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Fractionated Stem Cell Infusions for Patients with Plasma Cell Myeloma Undergoing Autologous Hematopoietic Cell Transplantation

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Abstract

We conducted a phase II trial investigating fractionated hematopoietic cell infusions on engraftment kinetics and symptom burden in patients with plasma cell myeloma (PCM) undergoing autologous hematopoietic cell transplant (AHCT). We hypothesized that multiple hematopoietic cell infusions would reduce duration of neutropenia and enhance immune recovery resulting in a better tolerated procedure. Twenty-six patients received high-dose melphalan followed by multiple cell infusions (Days 0, +2, +4, +6) and were compared to PCM patients (N= 77) who received high-dose melphalan and a single infusion (Day 0) (concurrent control group). The primary endpoint was number of days with ANC <500K/mcL. Symptom burden was assessed using the MSK-modified MD Anderson Symptom Inventory. Median duration of neutropenia was similar in study (4 days, range 3-5) and control patients (4 days, range 3-9) ($P = 0.654$). There was no significant difference in the number of red cell or platelet transfusions, days of fever, diarrhea, antibiotics, number of documented infections, or length of admission. Symptom burden surveys showed that AHCT was well-tolerated in both study and control patients. We conclude that fractionated stem cell infusions following high-dose melphalan do not enhance engraftment kinetics or significantly alter patients' clinical course following AHCT in PCM.

Keywords

myeloma; transplant; fractionated; engraftment; symptom burden

Introduction

High-dose chemotherapy followed by autologous hematopoietic cell transplantation (AHCT) is effective therapy and to date has been the standard of care for eligible patients with plasma

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cell myeloma (PCM). Multiple trials have shown superior event free and overall survival with AHCT compared to conventional chemotherapy.[1-3] With the advent of very active novel therapies, the role of AHCT as part of initial therapy is being reevaluated, but available data support its continued use.[4] However, the symptom burden of high-dose chemotherapy and AHCT must be considered. Despite improved outcomes, the obligate period of myelosuppression following transplant is associated with morbidity and a low but real risk of mortality.[5-7] During nadir, patients suffer from the most severe symptoms during their transplant course.[8] More rapid neutrophil recovery is associated with less febrile neutropenia, reduced antimicrobial use, and cost savings.[9] Enhancing immune reconstitution following AHCT has the potential to reduce symptom burden and improve the transplant experience, which would make the application of high-dose chemotherapy more acceptable.

In animal models, fractionated bone marrow stem cell infusions administered over a short period significantly impacts engraftment. Infusing the same total number of stem cells in multiple divided doses, when compared with a single infusion, results in more efficient and reliable engraftment.[10] The exact mechanism for this is unknown, but it is hypothesized that the initial dose “primes” the bone marrow microenvironment for engraftment by creating novel stem cell niches similar to those induced by stem cell mobilization. This allows subsequent infusions to utilize the new niches to more rapidly propagate cell division and speed engraftment.[11] Fractionating peripheral blood stem cell (PBSC) infusions to facilitate earlier hematopoietic recovery and enhance hematopoietic function has been evaluated in patients with breast cancer, but the data have been mixed.[12] This approach has not been studied in patients with PCM.

Based on these data, we designed this phase II clinical trial to determine whether or not a fractionated reinfusion strategy would shorten the duration of cytopenias and improve clinically relevant endpoints after high-dose melphalan in patients with PCM. Of particular interest was whether more rapid engraftment would be associated with reduced symptom burden.

MATERIALS AND METHODS

Patients

Patients ages 18–75 with histologically-confirmed symptomatic PCM that had responded to prior induction or salvage chemotherapy were enrolled from 2011 to 2013. Eligible patients were required to have at least 10 × 10^6 (+/− 0.5 × 10^6) CD34+ cells/kg frozen if AHCT was being performed as part of initial therapy and at least 7×10^6 (+/− 0.5 × 10^6) CD34+ cells/kg if the patient was being treated as part of a salvage (second) transplant strategy. Adequate organ function was required, including serum bilirubin <2.0 mg/dl; AST, ALT and alkaline phosphatase <3 times the upper limit of laboratory normal, creatinine clearance >40 ml/min, LVEF >45% by MUGA or rest ECHO, and diffusion capacity adjusted for hemoglobin >45% as determined by pulmonary function testing. The KPS performance status of all patients was ≥ 70%.

The study was approved by the Memorial Sloan Kettering (MSK) Cancer Center Institutional Review Board, and all participants gave written informed consent. The study is registered at Clinical-Trials.gov ().

Design

Following enrollment, patients in this single-arm study were treated with single agent melphalan 200mg/m2 or 140mg/m2 (if creatinine clearance was <50 and/or age >70 years) on day −2. Following 24 hours of rest, the first dose of CD34+ cells was administered on day 0 (2.5–5×10^6 CD 34+ cells/kg; ±0.5×10^6 CD34+ cells/kg), followed by 3 additional doses of CD34+ cells (1.5–2.5 × 10^6 CD34+ cells/kg; ±0.5×10^6 CD34+ cells/kg) on days +2, +4, and +6. Pegfilgrastim 6 microgram was administered on day +1. All patients were treated at MSK Cancer Center. After each hematopoietic cell infusion we had expected to see peripheral mobilization of the white cells and an increase in peripheral white cells, but did not. Therefore after the first 14 patients were enrolled, the protocol was modified to include granulocyte colony stimulating factor (G-CSF) 5 microgram/kg 12–24 hours after the 2nd, 3rd and 4th hematopoietic cell infusions in addition to Pegfilgrastim.

For comparison, all patients with plasma cell myeloma who underwent high-dose melphalan and AHCT at MSK Cancer Center during the study period (October 10, 2011-July 16, 2013) and received the standard one dose of CD34+ cells on day 0 served as a concurrent control group. All patients in the control group received Pegfilgastrim on day +1 as the standard growth factor support, with the exception of 10 patients who received G-CSF (day +5 through engraftment) rather than Pegfilgrastrim as per a national study on which the patients were enrolled (BMT CTN 0702).

The size (n) of the treatment group and control group were 26 and 77, respectively. Supportive care measures (including antimicrobial prophylaxis, red blood cell and platelet transfusions and treatment for neutropenic fever) were administered as per standard institutional practice.

Patient characteristics (age, sex, prior regimen(s), disease response, mobilization agents, 1st vs 2nd AHCT, number of cells collected/infused) were recorded at baseline. Clinical parameters (infusion reactions, diarrhea volume, infectious complications, days on antimicrobials, transfusions administered, and hospital days) were collected during the study. Neutrophil and lymphocyte engraftment were defined as absolute neutrophil count (ANC) and an absolute lymphocyte count (ALC) >500K/mcL x 10^6/L for 2 consecutive days. Platelet engraftment was defined as a platelet count ≥30 × 10^6/L (not transfused) for 1 day.

The MD Anderson Symptom Inventory (MDASI) assesses the severity of 13 common cancer-related symptoms (pain, fatigue, nausea, vomiting, dry mouth, shortness of breath, lack of appetite, numbness, difficulty remembering, drowsiness, disturbed sleep, sadness and distress) and 6 items related to symptom interference with functioning.[13] For this study, we used the Memorial Sloan Kettering modified MDASI (MSK-modified MDASI), which contains the 19 MDASI items plus 12 items relevant to patients with multiple myeloma undergoing AHCT (problems with taste, chills, mouth/throat sores, abdominal bloating,

constipation, diarrhea, urinary frequency, incontinence, dizziness, muscle aches, headache, skin problems) selected from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Patients rated symptom severity over the previous 24 hours/week/month ranging from “not present” to “as bad as you can imagine.” For the treatment group, MSK-modified MDASI assessments were conducted daily on days −2 through engraftment and then on days +30, +60, and +90 following AHCT. In contrast, the patients in the control group underwent MSK-modified MDASI assessment on days −2 (baseline), +6 (nadir), +11 (engraftment), +30, +60, +90 as part of routine care.

Endpoints

The primary endpoint was to determine engraftment kinetics as measured by the duration of neutropenia, defined as the total number of days with ANC <500K/mcL. The days to neutrophil (ANC > 500 × 10^6/L x 2 days) and platelet (>30 × 10^9/L x 1 day) recovery were assessed as secondary objectives. Other secondary endpoints included the days to lymphocyte (ALC >500 × 10^6/Lx 2 days) recovery, incidence of grade 3 and 4 non-hematologic toxicity, febrile neutropenia and documented infections, the number of red blood cell and platelet transfusions, and length of hospital admission. Response rates were evaluated based on International Myeloma Working Group Uniform Response Criteria at 3 months following AHCT. Symptom burden using the MSK Modified MDASI was summarized using descriptive statistics.

Statistical methods

The pilot study was designed to evaluate whether the average number of days with ANC < 500 decreases to 4.8 days from a historical average in a heterogenous AHCT population of 6.4 days with a standard deviation 2.5. With a total of 26 patients accruing, this provided 90% power to detect this mean decrease from the historical benchmark at alpha level 0.05. In addition to the primary endpoint, there were safety stopping rules for cardiovascular infusion reaction and engraftment syndrome.

Clinical and immune parameters for pilot study patients were compared to the concurrently accrued control patients using the Wilcoxon rank-sum test. In symptom burden survey, change from baseline was calculated as absolute difference for overall health state (score 0–100) and other symptoms (scale 0–10) at 6, 11, and 30 days. The Wilcoxon rank-sum tests were used to compare these changes in study patients and control patients. The area under the curve (AUC) of all symptoms were estimated under linear trapezoidal rule and compared between the two groups using a permutation sign test, where the AUC was calculated up to the minimum follow-up time for every pair of patients to account for informative dropouts. All analyses were performed using the R statistical platform.

RESULTS

Patient characteristics

Twenty-six patients were enrolled and underwent AHCT on the clinical trial. During the same period, 77 patients received high-dose melphalan and AHCT for a diagnosis of plasma cell myeloma, but did not receive fractionated hematopoietic cell infusions (N= 57 off

protocol, N= 20 on alternate study). Table I presents the demographic and clinical characteristics of the study patients and control population. All patients in both groups received lenalidomide, bortezomib or both in addition to corticosteroids prior to AHCT; 7 patients in the control group and 1 patient in the study population received a prior transplant. The majority of patients in both groups had hematopoietic cells mobilized with plerixafor and GCSF (N= 19 study patients, N= 43 control patients). The number of hematopoietic cells collected was similar in both groups (Table II).

Clinical course

Results are shown in Table II. Median number of hematopoietic cells infused was 8.9 × 10^6 CD34+ cells/kg in the study patients compared to 5.02 × 10^6 CD34+ cells/kg in the standard, control group ($P < 0.001$). Despite a higher cell dose, the median duration of neutropenia (days of ANC < 500 K/mcL) (both 4 days, $P = 0.654$) and lymphopenia (days of ALC < 500 K/mcL) (14 and 15 days, $P = 0.361$) were similar in the study and control patients, respectively. Time to neutrophil ($P = 0.475$), lymphocyte ($P = 0.363$) and platelet engraftment ($P = 0.045$) also did not differ. When the ten patients in the control arm who received G-CSF starting at day +5 (and not pegfilgrastim on day +1) were excluded from the analysis, outcomes were also similar (data not shown). Clinical characteristics were similar between the study patients who received pegfilgrastim only (N= 14) and study patients who received pegfilgrastim plus G-CSF (N= 12), except patients on pegfilgrastim only had fewer hospitalization days than the others (median (range): 15 (13–19) vs 17 (14–25), $P = 0.036$).

There was no significant difference in the median number of red cell (0 in both groups, $P = 0.329$) or platelet (2 in both, $P = 0.358$) transfusions required by each group. Total days of fever, diarrhea, empiric antibiotic use and number of documented infections were also similar. The length of hospital stay did not differ between patients who received fractionated cells (16 days) and those who received a single infusion (17 days) ($P = 0.157$). Although patients in the study group received a greater number of hematopoietic cells and more infusions, there was no significant difference in the proportion of patients who experienced infusion reactions (0 versus 4, $P = 0.570$) or engraftment syndrome (3 versus 5, $P = 0.413$).

Hematologic response was assessed at day + 90 following AHCT. Of the 26 patients in the treatment group, 7 patients (26.92%) achieved CR, 12 (46.16%) VGPR, and 7 (26.92%) PR for overall hematologic response rate of 100%. In the control population hematologic responses included 35/77 CR, 15/77 VGPR, 20/77 PR; 5 patients had SD and 2 relapsed. There were no deaths in the first 90 days in either group.

Symptom burden

Results from selected daily symptom burden surveys on study and control patients are summarized in the supplementary material. Of note, overall patient reported symptom scores were low and relatively constant with no significant change in the median value for any one symptom from day −2 to engraftment. This included the patient's view of their "overall health state" (Supplemental Figure I). Symptom scores in patients treated with a single stem cell infusion followed a similar trend (Supplemental Figure II) and there were no significant differences between the study and control groups when examined by area under the curve

with the exception that dry mouth was slightly better in study patients (Supplemental Table I). The overall health status decreased more in study patients than in control patients at day 11 and day 30 (Supplemental Table II) although AUCs were not different overall.

DISCUSSION

This study was designed to evaluate the benefit of fractionated hematopoietic cell infusions following high-dose therapy on engraftment kinetics and symptom burden in patients with plasma cell myeloma. In our study, there was no significant difference in the duration of neutropenia or clinical course between patients who received multiple hematopoietic cell infusions when compared to patients who received a single infusion. This is despite a significantly higher number of CD34+ cells/kg infused in patients who received multiple cell doses which has been associated with more rapid neutrophil and platelet engraftment in retrospective series' but not more recently when evaluated prospectively.[14-16]

Increased toxicities, specifically DMSO-related adverse effects and engraftment syndrome, are potential complications of administering multiple hematopoietic cell infusions. We did not observe a higher incidence of either condition in our study. This is consistent with a previous report showing multiple peripheral blood progenitor infusions to be safe and not associated with increased risk of toxicity as compared to a single infusion.[12]

Duration of neutropenia is highly associated with increased symptom burden and decreased quality of life.[17] Symptom severity typically peaks at nadir and is associated with functional compromise. Fractionated hematopoietic cell infusions did not significantly alter patient-reported symptom scores in our study. Although this was initially thought due to patient selection, a similar trend was noted in all patients who were transplanted for a diagnosis of PCM during the study period indicating that high-dose melphalan and AHCT is well-tolerated in PCM. This is supported by the finding that the median number of days with fever and diarrhea is zero for both parameters in both the study and control groups. Patients who are hesitant to undergo high-dose chemotherapy and should be reassured by these data that should be used as evidence that physicians should refer eligible patients for transplant rather than opting for less aggressive and possibly less effective treatment strategies.

While no significant differences were seen with respect to clinical course, engraftment kinetics or symptom burden scores between PCM patients who received fractionated infusions or a single infusion, this study has several limitations. First, the patients were not prospectively randomized and therefore subtle differences in patient characteristics may have implications on our power to detect a small difference between the groups. There were also more patients with relapsed disease and prior transplants in the control group although increased prior therapy would be expected to bias the results in favor of the study group. Second, while the symptom burden surveys were completed in both the control and study groups, they were administered daily to patients enrolled on the study and only at 3 selected time points in the control population due to limited resources. It is therefore possible that we did not capture the most severe symptoms in the control patients. Nevertheless, we believe the results of the daily surveys in the study group can be more broadly applied as there were

no significant differences in the engraftment kinetics or clinical course in either group, suggesting all patients had similar experiences.

We conclude that fractionated infusions provide no additional benefit in the setting of AHCT for plasma cell myeloma. Regardless, despite high-dose chemotherapy and a period of neutropenia, our data suggest the standard AHCT procedure is well-tolerated with minimal patient symptom burden and should be encouraged in eligible patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

Patient characteristics

	Study Patients (N = 26)	**Control Patients (N = 77)**
Patient characteristics		
Age , Median (range)	60 (38 – 73)	59 (29 – 74)
Gender		
Male, N (%)	18 (69)	52 (68)
Female, N (%)	8 (31)	25 (32)
First AHCT, N (%)	25 (96)	70 (91)
Prior lines of therapy, not including induction, N (range)	0 (0-2)	0 (0-5)
Hematologic response pre AHCT		
CR, N (%)	4/26	17/77
PR, N (%)	21/26	52/77
< PR, N (%)	1	8/77
Mobilization method		
Plerixafor & GCSF, N (%)	19 (73)	43 (56)
Chemo-mobilization, N (%)	7 (27)	34 (44)

Table II:

Clinical and immune parameters in study and control patients

	Study Patients (N=26)	Control Patients(N=77)	
	Median (Range)	**Median (Range)**	***P* value**
Cells Collected (10×10^6)	11.8 (9.9 – 37.1)	11.4 (2.0 – 34.5)	0.059
Cells Infused (10×10^6)	8.9 (7.0 - 14.0)	5.0 (1.5 - 9.3)	<.001
Days ANC <500	4 (3 - 5)	4 (3 - 9)	0.654
Days Abs Lymph <500	15 (12 - 32)	15 (5 - 68)	0.361
ANC Engraftment Day	10 (9 - 11)	9 (8 - 14)	0.475
Abs Lymph Engraftment Day	14 (11 - 31)	14 (9 - 66)	0.363
PLT Engraftment Day	14 (10 - 20)	13 (0 - 27)	0.045
Days Hospitalized	16 (13 - 25)	17 (0 - 43)	0.157
Days on Abx	3 (0 - 14)	4 (0 - 28)	0.319
RBC Transfusions	0 (0 - 3)	0 (0 - 10)	0.329
PLT Transfusions	2 (0 - 4)	2 (0 - 12)	0.358
Days of Fever >=38	0 (0 - 7)	0 (0 - 10)	0.468
Days Diarrhea >= 500cc	0 (0 - 7)	0 (0 - 6)	0.941
Engraftment syndrome (%)	3 (12%)	5 (6%)	0.413
Infusion rx (%)	0 (0%)	4 (5%)	0.570