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A Prospective Randomized Trial Examining Low - or Intermediate-Dose Cyclophosphamide for Stem Cell Mobilization in Multiple Myeloma Patients

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Abstract

We performed a randomized mobilization trial comparing intermediate-dose (3000 mg/m^2) with lower-dose cyclophosphamide (1500 mg/m^2) to determine if the lower dose would yield a similar number of CD34+ progenitor cells with fewer toxicities. Nineteen patients were randomized to receive the lower dose, while twenty-one patients received the higher dose. All patients in the lower dose arm mobilized cells, but one patient receiving the higher dose failed to mobilize. There was no difference between the two groups when comparing the number of CD34+ cells collected per patient (7.2 x 10^8 in the low dose arm versus 10.5 x 10^8 in the higher dose arm; p = 0.6) or the number of CD34+ cells/kg collected (8.2 x 10^6 in the low dose arm versus 13.9 x 10^6 in the higher dose arm; p = 0.12). One day cell collection occurred in 89% of patients in the lower dose cohort, and in 71% of patients in the higher dose cohort. Life-threatening toxicities occurred only in the higher dose arm (n= 5 patients). Engraftment following transplant was similar between the two groups. These results demonstrate non-inferiority and similar clinical efficacy of the lower dose cyclophosphamide in mobilizing progenitor cells in myeloma patients. (Clinicaltrials.gov: NCT02139280).

Keywords: Myeloma; Cyclophosphamide; Mobilization; Randomized; Transplantation

Introduction

The optimal method to mobilize autologous hematopoietic stem cells in patients with multiple myeloma is unknown. In the majority of myeloma patients, growth factors, with or without plerixafor (Sanofi Company, Bridgewater, NJ), are used. In a small subset of high-risk myeloma patients, a combination of growth factor and cyclophosphamide may be utilized, in an attempt to further treat the patient and mobilize stem cells. Advantages and disadvantages exist for each mobilization regimen. Growth factors alone provide a predictable mobilization schedule and fewer side effects, but may yield a lower cell collection when compared with the combination of chemotherapy and growth factors. The combination of chemotherapy and growth factors provides an unpredictable schedule but tends to yield more cells, in the setting of increased toxicities, including a 12-15% chance of hospitalization due to toxicities [1,2]. Growth factors with plerixafor often results in successful mobilization, but some clinicians are concerned about the cost of the plerixafor [3]. The optimal method for mobilizing autologous hematopoietic stem cells is crucial for these patients since myeloma patients will be receiving treatment chronically and, generally, there is only one opportunity to collect cells. The optimal mobilization treatment should provide the maximal number of stem cells with minimal amount of patient side effects and toxicity.

No prospective randomized trials have evaluated the optimal dose of cyclophosphamide to mobilize autologous stem cells [4-6]. Retrospective analyses have examined the doses of cyclophosphamide, ranging from 1.5 grams/m^2 to 7 grams/m^2 [4,5,7-11]. Historically, higher doses of cyclophosphamide (5 grams/m^2 to 7 grams/m^2) were used in the early 2000's [12]. With these higher doses of cyclophosphamide, there is an increased incidence of toxicities, but a larger number of cells are generally mobilized and collected. Weighing these two conflicting issues, over the past few years, transplant centers have been administering lower doses of cyclophosphamide for mobilization, in an attempt to achieve maximal cell yield with fewer side effects [13-15]. Many centers are now using 3000 mg/m2 for mobilization.

Since growth factors with cyclophosphamide is still occasionally used for mobilization, we wanted to identify an appropriate chemotherapy dose that would provide adequate cell yield with fewer toxicities. We designed a prospective randomized trial examining intermediate-dose (3000 mg/m^2) compared with lower-dose cyclophosphamide (1500 mg/m^2), in combination with filgrastim (rhG-CSF, Amgen, Thousand Oaks, California).

Methods

Patient Population

Newly diagnosed multiple myeloma patients between the ages of 18 and 75 years with treatment-sensitive disease were eligible for the trial. The Revised Multiple Myeloma International Staging System (R-ISS) was used for staging patients. The protocol did not dictate the treatment regimen prior to transplant but patients were required to have received a minimum of 4 cycles of treatment. Prior to mobilization, the response to treatment was evaluated using the International Myeloma Working Group (IMWG) definitions [16,17]. Standard transplant eligibility criteria were used to determine if a patient was a transplant candidate, including an ECOG performance status of 0 - 2, a DLCO > 40% of predicted, a left ventricular ejection fraction > 35%, a bilirubin level less than twice the upper limit of normal and transaminases less than three times normal. There could be no active or uncontrollable infection, no evidence of active hepatitis B or C and no evidence of a malignancy that would limit the patient's survival to less than two years. Patients were excluded if a significant co-morbid medical or psychiatric illness existed that would compromise the patient's clinical care or chances of survival. Each patient signed an IRB-approved informed consent and the trial was listed on Clinical Trial.gov (NCT02139280).

This was required to be the patient's first attempt at mobilization. The mobilization procedure was initiated 4 weeks or more after stopping immunomodulatory therapies (IMiDs) and 8 weeks or more after completing radiation therapy. Prior treatments and the duration of IMiDs therapies were recorded for each patient.

Trial Design and Treatment

Consecutive transplant-eligible myeloma patients were accrued. Patients were stratified based on risk factors

that affect stem cell mobilization including age (< or > 60 years), history of prior radiation (yes or no), number of prior regimens (< or > 2 prior treatments), duration of IMiD therapy (< or > 4 months) and platelet count at the time of mobilization (< or > 100,000/mcl) [1,5,18]. Once stratified, the patients were randomized by computer to receive either 1500 mg/m^2 or 3000 mg/m^2, based on actual body weight.

Cyclophosphamide was administered intravenously in a non-blinded fashion, as an outpatient over one hour. Patients received intravenous mesna (600 mg/m^2), fifteen minutes prior to cyclophosphamide and at four and eight hours afterwards. Oral mesna could be substituted for the two post-cyclophosphamide doses. Oral mesna doses (1200 mg/m^2) were administered at two and six hours after the start of cyclophosphamide.

Forty-eight hours after receiving cyclophosphamide, filgrastim was initiated as a daily subcutaneous injection until completion of collection. National Marrow Donor Program (NMDP) guidelines were used for dosing filgrastim, based on patient's weight [19]. Complete blood counts (CBC) were monitored three times a week.

Following cyclophosphamide administration and after the patient's absolute neutrophil count dropped to < 500 cells/mcl, prophylactic fluconazole (400 mg/day), acyclovir (800 mg twice a day) and levofloxacin (750 mg/day) were started and continued until completion of cell collection.

Leukapheresis Procedure

We previously demonstrated that the time to collection of autologous hematopoietic stem cells was ten to twelve days following cyclophosphamide and daily filgrastim [20]. Peripheral blood CD34+ cell numbers were examined beginning ten days after cyclophosphamide administration. Leukapheresis began once the blood CD34+ number reached 10 cells/mcl. Patients received consecutive days of leukapheresis, with the goal of collecting > 5 x 10^6 CD34+-cells/kg.

The collection process, concentration and storage of PBSC were similar for all patients. Briefly, a 4-blood volume leukapheresis PBSC collection was performed daily using a COBE Spectra cell separator (COBE BCT, Lakewood, CO). Collected cells were concentrated and cryopreserved. Cells were frozen in Cryocyte freezing bags (Nexell Therapeutics Inc.) in a controlled rate freezer (Custom BioGenic Systems, Shelby Township, MI). At the conclusion of this freezing, the cells were transferred to the vapor phase of a monitored liquid nitrogen freezer (CryoPlus III, Forma Scientific, Marietta, OH) at a temperature of –120 ^{0}C or below.

Evaluation of Toxicities

Toxicities were evaluated and graded using NCI Common Toxicity Criteria (CTCAE 5.0). Patients were monitored for toxicities and reported on a case report form during the mobilization process until completion of collection of stem cells. Monitoring terminated on the last day of collection; however, any life-threatening events possibly linked to the study within two weeks following mobilization or collection were reported.

In addition, any adverse reaction deemed related to the treatment that required medical intervention, either by requiring an office visit or treatment (ranging from medication administration, hydration or transfusion) were noted. In particular, each patient was monitored for the need of transfusions of red blood cells or platelets, hospitalization and the incidence of febrile neutropenia.

Trial Endpoints

The primary endpoint of this clinical trial was to determine if a lower dose of cyclophosphamide combined with filgrastim could mobilize a similar number of CD34+ progenitor cells, with less toxicity. Secondary endpoints included the post-transplant engraftment of neutrophils and platelets.

The failure to mobilize cells was defined by two criteria: if < 1 x 10^6 CD34 + cells/kg were obtained after two days of collection, and secondly, if a patient's peripheral blood CD34+ cell number remained less than 10 cells/mcl for two consecutive days.

Post-transplant engraftment was identified for each patient. Standard definitions of engraftment were used, defined as an absolute neutrophil count (ANC) of > 500/mm^3 for three days (defined as first day) and a platelet

count of 20,000/mm^3 (un-transfused for 7 days).

Statistical Analyses

The trial was designed as a non-inferiority trial by the investigators and biostatistician (JG). A non-inferiority trial was selected since the number of patients required to define superiority would require a large multi-institutional trial to meet accrual goals and to define a statistically significant result. Data were collected by transplant research nurses and the transplant data management team. Data analyses were performed by a biostatistician (JG). We examined if the lower dose of cyclophosphamide would mobilize a similar number of cells with fewer toxicities. Based on this assessment, approximately forty patients would need to be treated. With approximately twenty patients in each arm, there would be an 80% power to detect non-inferiority using a one-sided, two-sample t-test. If the difference between the average number of apheresis required to collect cells for lower dose arm and higher dose arm is no greater than 0.5. The true difference between the means was assumed to be 0. The significance level (alpha) of the test was 0.025 and standard deviations were 0.55 for both arms.

Results

Patient Demographics

Of the forty-three patients that signed an informed consent, three patients were excluded due to co--morbidities that excluded transplantation (Figure 1).

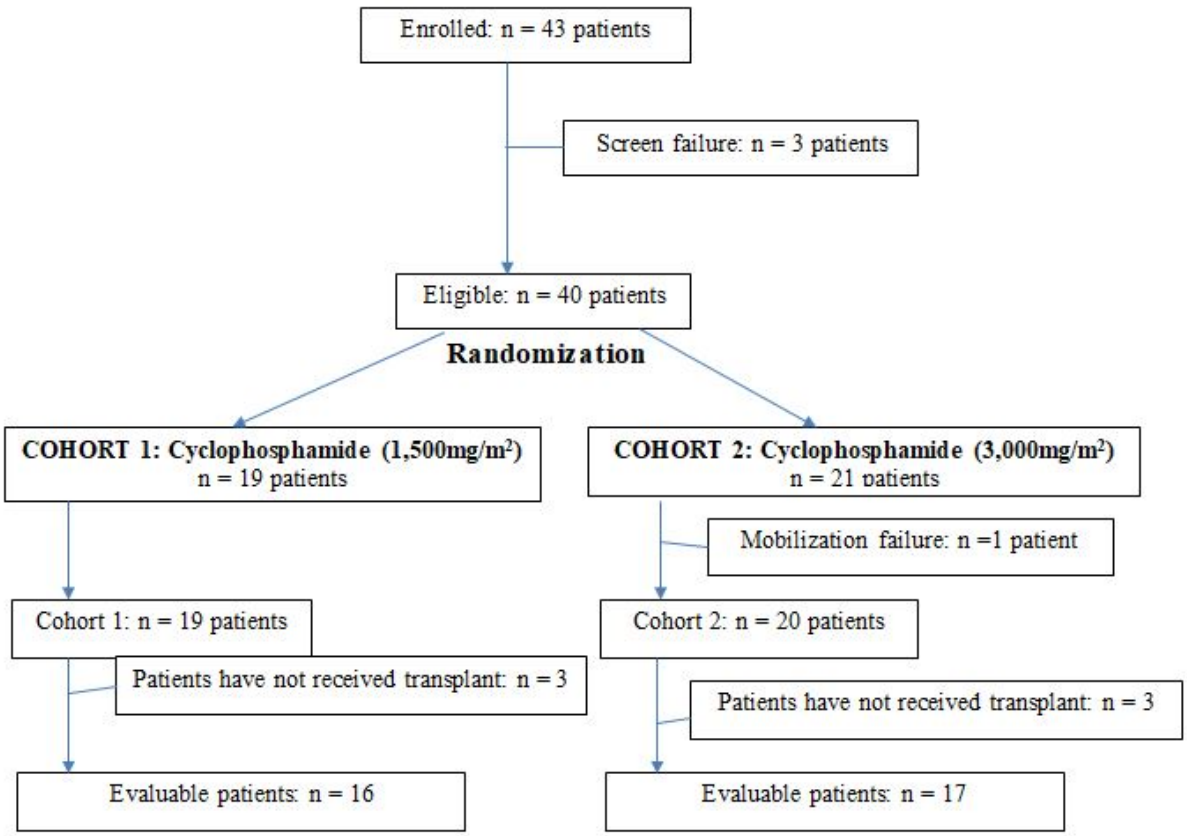

Figure 1: Patient Accrual

Nineteen patients received cyclophosphamide at 1500 mg/m^2 (lower dose are) and twenty-one patients received 3000 mg/m^2 (higher dose arm). Of the nineteen patients in the lower dose arm, sixteen patients have received a transplant and three patients await transplantation. Within the higher dose arm, twenty-one patients attempted mobilization but one patient failed to mobilize. Of the remaining twenty patients, seventeen patients have received a transplant, while three patients await transplantation.

There were no statistically significant differences

between the two groups. Both groups were similarly matched for age, sub-type of myeloma, stage of disease, number of prior therapies, the duration of IMiD therapy, the response to therapy, history of prior radiation and platelet counts at the time of mobilization (Table 1).

Table 1: Patient Demographics

PATIENT CHARACTERISTICS	Group 1 Cyclophosphamide 1500 mg/m2 n = 19 patients	Group 2 Cyclophosphamide 3000 mg/m2 n = 21 patients
Age (median; range)	59 years (37-74)	60.5 years (51-74)
Gender (male: female; n (%)	14 (74%): 5 (26%)	10 (48%): 11 (52%)
Myeloma isotype, n (%)		
IgA	4 (21%)	6 (29%)
IgG	12 (63%)	10 (48%)
Light chain	3 (16%)	5 (24%)
Number of prior therapies *(median; range)*	2 (1-3)	2 (1-3)
Therapies (n = number of patients who received that regimen) Lenalidomide, bortezomib/ dexamethasone	15	19
Bortezomib/ dexamethasone	5	5
Cyclophosphamide/bortezomib/dexamethasone	2	3
Lenalidomide/Dexamethasone	3	2
Pulse dexamethasone	2	1
Carfilzomib-based regimen	2	2
Lenalidomide alone	0	1
VD-PACE	0	1
IMiD therapy duration >4 months	12	18
< 4 months	7	3
Duration of IMiD therapies (*median; range*)	4 months (0 – 8)	4 months (3 – 15)
Disease stage at presentation (n, %)		
I	5 (26%)	7 (34%)
II	4 (21%)	3 (14%)
III	8 (42%)NA; 2 (10%)	10 (48%)NA; 1 (5%)
Response at time of mobilization (n, %)		
CR	7 (37%)	6 (29%)
VGPR	6 (32%)	8 (38%)
PR	6 (32%)	7 (34%)

Prior radiation (n, %)	6 (32%)	4 (19%)
Platelet count at mobilization(Platelets/mcl; median)	239,000	234,500

*There were no statistically significant differences between the two cohorts.

Legend: CR – complete response; VGPR-very good partial response; PR – partial response; NA = not available; IMiDs = Immunomodulatory imide drugs (lenalidomide, pomalidomide)

When comparing each value in cohort 1 to cohort 2, each p value was non-significant.

VD-PACE = bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide

Table 2: Summary of Progenitor Cell Collection

VARIABLE	Group 1 Cyclophosphamide 1500 mg/m2 n = 19 patients	Group 2 Cyclophosphamide 3000 mg/m2 n = 20 patients**	P value
Total number of CD34+ cells (10^8) (*median, range*)	7.2 (2.2-49.9)	10.5 (1.9 – 29.4)	0.6
Number CD34+ cells/kg (10^6) (*median, range*)	8.2 (3.8 – 45.5)	13.9 (4.3 -36.7)	0.12
Total number of MNC (10^{10}) (*median, range*)	5.2 (2.9 – 20.7)	3.8 (1.9 – 7.1)	0.03
Number MNC/kg (10^8) (*median, range*)	3.8 (1.3 – 7.7)	4.6 (2.8 – 14.8)	0.23
Starting Day of apheresis collection following cyclophosphamide (*median, range*)	10 (9 - 12)	10.5 (10 - 14)	
Number of apheresiscollections required			
One	17 (89%)	14 (70%)	
Two	1 (5%)	5 (25%)	
Three	1 (5%)	1 (5%)	

Legend: MNC = mononuclear cells; **One patient failed to mobilize in Cohort 2

Comparison of Collected Progenitor Cells (Table 2)

Number of Collected CD34+ Cells

When comparing the total number of CD34+ cells collected and the number of CD34+ cells/kg collected, there was a slight difference between the two groups, but neither reached statistical significance. The median number of CD34+ cells collected in the lower dose arm was 7.2 x 10^8 CD34+ cells (range: 2.2 – 49.9) compared with 10.5 x 10^8 CD34+ cells collected in higher dose arm (range: 1.9 -29.4; p = 0.6). A median number of 8.2 x 10^6 CD34+ cells/kg per patient were collected in lower dose arm (range: 3.8 - 45.5) and 13.9 x 10^8 CD34+ cells/kg per patient were collected in higher dose arm (4.3 -36.7; p = 0.12).

Number of Collected Mononuclear Cells

There was a statistically significant difference in the total median number of mononuclear cells collected per patient with 5.2 x 10^{10} MNC (median; range: 2.9 -20.7) collected in the lower dose arm compared with 3.8 x 10^{10} MNC per patient in the higher dose arm (median; range:1.9 -7.1; p = 0.03).When comparing the total median number of mononuclear cells/kg collected per patient, there was no difference between the two groups, with 3.8 x 10^8 mononuclear cells (MNC/kg) collected in the lower dose arm(median; range: 1.3 -7.7) and 4.6 x 10^8 (median; range:2.8 -14.8; p =

0.23) collected in the higher dose arm.

Number of Collections

The collection of cells was completed in one day in seventeen of nineteen patients (89%) in the lower dose arm and fourteen of twenty patients (70%) in the higher dose arm. Two days of collection were required for one patient in the lower dose arm compared with five patients in the higher dose arm.

The number of days following cyclophosphamide administration for the collection of cells was similar in both cohorts, on Day 10 (median; range Day 9 – 12) in the lower dose arm versus Day 10.5 (median; range day 10 – 14) in the higher dose arm.

Finally, all patients in the lower dose arm mobilized cells, but one patient in the higher dose arm failed to mobilize stem cells.

Infusion of Mobilized and Collected Cells

There was no difference between the number of CD34+ cells infused in the two groups, with 2.8 x 108 (range: 0.79 – 6.4 x 108) CD34+ cells infused per patient in the lower dose arm compared with 3.7 x 108 (1.5 – 7.8 x 108) CD34+ cells infused per patient in the higher dose arm (p = 0.06) (Table 3). Patients in the lower dose arm received 3.2 x 106 CD34 + cells/kg (range: 1.4 – 6.1 x 106) compared with 4.7 x 106 (range: 2.9 – 9.7 x 106) CD34 + cells/kg in the higher dose arm patients (p = 0.12).

When the two groups were compared, there was no statistical difference between the total number of MNC infused per patient (p=0.99) nor the number of MNC/kg per patient infused (p = 0.24).

Table 3a: Comparison of Cell Infusions

Cells Infused *(median; ranges)*	**Group 1 Cyclophosphamide 1500 mg/m2 n = 16 patients**	**Group 2 Cyclophosphamide 3000 mg/m2 n = 17 patients**	**P value**
Number of CD34+ cells infused (10^8)	2.8 (0.79 – 6.4)	3.7 (1.5-7.8)	0.06
Number of CD34+ cells/kg (10^6)	3.2 (1.4 – 6.1)	4.7 (2.9 – 9.7)	0.12
Number of MNC infused (10^{10})	3.5 (1.2 – 7.3)	1.7 (0.9 – 5.6)	0.99
Number of MNC/kg (10^8)	3.8 (1.3 – 7.7)	2.2 (1.3 – 12.7)	0.24

Legend: Abbreviations: MNC = mononuclear cells

Engraftment Following Transplantation (Table 3b)

Engraftment following transplantation was similar in both groups with engraftment of neutrophils on Day 11 (p = 0.6) and platelets on Day 12 (p = 0.9).

Table 3b: Comparison of Engraftment Following Transplant

Cells Infused *(median; ranges)*	**Group 1 Cyclophosphamide 1500 mg/m2 n = 16 patients**	**Group 2 Cyclophosphamide 3000 mg/m2 n = 17 patients**	**P value**
ANC engraftment (days)	11 (11 - 13)	11 (6 - 14)	0.6
Platelet engraftment (days)	12.5 (11 - 16)	12 (9 - 13)	0.9

Legend: Abbreviations: ANC = absolute neutrophil countTable 4: Toxicities

Toxicities Experienced During Mobilization and Collection (Table 4)

There were no toxic deaths in this trial. Severe (Grade 4) toxicities were not observed in the lower dose arm patients. In contrast, five patients experienced severe/life threatening toxicities in the higher dose arm.

Hospital admission for febrile neutropenia was the most severe side effect, observed in one patient in the lower dose arm, and three patients in the higher dose arm. One patient in the lower dose arm was admitted for four days (Grade 3) and three patients in the higher dose arm were admitted for three days (Grade 3; n = 2 patients; Grade 4, n = 1 patient) (median days hospitalized; range 3-6 days).

Table 4: Toxicities

Toxicities Experienced During the Mobilization and Collection Process (≥ Grade 3)				
	Group 1 1500 grams/m² (n = 19 patients)		**Group 2 3000 mg/m² (n = 21 patients)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Febrile Neutropenia	1	0	2	1
Thrombocytopenia	0	0	1	4
Hypotension	1	0	2	0
Pain	2	0	0	0
Nausea	1	0	1	0

Legend: CTCAE (V5); Grade 3 = severe or medically significant, but not immediately life-threatening. Grade 4 = life-threatening.

Toxicities Observed in the Lower Dose Patients

Moderate (Grade 3) toxicities experienced by patients during the mobilization and collection process included febrile neutropenia (n = 1 patient), hypotension after collection requiring intravenous fluid hydration (n = 1 patient), bone pain (n = 2 patients) or nausea (n = 1 patient).

Toxicities Observed in the Higher Dose Patients

Five patients in the higher dose arm experienced life-threatening (Grade 4) toxicities, including febrile neutropenia (n =1 patient) or thrombocytopenia (n = 4 patients). Moderate toxicities (Grade 3) included hypotension after collection requiring intravenous fluid hydration (n = 2 patients), febrile neutropenia (n = 2 patients), thrombocytopenia (n = 1 patient), or nausea (n = 1 patient).

Discussion

The optimal manner to mobilize autologous peripheral blood stem cells in myeloma patients is unknown. When higher doses of cyclophosphamide (> 4 grams/m^2) are administered with growth factors, more cells are mobilized and collected, but this is at the expense of increased toxicities [21,22]. Historical studies indicate that a dose of cyclophosphamide greater than 4 grams/m^2 offers no benefits and results in an increased incidence of toxicities. Although the authors realize that the growth factor/cyclophosphamide mobilization is not commonly used in myeloma patients, there remains a subset of high-risk patients that may benefit. Since the optimal dose of cyclophosphamide is not known, we proposed this prospective randomized trial to guide clinicians.

Our trial represents one of the first prospective clinical trials that examines the mobilization and collection efficacy of an intermediate-dose of cyclophosphamide (3000 mg/m^2) compared with a lower dose (1500 mg/m^2). Our results indicate that there is no statistically significant difference between the number of CD34+ cells collected ($p = 0.6$) nor the number of CD34+ cells/kg collected ($p = 0.12$). Although there was a slight difference in the total number of MNC collected per patient ($p = 0.03$), there was no difference in the number of MNC/kg collected per pa-

tient (p = 0.23). All patients in the lower dose arm mobilized cells, but one patient in higher dose arm failed to mobilize cells. There was an increased incidence of moderate and severe toxicities in the higher dose cohort. Five patients in the higher dose arm experienced severe toxicities (grade 4), compared with no patients in the lower dose arm. There was no difference in engraftment following transplant between the two cohorts.

When selecting the dose of cyclophosphamide to use for mobilization, the current conflict is that higher doses of cyclophosphamide generally yield a greater number of cells collected, but this is at the expense of an increased incidence of toxicities. Although no prospective trials compare varying doses of cyclophosphamide, a number of retrospective reviews have examined various doses of cyclophosphamide used in combination with rhG-CSF. Jantunen et al, performed a retrospective analysis comparing the use of rhG-CSF with low dose cyclophosphamide (ranging from 1.2 – 2 grams/m^2) to a higher dose (4 grams/m^2) in myeloma patients. Both regimens effectively mobilized progenitor cells. As anticipated, patients in the lower dose group experienced less toxicities, including fewer hospital days, but one patient failed to mobilize. These researchers recommended that a lower dose of cyclophosphamide should be used, due to a more favorable toxicity profile and lower resource utilization [24]. Another retrospective analysis compared lower dose cyclophosphamide (1 - 2 grams/m^2) to higher doses (3 - 4 grams/m^2) and noted that 42% of patients in the higher dose arm required hospitalizations, compared with only 16% of patients in the lower dose arm. Unfortunately, 26% of patients within the lower dose arm failed to mobilize enough cells for two transplants [15]. Finally, intermediate dose cyclophosphamide (3 - 4 grams/m^2) with rhG-CSF was compared to plerixafor and rhG-CSF in their mobilization abilities. Both arms mobilized an adequate number of cells, but the investigators noted that the cyclophosphamide arm was significantly cheaper when compared with the plexiform arm ($ 22,504 versus $ 28,980; p=0.001) [25].

Conclusions

Our study is one of the first prospective randomized trials to demonstrate non-inferiority and similar clinical efficacy of lower-dose cyclophosphamide in mobilizing progenitor cells in myeloma patients. Our results demonstrate that a lower dose of cyclophosphamide mobilizes a similar number of hematopoietic stem cells with fewer side effects and less toxicity. Although these results are clinically relevant and have changed the practice at our institution, readers need to acknowledge that this is a small, single institution study and results need to be interpreted in that setting. The benefit of this study is that it is a real-world trial with patients stratified based on risk factors, and then randomized. Both doses of cyclophosphamide mobilized enough CD34+ cells for two transplantations. Future studies should compare cell yield and toxicities of this mobilization regimen using a lower dose of cyclophosphamide with rhG-CSF to the use of rhG-CSF mobilization alone.Finally, although this is a prospective study, it was designed as a *non-inferiority* trial, since the number of patients needed to define superiority would require a large multi-institutional trial to meet accrual goals.

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