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Higher Stem Cell Dose Infusion after Intensive Chemotherapy Does Not Improve Symptom Burden in Older Patients with Multiple Myeloma and Amyloidosis

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Autologous hematopoietic stem cell transplantation (ASCT) for multiple myeloma (MM) is associated with high symptom burden, particularly for older patients and those with amyloid light-chain (AL) amyloidosis. Symptom burden peaks during leukopenia. We hypothesized that higher doses of $CD34^+$ stem cells would be associated with an improved symptom outcome. Patients undergoing ASCT for MM who were ≥60 years old or had AL amyloidosis were randomized to receive either a standard (4 to 6 × 10^6 cells/kg) or high dose (10 to 15 × 10^6 cells/kg) of $CD34^+$ cells after melphalan 200 mg/m^2. Symptom burden was assessed via the MD Anderson Symptom Inventory MM module. Eighty patients were enrolled. Median $CD34^+$ cell doses were 5.1 × 10^6 cells/kg (standard dose) and 10.5 × 10^6 cells/kg (high dose). The most severe symptoms during the first week were fatigue, lack of appetite, drowsiness, disturbed sleep, and pain. The area under the curve for the mean composite severity score of these symptoms was similar between treatment arms ($P = .819$). Median times to neutrophil, lymphocyte, and platelet engraftment were also similar between groups. IL-6 increased similarly for both groups throughout the ASCT course. Infusion of higher autologous stem cell dose after high-dose chemotherapy does not yield a difference in symptom burden or engraftment time in the first few weeks after ASCT.

INTRODUCTION

High-dose chemotherapy and autologous stem cell transplantation (ASCT) have become part of the standard of care for patients with multiple myeloma (MM). However, this process is often associated with a high symptom burden, including lack of appetite, fatigue, weakness, and disturbed sleep [1,2]. The underlying etiology of these symptoms is not completely clear but may be dependent on an ongoing systemic inflammatory response and cytokine flux [3].

We have previously shown that symptom burden during ASCT reaches a peak at the time of WBC nadir [3]. This increased burden has been associated with elevated serum levels of interleukin (IL)-6 as well as other inflammatory markers [4]. Furthermore, prospective analysis from our institution has suggested that older patients (age > 60 years) and those with albumin < 3 g/dL are more likely to have a higher symptom burden during their ASCT course [5].

Because the greatest symptom burden is temporally associated with the WBC nadir, we were interested in the possible beneficial effects of a higher stem cell dose on severity of symptoms during transplantation. Several studies have suggested a dose-response relationship between the number of $CD34^+$ cells and rate of hematological recovery during allogeneic or autologous stem cell transplantation [6,7]. In addition, a higher $CD34^+$ cells dose appears to correlate with rate of engraftment in patients with amyloid

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light-chain (AL) amyloidosis undergoing ASCT [8]. Finally, preliminary data from our institution have suggested that infusion of a higher stem cell dose during ASCT is associated with a lower symptom severity score [9].

On the basis of these findings, we hypothesized that a higher dose of $CD34^+$ stem cells in the autologous rescue graft would be associated with an improved symptom outcome, not only because of potentially shorter time to engraftment, but also through cytokine modulation. In addition, we theorized that this effect would best be elucidated in the setting of a population at higher risk for symptom burden, such as in older patients or those with AL amyloidosis. We, therefore, conducted a single-center, prospective, randomized controlled trial of 2 stem cell doses for MM patients older than 60 years or with AL amyloidosis undergoing ASCT after high-dose melphalan, 200 mg/m^2.

METHODS

Patients and Treatment

Patients were recruited from the Department of Stem Cell Transplantation at The University of Texas MD Anderson Cancer Center. Patients with MM were eligible if they were older than 60 years or had evidence of AL amyloidosis defined by a biopsy showing light-chain amyloid deposition at any site. Patients had to be deemed by their treating physicians as candidates for high-dose melphalan and ASCT and were required to have collected $>10 \times 10^6$ $CD34^+$ cells/kg. Patients who would be unable to complete the symptom inventory questionnaire were excluded.

At the time of enrollment, patients were randomized to receive either a standard dose of stem cells (4 to 6×10^6 $CD34^+$ cells/kg) or a high dose of stem cells (10 to 15×10^6 $CD34^+$ cells/kg). All patients were treated with melphalan 100 mg/m^2 intravenously on day −3 and day −2 and with autologous stem cell rescue (per assigned stem cell dose) on day 0. Standard supportive care measures, including granulocyte colony–stimulating factor and antimicrobial prophylaxis, were administered as per standard departmental practice. Patients were assessed by multiple modalities (detailed below) throughout the ASCT process. The study was approved by the MD Anderson institutional review board and registered at clinicaltrials.gov (NCT00651937). All patients provided written informed consent to participate.

Measurement of Symptom Burden

Treatment-related symptom burden was measured using the MD Anderson Symptom Inventory (MDASI), a validated tool for symptom assessment [10]. Specifically, the MM module (MDASI-MM) was employed for this patient population [11]. The MDASI-MM assesses the 13 core symptoms contained in the basic MDASI, including pain, fatigue, sleep disturbance, and lack of appetite, and 6 items measuring symptom interference with function. In addition, the MDASI-MM assesses 7 additional symptoms commonly associated with MM: bone aches, muscle weakness, sore mouth/throat, rash, difficulty concentrating, constipation, and diarrhea. Symptom severity over the previous 24 hours is rated on a 0 to 10 scale ranging from “not present” to “as bad as you can imagine.” The MDASI-MM was administered at baseline, before treatment with chemotherapy, and then every other day during the first week of the ASCT. Thereafter, the MDASI-MM was administered twice weekly for 2 weeks and then once in the fourth week after ASCT.

Functional Testing

Physical performance was measured by 2 methods: the 6-minute walk test and the sit-to-stand test. For the 6-minute walk test, we measured the distance (in feet) that patients could walk in 6 minutes, with rest periods allowed. In the sit-to-stand test, patients were timed as they stood up from a sitting position and sat back down twice. This cycle was repeated and the average time of the 2 attempts was used. Both of these tests are believed to be complementary to cancer patients’ self-reporting of symptoms [12].

Inflammatory Markers

Serum was isolated from peripheral blood samples collected from patients before they received high-dose melphalan and then on days −2, 0, +3, +5, +7, and then twice weekly after ASCT until 4 weeks. Sera were stored frozen at −80°C. On the day of cytokine assay, serum samples were thawed and subjected to enzyme-linked immunosorbant assay (ELISA; R&D Systems Inc, Minneapolis, MN) to measure levels of IL-6, IL-1 receptor antagonist, macrophage inflammatory protein-1α, TNF-α, IL-1β, soluble TNF receptor I, and soluble TNF receptor II. Results for each of the analytes were reported as pg/mL.

Statistical Analysis

The primary objective of this study was to determine if a higher stem cell dose would result in a lower increase in symptom severity 1 week after ASCT. We defined the 5 most severe symptoms as those that received the highest ratings during the first 7 days of transplantation. A composite symptom score was obtained by averaging those 5 symptom levels. The area under the curve (AUC) for each stem cell group was calculated using the composite scores for these 5 most severe symptoms over time, according to the trapezoidal rule [13]. AUCs were compared between treatment groups using a *t*-test. In addition, mean scores for these symptoms were calculated at each time point and compared between groups. Linear mixed models were applied to estimate the development of the 5 most severe symptoms during the first week and first 28 days after transplantation. Based on our previous experience, we estimated that the severity score in the standard dose group would increase by .85 points more than the increase in the high-dose group. We, thus, enrolled 50 patients per arm to have 80% power to detect this difference.

The other outcome measurements were also compared between the 2 groups. For functional tests, the mean scores for each test (time in seconds for sit-to-stand and feet for 6-minute walk) were compared between treatment groups at each time point. In addition, the mean change from baseline to day 28 was analyzed and compared between groups by linear mixed models. For cytokine analyses, we first normalized the values using natural-based log transformation. Linear mixed models were used to compare means of transformed values between treatment groups over 7 days after ASCT. SAS version 9.3 statistical software (SAS Institute, Cary, NC) was used to perform all analyses. All statistical tests were 2-sided, and P values $< .05$ were considered statistically significant.

RESULTS

Patient Characteristics

Between March 2008 and May 2013, 80 patients were enrolled. On the basis of preliminary data, we had planned to enroll 50 patients per group. Because of funding constraints, we performed an unplanned interim analysis for futility/superiority after 77% of the targeted number of patients had completed assessment. This analysis indicated that the predicted probability of demonstrating a significant difference between treatment groups would be 3% if the trial were to continue to full enrollment. Thus, the trial was halted early with 41 patients in the high-dose group and 39 patients in the standard-dose group.

Patient characteristics are detailed in Table 1. There were no significant differences between the 2 treatment groups with regard to demographic or clinical characteristics. Twenty-two patients had AL amyloidosis. The median $CD34^+$ cell dose was 5.1×10^6 cells/kg in the standard-dose arm and 10.5×10^6 cells/kg in the high-dose arm. Median number of stem cells collected was also similar between the 2 arms (13.80×10^6 cells/kg in the standard-dose arm and 13.93×10^6 cells/kg in the high-dose arm). All patients collected at least 10×10^6 cells/kg as per eligibility criteria. Two patients in the high-dose arm were unable to receive the appropriate dose (in 1 case because of contamination and in another because of physician ordering error). One patient in the standard-dose arm received more than 6×10^6 cells/kg because of cryopreservation of all cells in 1 bag.

Symptom Data

The primary endpoint of the study was symptom burden during the first week after ASCT. Of the 80 patients enrolled on the study, 74 were evaluable for the primary endpoint (Figure 1). The 5 most severe symptoms during the first 7 days after ASCT were fatigue, lack of appetite, drowsiness, disturbed sleep, and pain. During this time, the AUC for the mean composite severity score of these 5 symptoms did not differ between the 2 treatment arms (Figure 2A, $P = .819$).