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Bendamustine, Prednisone and Bortezomib (BPV) Induction Therapy Prior Autologous Stem Cell Transplantation (ASCT) in 135 Newly Diagnosed Multiple Myeloma Patients: Comparison Between Patients with Normal and Impaired Renal Function

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Abstract

Introduction: Autologous stem cell transplantation (ASCT) is the standard first line treatment for younger patients with multiple myeloma (MM). Bortezomib and bendamustine have both been identified as rapidly acting and well-tolerated drugs for patients with MM-induced renal failure. In this retrospective study we analyzed the efficacy of induction therapy with a combination bendamustine, prednisone and bortezomib (BPV) prior to ASCT in newly diagnosed MM-patients (NDMM) depending on severity of renal impairment.

Methods: 135 patients with NDMM were treated with BPV-induction.

Results: The majority of patients (n=117; 87%) responded after BPV-induction with 9 sCR, 3 CR, 51 VGPR, and 54 PR. After first ASCT ORR increased to 99% with 33 sCR, 10 CR, 73 VGPR and 17 PR. Median PFS was 47 months and OS at 60 months was 67%. Patients were divided into four groups depending on severity of renal impairment: A (n=13) with eGFR<15mL/min, B (n=15) 15–29mL/min, C (n=19) 30-59mL/min and D (n=88) ≥60mL/min. We observed no significant difference in PFS between patients with normal/mild, moderate, severe renal dysfunction and renal failure/dialysis (50 vs 47 vs 34 vs 24 months, p=0.05) and in 60 months OS (69 vs 72 vs 58 vs 70%, p=0.23). The renal response rate improved from 68% after BPV to 74% following ASCT.

Conclusion: These results indicate that BPV-induction followed by ASCT is feasible, effective and well tolerated in patients with MM-induced renal failure. Furthermore, we showed that pretreatment with short-term bendamustine had no negative impact on stem cell mobilization.

Keywords: Multiple Myeloma; Autologous Stem Cell Transplantation; Renal Insufficiency; Cast Nephropathy; Bendamustine; Bortezomib

1. Introduction

Multiple myeloma (MM) is the most common B-cell neoplasm in Germany with about 7,100 new cases (more than 8 new cases per 100,000 of the population) each year [1]. The median age at diagnosis is 72-74 years, with about 35% of MM patients being younger than 65 years [2]. For these patients, high-dose therapy followed by autologous stem cell transplantation

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(ASCT) is the standard treatment [3]. However, an increasing number of reports suggest this to be both feasible and safe in MM patients older than 65 years [4,5,6]. Approximately 20–50% of all patients with MM have impaired renal function at diagnosis [7,8], with around 5-10% of them requiring hemodialysis [9].

Renal dysfunction is caused by the toxic effect of monoclonal free light chains (FLCs), although other factors such as amyloidosis, light chain deposition disease, dehydration, hypercalcemia, hyperuricemia, the use of nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, antibiotics, contrast media, etc.), and in rare cases, myeloma cell infiltration or hyperviscosity also contribute. However, the main cause of renal impairment is the overproduction of monoclonal FLCs, which can surpass the absorptive and catabolic capacity of proximal tubule cells and the resulting cell damage [10]. Necrotic tubular cells and excess FLCs form intratubular casts, resulting in renal tubular dysfunction. This process can only be stopped or reversed by a rapid, significant reduction in the production of toxic FLCs. Persistent renal impairment (particulary end-stage renal disease) results in higher morbidity and mortality, and severely impacts quality of life [11].

The introduction of new substances, especially bortezomib, has led to a significant improvement in overall survival (OS) in patients with severe renal impairment from 19 months before 2000 to 32 months after 2005 [12]. A retrospective French study in patients with severe renal impairment showed that ASCT increased survival to 76 months [13]. Previous studies with small numbers of patients suggest that treatment with new substances and/or conventional chemotherapy results in recovery of renal function in more than 50% of the cases [7,8]. An example of the use of the new drugs is the combination of bortezomib with bendamustine and corticosteroids, which has been assessed in several studies in the first line setting [14,15,16,17]. The combination of bendamustine, prednisone and bortezomib (Velcade®) (BPV) was particularly effective in 18 MM patients with severe renal insufficiency with a hematological overall response rate (ORR) of 83% and an improvement of renal function in 72% [18]. Ramasamy et al. [17] were also able to demonstrate the high efficacy of bendamustine and bortezomib in combination with steroids in patients with severe renal insufficiency in a randomised phase II trial (OPTIMAL). A rapid reduction of involed FLCs (iFLCs) after 2 cycles in 94% of patients with newly diagnosed MM (NDMM) resulted in a renal response rate of 50% after 4 cycles. Furthermore, we have gone on to use the BPV-combination as induction therapy prior to ASCT in patients with NDMM. Meanwhile, we published preliminary results in 35 MM patients [19]. This study demonstrated that BPV is a well-tolerated and highly effective induction treatment prior to ASCT. In addition, we showed that pretreatment with a median of two BPV cycles had no negative impact on stem cell mobilization and hematopoietic recovery after ASCT. In the present retrospective study, we have analyzed the efficacy of BPV induction before ASCT in NDMM patients depending on the severity of renal impairment.

2. Methods

2.1 Patients

This analysis included consecutive patients with NDMM with intended stem cell mobilization and subsequent ASCT after completion of BPV induction therapy. All patients met CRAB-criteria [20] or had another myeloma-related end-organ damage, with measurable myeloma protein in the serum and/or urine as confirmed by protein electrophoresis or serum FLC assay (Freelite®). Patients were divided into four groups: group A consisted of patients with renal failure/dialysis (eGFR <15 mL/min), group B patients with severe renal dysfunction (eGFR 15-29 mL/min), group C patients with moderate renal dysfunction (eGFR 30-59 mL/min) and group D patients with normal renal function or mild dysfunction (eGFR ≥60 mL/min) [21]. All patients gave written informed consent for the treatment and the use of anonymised personal data for clinical research. The study was approved by the Ethical Committee at the Medical Faculty, Leipzig University (IRB 00001750; registration number 118/18-ek).

2.2 Treatment protocol

2.2.1 BPV Induction Therapy

Bendamustine (60 mg/m^2) was given as 30-minute infusion on days 1 and 2 in combination with prednisone (100 mg) given orally on days 1, 2, 4, 8 and 11, and bortezomib (1.3 mg/m^2) as intravenous push or subcutaneously on days 1, 4, 8 and 11 [18]. In dialysis dependent-patients bendamustine and bortezomib were given 30 minutes after the end of dialysis. Cycles were repeated every 21 days up to 6 cycles or until a maximum response was observed. Maximum response was achieved if 3 weeks of therapy did not further reduce myeloma protein by more than 10% in the serum and/or urine.

2.2.2 Peripheral blood stem cell (PBSC) collection

PBSC collection was performed 2-3 weeks after BPV induction. The mobilization regimen consisted of cyclophosphamide 4 g/m^2 or 1-2 g/m^2 in case of severe renal insufficiency or preexisting heart disease. All patients received G-CSF (2x5 µg/kg body weight) until completion of stem cell collection. PBSC collection was started when the required number of CD34+ cells ≥20x10^6/L was detected. The target for all patients was to collect stem cells for 2-3 transplants. In patients with a poor stem cell yield in the first leukapheresis session, plerixafor (0.24 mg/kg body weight) was additionally administered before the next apheresis.

2.2.3 High dose therapy and ASCT

The pretransplantation conditioning therapy consisted

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of melphalan 200 mg/m^2. In case of concomitant heart amyloidosis or severe renal insufficiency, the melphalan dose was reduced to 100 or 140 mg/m^2. G-CSF (5 µg/kg body weight) was given on day 4 after stem cell reinfusion and continued until reconstitution of leukocytes ≥1.0x10^9/L.

2.3 Definitions of response

Evaluation of hematological response was based on the international uniform response criteria for multiple myeloma [22]. The degree of improvement of renal function was evaluated according to the criteria of the consensus statement on behalf of the International Myeloma Working Group [8,21]. Renal complete response (CRrenal) was defined as an improvement of eGFR from <50 mL/min at baseline to ≥60 mL/min, lasting at least 2 months. Renal partial response (PRrenal) was defined as improvement of eGFR from <15 mL/min at baseline to 30-59 mL/min. Renal minor response (MRrenal) was documented if baseline eGFR improved from <15 to 15-29 mL/min or from 15-29 to 30-59 mL/min.

2.4 Evaluation of efficacy

Patients were examined within a 48 hours period before inclusion into the BPV protocol. A staging examination was performed for each patient, incorporating medical history, physical examination including a detailed neurological examination, determination of World Health Organization Performance Status, determination of laboratory parameters (including β2-microglobulin, serum protein, serum protein electrophoresis, myeloma typing of serum and urine, serum FLC assay (Freelite®), serum creatinine, serum calcium and LDH), electrocardiogram, low dose CT and bone marrow biopsy. The value of iFLCs was defined as being above the upper standard level and an abnormal ratio of involved to uninvolved FLCs ≥8. Renal function was assessed by the eGFR using the Modification of Diet in Renal Disease (MDRD) formula [23]. Response data was collected on day 1, 8, 15 and 22 of each BPV cycle and 90 days after 1st ASCT.

2.5 Statistical methods

Descriptive statistical analyses were obtained for demographic and baseline variables. Patients were followed to a closeout date of at least 30st of November 2019. All patients who commenced treatment were included in the analysis of OS and progression free survival (PFS). OS was measured from the time of inclusion in the protocol to the time of death, and PFS from the inclusion in the protocol to the first occurrence of relapse, progression or death. OS and PFS rates were estimated using the Kaplan-Meier survival analysis and compared using the Log Rank test (IBM SPSS Statistics, Version 24). P-values were based on the Wilcoxon rank sum test. Categorical variables were compared using the x2-test. P-values were considered significant when <0.05.

3 Results

3.1 Patient characteristics

135 patients with NDMM were enrolled in this retrospective analysis. These patients were treated in the Clinic of Hematology at the University of Leipzig between October 2008 and November 2019. Two patients without CRAB criteria, one patient with multiple plasma cell organ infiltration (liver, spleen and lymph nodes) and a second patient with cardiac amyloidosis, were included in this cohort. Three additional patients treated with BPV induction with the initial intention of ASCT did not received transplantation due to multisystem amyloidosis with atrial fibrillation (n=1) or recurrent severe infections (n=2).

Baseline demographics and disease characteristics are shown in Table 1. Patients were divided into four groups depending on the severity of myeloma related renal impairment: group A 13 patients with eGFR <15 mL/min, group B 15 patients with eGFR 15-29 mL/min, group C 19 patients with eGFR 30-59 mL/min and group D 88 patients with eGFR ≥60 mL/min. At the time of diagnosis, 8 out of 13 patients with renal failure/dialysis (group A) were dialysis dependent. Of the 47 patients with renal impairment (group A–C), 38 had an eGFR <50 mL/min and were therefore used for the assessment of renal response [8]. In 3 patients (group A–C) with initially inconclusive results (iFLCs <500 mg/L) a renal biopsy was performed. Median age was 59 (range 35-73) years, with both age and male/female ratio being comparable between the four groups. The proportion of patients with a poor general condition (ECOG PS grade 3/4) was markedly higher in group A/B (n=9; 32%) compared to group C/D (n=10; 9%) (p<0.01). Patients with eGFR <30 mL/min (group A/B) presented with a higher frequency of light chain myeloma (n=16; 57% vs n=24; 23%; p<0.001). While in group A/B predominantly MM patients with light chain type lambda (57%) were found, in group C/D we observed a significantly lower number of patients with this light chain type (32%; p<0.03). The levels of iFLCs were significantly higher in patients with at least severe renal insufficiency (group A/B) with median 6,110 (range 83-28,700) mg/L, compared to median 281 (34-15,900) mg/L in group C/D (p<0.0003). Moderate, short-term hypercalcemia (2.61-2.98 mmol/L) occurred in 11 patients (8%) and severe hypercalcemia (3.04-3.97 mmol/L) in 7 patients (5%).

3.2 Induction therapy with BPV

Median time from first diagnosis to initiation of BPV therapy was 10 (range 0-240) days. This time was significantly shorter in patients with severe renal impairment with median 5 (range 0-36) versus 14 (range 0-240) days in patients with better renal function (p<0.01). The majority of patients (n=117; 87%) responded to the induction with a median of 2 (range 1-6) BPV cycles with 9 sCR (7%), 3 CR (2%), 51

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Table 1: Baseline characteristics of the 135 patients with newly diagnosed/untreated MM

Parameter eGFR (ml/min)		Group A (n = 13) < 15	Group B (n = 15) 15 – 29	Group C (n = 19) 30 – 59	Group D (n = 88) ≥ 60
Median age, years (range)		61 (35–68)	56 (43–67)	61 (46–72)	58 (36–73)
Male, n (%)		8 (62)	10 (67)	12 (63)	49 (56)
Female, n (%)		5 (38)	5 (33)	7 (37)	39 (44)
ECOG PS	0 – 2, n (%)	9 (69)	10 (67)	16 (84)	81 (92)
	3 + 4, n (%)	4 (31)	5 (33)	3 (16)	7 (8)
MM-Typ	IgG, n (%)	1 (8)	5 (33)	9 (47)	41 (47)
	IgA, n (%)	3 (23)	3 (20)	4 (21)	27 (31)
	IgD, n (%)	0	0	0	2 (2)
	Light chain, n (%)	9 (69)	7 (47)	6 (32)	18 (20)
Light chain-Typ	Kappa, n (%) Lambda, n (%)	4 (31) 9 (69)	8 (53) 7 (47)	13 (68) 6 (32)	60 (68) 28 (32)
Involved FLCs*, n (%) mg/L, median (range)		13 (100) 3648 (201-14000)	15 (100) 8440 (83-28700)	19 (100) 1055 (35-15900)	74 (84) 214 (34-15253)
ISS stage	I, n (%)	0	0	2 (11)	53 (60)
	II, n (%)	0	1 (7)	11 (58)	27 (31)
	III, n (%)	13 (100)	14 (93)	6 (32)	8 (9)
High risk (FISH) **	del 17p	0	2 (18)	4 (27)	12 (16)
	t (4;14)	4 (33)	1 (9)	3 (18)	8 (11)
	t (14;16)	0	0	1 (6)	4 (5)

*Involved FLCs was defined as being above the upper standard level and an abnormal ratio of involved to uninvolved FLCs ≥8.
**results available from 114 patients

VGPR (38%), and 54 PR (40%) (Fig. 1). The ORR in 34 patients with high-risk cytogenetic profile [del 17p, t(4;14) and t(14;16)] was 91% [2 sCR (6%), 2 CR (6%), 14 VGPR (41%) and 13 PR (38%)]. The BPV regimen resulted in a rapid decrease in M-protein, with 38 (28%) patients reaching the best response after the first and 68 (50%) additional patients after the second cycle. The first hematological response was observed after a median of 21 days (Table 2). We found no difference in ORR and CR rate between the four groups with different renal impairment (Table 3). An initial improvement of renal function occurred in 13/38 (34%) patients with renal impairment (eGFR <50 mL/min) after the first BPV cycle (3 CRrenal, 10 MRrenal) (Fig. 2). After completion of BPV induction, a total of 26 (68%) patients with renal impairment improved their renal function: 14 patients achieved CRrenal, 3 PRrenal and 9 MRrenal (Table 5a). Four of the eight dialysis dependent patients became dialysis independent (two patients after the first BPV cycle, one patient after 2 cycles and one patient after 3 cycles).

Table 2: Number of induction-cycles with bendamustine, prednisone and bortezomib (BPV) and outcome in 135 patients with newly diagnosed/untreated MM

Parameter	
Number of applied BPV cycles (median, range)	2 (1–6)
Number of cycles to first response (median, range)	1 (1–3)
Number of cycles to first maximum response (median, range)	2 (1–6)
Progression free survival (median, months)	47
Overall survival (median, months)	80

3.3 Peripheral blood stem cell mobilization

A period of median 64 (range 26-199) days elapsed from the start of BPV induction to first day of chemomobilization. For optimal stem cell mobilization and further reduction of the tumor burden, 111 patients received cyclophosphamide 4 g/m^2 and 24 patients with severe renal failure or pre-existing heart disease 1 to 2 g/m^2. Stem cell counts of CD34+

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Table 3: Best confirmed hematological response after induction therapy with bendamustine, prednisone and bortezomib (BPV) and after first ASCT in 135 patients with newly diagnosed/untreated MM

Parameter	Group A (n = 13)	Group B (n = 15)	Group C (n = 19)	Group D (n = 88)
eGFR (ml/min)	< 15	15 – 29	30 – 59	≥ 60
Response after BPV induction				
Stringend complete response (sCR)	2 (15)	1 (7)	0	6 (7)
Complete response (CR)	1 (8)	0	0	2 (2)
Very good partial response (VGPR)	7 (54)	10 (67)	9 (47)	25 (28)
Partial response (PR)	3 (23)	3 (20)	9 (47)	39 (44)
≥ CR	***3 (23)***	***1 (7)***	***0***	***8 (9)***
≥ VGPR	***10 (77)***	***11 (73)***	***9 (47)***	***33 (38)***
ORR	***13 (100)***	***14 (93)***	***18 (95)***	***72 (82)***
Response after ASCT				
Stringend complete response	5 (39)	7 (47)	1 (5)	20 (23)
Complete response	1 (8)	1 (7)	0	8 (9)
Very good partial response	7 (54)	6 (40)	16 (84)	44 (50)
Partial response	0	1 (7)	2 (11)	14 (16)
≥ CR	***6 (46)***	***8 (53)***	***1 (5)***	***28 (32)***
≥ VGPR	***13 (100)***	***14 (93)***	***17 (89)***	***72 (82)***
ORR	***13 (100)***	***15 (100)***	***19 (100)***	***86 (98)***

≥20x10^6/L in the peripheral blood were achieved in 131 (97%) patients after a median of 12 (range 9-17) days. A further four patients with poor stem cell mobilization on day 15 received additional plerixafor. In 96 of 135 patients (71%) a single apheresis was sufficient to reach the target of 8x10^6 CD34+/kg body weight (Table 4). The median number of aphereses was one (range 1-4) and the median total stem cell yield was 14 (range 2-33) x10^6/kg. The severity of the renal impairment had no effect on CD34+ yield. The restaging after stem cell mobilization showed an ORR of 91% [17 sCR (13%), 5 CR (4%), 61 VGPR (45%) and 40 PR (30%)] (Fig. 1).

3.4 Autologous stem cell transplantation

A total of 135 patients received an ASCT. The median time between the first day of BPV induction and start of pretransplantation conditioning therapy was 116 (range 69-260) days. The conditioning therapy in 108 patients consisted of melphalan 200 mg/m^2. In 27 patients with age ≥70 years (n=6), concomitant heart amyloidosis (n=4) or severe renal insufficiency (n=17), melphalan dose was reduced to 100 or 140 mg/m^2. Autografts contained median 5 (range 2-17) x10^6 CD34+ cells/kg (Table 4). Transplant related mortality (TRM) was 0.7% (n=1), with one patient dying following respiratory tract infection and septicemia on day 8 prior hematological regeneration. Engraftment was successful in all other patients. The median time to leukocyte count >1x10^9/L was 11 (range 9-23) days and the time to untransfused platelet count of >50x10^9/L was 13 (range 9-120) days.

3.5 Response and Survival

After the first ASCT the ORR increased to 99% with 33 sCR (24%), 10 CR (7%), 73 VGPR (54%) and 17 PR (13%) (Fig. 1). With a median observation time of surviving patients of 51 months, the median PFS was 47 months, and the 60 months OS was 67% (Fig. 3).

Analysis of PFS according to the severity of kidney impairment also revealed a trend that failed to reach significance, with median PFS of 50 vs 47 vs 34 vs 24 months (p=0.05) in patients with normal/mild-, moderate-, severe-renal dysfunction and renal failure/dialysis. Here, too, there was no difference in OS at 60 months (69 vs 72 vs 58 vs 70%; p=0.23) (Fig. 4 a, b). Also, there was no relevant difference in ORR and ≥VGPR rate between the four groups with different renal function (Table 3). Following the first ASCT, the renal response rate improved from 68% after induction to 74% (Fig. 2) with 18 CRrenal (47%), 3 PRrenal (8%) and 7 MRrenal (18%) (Table 5b). The remaining four dialysis dependent patients after BPV induction therapy showed no further improvement in their renal function.

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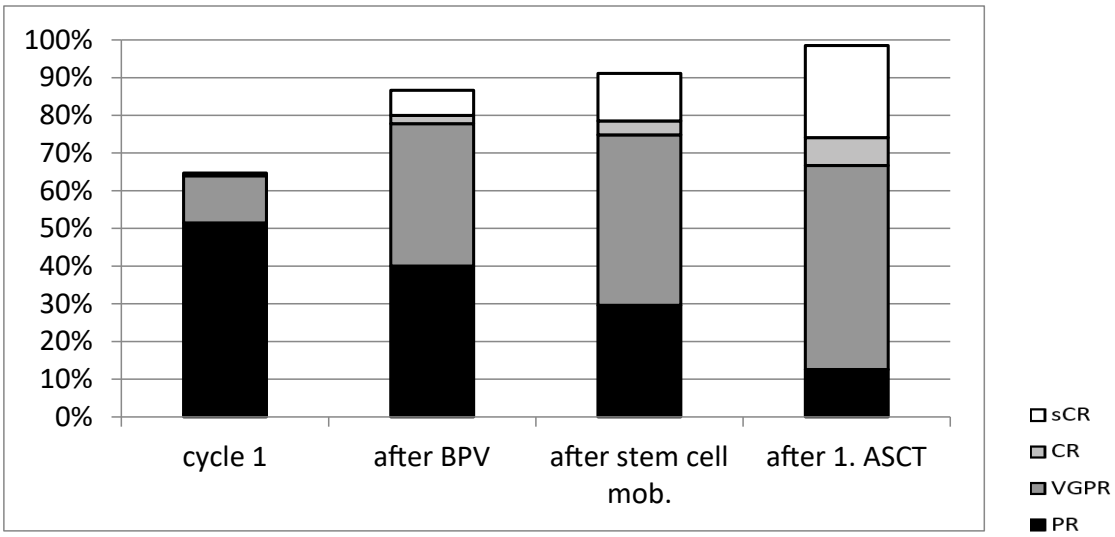

Figure 1: Hematological response in 135 newly diagnosed MM patients after each treatment phase

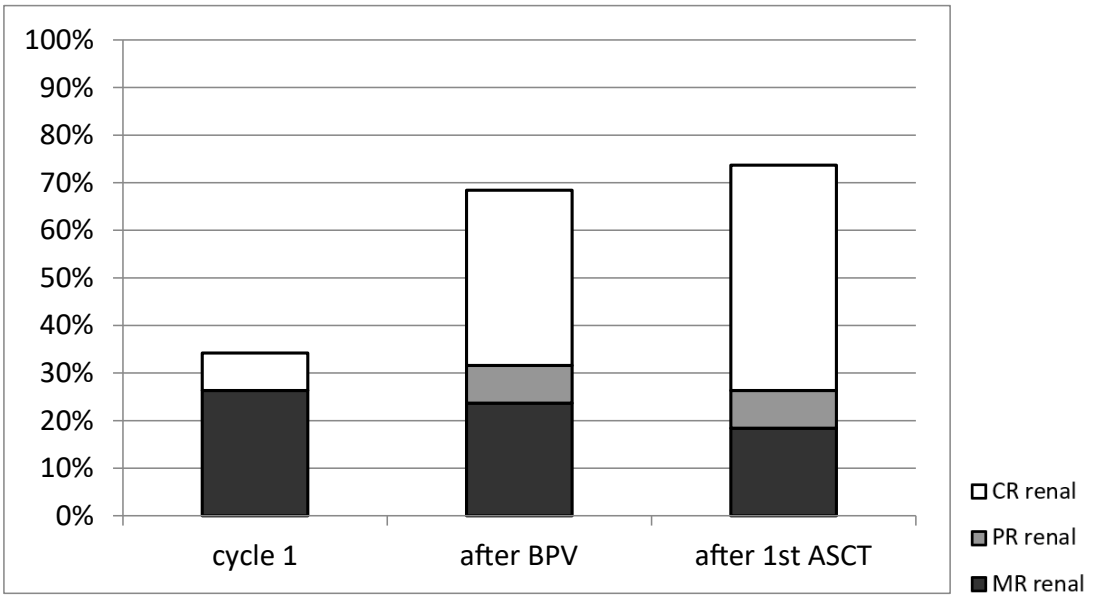

Figure 2: Renal response in 38 MM patients with renal impairment (eGFR <50 mL/min) after each treatment phase

Table 4: Leukapheresis and engraftment data in 135 patients with newly diagnosed/untreated MM

Parameter	Group A	Group B	Group C	Group D
	(n = 13)	(n = 15)	(n = 19)	(n = 88)
eGFR (ml/min)	< 15	15 – 29	30 – 59	≥ 60
Leukapheresis				
Day of first apheresis (range)	12 (11–14)	12 (9–15)	13 (10–16)	12 (10–17)
$CD34^+$ cells in peripheral blood on first day of apheresis (10^6/L), (range)	68 (27–121)	78 (20–266)	99 (17–281)	98 (10–478)
Total number of apheresis, n (range)	1 (1–2)	1 (1–4)	1 (1–3)	1 (1–4)
Total number of harvested $CD34^+$ cells (x10^6/kg), (range)	10 (4–18)	16 (2–24)	14 (5–30)	15 (2–33)

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Amount of harvested CD34⁺ cells per apheresis (x10⁶/kg), (range)	9 (4–18)	12 (2–24)	13 (3–30)	13 (1–33)
Stem cell transplantation				
Transplanted CD34⁺ cells (x10⁶/kg), (range)	4 (3–6)	5 (3–13)	5 (3–10)	5 (2–17)
Days to leukocyte ≥1.0x10⁹/L, (range)	11 (9–13)	11 (10–18)	11 (10–13)	11 (9–23)
Days to platelets ≥50x10⁹/L, (range)	15 (12–30)	15 (11–70)	14 (9–18)	13 (9–120)

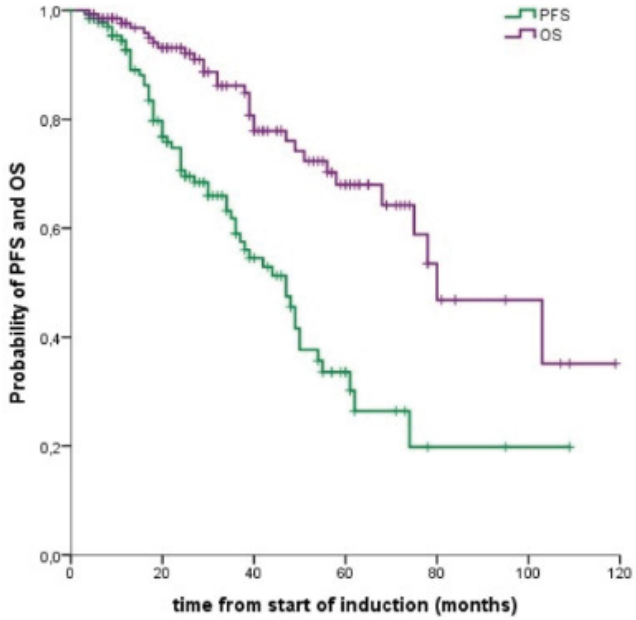

Figure 3: Progression free survival (PFS) and overall survival (OS) in 135 newly diagnosed MM patients. The median PFS was 47 months, and the 60 months OS was 67%.

The median PFS was 61 months in patients with ISS stage I, 47 months in stage II and 34 months in stage III, and OS at 60 months was 77%, 65% and 62%, respectively. While the difference in PFS between patients in stage I compared to stage II and stage III was significant ($p<0.05$), there was no difference in OS.

Chromosomal aberrations were examined with interphase fluorescence in situ hybridization (FISH) in 114 patients. Thirty-four patients (30%) had at least one high-risk cytogenetic abnormality: del17p (n=18; 16%), t(4;14) (n=16; 14%); t(14;16) (n=5; 4%). In patients with high risk cytogenetics we found no difference in PFS (26 vs 46 months, p=0.24) or in 60 months OS (57 vs 69%, p=0.24) compared to 80 patients with standard risk (Fig. 5 a, b).

4. Discussion

In the last 15 years, bortezomib-containing combinations have predominantly prevailed as induction therapies before ASCT [3,24,25,26], also in patients with advanced renal failure [8,27]. In the present retrospective study, we investigated the treatment of transplant eligible NDMM patients with normal or impaired renal function with a triple combination of bortezomib, bendamustine and prednisone. Our study of 135 patients provides confirmation of a previous preliminary study of just 35 patients covering a shorter period of follow up, in which BPV was identified to be a potentially effective and well-tolerated induction therapy [19].

The ORR of 87% (47% ≥VGPR and 9% ≥CR) after BPV induction observed in our study compares favorably to those reported for other bortezomib-containing triplets, which have ORR between 78-92%, including ≥VGPR rates between 34 and 67% and ≥CR rates between 7 and

Table 5a: Renal response after induction therapy with bendamustine, prednisone and bortezomib (BPV) in 38 patients with newly diagnosed/untreated MM and advanced renal failure (eGFR <50 mL/min).

Parameter	Group A	Group B	Group C	All patients
	(n = 13)	(n = 15)	(n = 10)*	(n = 38)
eGFR (mL/min)	< 15	15 – 29	30 – <50	< 50
Complete response renal	1 (8)	7 (47)	6 (60)	14 (37)
Partial response renal	3 (23)	–	–	3 (8)
Minimal response renal	2 (15)	7 (47)	–	9 (24)
ORRrenal	***6 (46)***	***14 (93)***	***6 (60)***	***26 (68)***

*Subgroup of Group C with eGFR 30 – <50 mL/min

Table 5b: Renal response after the first ASCT in 38 patients with newly diagnosed/untreated MM and advanced renal failure (eGFR <50 mL/min).

Parameter	Group A	Group B	Group C	All patients
	(n = 13)	(n = 15)	(n = 10)*	(n = 38)
eGFR (mL/min)	< 15	15 – 29	30 – <50	< 50
Complete response renal	3 (23)	8 (53)	7 (70)	18 (47)
Partial response renal	3 (23)	–	–	3 (8)
Minimal response renal	1 (8)	6 (40)	–	7 (18)
ORRrenal	***7 (54)***	***14 (93)***	***7 (70)***	***28 (74)***

*Subgroup of Group C with eGFR 30 – <50 mL/min

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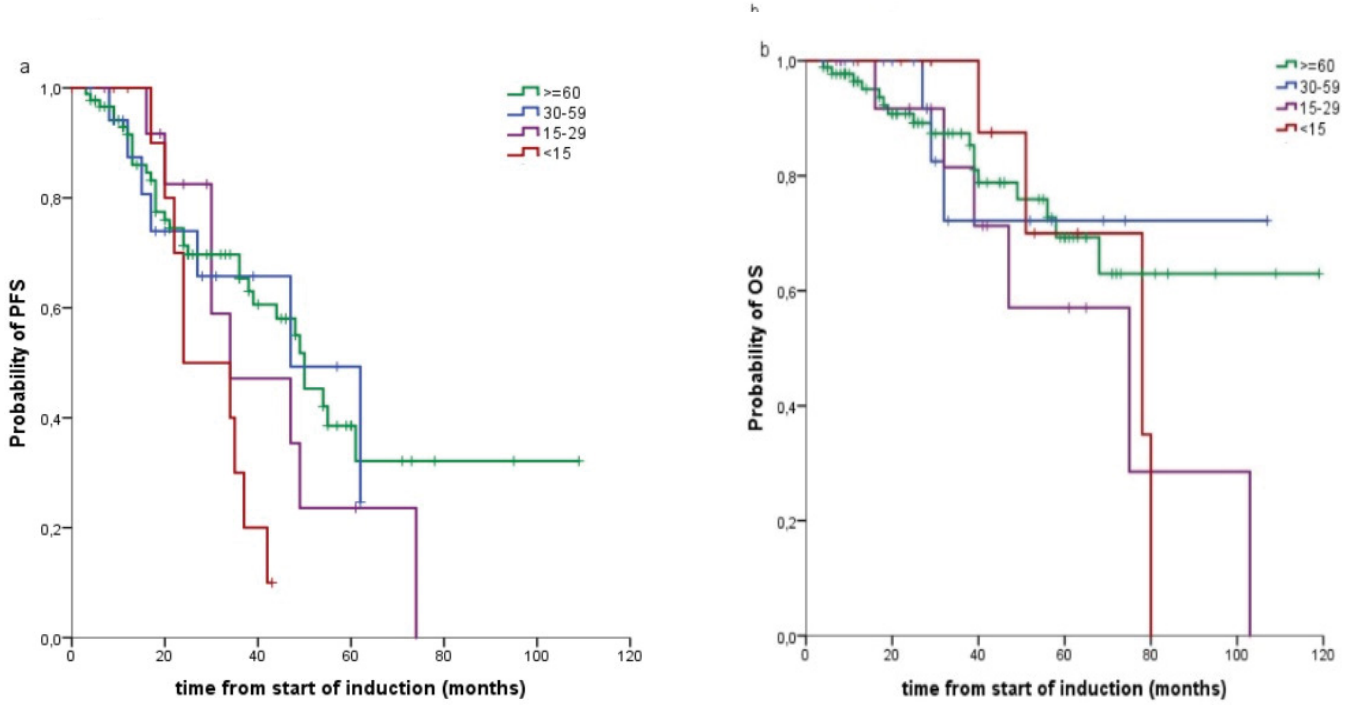

Figure 4: Progression free survival (PFS) (a) and overall survival (OS) (b) according to the renal function: eGFR ≥60 mL/min (n=88), eGFR 30-<60 mL/min (n=19), eGFR 15-<30 mL/min (n=15), and eGFR <15mL/min (n=13). There was no difference in median PFS in patients with normal/mild, moderate severe reanl dysfunction and renal failure/dialysis (50 vs 47 vs 34 vs 24 months; p=0.05) and in 60 months OS (69 vs 72 vs 58 vs 70%; p=0.23).

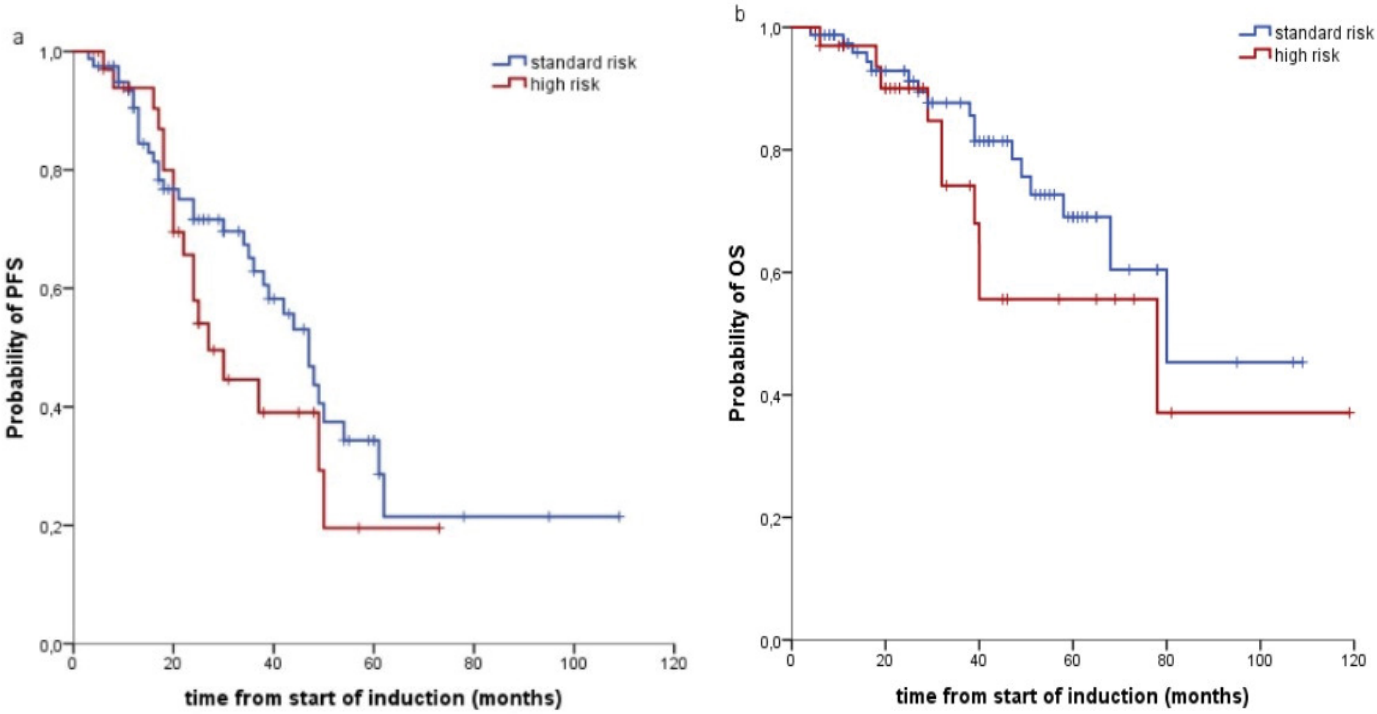

Figure 5: Progression free survival (PFS) (a) and overall survival (OS) (b) in patients with (n=34) or without (n=80) high risk cytogenetics [del17p, t(4;14), t(14;16)]. There were no difference in median PFS (26 vs 46 months; p=0.24) and 60 months OS (57 vs 69%; p=0.24).

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35% [28,29,30,31,32,33]. Due to the high efficacy of BPV induction, a median of just two 3-weekly cycles was requiered to achieve maximum response. This average 6-week induction period is significantly shorter than the 9 to 16 weeks required for other bortezomib triplets to achieve equivalent remissions [26,30,31,32,34]. The short time to first response (21 days) and to best response (42 days) is reflected in a rapid improvement in clinical symptoms and reduces the risk of developing peripheral polyneuropathy [19].

Until now, there is only limited information about stem cell toxicity of bendamustine. Successful stem cell mobilization after pretreatment with bendamustine has been reported in three previous studies involving lower numbers of myeloma patients [15,19,35]. In the present study of a larger cohort, we show that stem cell harvesting is easily feasible using a mobilization regimen consisting of cyclophosphamide and G-CSF following an induction with a median of two BPV cycles. The median yields of CD34+ cells collected ($14x10^6$/kg) compare very well to those reported for other stem cell mobilization protocols [31,36]. This indicates that short-term bendamustine therapy has no significant stem cell toxicity. The varying levels of renal impairment do not appear to effect either the CD34+ yield or subsequent engraftment.

Following first ASCT, the ORR increased to 99% in our patient cohort, with a ≥VGPR rate of 86% and a ≥CR rate of 32%. These response rates are similar to those of other ASCT studies involving bortezomib-containing inductions, in which ORR ranged from 81 to 98%, ≥VGPR rates from 62 to 88% and ≥CR rates from 21 to 59% [29,30,33,34]. Clinical outcomes in our study are promising, with a median PFS of 47 months and an OS of 67% at 60 months. These results compare well with the survival data achieved with other bortezomib-containing triplet inductions with median PFS between 35 and 60 months and 60 months OS between 60 and 80% [24,30,32,37,38].

Patients with renal insufficiency are not considered or underrepresented in most transplant studies [10,32,38,39]. In recent years, the two daratumumab- based induction therapies D-VTd and D-RVd have prevailed before ASCT. However, there is still no reliable data on its use in patients with renal impairment, as the phase 3 studies CASSIOPEIA [34], GRIFFIN [40] and PERSEUS [41] excluded patients with severe renal insufficiency. In contrast, the incidence of patients with at least moderate renal insufficiency (eGFR <50 ml/min) in our analysis was 28% (n=38) and corresponded to the frequency between 25 and 31% in large demographic MM studies [11,39,42]. Our study demonstrates that BPV induction followed by ASCT has very high efficacy in patients with NDMM and advanced renal impairment. The resulting hematological ORR of 100% with 50% CR in patients with stage 4/5 renal insufficiency, compares favorably with those reported in other transplant studies using bortezomib-containing inductions. For example, in the HOVON-65/GMMG-HD4 trial with the combination of bortezomib with adriamycin and dexamethasone, the ORR was 89% with 37% CR and in the SFGM-TC trial with predominantly bortezomib-based inductions the ORR was 89% with 40% CR [13,27]. The favorable hematological remission rates we observed in patients with at least severe renal impairment were associated with an only slight reduction in PFS and a similar 60 months OS compared to the remaining patients with superior renal function.

A rapid reduction of the MM protein, and in particular of the iFLCs, is decisive for the sustained improvement in kidney function. This early decrease in the iFLCs can be achieved both by high cutoff hemodialysis (HCO-HD) and by highly efficient systemic therapy. However, there are contradictory results on the use of HCO-HD. While the EuLITE study did not achieve any benefit in terms of dialysis independence, a French study using HCO-HD reported a significantly higher rate of hemodialysis independency after 6-12 months [43,44]. Using induction therapy with BPV, our study group has also demonstrated a similarily rapid reduction in iFLCs within the first week of treatment in the majority of MM patients [45]. In the present study, we observed a favorable renal response rate of 68% after BPV induction, comparable to those observed for other regimes containing novel agents [8,10]. Four of eight dialysis patients became dialysis independent. After completion of the induction therapy, only a few patients experienced a further improvement in renal function during the subsequent course of therapy including ASCT, in particular no additional patient became dialysis independent. This demonstrates the necessity of immediately initiating rapid-acting induction therapy in patients with renal impairment.

5. Conclusion

The combination of bendamustine, prednisone and bortezomib is a highly effective induction treatment prior to ASCT in patients with NDMM over varying levels of renal impairment. The rapid hematological response to BPV induction leads to an improvement in kidney function in the majority of patients.

Declarations

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Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Susann Fricke, Wolfram Pönisch and Tanja Holzhey. The first draft of the manuscript was

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Competing interests

The authors declare no competing interests.

Conflict of interest

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