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ORIGINAL PAPER

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Treatment of Bendamustine and Prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with Melphalan and Prednisone—a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO)

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Abstract *Purpose*: This randomized phase III study compared bendamustine and prednisone (BP) to standard melphalan and prednisone (MP) treatment in previously untreated patients with multiple Myeloma (MM).

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Patients and Methods: To be included, patients had to have histologically and cytologically proven stage II with progressive diseases or stage III MM. They were randomly assigned to receive BP ($n = 68$) or MP ($n = 63$). The primary endpoint was the time to treatment failure (TTF). Secondary endpoints included survival, remission rate, toxicity and quality of life. *Results*: The overall response rate was 75% in the BP and 70% in the MP group. A significantly higher number of patients treated with BP achieved a complete remission than did patients receiving MP (32 vs. 13%; $P = 0.007$), and the maximum response was achieved more rapidly in patients treated with BP compared to those receiving MP (6.8 vs. 8.7 cycles; $P < 0.02$). TTF and remission duration were significantly longer in the BP group. Patients receiving BP had higher QoL scores and reported pain less frequently than patients receiving MP. *Conclusion*: BP is superior to MP with respect to complete remission rate, TTF, cycles needed to achieve maximum remission and quality of life and should be considered the new standard in first-line treatment of MM patients not eligible for transplantation.

Keywords Bendamustine · Prednisone · Multiple myeloma · Melphalan · Prednisone

Introduction

Multiple myeloma (MM) involves the abnormal growth and/or dysregulation of plasma cells and usually results in the accumulation of malignant plasma cells in the bone marrow along with the production of monoclonal proteins, generally of the immunoglobulin G or A class (IgG or IgA). Depending on the tumor location, patients with MM are at risk of developing a wide range of clinical complications such as renal insufficiency, recurrent bacterial infections, lytic bone lesions, hypercalcemia, anemia and neurological symptoms (Kyle 1975).

Multiple myeloma accounts for approximately 10% of all hematologic malignancies occurring in the USA. Around 14,400 new cases of MM were thought to have occurred in the USA in 2001 alone, resulting in an estimated 11,200 deaths (Greenlee et al. 2001). It is regarded as a disease of older patients, presenting most commonly in individuals over 50 years of age, with a median age of 70 years for women and 68 years for men at the time of diagnosis (Kyle 1975). The overall median survival of MM patients is approximately 2.5–3 years, however—because the course of the disease shows great variation—survival can range from less than 1 year to over 10 years. Several staging systems have been devised for MM, but the Durie and Salmon system is the most commonly used (Durie 1975). This system, which categorizes patients into stages I, II or III, is based on clinical symptoms and tumor cell mass at the time of diagnosis, and it is used to predict patients' clinical outcome following standard chemotherapy.

Approximately 40 years ago, the combination of oral melphalan and prednisone (MP) was introduced and shown to be the first successful chemotherapy for patients with MM (Bergsagel et al. 1962). Since then, intermittent courses of MP have been the standard form of therapy and numerous prospective trials have shown overall response rates of 40–50% (complete remissions < 5%) with remission durations of approximately 18–24 months, and a median overall survival of 24–30 months (Alexanian 1994). However, failure to respond to melphalan may be related to variable individual absorption and differences in the cell sensitivity to the drug; thus prompting dose escalation (Bosanquet 1982; Ehrsson et al. 1989; Fernberg et al. 1990; Raaijmakers et al. 1998). Furthermore, melphalan is leukemogenic, resulting in cytopenia and eventually myelodysplastic changes in the bone marrow, which increases the risk of therapy-induced myelodysplastic syndrome and acute myeloid leukemia (Bergsagel et al. 1979; Oken 1994).

Despite these problems, MP is still considered the "gold standard" of treatment, particularly for those patients not scheduled to undergo subsequent intensive chemotherapy with autologous or allogeneic peripheral blood stem cell or bone marrow transplantation (PBSCT or BMT) (Raje 2000; Weber 2002). While an alternative option is to use more aggressive combination treatment, a 1998 meta-analysis by The Myeloma Trialists Collaborative Group showed that alternative combination chemotherapy was equivalent to MP in terms of survival.

Therefore, a more effective treatment offering an improved tolerability profile to that of MP is needed. Initial results with bendamustine hydrochloride (hereafter referred to as "bendamustine") and prednisone suggests that similar or better results might be achieved with minimal adverse effects in comparison to MP.

Bendamustine is a bifunctional alkylating agent with a purine-like benzimidazole ring that has been administered successfully to patients with MM (Anger et al. 1969). It causes only partial cross-resistance to other alkylating agents and anthracyclines (Anger et al. 1975; Hoeffken et al. 1998). Apart from these clinical observations, in vitro data have also revealed only partial cross-resistance to melphalan, cyclophosphamide, cisplatin and anthracyclines (Strumberg et al. 1996). Recently, in vitro studies showed that bendamustine possesses a unique profile of activity, which was clearly divergent from other common nitrogen mustard drugs (Leoni et al. 2003) These properties turn bendamustine into an important agent that qualifies for front-line treatments as well as for salvage therapy after failure of other drugs. In a comparative study, treatment of previously untreated MM patients with either bendamustine or cyclophosphamide achieved comparable overall remission rates of 73 and 67%, respectively (Anger et al. 1975).

In a small phase III study involving 83 patients being treated for MM and followed over a period of 48 months Blumenstengel et al. (1998) observed equivalent efficacy when comparing a combination of bendamustine 50 mg/m^2 days 1–5 and prednisone 100 mg days 1–5 (BP) every 28 days with melphalan 7.5 mg/m^2 days 1–5 and Prednisolone 100 mg days 1–5 every (MP)

28 days. After six courses of therapy, 38% of the patients receiving BP and 34% of those receiving MP achieved a remission. Overall response rates in this study were 64 and 71%, respectively.

The current prospective randomized study was conducted to compare the efficacy and toxicity of BP and MP for the primary treatment of patients with MM. MP was administered according to Pest et al. (1993, 1995) and bendamustine was given as a fixed dosage of 150 mg/m^2 on day 1 and 2. As the enteral resorption of melphalan following oral administration shows individual differences (Alberts et al. 1979), the drug was administered intravenously.

The primary endpoint of the study was time to treatment failure (TTF). Secondary endpoints were overall survival, remission rate, the duration of remission, toxicity and quality of life.

Patients and methods

The current study was a prospective, open-label, randomized, multicenter, phase III trial of BP compared to the standard MP regimen as a first-line treatment for patients with MM.

Patient selection

From June 1994 to July 1999, 136 patients between 18 and 80 years of age were enrolled in the study. They all fit the Durie and Salmon (Durie 1975) criteria for histologically or cytologically proven stage II with progression or stage III MM. Other inclusion criteria were: quantitatively measurable myeloma proteins in the serum and/or urine by protein electrophoresis, leukocyte count ≥2,000/μl, platelet count ≥50,000/μl, Karnofsky performance status of ≥60%, life expectancy of ≥3 months, no prior chemotherapy or radiotherapy and full written informed consent was obtained.

Patients with nonsecretory and local plasmacytoma, HIV or Hbs-AG positivity or active hepatitis, secondary malignancy, pregnancy, lactation or inadequate contraception were excluded from the study. Also excluded were patients who had participated in clinical experimental studies within 1 month of the current study or who had serious concomitant diseases such as overt heart insufficiency, myocardial infarction within 6 months prior to the trial, arrhythmias ≥Lown 4b, chronic respiratory disease with hypoxemia, bilirubin ≥35 μmol/l or serum creatinine ≥300 μmol/l, autoimmune disease or allogeneic organ transplantations, severe CNS-diseases, pheochromocytoma, glaucoma and severe, poorly controlled diabetes mellitus.

The ethical committees of the participating centers approved the study and written informed consent was obtained from all patients. Patients were free to withdraw from the study at any time.

Therapy

Patients were randomly assigned to chemotherapy with either BP or MP. Randomization was stratified by the stage of the disease. All patients received prednisone (60 mg/m^2 intravenously or orally) on days 1–4 in combination with bendamustine on days 1 and 2 or melphalan on day 1. Bendamustine (150 mg/m^2 in 500 ml NaCl 0.9%) was administered as an intravenous infusion over 30 min. Melphalan (15 mg/m^2 in 100 ml NaCl 0.9%) was also administered intravenously over 30 min.

Treatment with BP or MP was administered every 28 days until maximum remission or disease progression was observed. Patients had to receive at least two cycles of chemotherapy for efficacy to be evaluated.

Evaluation of response was based on the SWOG criteria (Alexanian et al. 1972) that had been further defined by the German Myeloma Study Group (Peest et al. 1993, 1995).

Definitions of response

Complete remission (CR): decline in serum myeloma protein by ≥75% to ≤ 25 g/l, reduction in 24-h urinary protein by ≥90% to ≤ 200 mg/24 h, no increase in skeletal destruction, serum calcium within normal range, no blood transfusion required in the previous 3 months.

Partial remission (PR): decline in myeloma protein of 25–74% in serum myeloma protein reduction in 24-h urinary myeloma protein of 25–89%, no increase in skeletal destruction, serum calcium within normal range.

No change (NC): only minor variations ($< \pm 25\%$) in serum myeloma protein and/or 24-h urinary protein.

Progressive disease (PD): increase in serum myeloma protein and/or 24-h urinary protein by at least 25%, appearance of new osteolytic lesions or occurrence of hypercalcemia, progressive worsening of anemia with increased infiltration of plasma cells into the bone marrow.

Maximum remission was achieved if three additional courses of therapy did not further reduce the myeloma protein by $> 10\%$ in the serum and/or urine (24-h urine protein) and if no disease progression was observed. BP and MP therapies were discontinued after maximum remission was achieved. In cases of late relapse, (i.e., disease progression after at least a 3-month therapy-free interval), a reintroduction of the same therapy regimen was recommended until maximum remission was achieved. In cases of early relapse, (i.e., disease progression while on therapy or within the 3-month therapy-free interval), it was recommended to switch patients to the other therapy arm. In cases of further disease progression, alternative therapies were to be administered on an individual basis.

The next cycle of BP and MP was delayed by 1 week if leukocyte counts were still $< 3{,}000/\mu l$ and/or platelet counts $< 75{,}000/\mu l$. While the dosage of prednisone was kept constant, the bendamustine or melphalan dosage of

subsequent courses were modified according to WHO leukocyte/platelet counts and toxicity. The full chemotherapeutic dosage was given in case of leukocyte counts ≥3,000/μl and/or platelet counts ≥75,000/μl and/or non-hematologic toxicity grade 1; the dosage was reduced by 25% in case of leukocyte counts ranging from ≥2,000/μl to <3,000/μl and/or platelet counts ranging from ≥50,000/μl to <75,000/μl and/or non-hematologic toxicity grade 2; the dosage was reduced by 50% if the leukocyte counts were <2,000/μl and/or platelet counts <50,000/μl and/or non-hematologic toxicity grade 3. The dosage of bendamustine or melphalan was also reduced by 50% in cases of renal failure with an increase of creatinine to ≥500 μmol/l.

Patients could receive supportive measures as indicated, e.g., treatment of bone lesions at risk of fracture with radiotherapy or conservative therapy, transfusion of platelets or erythrocytes in cases of thrombocytopenia <20,000/μl or anemia and substitution with 10 g of an immunoglobulin preparation at 4-week intervals in cases of symptomatic antibody deficiency syndrome. Therapy-induced granulocytopenia (<1,000/μl) was treated with growth factors and therapeutic or prophylactic administration of antibiotics and antimycotics was permitted. Hypercalcemia was treated with bisphosphonates (preferably intravenously) and hydration.

Evaluation of efficacy and toxicity

Before the start of the study, a detailed staging examination was performed in each patient including a medical history, physical examination, determination of Karnofsky performance status, quality of life assessment (based on EORTC QLQ 30), determination of laboratory parameters, electrocardiogram (ECG), recording of X-ray findings and bone marrow biopsy. The myeloma protein concentration had to be determined by measuring the integral of the area under the myeloma protein curve using electrophoresis and calculating its portion of the total serum protein. During the first and second course of therapy, weekly blood counts (including platelets) were performed. After each course of therapy, the initial clinical and laboratory examinations were repeated, including an assessment of toxicity according to WHO criteria. Following courses 6 and 12, and in cases of maximum remission or disease progression, laboratory tests, ECG, X-ray and bone marrow biopsy were performed. During the first 3 months after the end of treatment, patients were followed up at 4-week intervals, and thereafter at 8-week intervals until disease progression.

It is important to note that the criteria used to define response to treatment in this study had originally been developed by Alexanian and the South Western Oncology Group (SWOG) in the early 1970s and further defined by the German Myeloma Treatment Group (Peest et al. 1993). The Myeloma Subcommittee of the European Group for Blood and Bone Marrow Transplant (EBMT) published response criteria for patients with MM (treated with high-dose chemotherapy and PBSCT) in 1998 after this study was started and, therefore, not used in this analysis (Blade et al. 1998).

Statistical methods

The study pooled data across all study sites, listed patient demographics, disease stage and histology by treatment group and evaluated comparability of the two groups using the Wilcoxon test.

Remission rates were estimated using 95% confidence intervals. The Mantel-Haenszel test compared remission rates after at least three cycles of chemotherapy. TTF (defined as the time from randomization to the occurrence of PD during the first cycle or any time thereafter, therapy switch, discontinuation of therapy or death) was compared in the two groups using the Cox regression model. Overall survival was estimated using Kaplan–Meier survival analysis and compared using the Log Rank test.

The statistical comparison of hematological toxicity between groups was based on the most severe toxicities across the entire treatment period.

Results

Patient characteristics

Of the 136 patients with MM enrolled in the trial, 11 of whom presented with stage II disease with progression and 125 with stage III disease, a total of 131 patients could be evaluated for this analysis. Five patients had not received the assigned treatment and were thus not evaluable. Patient outcomes were analyzed after an observation period of 48 months.

Baseline characteristics of the 131 evaluable patients appear in Table 1. Median age, proportion of male/female patients, mean serum hemoglobin, creatinine, β_2-microglobulin and calcium levels, together with the proportion of patients with advanced bone destruction or spontaneous fractures, IgG, IgA, IgE and Bence Jones protein levels, as well as Durie–Salmon stage II with progress or stage III disease at diagnosis, were comparable in the BP ($n=68$) and MP ($n=63$) arms.

Type and duration of response

The overall remission rate (CR + PR) was 75% in the BP group and 70% in patients receiving MP (Table 2). A significantly higher number of patients treated with BP achieved a CR compared to patients receiving MP (32 vs. 13%, $P=0.007$). The proportion of patients achieving a PR was comparable in the BP and MP groups (43 vs. 57%), as were the percentage of patients

Table 1 Patient characteristics at diagnosis

	Treatment regimen		
	BP ($n=68$)	MP ($n=63$)	P value
Age; median (range) years	62 (38–76)	62 (42–80)	0.64
Sex (male/female)	38/30	35/28	0.97
Hemoglobin [median (range) g/dl]	11.1 (6.7–5.5)	11.0 (6.1–15.5)	0.34
Serum creatinine [median (range) μmol/l]	91 (58–327)	99 (65–272)	0.38
Serum β_2 microglobulin [median (range) mg/l]	3.4 (1.1–7.5)	3.3 (1.1–16.4)	0.75
Serum calcium [median (range) mmol/l]	2.3 (2.0–4.2)	2.4 (1.2–3.5)	0.80
Advanced bone destruction	50 (74%)	48 (76%)	0.84
Spontaneous fractures	17 (25%)	14 (22%)	0.84
Immunoglobulin-type			
IgG	47 (69%)	45 (71%)	0.85
IgA	17 (25%)	14 (22%)	0.84
IgE	0 (0%)	1 (2%)	0.48
Bence–Jones protein	4 (6%)	3 (5%)	1.00
Durie-Salmon stage			
Stage II (with progression)	7 (10%)	4 (6%)	0.53
Stage III	61 (90%)	59 (94%)	0.53

Table 2 Maximum response following first-line therapy with BP or MP in 131 patients with multiple myeloma

	Treatment regimen		
Response	BP ($n=68$)	MP ($n=63$)	P value*
ORR	51 (75%)	44 (70%)	NS
CR	22 (32%)	8 (13%)	$P=0.007$
PR	29 (43%)	36 (57%)	NS
SD	16 (23%)	17 (27%)	NS
PD	1 (2%)	2 (3%)	NS

ORR overall remission rate (CR and PR); *CR* complete remission; *PR* partial remission; *SD* stable disease; *PD* progressive disease; *NS* not significant*Fisher's exact test

having stable disease (23 vs. 27%) or disease progression (2 vs. 3%). The maximum response was achieved more rapidly in patients treated with BP compared to those receiving MP (mean number of cycles to maximum response 6.8 vs. 8.7, Table 3).

TTF and overall survival

The primary endpoint of the study, TTF, was significantly longer in BP-treated patients compared to MP-treated patients (14 vs. 10 months; $P<0.02$, Fig. 1, Table 3). Remission duration in patients achieving a CR or PR was 18 vs. 12 months ($P<0.02$). The benefits of BP over MP in terms of TTF were maintained beyond 30 months (Fig. 1).

Table 3 Required number of Cycles, TTF, duration of remission and median overall survival after treatment with BP or MP in 131 patients with multiple myeloma

	BP ($n=68$)	MP ($n=63$)	P value
Number of cycles	6.8	8.7	$P<0.02$*
TTF (months)	14	10	$P<0.02$**
Duration of remission (months)	18	12	$P<0.02$**
Median overall survival (months)	32	33	NS**

BP bendamustine and prednisone; *MP* melphalan and prednisone; *TTF* time to treatment failure; *NS* not significant
*Wilcoxon test
**Log-Rank test

The number of patients who died during the course of the study was comparable in the BP and MP groups: 43 (63%) and 42 (67%) patients, respectively. However, the overall median survival rate did not differ significantly between patients receiving BP or MP treatment (32 vs. 33 months, $P=$ NS, Fig. 2). Furthermore, the 5-year survival rate was 29% in the BP arm and 19% in the MP arm.

The study design allowed crossover to the alternative treatment in case of disease progression on therapy or within the 3-month therapy-free interval. Since only 9 patients received MP after BP and 13 patients received BP after MP, no crossover analysis was carried out.

Quality of life

Evaluable baseline questionnaires were available for 23 patients in the BP group and 19 MP patients. Analysis of the questionnaires revealed that the global status of health and emotional functioning were superior in BP-treated patients compared to the MP-treated ones, 4 months after treatment and remaining so beyond 6 months (Fig. 3a, b). Furthermore, 4 months after the start of treatment, BP-treated patients reported (mostly bone) pain less frequently than those receiving MP (Fig. 3c).

Toxicities

Both bendamustine and melphalan were well tolerated, although severe (grade 3/4) nausea and vomiting was

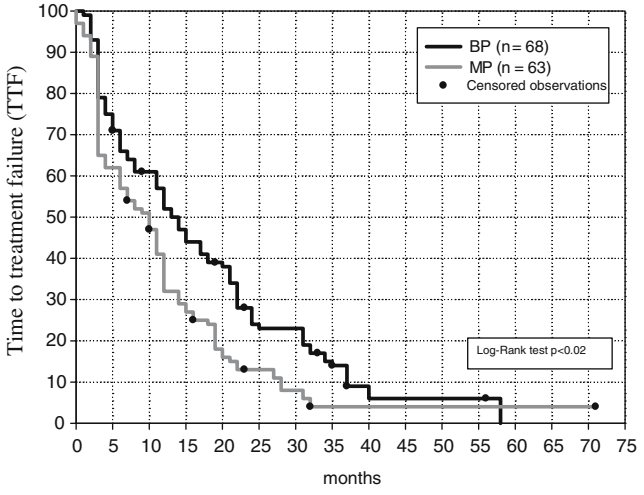

Fig. 1 Comparison of time to treatment failure following BP or MP in 131 patients with multiple myeloma (Log-Rank test)

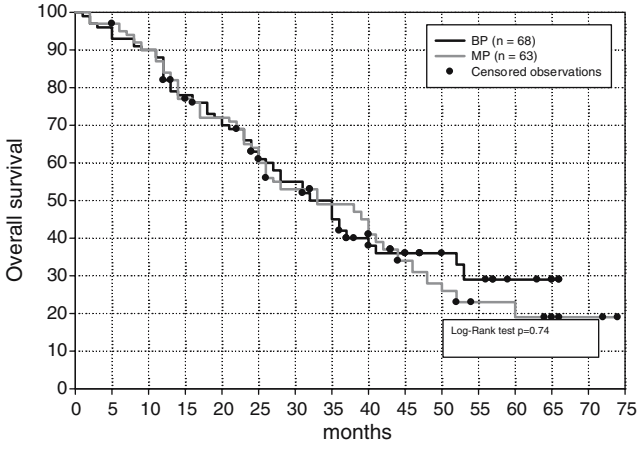

Fig. 2 Comparison of overall survival following BP or MP in 131 patients with multiple myeloma (Log-Rank test)

noted in 12% of patients in the BP group but none among the MP-treated patients (Table 4). If vomiting was noted in the first cycle of treatment, patients received anti-emetics in the second cycle (about 20% of patients).

Hematologic toxicity

No significant differences in toxicity were observed. Grade 3 and 4 anemia occurred in 24% of patients in both arms; similarly, grade 3 and 4 leukocytopenia was observed in 40 and 31% of patients and thrombocytopenia in 10 and 15% of patients after treatment with bendamustine or melphalan, respectively.

Furthermore, no treatment-related toxicities resulted in discontinuation of therapy. The vast majority of treatment cycles (80% BP and 92% MP) were completed without a dose reduction. The percentage of patients receiving bendamustine who required a dose reduction because of leukocytopenia (8.6 vs. 4.1%) or thrombocytopenia (1.8 vs. 0.9%) was twice that of patients receiving melphalan.

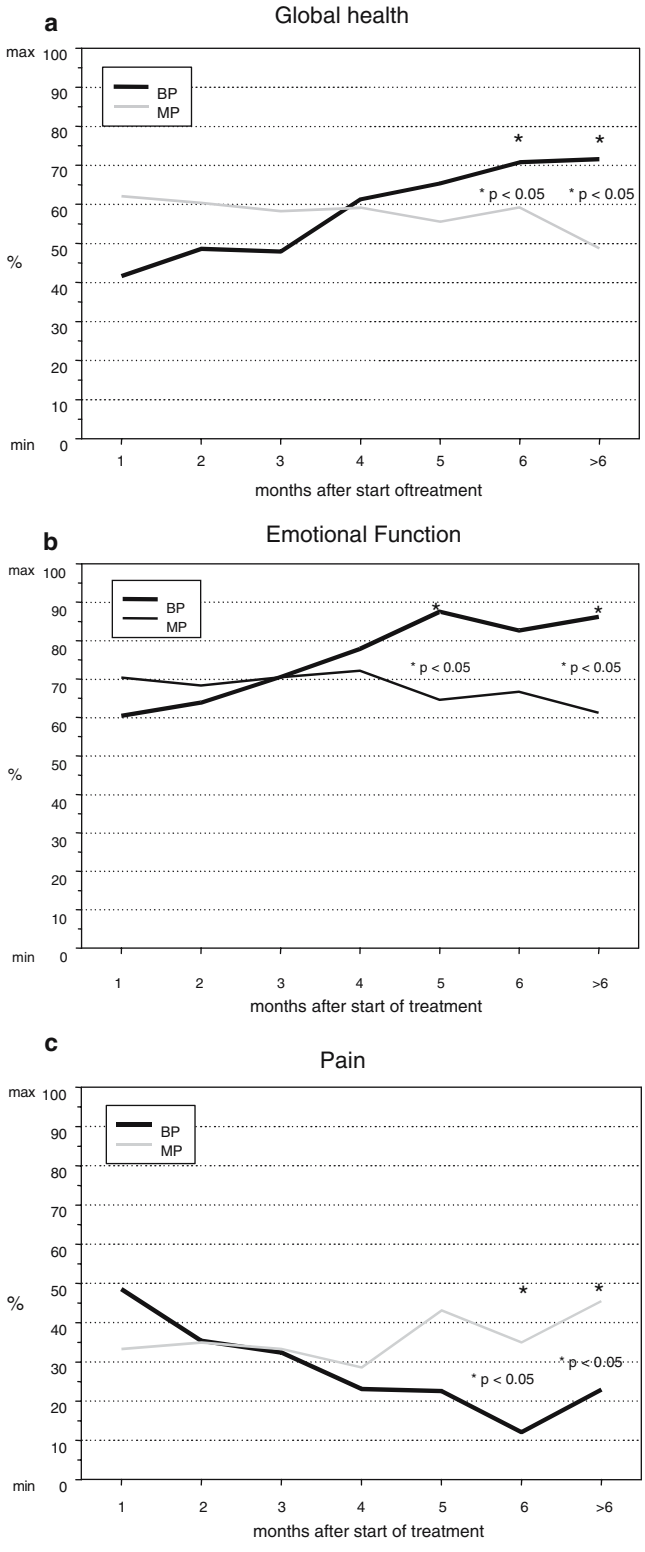

Fig. 3 Comparison of QoL parameters during therapy with BP or MP in patients with multiple myeloma: **a** Global status of health; **b** Emotional functioning; **c** Pain

Table 4 WHO grade 1–4 toxicities following treatment with BP or MP in 131 patients with newly diagnosed multiple myeloma

WHO Grade		1	2	3	4	Mantel–Haenszel test
Anemia	BP	25%	16%	21%	3%	$P = 0.1878$
	MP	19%	35%	21%	3%	
Leukocytopenia	BP	10%	25%	28%	12%	$P = 0.2808$
	MP	14%	27%	25%	6%	
Thrombocytopenia	BP	10%	4%	6%	4%	$P = 0.3392$
	MP	11%	18%	10%	5%	
Fever	BP	12%	27%	2%	0	$P = 0.4267$
	MP	10%	18%	0	0	
Infection	BP	18%	15%	10%	2%	$P = 0.8270$
	MP	18%	5%	10%	2%	
Mucositis	BP	13%	0	4%	0	$P = 0.0135$
	MP	3%	0	2%	0	
Nausea/vomiting	BP	19%	21%	12%	0	$P = 0.0009$
	MP	18%	10%	0	0	

Discussion

For patients not eligible for transplantation, a variety of alternative primary regimens to standard MP, the benchmark of MM treatment for over 30 years, have been evaluated over the past 10–15 years, including combinations of various alkylating agents and doxorubicin, vincristine or nitrosourea. However, while these newer combination regimens appeared to offer higher response rates (60 vs. 53%) in the first-line treatment of MM, a meta-analysis of 18 randomized controlled trials showed no significant differences in the 2-year survival rates (50–71 vs. 45–87%) among the newer regimens and the standard MP therapy (Myeloma Trialist's Collaborative Group 1998; Gregory et al. 1992). Consequently, new therapeutic options for patients with MM are needed.

The prospective, randomized, phase III trial presented here reveals that bendamustine in combination with prednisone (BP) is demonstrably superior to MP in respect to complete remission rate, TTF, cycles needed to achieve a maximum remission and quality of life.

The number of patients who died during the course of the study was comparable in the BP and MP groups and the median overall survival did not vary between patients receiving BP or MP treatment (32 vs. 33 months). Due to the crossover design and to the other salvage chemotherapy regimens applied in the two treatment arms, the overall survival benefit of bendamustine may have appeared less effective than its true potential and deserves further investigation without such constraints. Additional treatment after second progress may have also influenced overall survival.

In addition to bendamustine, several alternative regimens have shown promising results in MM, including high-dose chemotherapy with PBSCT or BMT support, the use of chemosensitizers to overcome drug resistance, interferon (IFN)-α, and various immunotherapies. Other emerging treatments include thalidomide-dexamethasone as first-line therapy, the proteosome inhibitor Bortezomib (PS 341) in patients relapsing after first-line induction treatment of more than two lines of previous treatment (Richardson et al. 2003), immunomodulatory thalidomide analogs in patients who fail to respond to previous treatments and farnesyl-transferase inhibitors. Therefore, it is useful to put our current findings into context with these other potentially important developments.

The administration of high-dose chemotherapy (mainly melphalan-based therapy) with PBSCT or BMT has been shown to increase CR rates and prolong EFS and overall survival in both previously untreated and relapsed/refractory patients when compared to conventional chemotherapy. Indeed, autologous SCT accelerated the restoration of hematopoiesis following high-dose melphalan and increased CR rates to 30—50% in the first-line treatment of MM (Harousseau et al. 1995; Attal et al. 1996). Furthermore, long-lasting remissions (almost 10 years) were observed in approximately 10% of patients receiving autologous PBSCT or BMT for advanced/refractory MM, suggesting that cure might be achievable (Vesole et al. 1996; Barlogie et al. 1999). Allogeneic BMT produces a CR rate between 33 and 58% (Bensinger et al. 1997), although transplant-related morbidity/mortality, particularly graft-versus-host disease, remains an important problem. Consequently, only younger patients who have a human leukocyte antigen (HLA)-identical sibling donor and do not respond to autologous transplantation should be evaluated for allogeneic BMT/PBSCT (Gahrton et al. 2001).

A meta-analysis conducted by The Myeloma Trialists' Collaborative Group in 1998 demonstrated that combination chemotherapy (CCT) and melphalan/prednisone are approximately equivalent. However, CCT decreases the quality of life and increases toxicity. In our study, quality of life improved continuously in the BP arm, becoming significantly better after 4–6 months, whereas it remained at the same level in the MP arm. The slight difference in QoL in the initial evaluation may be due to the stronger gastrointestinal toxicity of BP.

In a current phase III study in the East Germany Study Group of Hematology and Oncology, the impact of an intensified dose of prednisone is tested in a randomized setting in combination with either BP or MP. We are currently investigating a new combination therapy based on the BP regimen with the addition of

thalidomide (BPT) in relapsed or refractory patients with MM who do not qualify for transplantation.

In conclusion, the current findings provide evidence that bendamustine is an important advance over melphalan in patients with previously untreated MM. In particular, BP offers significant benefits in terms of CR rates, required duration of treatment, TTF, and quality of life when compared to MP. Therefore, BP should be considered the new standard in the first-line treatment of patients with MM who are not eligible for transplantation.

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