Transfusion and Apheresis Science 57 (2018) 204–207

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Stem cell mobilization kinetics in elderly patients with multiple myeloma

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ARTICLE INFO

Article history:
Received 25 October 2017
Received in revised form
17 December 2017
Accepted 23 January 2018

Keywords:
Multiple myeloma
Mobilization
Apheresis

ABSTRACT

In this study, we aimed to investigate whether the procedure and product kinetics differ according to age groups in advanced-age MM patients who underwent autologous HSCT. 59 patients who underwent autologous HSCT were retrospectively analyzed. Then, the patients were divided into two groups as 60–65 years and ≥65 years. It was significantly lower in ≥65 years group ($p = 0.008$) and proportionally, the procedure duration was also significantly shortened in this group ($p = 0.013$). Total number of collected CD34 positive stem cells was 6.20×106 (± 3.83) in 60–65 years group while it was 5.51×106 (± 2.48) in ≥65 years group with no statistically significant difference ($p = 0.825$). In conclusion, there was no significant difference in terms of the number of collected CD34-positive stem cells in this study that investigates the mobilization data, procedure and product kinetics, we think that successful stem cell mobilization can be performed in appropriately selected patients regardless of age.

1. Introduction

Multiple myeloma (MM), a plasma cell-derived hematological malignancy, manifests itself with monoclonal immunoglobulin production which frequently leads to organ damage such as renal failure, hypercalcemia, anemia and lytic bone lesions [1,2]. Most of MM patients are in advanced age, so the prevelance of MM rises as the average life span of the general population is increasing [3]. The standard treatment approach for young MM patients is autologous hematopoietic stem cell transplantation after induction chemotherapy. This approach can also be applied to the patients who are 65 years or older with satisfactory performance status [4,5].

Autologous hematopoietic stem cell transplantation (HSCT) is a treatment modality with increasing importance in many hematological malignancies including MM. It comprises intravenous infusion of hematopoietic stem cells to the patients who are already treated with high-dose chemotherapy prior to the infusion [6–11]. In recent years, the stem cells are collected from the peripheral blood of the patients by means of mobilization, which is a method used to increase the content of stem cells in peripheral blood. The medications used for this purpose are called mobilization regimens and an optimal mobilization regimen should support the hematopoietic reconstruction and allow sufficient stem cell collection with minimum number of apheresis. Lately, the role of mobilization regimens and strategies to decrease the mobilization failure has gained importance, because of the growing data about the efficiency and safety of autologous HSCT in patients 65 years or older [12,13].

For stem cell collection, peripheral blood is preferred over bone marrow as the source of hematopoietic stem cells in autologous HSCT [14]. Usually, a central venous line is used during apheresis procedure while a peripheral venous line may be employed only in selected patients. In stem cell mobilization regimens, growth factors may be used solely or combined with chemotherapeutic agents. There are many studies comparing different mobilization regimens [15] including the study by Bozdag et al. [16]. In addition, the use of CXCR-4 chemokine receptor antagonists has been recently on the rise [17,18].

In this study, we aimed to investigate whether the apheresis procedure and product kinetics differed according to the age groups

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https://doi.org/10.1016/j.transci.2018.01.010
1473-0502/

in advanced-age MM patients who underwent autologous HSCT after high-dose chemotherapy.

2. Patients and method

2.1. Patients

This study was performed with patients who were 60 years or older and underwent autologous HSCT with the diagnosis of MM. Demographic and mobilization data of a total of 59 MM patients who underwent autologous stem cell transplantation were retrospectively analyzed. The patients were divided into two groups as 60–65 years and ≥65 years, and then mobilization and stem cell parameters were compared between two groups.

2.2. Mobilization

The stem cell mobilization regimens were granulocyte colony-stimulating factor (G-CSF) alone, G-CSF with chemotherapy, or plerixafor with G-CSF and/or chemotherapy in patients with inadequate stem cell yield. Either a central venous route or a peripheral venous route was chosen for stem cell apheresis procedure according to the availability of a peripheral vein. As for product kinetics acquired with apheresis, the total amount of product was measured in milliliters and $CD34^+$ cells were estimated from the product as number 10^6/kg. As for procedure kinetics, the volume amount of processed blood, procedure duration, total days of apheresis and total amount of anticoagulant ACD solution used were determined.

2.3. Statistics analysis

Statistical evaluation was made by SPSS 17 program. Data were described as numbers and percentage or mean (±), when appropriate. x^2 Fisher's exact test was used for evaluating categorical values and Mann Whitney U test for continuous values. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

3. Results

The patient characteristics are presented in Table 1. The median age was 65 (range: 60–75). 34 of the patients were male and 25 were female. Twenty-seven of the 59 patients who underwent peripheral stem cell mobilization were 60 to 65 years while 32 patients were ≥65 years. For mobilization, chemotherapy plus G-CSF was used in 35 (59.3%) patients; G-CSF alone was used in 21 (35.6%) patients and plerixafor plus G-CSF was used in 3 (5.1%) patients. When the patients were compared in two age groups, both groups were found to be similar in terms of age, height, weight and plasma volume of patients ($p > 0.05$). There was no significant difference in mobilization protocols between two groups (Table 1). The median number of days of procedure performed was 2 (1–4) days in patients 60–65 years as it was also 2 (1–3) days in patients ≥65 years ($p = 0.326$). Similar results were observed regarding the preferred venous route in both groups and central venous line was prominently favored (74% v.s. 75%). The volume of processed blood was the only parameter with significant difference between two groups. It was significantly lower in patients ≥65 years ($p = 0.008$) and proportionally, the procedure duration was also significantly shortened in this group ($p = 0.013$). The total number of collected $CD34^+$ stem cells was 6.20×10^6/kg (±3.83) in patients 60–65 years and 5.51×10^6/kg (±2.48) in patients ≥65 years ($p = 0.825$). The total volume of product yielded at the end of mobilization was 559 (±413) milliliters in patients 60–65 years and 359 (±230) milliliters in patients ≥65 years. The product volume was apparently lower in patients ≥65 years, yet the difference did not reach statistical significance ($p = 0.056$) (Table 2).

Table 1
Characteristics of patients.

Age	60–<60 years n (%)	≥65 years n (%)	p value
	27 (45.8%)	32 (54.2%)	NS
Gender			
Female	13 (22.1%)	12 (20.3%)	NS
Male	14 (23.7%)	20 (33.9%)	NS
Height (cm)	165 (155–182)[b]	165 (149–180)[b]	NS
Weight (kg)	77 (49–105)[b]	74.5 (52–95)[b]	NS
Blood Volume (ml)	5217 (±753)[a]	5145 (±649)[a]	NS
Plasma Volume (ml)	3307 (±587)[a]	3165 (±555)[a]	NS
Mobilization Regimen			
G-CSF	11 (18.6%)	10 (16.9%)	NS
Chemotherapy + G-CSF	15 (25.4%)	20 (33.9%)	
Plerixafor	1 (1.7%)	2 (3.4%)	
Venous Access			
Central	20 (33.9%)	24 (40.7%)	NS
Peripheral	7 (11.9%)	8 (13.6)	

NS (not significant).
[a] Mean.
[b] Median.

Table 2
The kinetics of the mobilization.

	60–<60 years n	≥65 years n	p value
Number of days of apheresis (days)	2 (1–4)	2 (1–3)	NS
Total time of apheresis (minute)	426 (241–910)[b]	360 (180–761)	**p = .013**
TVBP (L)	22.51 (±8.44)[a]	17.87 (± 6.57)[a]	**p = .008**
CD 34 × 10^6/kg	6.20 (±3.83)[a]	5.51 (± 2.48)[a]	NS
TVP (ml)	559 (±413)[a]	359 (±230)[a]	**p = .056**
ACD Solution (ml)	1500 (±610)[a]	1394 (±490)[a]	NS

TVBP: Total volume of blood processed; TVP:Total volume of product.
[a] Mean.
[b] Median.

4. Discussion

Autologous HSCT after high dose chemotherapy is a treatment modality that increases remission rates and survival in various hematological diseases, one of which is MM. Although the bone marrow was the main source of hematopoietic stem cells in the past years in patients undergoing autologous HSCT, currently the peripheral blood is preferred as the main source of stem cells. Preference of the peripheral blood as the stem cell source, provides some benefits such as avoiding hospitalization and general anesthesia, patient comfort during the procedure and post-transplant rapid engraftment kinetics with an acceptable toxicity in patients particularly in advanced-aged ones [19,20]. In this study, stem cell source was peripheral blood in all patients undergoing autologous HSCT.

When the peripheral blood is used as the stem cell source, mobilization procedure, which is defined as moving the stem cells in the bone marrow out to the peripheral circulation, is applied to the patients. Mobilization can be performed by means of using either growth factors alone or in combination with different chemotherapy regimens [21,22]. After mobilization, stem cells are collected from the peripheral blood via apheresis procedure, and stem cell kinetics can be affected from the devices used in apheresis [23,24] and the route of venous access [25,26] as well as the mobilization regimen. While a number of studies recommended the antecubital vein route for apheresis procedure, two recent studied showed that type of the access could alter the total volume of the product and

the total processed volume [27,28]. Despite the recommendation of usage of the antecubital vein, requirement of central venous catheter was distinctly high in both age groups (74% v.s. 75%) in our study, which could be the result of the inapplicability of peripheral vascular structures for long-duration process due to the advanced-age.

Older age was demonstrated to have a negative impact on mobilization results in a study including relatively high number of MM patients undergoing autologous HSCT [29]. But to our knowledge, the effect of age on the stem cell kinetics in mobilized MM patients has not been investigated previously. We investigated the stem cell kinetics according to the age groups in the advanced-age MM patients who were applied mobilization. The days of apheresis procedure and number of collected $CD34^+$ stem cells were comparable in two groups which signifies that old age is not an obstacle to mobilization in MM patients. Also total volume blood processed and furthermore procedure duration decreased in patients ≥65 years which suggests that shortened procedure duration may lead to reduced mobilization-related complications in this patient group. Two other important findings in this study were the lower volume of product yielded and lower acid citrate dextrose (ACD) used in patients ≥65 years though they did not reach a statistical significance. The low volume of the product ensures the usage of decreased amount of dimethyl sulfoxide (DMSO), which is used for preserving stem cells and furthermore it might be toxic in increased volumes [30]. Beside the significance of DMSO toxicity, ACD, an anticoagulant agent used during apheresis, might cause side effects such as muscle cramps, shaking, sweating, nausea, vomiting, vague vision and tachycardia [31,32] and the volume of citrate infused to the patients was shown to affect the rate of these side effects [33].

In conclusion, stem cell mobilization and autologous HSCT are complex processes comprising many procedures and treatment applications. On the other hand, there was no significant difference in terms of either procedure duration or the number of collected $CD34^+$ stem cells in older MM patients, in this study. Hence, advanced-age would not avoid physicians from planning autologous HSCT for all MM patients with satisfactory performance status.

Acknowledgements

We thank the staff in stem cell apheresis units for their endeavors and technical support.

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