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

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



## 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

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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 complete remission (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 at a dose of 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 contemporary 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 $\geq 20 \times 10^9$/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−6and −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 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