reactions being haematological (leukopenia, thrombocytopenia) and gastro-intestinal (nausea, vomiting) and
- Favourable quality of life outcomes.

The experience of bendamustine in myeloma is still limited, and data from phase III studies demonstrating its effectiveness in terms of overall survival are not yet available.

However, a recent retrospective analysis of survival of relapsed myeloma patients has provided good benchmarking data to compare treatment regimens [44]. The OS and TTF of 286 such patients (with a median of 4 prior treatments) were 9 and 5 months, respectively. Data on bendamustine use in similar- or poorer-risk patients compares favourably:

Damaj *et al.* [32] - OS 12.4 months, PFS 9.3 months

Michael *et al.* [31] - OS 17 months, event-free survival 7 months

Grey-Davies *et al.* [36] - OS 13 months, PFS 3 months.

These retrospective data are consistent in demonstrating improved OS for relapsed/refractory patients treated with a bendamustine and steroid regimen. Further studies would inform most effective treatment combinations, particularly for the heavily pretreated population, and the optimal dose to use.

LICENSED INDICATION AND CURRENT USE

Bendamustine is licensed for use, under the name Levact[®], in the European Union for the treatment for myeloma in combination with prednisolone for patients older than 65 years who are not candidates for HDT-ASCT and who have clinical neuropathy at the time of diagnosis precluding the use of thalidomide or bortezomib.

At present, in the UK, there are no National Institute for Health & Excellence (NICE) guidelines recommending the availability of bendamustine on the National Health Service (NHS) for patients with myeloma. The Scottish Medicines Consortium (SMC) does not recommend bendamustine be made available in this situation.

Until recently, bendamustine was available as part of the MUK *one* clinical trial in combination with thalidomide and dexamethasone. Preliminary data should become available early next year.

At present, access to bendamustine can be made through application for an Individual Funding Request or via the Cancer Drugs Fund. Bendamustine is available as 25-mg vials at a commercial price of £1379.04 (excl. VAT) for a pack of 20 vials. The mean cost per patient assuming a dose of 100 mg/m², average body surface area of 1.72 m² and an average treatment course of 5 cycles is approximately £4800. A quality-adjusted life year (QALY) has not been formally calculated.

In practice, only a very small number of patients in the UK (approximately 20 per year) are eligible to receive bendamustine. As it stands, the way bendamustine is currently approved for the use does not match the high level of unmet need at multiple relapse.

THE FUTURE

For bendamustine to become recognized as a bona fide antimyeloma treatment and be integrated into current practice, it is imperative that evidence of its most effective use, in terms of combination, clinical setting, optimal dose and schedule, is sought. This is being addressed to some extent in the MUK *one* trial in the relapsed setting, but further randomized trials will be required.

As bendamustine is increasingly used as antimyeloma treatment, it is important that a systematic collection of clinical data, including quality of life, continues to be made. Effective use of the data will thus help inform myeloma physicians across the world as to its optimal uses, support commissioning and drive future research.

Current recommendations for the use of bendamustine

Bendamustine is effective as a monotherapy, and this effectiveness is increased when used in combination with other agents. We recommend the following:

- How it should be used
 - Studies demonstrate bendamustine has clinical activity in relapsed myeloma patients in combination with both steroids and novel agents.
 - Bendamustine can be given as an intravenous infusion on days 1 and 8 of a 28-day cycle or on days 1 and 2 of a 28-day cycle, ideally for a minimum of 6 cycles and up to best response plus 2 cycles (maximum of 10 cycles).
 - Doses of between 60 and 100 mg/m² are well tolerated, but dose modifications are often dependent on prior treatments especially previous HDT-ASCT. Therefore, a starting dose of 60 mg/m² is recommended and can be increased as tolerated to 80 mg/m² or 100 mg/m².
- When it should be used
 - Outside of clinical trials, bendamustine, or dexamethasone (or other steroid) with or without a

novel agent is recommended as a treatment for multiply-relapsed patients who have had bortezomib and lenalidomide treatment or who are contra-indicated to these agents.

- Supportive measures

- Toxicity is generally haematological and mild when used alone with dexamethasone or other steroids. No specific measures other than standard anti-emetics are necessary although careful monitoring of blood counts and the addition of GCSF may be necessary for heavily pretreated patients. Patients should receive irradiated blood products for life [45]. This recommendation is based on the theoretical risk posed from the purine-like activity of bendamustine and may be revised as further evidence accumulates. Consideration should be given to test patients with risk factors for latent hepatitis B virus infection since reactivation has been reported [46]. Prophylactic antivirals may be required to prevent reactivation. Specific supportive care measures for patients with myeloma are addressed in the published guidelines for supportive care in multiple myeloma [47].

DISCLAIMER

While the advice and information in this position paper is believed to be true and accurate at the time of going to press, neither the authors, the UKMF nor the publishers accept any legal responsibility for the content of these guidelines.

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