Bendamustine in Patients with Relapsed or Refractory Multiple Myeloma

M. Michael¹, I. Bruns¹, E. Bölke², F. Zohren¹, A. Czibere¹, N. N. Safaian¹, F. Neumann¹, R. Haas¹, G. Kobbe¹, R. Fenk¹

¹Department of Hematology, Oncology and Clinical Immunology, ²Department of Radiooncology, Heinrich-Heine-University, Düsseldorf, Germany

Abstract

Objective: In patients with multiple myeloma, bendamustine monotherapy is effective as 1st and 2nd line therapy. However, data for patients with advanced multiple myeloma is rare.

Methods: In this retrospective analysis we have identified 39 patients with relapsed or refractory multiple myeloma by means of case research, who have been treated at our institution with bendamustine as salvage therapy. After median 2 lines of prior therapy (range: 1-5) patients received median 3 (range: 1-10) cycles of bendamustine. Bendamustine dosage was 80-150 mg on day 1+2 of a monthly cycle. Bendamustine was administered as monotherapy in 39% of patients, whereas 61% received concomitant steroids.

Results: Toxicity was mild to moderate. Response rates were as follows: 3% vgPR, 33% PR, 18% MR, 26% SD and 20% Pd. The median event-free and overall survival were 7 and 17 months, respectively.

Conclusions: In conclusion, in patients with advanced multiple myeloma bendamustine is effective and associated with mild toxicity. Therefore, the role of bendamustine in patients with multiple myeloma should be investigated in further clinical trials.

Key words: Bendamustine, multiple myeloma, relapsed/refractory

1. INTRODUCTION

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) has improved response rates and survival in patients with multiple myeloma [1, 2]. Despite further dose escalation, almost all patients ultimately suffer from disease progression [3, 4]. Therefore, there is a continuous need to broaden the spectrum of salvage therapies for those patients [5]. In addition to novel agents such as thalidomide [6], lenalidomide [7] and bortezomib [8], conventional cytotoxic chemotherapy remains a treatment option in this situation. In this respect one may consider bendamustine, which is a bifunctional alkylating agent. It is characterised by a unique profile of cytotoxicity and there is only partial cross-resistance with other alkylating agents or anthracyclines [9, 10; 12]. Bendamustine is used for the treatment of non-Hodgkin-lymphoma and chronic lymphatic leukaemia, but also for therapy of lung and breast cancer [10-19].

In myeloma cells, bendamustine induces a G2 cell cycle arrest and p53-mediated apoptosis [20]. In patients with multiple myeloma, efficacy has been reported as a single-agent as well as in combination with other agents, while the toxicity observed was mild and mainly haematological [21-26]. Poenisch et al. randomized patients with newly diagnosed multiple myeloma to either a bendamustine/prednisone regimen or standard melphalan/prednisone. The overall response rate (minimal response (MR) + partial response (PR) + complete response (CR)) was the same with both regimens, but the treatment with bendamustine led to an increased CR rate (32% vs. 13%, p = 0.007). The duration of remission in patients with CR or PR was also significantly longer (18 months vs. 12 months, p < 0.02), while the median overall survival (OS) was not significantly different (32 vs. 33 months). Still, the quality of life was better in the group of patients who received bendamustine [23].

In patients with first relapse after high dose therapy and autologous PBSCT, Knop et al. observed an overall response rate of 55% with bendamustine as salvage therapy. In this study a median event-free survival (EFS) of six months was observed [24]. In combination with prednisolone and thalidomide bendamustine resulted in response rates of 80% in patients with relapsed and refractory multiple myeloma [25]. In another trial patients not responding to a bortezomib/dexamethasone regimen received a triple therapy consisting of bortezomib, dexamethasone and bendamustine, which resulted in a 57% response rate [26], another study reports an overall response rate of 88% in this combination [27].

In conclusion, there is evidence that bendamustine is effective in different stages of multiple myeloma. However, there is no data for bendamustine monotherapy in patients with advanced disease. Therefore, we report on 39 patients in this situation.

2. MATERIAL, METHODS AND STATISTICS

2.1 Patients

We conducted a retrospective analysis of patients with advanced multiple myeloma who have been treated with bendamustine at our institution between April
2. Bölke_Umbruchvorlage  20.01.10  12:39 Seite 14

2000 and May 2005. Based on the institutional pharmacy records we identified patients with multiple myeloma who have been treated with bendamustine. As concomitant treatment, only steroids and radiation therapy were allowed. Exclusion criteria for this retrospective analysis were treatment with other combination partners, dosage of less than 80 mg/m², prior bendamustine treatment, first-line treatment or missing data concerning remission rate and event-free survival. Clinical data of patients included in the analysis was obtained by the means of case research. Bendamustine was approved for treatment of myeloma patients in Germany and all patients gave written informed consent for treatment with bendamustine.

2.2 Treatment Schedule

Bendamustine hydrochloride was administered intravenously at a dose of 80-150 mg/m² in 500 ml NaCl 0.9% over 30 minutes on day 1 + 2. The dose was assessed by the physician according to the health state and the comorbidity of the patient. Corticosteroids were chosen as concomitant treatment according to the treating physicians decision, without any detectable pattern for decision making. The steroids used were either prednisolone 100 mg on day 1-5 or dexamethasone 40 mg on day 1-4. Cycles were repeated in median after 28 days (range: 14-90 days). Growth factors and antibiotic prophylaxis were not used. Treatment was continued until either induction of remission (≥ PR) or disease progression occurred.

2.3 Statistical Methods

Treatment response and duration of remission were assessed according to the EBMT criteria [28]. The EFS was calculated for all patients, who achieved at least a minimal response, from the date of first bendamustine treatment to the time of disease progression, relapse or death. OS was calculated from the date of starting bendamustine treatment to the date of death. Kaplan-Meier curves for EFS and OS were plotted and compared with the use of the log-rank test. Adverse events were assessed as documented in patients records according to CTC AE criteria version 3.0. The two-sided Fisher exact test was used to compare the response rates or the number of adverse events. Prognostic factors were determined by univariate analysis and the use of the log rank test. The following parameters were included in the univariate analysis: age (≤/≥ 65 years), refractory (not achieving at least stable disease by last treatment line) or relapsed (progressive disease after achieving at least stable disease by last treatment line) disease, monotherapy versus concomitant steroids, bendamustine dose (80-100 or 120-150 mg/m²), prior thalidomide or prior high-dose therapy and autologous stem cell transplantation (yes or no), extramedullary manifestation (yes or no), cytogenetic abnormalities (karyotypic normal versus abnormal), osteolytic lesions (yes or no), ISS stage (I vs. II/III), LDH (≤/≥ 200 U/l), CRP (≤/≥ 0.6 mg/dl), haemoglobin level (≤/≥ 10 g/dl), platelet count (≤/≥ 200.000/µl), hypercalcemia (≤/≥ 2.6 mmol/l), elevated creatinine (</> 1.2 mg/dl). SSPS V14.1 was used for statistical analysis.

3. Results

3.1 Patient Characteristics

Using pharmacy records we could identify 75 patients with multiple myeloma who received bendamustine treatment in our institution. Of all, 39 patients entered the retrospective analysis. Reasons for exclusion from the analysis were insufficient data (n = 19), combination partners other than steroids (n = 10), first-line treatment (n = 3), total bendamustine dosage of less than 80 mg/m² (n = 2). The patients in our study had an advanced stage of disease as reflected by a median of two lines of prior treatment regimen (range: 1-5). This includes high-dose therapy and autologous PBSC in 64% of the patients and a second high-dose therapy as salvage treatment in 23%. Prior thalidomide treatment had been administered in 59% of the patients. Of all patients, 54% were refractory to the last salvage therapy, whereas 46% suffered from progressive disease after a remission or stable disease had been achieved by the antecedent therapy. About one third of patients presented with extramedullary manifestations (28%). Patient characteristics before the begin of bendamustine treatment are shown in Table 1.

3.2 Treatment Profile

Patients received a median of 3 (range 1-10) cycles of bendamustine. Of all, 25 patients (64%) received bendamustine treatment until disease progression. These patients were treated with in median 4 cycles (1-10). In 13 patients (33%) bendamustine treatment was stopped after in median 3 cycles (1-9) during ongoing remission.

The median dose was 100 mg/m² (range 80-150 mg/m²) on day 1+2. For our evaluation the patients were retrospectively allocated to two different groups according to the administered dose of 80-100 mg/m² (n = 20) versus 120-150 mg/m² (n = 19).

Dose reduction was necessary in 28% (n = 11) of the patients because of haematological side effects, while a discontinuation was not necessary for any of the patients. 31% of the patients received bendamustine monotherapy and 69% received bendamustine in combination with corticosteroids.

3.3 Response Rates

The overall response rate (CR+PR) was 36% (Table 2). No CR was observed. In one case (3%), a very good PR could be achieved while 13 patients entered into a PR (33%). A MR was observed in 7 patients (18%), whereas stable and progressive disease were noted in 10 (26%) and 8 (20%) patients, respectively.

Subgroup analysis showed no significant differences in outcome in relation to the dose of bendamustine administered (Table 2). Within the subgroup of patients who had received a dose of 80-100 mg/m², the rate of PR was 33% compared with 38% in the group
| Table 1. Patient characteristics. | Total | Subgroups therapy mode | Subgroups dosage | p |
|---------------------------------|-------|------------------------|------------------|---|
| | | Monotherapy | + Steroids | 80-100 mg/m² | 120-150 mg/m² |  |
| Age | 61 (41-83) | 61 (41-83) | 61 (47-68) | 0.4 | 63 (41-76) | 61 (42-83) | 0.7 |
| Sex | | | | | | | |
| male | 15 (38%) | 8 (67%) | 16 (59%) | 0.7 | 13 (62%) | 11 (61%) | 1 |
| female | 24 (62%) | 4 (33%) | 11 (41%) | 0.7 | 8 (38%) | 7 (39%) | 1 |
| Myeloma subtype | | | | | | | |
| IgG | 35 (90%) | 11 (92%) | 24 (89%) | 1 | 20 (95%) | 15 (83%) | 0.3 |
| Other | 4 (10%) | 1 (8%) | 3 (11%) | 1 | 1 (5%) | 3 (17%) | 0.3 |
| ISS stage | | | | | | | |
| I | 16 (41%) | 1 (8%) | 15 (56%) | 0.01 | 9 (43%) | 7 (38%) | 1 |
| II | 11 (28%) | 6 (50%) | 5 (19%) | 0.1 | 6 (29%) | 5 (28%) | 1 |
| III | 7 (18%) | 3 (25%) | 4 (15%) | 0.7 | 4 (19%) | 3 (17%) | 1 |
| Not available | 5 (13%) | 2 (17%) | 3 (11%) | 0.6 | 2 (9%) | 3 (17%) | 0.6 |
| Salmon & Durie stage | | | | | | | |
| I | 2 (5%) | 2 (17%) | 0 (0%) | 0.1 | 1 (5%) | 1 (6%) | 1 |
| II | 7 (18%) | 0 (0%) | 7 (26%) | 0.1 | 2 (10%) | 5 (28%) | 0.2 |
| III | 30 (77%) | 10 (83%) | 20 (74%) | 0.7 | 18 (86%) | 12 (67%) | 0.3 |
| Metaphase cytogenetics | | | | | | | |
| Normal | 26 (67%) | 8 (67%) | 18 (67%) | 1 | 15 (71%) | 11 (61%) | 0.5 |
| Abnormal | 7 (18%) | 2 (17%) | 5 (19%) | 1 | 4 (19%) | 3 (17%) | 1 |
| Not done | 6 (15%) | 2 (17%) | 4 (15%) | 1 | 2 (10%) | 3 (17%) | 0.4 |
| Osteolytic lesions | 29 (84%) | 9 (75%) | 20 (74%) | 1 | 17 (81%) | 12 (67%) | 0.5 |
| Extranodal disease | 11 (28%) | 5 (25%) | 8 (30%) | 1 | 6 (29%) | 5 (28%) | 1 |
| Previous Therapy | | | | | | | |
| Refractory disease | 22 (56%) | 7 (58%) | 15 (56%) | 1 | 11 (52%) | 11 (61%) | 0.8 |
| Relapsed disease | 17 (44%) | 5 (42%) | 12 (44%) | 1 | 10 (48%) | 7 (38%) | 0.8 |
| Prior lines of therapy | 2 (1-5) | 2 (1-5) | 2 (1-5) | 1 | 2 (1-5) | 2 (1-5) | 1 |
| Prior radiotherapy | 27 (69%) | 9 (75%) | 18 (67%) | 0.7 | 15 (71%) | 12 (67%) | 1 |
| Prior thalidomide | 23 (59%) | 5 (42%) | 18 (67%) | 0.2 | 11 (52%) | 12 (67%) | 0.5 |
| Prior HDT | 25 (64%) | 5 (42%) | 20 (74%) | 0.1 | 11 (52%) | 14 (78%) | 0.2 |
| Prior 2nd salvage HDT | 9 (23%) | 2 (17%) | 4 (15%) | 1 | 2 (10%) | 4 (22%) | 0.4 |
| β2-microglobulin [mg/l] | 3.0 (1.3-8.4) | 4.8 (2.2-7.7) | 2.6 (1.3-8.4) | 0.2 | 2.7 (1.7-7.7) | 3.4 (1.3-8.4) | 0.9 |
| LDH [U/l] | 178 (95-988) | 244 (137-536) | 174 (95-988) | 0.6 | 185 (114-613) | 172 (95-988) | 0.8 |
| Calcium [mmol/l] | 2.6 (1.9-3.1) | 2.46 (2.1-2.5) | 2.3 (1.9-3.1) | 0.5 | 2.3 (2.0-2.5) | 2.6 (1.9-3.1) | 1.0 |
| CRP [mg/l] | 0.8 (0.1-14.2) | 1 (0.1-3.1) | 0.8 (0.1-14.2) | 0.5 | 0.8 (0.1-11.3) | 0.8 (0.1-14.2) | 0.8 |
| Haemoglobin level [g/l] | 11.5 (7.4-17.4) | 11.4 (7.9-14.4) | 12.2 (7.4-17.4) | 0.3 | 11.6 (7.9-14.4) | 11.4 (7.4 – 14.3) | 0.8 |
| Platelet counts [x 1.000/µl] | 148 (20-455) | 161 (20-319) | 140 (38-455) | 0.8 | 140 (20-319) | 168 (38-455) | 0.1 |
| Creatinine [mg/ml] | 0.9 (0.4-5.2) | 1.2 (0.4-5.2) | 0.9 (0.4-1.6) | 0.2 | 0.9 (0.4-1.5) | 1.0 (0.4-5.2) | 0.5 |
of patients who had received 120-150 mg/m² (p = 0.75).

In the same way, bendamustine monotherapy resulted in a PR rate of 25%, which was not statistically different from combination therapy of bendamustine with corticosteroids (40%, p = 0.48, Table 2).

Table 3. Univariate analysis.

|                      | EFS  | OS   |
|----------------------|------|------|
| ISS stage (I vs. II+II) | 0.2  | 0.001|
| Cytogenetics (normal vs. abnormal karyotype) | 0.05 | 0.2  |
| LDH (</> 200 U/l)     | 0.5  | 0.02 |
| CRP (</> 0.6 mg/dl)   | 0.7  | 0.001|
| Haemoglobin level (</> 10 g/dl) | 0.2  | 0.04 |
| Platelet count (</> 200.000/µl) | 0.6  | 0.1  |
| Chemosensitivity (relapse vs. refractory) | 0.4  | 0.01 |
| Prior thalidomide     | 0.4  | 1.0  |
| Prior high-dose therapy | 0.5  | 0.4  |
| Extramedullary manifestion | 0.4  | 0.2  |
| Osteolytic lesions     | 0.5  | 0.3  |
| Bendamustine dosage (</> 120 mg/m²) | 0.6  | 0.9  |
| Monotherapy vs. Steroid combination therapy | 0.7  | 0.3  |

There were no significant differences in terms of remission rates for patients older than 65 years or younger patients. The same was true for patients who had received a prior high-dose therapy with PBSCT or who were treated with conventional chemotherapy (data not shown).

3.4 Event-free and Overall Survival

For the entire group of patients, the median EFS was 7 months and the median time of OS was 17 months (Fig. 1). The major reason for the relatively short survival time was disease progression and not toxicity.

Univariate analysis did show metaphase cytogenetics as a prognostic parameter for EFS. This was different for OS. Patients with ISS stage II or III, refractory disease, elevated LDH (> 200 U/l), elevated CRP level (> 0.6 mg/dl), and anaemia (haemoglobin level < 10 g/dl) had a significantly shorter OS time (Table 3).

There were no significant differences in outcome between the two subgroups receiving either bendamustine monotherapy or combination therapy with steroids. The dose of bendamustine also had no influence on the patients’ outcome. There also were no statistically differences between patients older than 65

![Overall survival](image1)

![Event-free survival](image2)

Fig. 1. Overall survival of 39 patients with refractory or relapsed MM treated with bendamustine and event-free survival of 21 patients with refractory or relapsed MM responding (MR+PR+CR) to bendamustine treatment.
years and younger patients or patients, which were treated with a prior PBSCT or not.

3.5 Toxicity

In our study, toxicity was mild (Table 4) and consisted mainly of haematological adverse events. In 95% of the patients, haematological side effects were observed after administration of one cycle of bendamustine. In most cases (69%) grade 1 and 2 cytopenia were observed, which did not postpone further treatment. severe anaemia requiring red blood cell transfusions (grade 3/4) developed in 4 patients (10%), while severe thrombocytopenia (grade 3/4) was observed in 10 (26%) patients. There were 16 (41%) patients with grade 3/4 neutropenia and 6 of them (15%) required iv antibiotic treatment and hospitalisation. one patient had a paravertebral abscess with spondylodiscitis requiring surgical intervention. this patient had received concomitant steroids.

Non-haematological toxicity included mainly gastrointestinal complaints. Grade 1 and 2 nausea and vomiting was observed in 8% (n = 3). In two patients (5%), grade 1/2 diarrhea was developed. Other grade 1/2 toxicities consisted of fatigue (n = 2), increase of creatinine (n = 3), paraesthesia (n = 1) and urticaria after application of bendamustine (n = 1). As a result, no grade 3/4 non-haematological toxicities were encountered. Alopecia was not reported for any of our patients.

There was no statistically significant difference with regard to haematologic toxicity between the different treatment groups. As far as the dose of bendamustine is concerned, there was no correlation between the dose level of bendamustine and the degree and type of toxicity. Concentrating on differences between bendamustine monotherapy and concomitant steroid therapy, haematological side effects were similar in both groups. On the other hand, infections were significantly more frequent in patients receiving corticosteroids (0% vs. 33%, p = 0.04, Table 4).

There were no differences in terms of toxicity for patients older than 65 years or younger patients. In the same way patients who had received a prior high-dose therapy with autologous stem cell transplantation showed the same toxicity as patients who were treated with conventional chemotherapy.

4. Discussion

Bendamustine is a treatment option for patients with relapsed and refractory multiple myeloma in particular because of its low toxicity either as single agent or in combination. Herein, we present retrospective data of 39 patients with advanced multiple myeloma, showing that bendamustine is an effective agent in this treatment situation. The rate of PR was 36%, which is similar to other salvage therapies. Noteworthy, in our study with a heterogeneous patient population we did not observe a better therapeutic efficacy when steroids were added. In contrast the concomitant administration of steroids was associated with a significantly higher rate of infections.

The major finding of our study is, that bendamustine is effective in patients with advanced multiple myeloma, while published data mainly focus on the role of bendamustine in early stages of the disease [23, 24]. Salvage therapies with single agents generally results in a CR or PR in one third of patients with multiple myeloma. This also holds true for novel agents such as thalidomide [6] or bortezomib [8]. Thus, the rate of 36% PR, which we observed in patients with in median 2 lines of prior therapy, including 56% of patients not achieving at least SD to their last line of therapy, meets the expected overall remission rate for an effective anti-myeloma agent. However, only one vgPR and no immunofixation negative CR could be achieved. This result scales down the expec-
Conflict of interest: Dr. Kobbe and Dr. Fenk received research funding by Celgene and Ortho Biotech and were involved in paid consultancy.

Acknowledgement: We thank the clinical staff of the Department of Hematology, Oncology and clinical Immunology for patient care.
27. Hrusivsky I, Heidtmann HH. Combination therapy of bendamustine and dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia & lymphoma (2005), 48 (12): 2345-2351.

28. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Guettet F et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haematopoietic stem cell transplantation. Myeloma subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British Journal of Haematology (1998), 102(5):1115-1123.

29. Atal M et al. The prognostic impact of complete remission (CR) plus very good partial remission (VGPR) in a double-transplantation program for newly diagnosed multiple myeloma (MM). Combined results of the IFM 99 trials. New England Journal Of Medicine (1996).

30. Lahuerta J, Mateos MV, Martínez-López J, Rosiñol L, Sureda A, de la Rubia J, García-Larriba J, Martínez-Martínez R, Hernández-Garcia MT, Carrera D, Besaldúch J, de Arriba F, Ribera JM, Escoda I, Hernández-Ruiz B, García-Frade J, Rivas-González C, Alegre A, Bladé J, San Miguel JF. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. Journal of Clinical Oncology (2008), 26 (35):5775-82.

31. Jagannath S, Barlogie B, Berenson JR, Siegel DS, Irwin D, Niesvizky R, Rajkumar SV, Coleman M, Rostiñol L, Sonneveld P, Andersen K, Anderson KC. Updated survival analyses after prolonged follow-up of the phase 2 multicenter REST study of bortezomib in relapsed or refractory multiple myeloma. British journal of haematology (2008); 143 (4): 537-40.

32. Niesvizky R, Richardson PG, Rajkumar SV; Coleman M; Rostiñol L; Sonneveld P; Schuster MW; Irwin D; Stadtmauer E; Facon T; Harousseau JL; Boral A; Esseltine DL; Anderson KC; Bladé J. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEx trial in relapsed multiple myeloma. British journal of haematology (2008); 143 (1): 6-53.

33. Hussein MA, Baz R, Skalovics G, Agrawal N, Suppiah R, Hsi E, Andresen S, Karam MA, Reed J, Faiman B, Kelly M, Walker E. Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed/refractory multiple myeloma. Mayo Clin Proc. (2006); 81(7): 889-95.4.

34. Büssing A, Fischer J, Haller A, Heusser P, Ostermann T and Matthies PF. Validation of the brief multidimensional life satisfaction scale in patients with chronic diseases. European Journal of Medical Research (2009), 14(4):171-177.

35. Büssing A, Girke M, Heckmann C, Schad F, Ostermann T, Kroź M. Validation of the self regulation questionnaire as a measure of health in quality of life research. European Journal of Medical Research (2009), 14(5): 223-227.

Received: October 14, 2009 / Accepted: November 27, 2009

Address for correspondence: PD Dr. med. Roland Fenk Heinrich-Heine-Universität Düsseldorf Klinik für Hämatologie, Onkologie und klinische Immunologie Moorstr. 5 40225 Düsseldorf Tel: +49-211-811-7760 E-mail: fenk@med.uni-duesseldorf.de