ASBMT
American Society for Blood and Marrow Transplantation

Chemomobilization with Etoposide is Highly Effective in Patients with Multiple Myeloma and Overcomes the Effects of Age and Prior Therapy

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The optimal mobilization strategy prior to autologous stem cell transplantation for patients with multiple myeloma remains unclear. Mobilization with cytokines alone appears to yield suboptimal results in older patients as well as patients who have received prior lenalidomide. To avoid the marked cytopenias and risks of hemorrhagic cystitis associated with the administration of cyclophosphamide, we investigated the efficacy and safety of chemomobilization with an intermediate dose etoposide (VP-16; 375 mg/m^2 on days +1 and +2) and granulocyte-colony stimulating factor (G-CSF) (5 μg/kg twice daily from day +3 through the final day of collection). We reviewed our institutional experience with 152 myeloma patients mobilized with this regimen. The addition of VP-16 to G-CSF resulted in successful mobilization in 100% of patients, including 143 (94%) who collected successfully in a single day. A total of 99% of patients, including those with prior XRT and/or prior lenalidomide or thalidomide therapy, collected at least 5 × 10^6 cells/kg in 1 or 2 days of apheresis, and the median total number of CD34$^+$ cells collected in the entire population was 12 × 10^6 cells/kg. Collection was predictable, with 61% of patients collecting on day +11, and the rest between days +7 and +13. There were no variables, including age, prior imid exposure, radiation therapy, or total amount of prior therapy that were associated with suboptimal mobilization. Adverse effects of the regimen included supportive transfusions required in 31 (20%) patients, and fevers requiring hospitalization or intravenous antibiotics in 26 (17%) patients. VP-16 and G-CSF appears to be a safe and effective mobilization regimen for patients with multiple myeloma undergoing autologous stem cell transplantation, producing excellent stem cell yield with the majority of patients requiring 1 day of apheresis.

Biol Blood Marrow Transplant 17: 141-146 (2011) © 2011 American Society for Blood and Marrow Transplantation

KEY WORDS: Stem cell mobilization, Myeloma, Etoposide, Lenalidomide, Autologous stem cell transplantation

INTRODUCTION

Despite the development of new and effective agents, autologous stem cell transplantation (ASCT) remains an important therapeutic component of the management of patients with multiple myeloma (MM), and the use of this procedure has continued to increase nationally and internationally [1]. Stem cell mobilization can be accomplished by using cytokine, most commonly granulocyte-colony stimulating factor (G-CSF), alone or in combination with chemotherapy [2,3]. The efficacy of G-CSF alone in certain patient groups is quite good, although there have been several different patient populations identified as difficult to mobilize [4]. "Failure rates" of G-CSF alone have been variably reported between 1% and 40% [5,6]. In a recent, large phase 3 study, only 34% of patients mobilized with G-CSF alone were able to collect 6 × 10^6 CD34$^+$ cells/kg in 2 days of apheresis [7]. Recent data demonstrates the adverse impact of receipt of prior lenalidomide therapy on stem cell mobilization, with the inability to collect >2 × 10^6 CD34$^+$ cells/kg in less than 4 days in 25% to 43% of this patient population when G-CSF alone is used [8,9].

In contrast, mobilization with chemotherapy in addition to cytokine has been previously demonstrated to increase stem cell yields at the time of collection [10-12]. Most of this data has been reported

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Financial disclosure: See Acknowledgments on page 145.

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Received April 23, 2010; accepted June 30, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.06.021

with the use of cyclophosphamide (Cy) in addition to G-CSF, in which stem cell yields and failure rates have been improved in comparison to G-CSF alone. One recent publication suggests that Cy can overcome the effects of prior lenalidomide exposure [13], although other data suggest that the use of Cy may impair stem cell engraftment [14]. Other potential disadvantages of adding chemotherapy to mobilization include increased complications such as cytopenias requiring transfusion support, febrile neutropenia requiring hospitalization, and intravenous antibiotics, and unpredictability regarding the optimal day for stem cell collection [15,16].

Although there are data that support the ability of high-dose etoposide (VP-16) to effectively mobilize progenitor cells [17], there is little to no data available regarding the routine addition of VP-16 to G-CSF in the mobilization of patients with MM. We have chosen to use an intermediate dose of etoposide (375 mg/m^2 per day for 2 days) to preserve progenitor cell mobilization and antitumor properties, while limiting other potential toxicities including myelodysplasia, mucositis, hepatic dysfunction, or prolonged cytopenias associated with higher doses of this or other agents. We now report our institutional experience with the safety and efficacy of this regimen.

METHODS

Patients and Treatment

This analysis included patients between the ages of 27 and 72 who received mobilization with VP-16 and G-CSF prior to ASCT for MM at our institution between 2004 and 2009. The mobilization regimen consisted of placement of a central apheresis catheter followed by outpatient administration of intravenous VP-16 (375 mg/m^2) once daily on days +1 and +2. Patients received ondansetron 24 mg orally and dexamethasone 20 mg orally 30 minutes prior to each VP-16 infusion, as well as prochlorperazine 10 mg every 4 hours for nausea or emesis. Each VP-16 infusion was diluted to a concentration of 0.4 mg/mL and infused over 4 hours, followed by a 20-mL postinfusion saline flush. G-CSF was administered at a dose of 5 μg/kg twice daily starting on days +3 and continuing through the last day of stem cell collection. Antimcrobial prophylaxis was given concurrently using levofloxacin 500 mg orally once daily to all patients starting on day +5. Peripheral blood CD34$^+$ cell counts were checked routinely starting on day +11, except for circumstances in which patients were noted to have normal or high total white blood cell counts prior to day +11. Apheresis was initiated when the peripheral blood CD34$^+$ cell count was ≥7/μL [18], and all patients had stem cells collected between days +7 and +13. Target volumes were calculated based on an algorithm that includes the patient's weight in kilograms, the peripheral precollection CD34$^+$ count, and the requested cell dose (usually a minmum of 5×10^6 CD34$^+$ cells/kg and a target of 8×10^6 CD34$^+$ cells/kg). These were large volume aphereses in approximately one-third of cases. All collections were done using the COBE Spectra machine (CaridianBCT, Lakewood, CO). Platelet transfusions were administered routinely for platelet counts ≤10,000, with higher thresholds used for patients at a higher risk for clinically significant bleeding. ASCT was performed using melphalan (200 mg/m^2, reduced to 140 mg/m^2 for patients with renal dysfunction, age over 65, or other comorbid illness), followed by stem cell infusion the next day.

Statistical Methods

The Kaplan-Meier (or product limit) method was used to estimate the time to event functions of overall survival (OS), time to relapse, and progression-free survival (PFS). Fisher's exact test was used for data categorized into 2 × 2 contingency tables. The nonparametric Jonckheere-Terpstra method was used to test for ordered differences among categories for larger contingency tables. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. For continuous covariates of interest, the median values with its distribution free 95% confidence intervals (CIs) were given. "Poor mobilizers" were defined as those patients who required >2 collections to obtain $>5 \times 10^6$ CD34$^+$ cells/kg. "Poor engrafters" were defined as patients who engrafted either neutrophils or platelets beyond 1 standard deviation from the median times to neutrophil or platelet engraftment for the entire cohort. Univariable logistic regression was used to investigate for a possible association between covariates of interest and either "poor mobilization" or "poor engraftment."

All analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC). This research was approved by the UNC institutional review board.

RESULTS

Patients

Between 2004 and 2009, a total of 152 patients with MM underwent stem cell mobilization and collection with VP-16 and G-CSF followed by ASCT in 151 patients. Among these, 65 (43%) were male and 87 (57%) were female. The median age at the time of transplant was 56 years, with a range of 27 to 72 years. Patients had received a median 5 prior months of antimyeloma treatment (range: 1.5-36 months), with 103 patients (68%) having received 1