Busulfan, Melphalan, and Bortezomib versus High-Dose Melphalan as a Conditioning Regimen for Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma

Tulio E. Rodriguez[1],[*], **Parameswaran Hari**[2], **Patrick J. Stiff**[1], **Scott E. Smith**[1], **Danielle Sterrenberg**[3], and **David H. Vesole**[4],[5]

[1]Division of Hematology and Oncology, Department of Medicine, Cardinal Bernardin Cancer Center, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois

[2]Department of Medicine and Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin

[3]Division of Hematology and Oncology, Department of Medicine, Loyola University Medical Center, Maywood, Illinois

[4]Multiple Myeloma Division, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, New Jersey

[5]Multiple Myeloma Program, MedStar Georgetown University Hospital, Washington, DC

Abstract

High-dose melphalan 200 mg/m^2 (MEL 200) is the standard of care as a conditioning regimen for autologous hematopoietic stem cell transplantation (AHSCT) for multiple myeloma (MM). We compared a novel conditioning combination incorporating busulfan, melphalan, and bortezomib (BUMELVEL) versus standard MEL 200 in newly diagnosed patients undergoing AHSCT for MM. Between July 2009 and May 2012, 43 eligible patients received BUMELVEL conditioning followed by AHSCT. BU was administered i.v. daily for 4 days to achieve a target area under the concentration-time curve total of 20,000 mM·min based on pharmacokinetic analysis after the first dose. MEL 140 mg/m^2 (MEL 140) and VEL 1.6 mg/m^2 were administered i.v. on days –2 and –1, respectively. Outcomes were compared with a contemporaneous North American cohort (n = 162) receiving MEL 200 matched for age, sex, performance status, stage, interval from diagnosis to AHSCT, and disease status before AHSCT. Multivariate analysis of relapse, progression-free survival (PFS), and overall survival (OS) was performed. The median follow-up was 25 months. No transplant-related mortality was observed in the study cohort at 1 year. PFS at 1 year was superior in the BUMELVEL cohort (90%) in comparison with 77% in MEL 200 historical control subjects (*P* = .02). Cumulative incidence of relapse was lower in the BUMELVEL group versus the MEL 200 group (10% at 1 year versus 21%; *P* = .047). OS at 1 year was similar between cohorts (93% versus 93%; *P* =.89). BU can be safely combined with MEL 140 and VEL without

*Correspondence and reprint requests: Tulio E. Rodriguez, MD, Cardinal Bernardin Cancer Center, Loyola University Chicago Stritch School of Medicine, 2160 S. First Avenue, Maywood, IL 60153. trodriguez@lumc.edu (T.E. Rodriguez).

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an increase in toxicities or transplant-related mortality. We observed a superior PFS in the BUMELVEL cohort without maintenance therapy, warranting further trials.

Keywords

Stem cell transplantation; Multiple myeloma; Conditioning regimen; Busulfan; Melphalan; Bortezomib

INTRODUCTION

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (AHSCT) is an effective therapy for transplant-eligible patients as consolidation after induction therapy in newly diagnosed multiple myeloma (MM). The benefit of AHSCT also extends to patients with relapsed disease who remain transplant eligible. The effectiveness of AHSCT for patients with MM remains relevant despite significant therapeutic advances achieved with the introduction of novel agents such as proteasome inhibitors and immunomodulatory agents. MM remains the most common indication for AHSCT in North America and Europe [1]. Single-agent melphalan, at a dose of 200 mg/m^2 (MEL 200), is the international standard for conditioning before AHSCT for MM [2]. Other chemotherapy and chemoradiotherapy regimens have been used in preparation for AHSCT but with no clear superiority over MEL 200 [3]. These other combination regimens are generally associated with increased hematologic and nonhematologic toxicities without improvement in efficacy.

High-dose busulfan (BU) and melphalan (MEL) are myeloablative chemotherapeutic agents. Both are effective and well-tolerated agents that have been used for over 20 years in MM and other malignancies as conditioning regimens for AHSCT. The combination of BU and MEL was associated with superior progression-free survival (PFS) compared with MEL 200 in patients who had not achieved European Group for Blood and Marrow Transplantation criteria (CR) before AHSCT [4,5]. Additionally, the combination of bortezomib (VEL) and MEL appears to be synergistic, especially when VEL is administered after MEL 200 [6].

We prospectively evaluated a conditioning regimen consisting of high-dose i.v. BU and MEL followed by VEL (BUMELVEL) in an open-label, phase I/II fashion aimed at improving PFS after AHSCT for MM patients. A predefined maximum tolerated dose was used in this trial and consisted of BU 130 mg/m^2 daily for 4 days and adjusted to achieve a target area under the concentration-time curve (AUC) total of 20,000 μM·min, MEL 140 mg/m^2, and VEL 1.6 mg/m^2. We then compared the results of patients who received the predefined maximum tolerated dose against a contemporaneous matched cohort of patients with similar characteristics who received single-agent MEL 200.

METHODS

Between July 2009 and May 2012, 43 patients received BUMELVEL conditioning followed by AHSCT in a single-center, open-label phase I/II protocol. Inclusion criteria included adults with MM who had a creatinine of less than 2.5 mg/dL, without active infections or severe obstructive and/or restrictive pulmonary disease determined by pulmonary function

testing (ie, $DL_{CO} < 50\%$ and/or $FEV_1 < 50\%$ and/or $FVC < 50\%$) and cardiac ejection fraction greater than 40%. Response criteria were assessed according to the International Myeloma Working Group Uniform Response Criteria [7].

Neutrophil and platelet engraftment were defined as the first of 3 days with a neutrophil count $> .5 \times 10^9$/L and first date of 3 consecutive laboratory values with an untransfused platelet count 20×10^9/L. Because BU has been associated with the risk of sinusoidal obstructive syndrome (SOS), we monitored for SOS using the Baltimore diagnostic criteria [8]. It is known that SOS risk is higher when the total BU AUC exceeds 24,000 μM·min [9]. Therefore, BU was administered i.v. daily for a total of 4 days with the first 2 days (days −6 and −5) at fixed dose of 130 mg/m^2 over 3 hours and the subsequent 2 doses (days −4 and −3) adjusted to achieve a target AUC total of 20,000 μM·min determined by pharmacokinetic analysis after the first dose of i.v. BU. MEL 140 mg/m^2 and VEL 1.6 mg/m^2 were administered i.v. on days −2 and −1, respectively.

Patients received prophylaxis for oral mucositis with palifermin: 2 doses of 6.25 mg were administered by i.v. bolus injection for 2 consecutive days before the first BU dose (days −8 and −7), and a third dose of 6.25 mg was administered on day 0 after stem cell infusion. This study was approved by the Loyola University Chicago Stritch School of Medicine Institutional Review Board, and all patients voluntarily signed informed consent.

STUDY DESIGN

Data from this phase I/II clinical trial in MM patients transplanted at Loyola University Chicago Medical Center using the BUMELVEL conditioning regimen were compared against a matched control cohort of contemporaneous North American MM patients (n = 162) receiving single-agent MEL 200 conditioning. Only patients who received the predefined maximum tolerated dose were included in the comparison analysis. The control subjects were identified from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. The comparison was done on a 1:3 match (Loyola-to-CIBMTR). Control subjects were randomly selected and matched by age, sex, Karnofsky performance status (KPS), disease stage, interval from diagnosis to AHSCT, and disease status before AHSCT. Fifty-four centers, not including the study center, contributed with patients for the control group. Multivariate analysis of relapse, PFS, and overall survival (OS) was performed. Maintenance therapy was not administered to patients or control subjects.

Control Cohort Database

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry and the National Marrow Donor Program (NMDP) and receives data from over 500 transplantation centers worldwide on allogeneic and autologous hematopoietic stem cell transplantation. Data are submitted to the Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis, where computerized checks for discrepancies, physicians' reviews of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the

CIBMTR are performed with approval of the institutional review boards of the NMDP and the Medical College of Wisconsin.

Statistical Analysis

The primary endpoint of the study was the 1-year PFS after a myeloablative preparative regimen consisting of i.v. BUMELVEL versus MEL 200. Using a 1:3 match comparison, the study included 43 patients on the BUMELVEL regimen and 162 patients from the CIBMTR database. Descriptive statistics were used to report results including demographics, disease-related factors, transplant-related factors, incidence and severity of mucositis, incidence and severity of SOS, remission rates, and relapse rates. Survival analysis was done using a Cox proportional hazards regression to adjust for differences between the groups. *P* values were always 2-tailed and considered significant when <.05.

Medians and ranges are listed for continuous variables. The total number of patients and the percentage of each subgroup were calculated for categorical variables. Characteristics of patients in the 2 study cohorts were compared using the Mann-Whitney-Wilcoxon test for continuous variables and chi-square test for discrete variables. For discrete variables with small group size, the Fisher's exact test was used for comparison. Probability of PFS and OS was calculated using the Kaplan-Meier estimator, with the variance estimated by the Greenwood's formula. Probabilities of treatment-related mortality (TRM) and relapse were generated using cumulative incidence estimates to accommodate the competing risk event. The point-wise comparison was used to analyze outcomes of 2 study cohorts. All tests were 2-sided with a significant level of .05.

Multivariate analysis of TRM, relapse, PFS, and OS were performed using Cox proportional hazards regression models. The variables considered in the multivariable were preparative regimen, age, gender, KPS, isotype, international stage for MM, Mayo risk stratification at diagnosis, number of prior chemotherapy regimens before transplantation, chemotherapy regimens before transplantation, disease status before transplantation, time from diagnosis to transplantation, and year of transplantation. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. A backward stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect for 2 different regimens. Factors significant at a 5% level were kept in the final model. The potential interactions between main effects and all significant risk factors were tested.

RESULTS

Patient Characteristics

Both cohorts were balanced for age, gender, KPS, MM isotypes, time from diagnosis to transplantation, disease stage, and disease status before transplantation (Table 1). Patient demographics in the BUMELVEL and MEL 200 groups included the following: median age 62 years and 61 years, respectively; KPS 90% in 74% and 75%, respectively; and chemotherapy-sensitive disease before transplantation in 95% and 91%, respectively. All patients underwent AHSCT within 12 months from diagnosis.

Of note, the MEL 200 control cohort had more standard-risk patients per Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) [10] (78% versus 40% in BUMELVEL, $P < .0001$) and more patients with only 1 prior line of therapy pre-AHSCT (67% versus 47%, $P = .02$). Patients in the BUMELVEL group had received induction combination regimens involving VEL, lenalidomide, and dexamethasone (51%); VEL and dexamethasone (35%); or VEL, thalidomide, and dexamethasone (14%) before AHSCT. At the time of transplantation, 3 (7%) and 15 (35%) patients were in CR and very good partial remission (VGPR), respectively. Median follow-up for the BUMELVEL and MEL 200 cohorts were 25 months and 35 months, respectively. Sixty-two percent of the control group received VEL either as a doublet or in combination with thalidomide or lenalidomide. Thirty-six percent received induction therapy with other novel agents consisting of doublets with thalidomide or lenalidomide.

Outcomes

The BUMELVEL regimen resulted in an overall response rate of 98%, including at least VGPR in 70% and CR in 42% (Table 2). At 1 year post-AHSCT, 90% of patients on the BUMELVEL cohort remained progression free in comparison with 77% of MEL 200 recipients ($P = .02$) (Figure 1). OS was similar between both cohorts (93% versus 93% at 1 year; $P = .89$) (Figure 2). Cumulative incidence of relapse at 1 year was lower in the BUMELVEL group versus MEL 200 (10% versus 21%; $P = .047$). Neutrophil and platelet engraftment kinetics were similar between both groups (Figures 3 and 4).

In multivariate analysis, PFS was superior in the BUMELVEL cohort (hazard ratio for relapse/death, 1.87 for MEL 200 cohort; $P = .04$). BUMELVEL therapy was not associated with any difference in OS or relapse risk at the time of the analysis. Patients who achieved at least a VGPR before AHSCT had a superior PFS post-AHSCT (CR, 1.000 [95% confidence interval {CI}, 1.000 to 1.000]; VGPR, 1.983 [95% CI, .876 to 4.489]; PR, 2.668 [95% CI, 1.260 to 5.652]; and stable disease, 3.468 [95% CI, 1.337 to 8.996]), whereas lower KPS (80) and higher international stage were associated with inferior OS (relative risk for OS, 2.283 [95% CI, 1.093 to 4.769] for KPS 80, $P = .02$; hazard ratio for OS, 3.568 [95% CI, 1.326 to 9.598] for stages II to III, $P = .0086$).

Regimen-Related Toxicity

There was no TRM in the BUMELVEL group and no episodes of SOS disease. There was a small but statistically significant TRM in the MEL cohort (relative risk for TRM, .03 [95% CI, .01 to .06]). The most common grade 3 adverse events (Table 3) included the expected febrile neutropenia, mucositis, and hypophosphatemia. Other adverse events presenting in less than 10% of the patients on the BUMELVEL group were diarrhea, nausea, hypocalcemia, transaminitis, and hyperglycemia. The median hospital stay for the BUMELVEL group was 19 days.

Dose Targeting of BU

The first 2 daily infusions of BU on the BUMELVEL regimen were given at a fixed dose of 130 mg/m^2 over 3 hours from days −6 to −5. This dose has been found to be safe and equivalent to the standard daily dose of 3.2 mg/kg [11]. The third and fourth daily doses of

i.v. BU were adjusted to yield a systemic plasma drug exposure, represented by a targeted AUC of 5000 μM·min per dose for a total of 20,000 μM·min. Only 23% of patients had an AUC outside an acceptable range of 5000 μM·min ± 20% (<4000 or >6000 μM·min). Doses were adjusted on days −4 and −3 to achieve the total desired AUC of 20,000 μM·min.

DISCUSSION

High-dose chemotherapy followed by AHSCT is considered a standard approach by the International Myeloma Working Group for transplant-eligible MM patients. The addition of novel agents, like the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide and the proteasome inhibitors VEL and carfilzomib, in treatment paradigms has led to unprecedented survival improvement in patients with MM [12–14].

In the context of stem cell transplantation for MM, there is a relationship between the achievement of CR or VGPR and PFS or OS [15]. VEL-based induction regimens result in significant improvements in response, PFS, and OS compared with non-VEL-based induction regimens [16]. In our study 100% of patients in the BUMELVEL cohort received induction with VEL combination regimens before AHSCT versus 62% of patients in the control group. Because control subjects were matched with patients for disease status before transplantation, we believe the lack of VEL in the induction therapy is not impacting the outcomes observed. More patients in the control group were in CR prior to transplantation compared with the BUMELVEL group (20% versus 7%, respectively). The higher CR rate in the control group might be related to a higher representation of standard-risk patients per mSMART and more patients with only 1 prior line of therapy pre-AHSCT in this group.

The study group was treated before the availability of other proteasome inhibitors. Carfilzomib, which was approved by the US Food and Drug Administration in 2012 for the treatment of patients with MM who have received at least 2 prior therapies, including VEL and an immunomodulatory agent, has shown activity in patients with newly diagnosed as well as relapsed or refractory MM [17]. In a randomized, phase III, open-label, multicenter study for patients with relapsed or refractory MM, carfilzomib with dexamethasone was found to deliver better response and PFS rates when compared with VEL with dexamethasone [18]. These observations suggest that carfilzomib-based regimens could deliver better responses before AHSCT in comparison with VEL-based regimens. Obviously, this will need to be validated in prospective clinical trials while paying special attention to therapeutic index.

Despite achievements of impressive response rates after inductions with novel therapy regimes, AHSCT continues to deliver improvement in PFS and OS as consolidation of these responses [19]. A phase II study of extended treatment with carfilzomib, lenalidomide, and dexamethasone (KRd) plus AHSCT in newly diagnosed MM patients showed that this regimen resulted in higher stringent CR rates than KRd without AHSCT. There was also a higher rate of minimal residual disease negativity in the transplantation group [20]. The improvement in response rate after induction was observed in our analysis where the CR plus VGPR after BUMELVEL followed by AHSCT increased from 42% pre-transplantation to 70% post-AHSCT. Our analysis suggests that the novel preparative regimen BUMELVEL

followed by AHSCT is a complementary, nonredundant therapy that can be effectively included in the management of MM supporting the trends in utilization and outcomes of autologous transplantation as a therapy for MM [2].

In an older study reported by Mansi et al. [21], a 46% response rate was observed after high-dose single-agent oral BU (16 mg/kg) followed by AHSCT in heavily pretreated patients with MM. The absorption of oral BU is unpredictable and may lead to unacceptable nonhematologic toxicity. We used an i.v. BU formulation for our regimen that has been found to deliver effective myeloablation with less nonhematologic toxicity and higher 100-day survival compared with oral BU [22]. Single-agent high-dose MEL 200 has been used almost exclusively as the preferred preparative regimen for MM since a randomized study established the superiority of this regimen over MEL 140 mg/m^2 with total body radiation [23].

There is now evidence of clonal heterogeneity and clonal evolution throughout the natural history of MM [24]. Based on these observations, a response to therapy might represent the suppression of a sensitive clone, whereas resistant clones remain unperturbed and become proportionally more dominant over time, leading to inevitable relapse. This rationale supports the development of preparative regimens combining synergistic agents to achieve deeper responses to circumvent the possibility of heterogeneous resistant clones leading to relapse while maintaining an acceptable therapeutic index. The combination of BU with either MEL or cyclophosphamide has been used for over 20 years as an alternative preparative regimen in MM before AHSCT [25–28].

Proteasome inhibitors such as VEL have a consistent anti-tumor activity against chemoresistant and chemosensitive myeloma cells. The sensitivity of chemoresistant myeloma cells to this chemotherapeutic agent is markedly increased (100,000- to 1,000,000-fold) without affecting normal hematopoietic cells [29]. This observation allowed us to deliver this drug 24 hours before the stem cell infusion without potentially affecting engraftment. We did not observe graft failure or delayed engraftment in the BUMELVEL cohort.

It has been suggested that VEL up-regulates the anti-apoptotic protein MCL-1, and the sequence of administration may be critical to the combination of VEL and MEL 200 [30]. Doses of VEL were escalated from 1.0 mg/m^2 up to 1.6 mg/m^2. The increase in apoptosis on samples obtained from patients who were treated with MEL followed by VEL was superior to the apoptosis observed with VEL preceding MEL [31]. The combination of MEL and VEL has been found to be effective in the relapse setting as well [32,33].

Nishihori et al. [34] completed a phase I/II study of VEL in combination with MEL followed by tandem autologous transplants in primary refractory MM patients. However, with the availability of new potent novel agents, the role of tandem transplantation in patients with MM is in question.

Our novel combination of BUMELVEL delivered an impressive overall response rate of 98%, including at least a VGPR of 70% and a CR rate of 42%. These responses compare favorably with reported responses using single-agent MEL 200 (20% to 40% CR and 40% to

55% CR/VGPR) [15]. The primary endpoint of the study, 1-year PFS, was significantly improved in the BUMELVEL cohort in comparison with single-agent MEL 200 (90% versus 77%, respectively; P =.02). The improvement in PFS was achieved despite a higher proportion of standard-risk patients in the control group in comparison with the BUMELVEL cohort by mSMART criteria and more patients with >1 prior line of therapy pre-AHSCT in the BUMELVEL group. OS was similar between the 2 groups, probably due to the relatively short median duration of follow-up and the multitude of treatment options available in relapsed MM. The main adverse events were manageable and included neutropenic fever, mucositis, and hypophosphatemia. Adverse events did not translate into transplant-related mortality. The incidence of febrile neutropenia (77%) is similar to that reported by Lahuerta using BU and MEL [21]. Among recipients of high-dose chemotherapy in high-risk protocols (eg, BU, cyclophosphamide, etoposide), severe mucositis is reported in excess of 60% to 90% [35]. In our study only 37% and 2% of patients developed grade 3 and grade 4 mucositis, respectively. Thus, collectively, the addition of VEL to BUMEL does not appear to increase adverse events. The lower incidence of adverse events may be due to the use of a targeted dose of BU and the incorporation of palifermin as a mucoprotectant.

Engraftment was prompt and predictable and was not different from historical control subjects with single-agent MEL 200. Moreover, the once-daily dosing of BU allowed us to perform outpatient transplantation using the BUMELVEL regimen.

Our analysis has the limitations of being a case-control retrospective comparison with a registry population. This type of analysis could potentially introduce a selection bias through center effects. However, no center effect has ever been identified in autologous transplant studies for MM in the CIBMTR. The improvement in PFS observed in the BUMELVEL cohort could be related to the targeted BU therapy used in this regimen, the synergism observed in prior studies between MEL and VEL, or both. Randomized prospective clinical trials would probably help in answering these questions.

In conclusion, pharmacokinetic-directed dosing of BU can be safely combined with MEL 140 mg/m^2 and VEL 1.6 mg/m^2 (BUMELVEL) without adding nonhematologic toxicity or transplant-related mortality. This novel regimen delivered high response rates and a better PFS compared with MEL 200 and warrants further study in a prospective randomized clinical trial.

Acknowledgments

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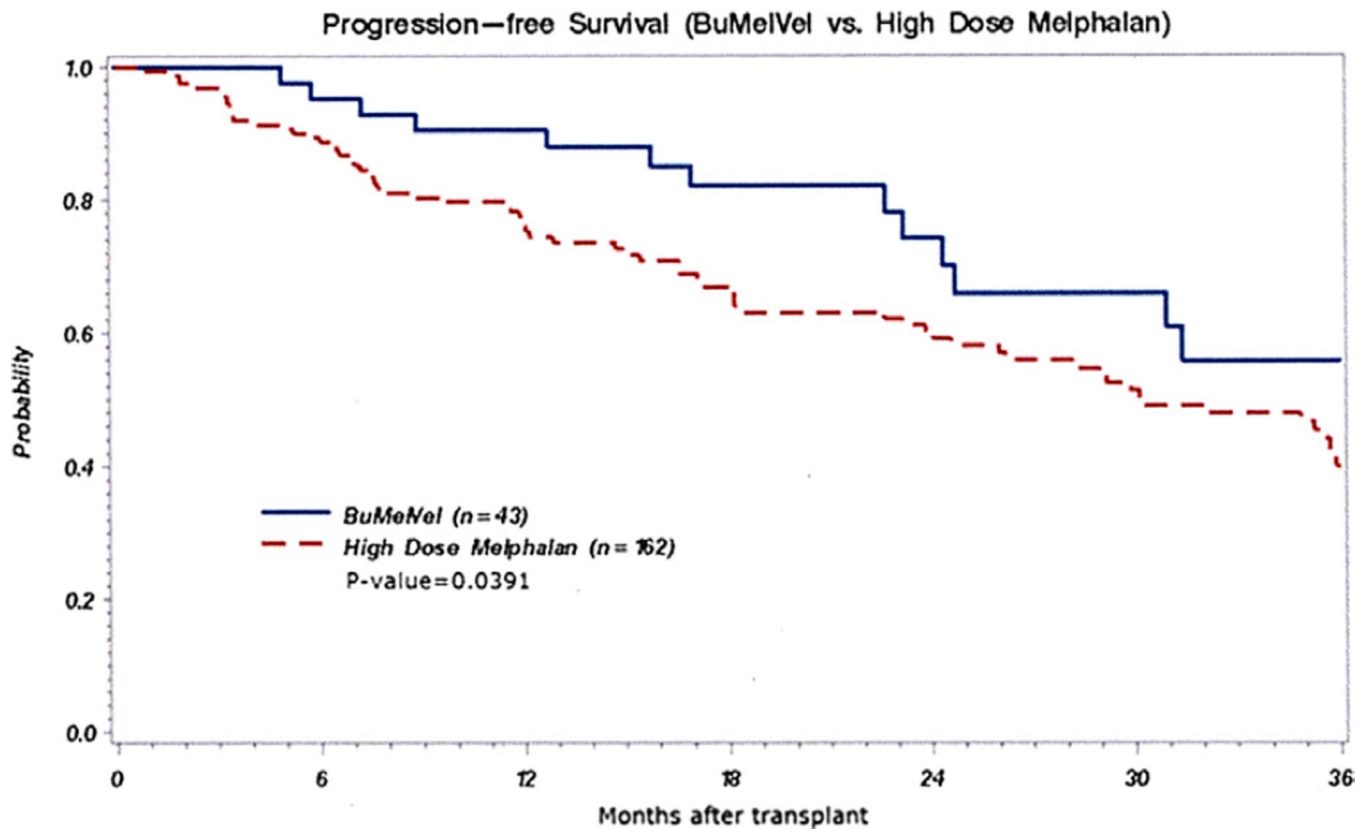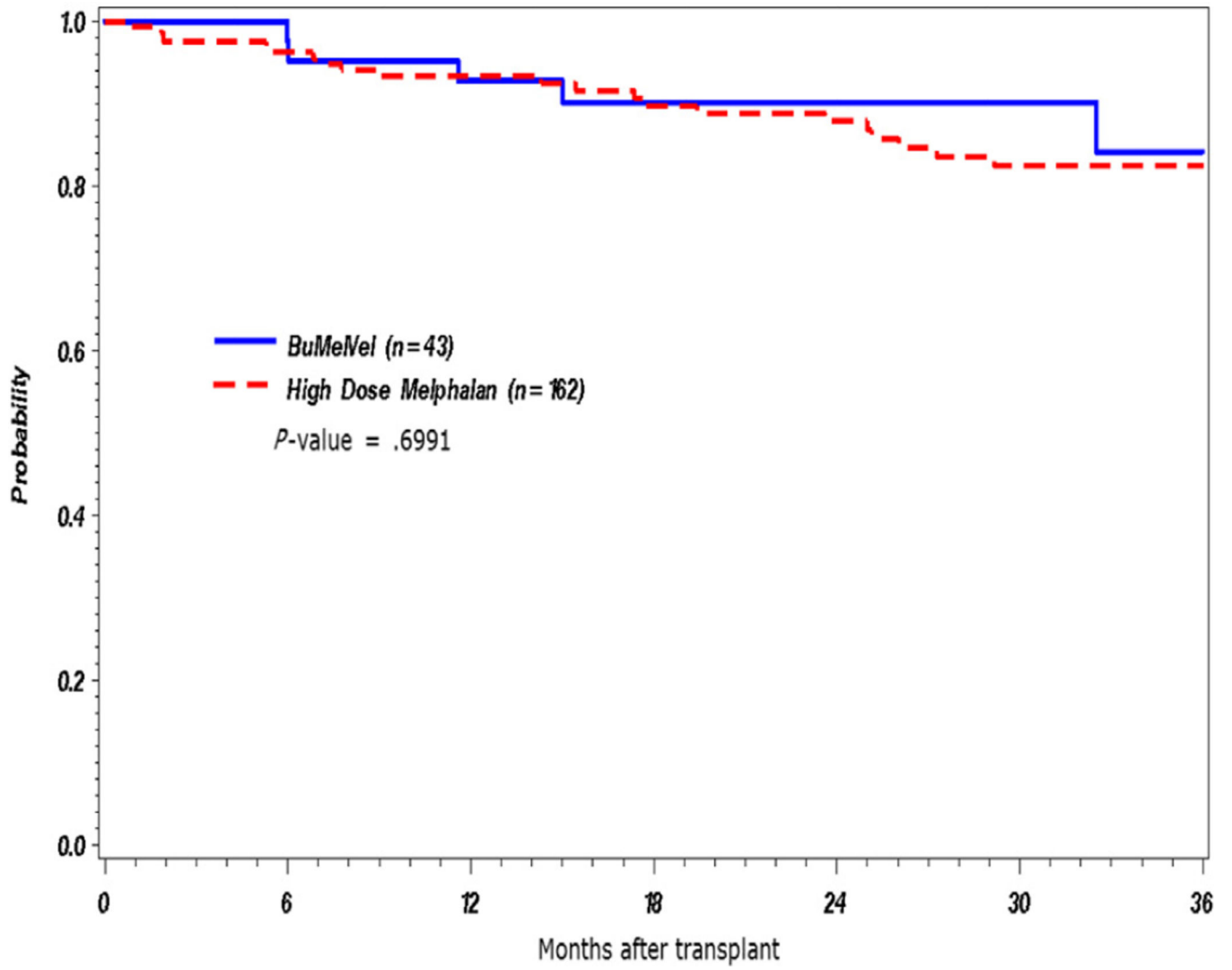
Figure 1.
PFS in BUMELVEL versus high-dose MEL.

Figure 2.
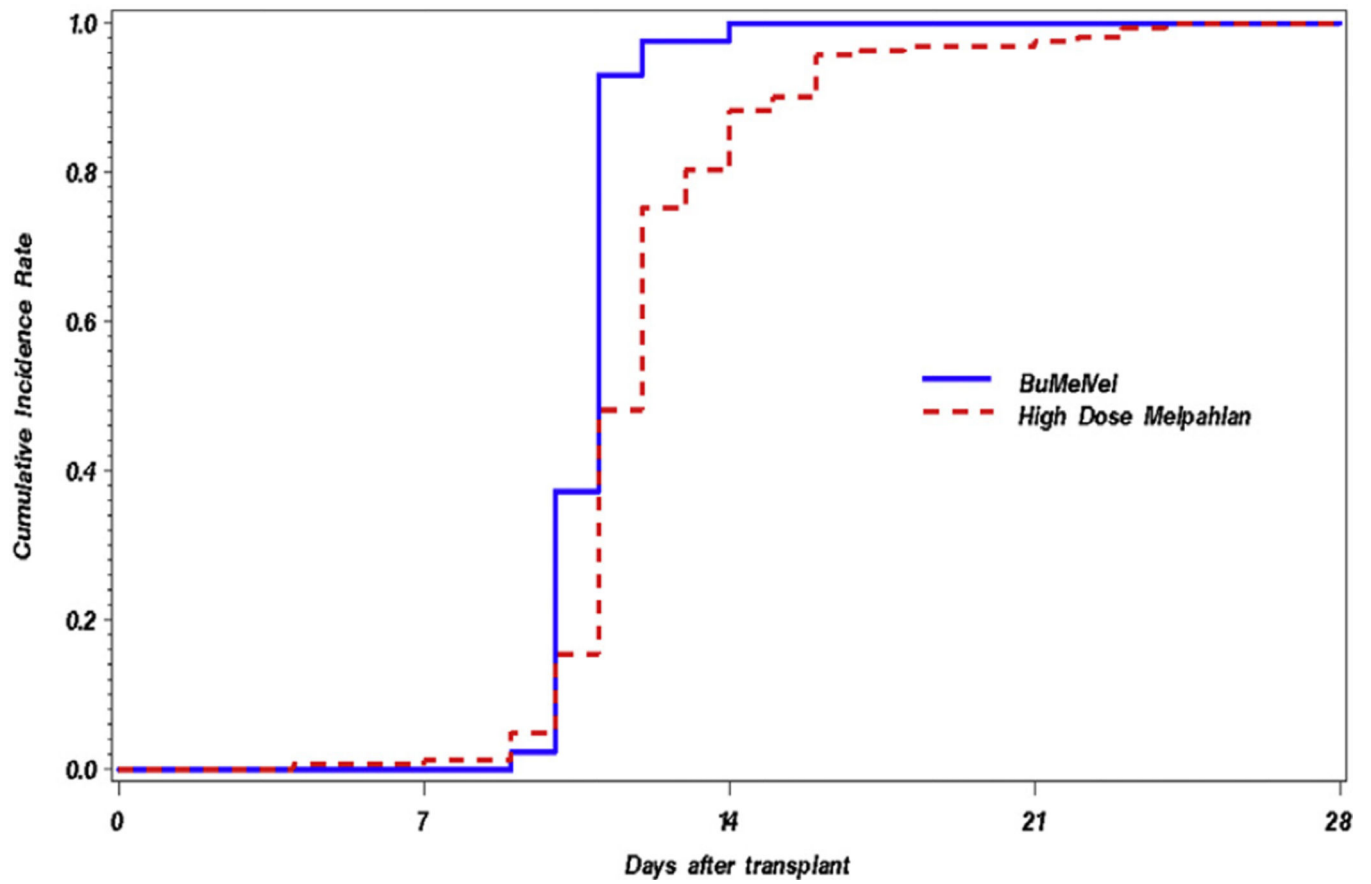OS in BUMELVEL versus high-dose MEL.

Figure 3.
Cumulative incidences of neutrophil engraftment in BUMELVEL versus high-dose MEL.
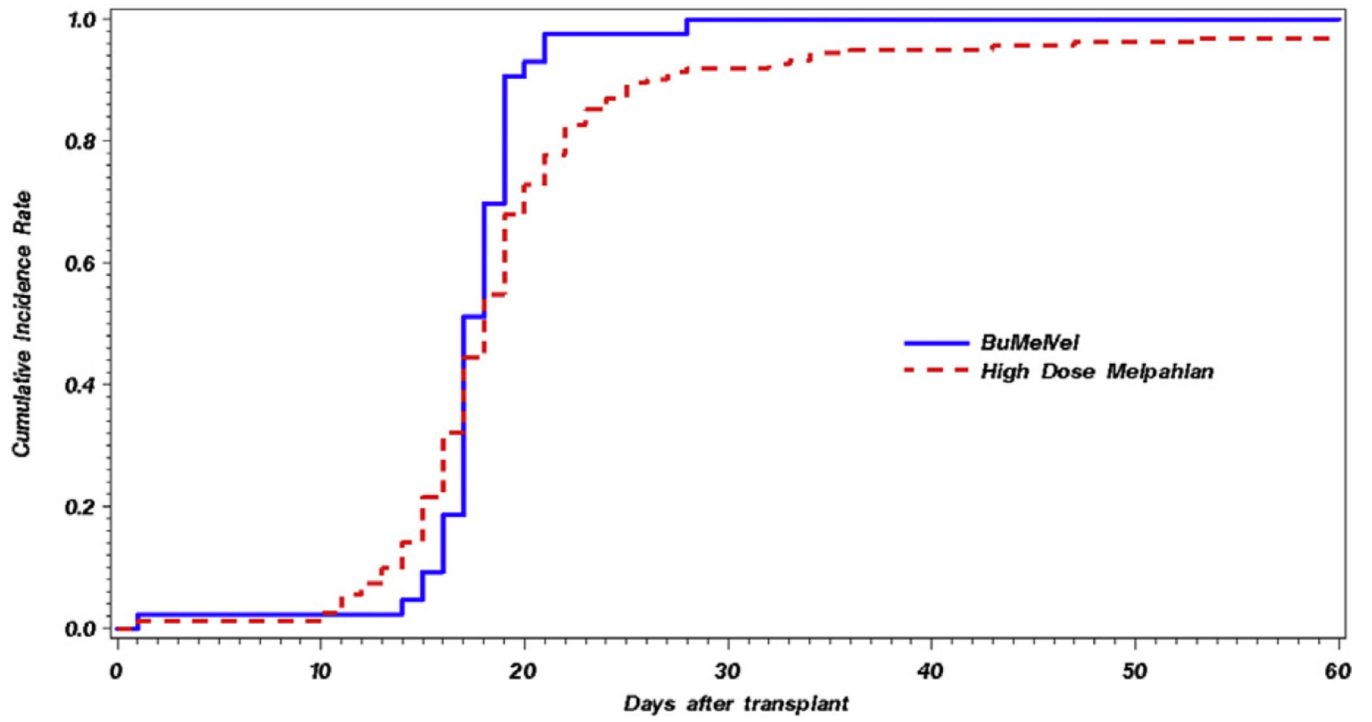
Figure 4.
Cumulative incidences of platelet engraftment in BUMELVEL versus high-dose MEL.

Table 1

Characteristics of Patients Who Underwent Single Autologous Transplant with i.v. BU, MEL Followed by VEL and High-Dose MEL between 2009 and 2012

Characteristics	BUMELVEL	MEL 200	P
Number of patients	43	162	
Number of centers	1	54	
Age at transplant, median (range), yr	62 (46–69)	61 (41–69)	
18–59	9 (21)	56 (35)	.17
60–64	17 (40)	61 (38)	
65–70	17 (40)	45 (28)	
Gender			
Male	24 (56)	91 (56)	.97
Female	19 (44)	71 (44)	
KPS at transplant			
80	11 (26)	40 (25)	1
90–100	32 (74)	122 (75)	
Isotype			
IgG	26 (60)	100 (62)	.86
IgA	8 (19)	32 (20)	
Light chain	7 (16)	27 (17)	
IgD	1 (2)	1 (<1)	
Nonsecretory	1 (2)	2 (1)	
International stage at transplant			
Stage I	16 (37)	51 (31)	.74
Stage II/III	20 (47)	79 (53)	
Unknown	7 (16)	25 (15)	
Mayo risk stratification at diagnosis (mSMART)			
Standard risk	17 (40)	127 (78)	<.0001
High risk	4 (9)	18 (11)	
Unknown	22 (51)	17 (10)	
Number of chemotherapy sessions			
1	20 (47)	108 (67)	.02
>1	23 (53)	54 (33)	
Disease status before AHSCT			
CR	3 (7)	33 (20)	.19
VGPR	15 (35)	43 (27)	
PR	23 (53)	72 (44)	
Stable disease	1 (2)	11 (7)	
Relapse/progression	1 (2)	3 (2)	
Median follow-up of survivors (range), mo	25 (2–50)	35 (3–50)	

Values are number of cases with percents in parentheses, unless otherwise noted.

Table 2

Response Status before and after AHSCT using BUMELVEL Regimen

Response Status	Patients before AHSCT	Patients after AHSCT
CR	3 (7%)	18 (42%)
VGPR	15 (35%)	12 (28%)
PR	23 (53%)	12 (28%)
Less than PR	2 (4%)	1 (2%)

Table 3

BUMELVEL Toxicities per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Toxicities	No. of Cases
Grade 3	
Febrile neutropenia	33 (77%)
Mucositis	16 (37%)
Hypophosphatemia	8 (19%)
Diarrhea	4 (9%)
Nausea	4 (9%)
Hypocalcemia	3 (7%)
Transaminitis	3 (7%)
Hyperglycemia	2 (5%)
Grade 4	
Hypocalcemia	2 (5%)
Mucositis	2 (5%)
Transaminitis	1 (2%)