Transfusion and Apheresis Science 56 (2017) 800–803

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

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

Original Article

Peripheral blood stem cell collection for allogeneic hematopoietic stem cell transplantation: Practical implications after 200 consequent transplants

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ARTICLE INFO

Article history:

Keywords:
Allogeneic stem cell transplantation
Peripheral bood stem cell
Stem cell mobilization

ABSTRACT

Background: Proper stem cell mobilization is one of the most important steps in hematopoietic stem cell transplantation (HSCT). The aim of this paper is to share our 6 years' experience and provide practical clinical approaches particularly for stem cell mobilization and collection within the series of more than 200 successive allogeneic HSCT at our transplant center.
Subjects & Methods: Two hundred and seven consecutive patients who underwent allogeneic peripheral blood stem cell transplantation were included in this study. Age, sex, weight, complete blood counts, $CD34^+$ cell counts, total collected amount of $CD34^+$ cells, $CD34^+$ cells per 10l processed, mobilization failure and adverse events were reviewed.
Results: Median age was 40.2 ± 12.9 (21–68) years and 46.4 ± 13.4 (17–67) years for donors and patients, respectively. The number of donors who had undergone adequate $CD34^+$ cell harvesting and completed the procedure on the fourth day was 67 (32.8% of all patients). Only 12 patients required cell apheresis both on day 5 and 6. Apheresis was completed on day 4 and/or day 5 in 94.2% of all our donors. There was no significant association between $CD34^+$ stem cell volume and age, gender and weight values of donors. Mobilization failure was not seen in our series.
Conclusions: G-CSF is highly effective in 1/3 of the donors on the 4th day in order to collect enough number of stem cells. We propose that peripheral stem cell collection might start on day 4th of G-CSF treatment for avoiding G-CSF related side effects and complications.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important and potentially curative treatment option for variety of malignant and nonmalignant hematological disorders. More than five decades have passed since the very first HSCT. Within these 50 years, significant developments have been made with parallel to the advancements in biotechnology. One of the most important aspects of these advancements is the emergence of especially peripheral blood and cord blood as additional sources of stem cells other than bone marrow, which has dramatically expanded the applicability of HSCT [1–6]. However, this big step forward has brought some inherent new problems into the clinical practice due to the qualitative and quantitative differences in immune cells in the grafts from these three sources. As a consequence, transplants from different sources have different kinetics of hematological recovery as well as different risks for developing graft-versus-host disease (GVHD) [7,8]. Currently, mobilized peripheral stem cells have largely replaced bone marrow as the graft source for allogeneic stem cell transplantation. In a recent study by Passweg et al., 17.302 patients underwent allogeneic stem cell transplantation and peripheral stem cells were used as stem cell source in 75.5% (n = 13077) of these cases [9]. Based on this 2015 European Society for Blood and Marrow Transplant activity survey report, it was clearly found that the use of peripheral blood as a stem cell source has surpassed the use of bone marrow [9]. However, stem cell mobilization is still a problem in some cases.

Proper stem cell mobilization is one of the most important parts of successful HSCT. Weaver et al. first reported a successful case using granulocyte colony stimulating factor (G-CSF) to mobilize peripheral blood stem cell (PBSC) in a syngeneic transplantation procedure in 1993 [10]. From then to now, G-CSF has become the

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https://doi.org/10.1016/j.transci.2017.11.009
1473-0502/

standard medication used to mobilize hematopoietic stem cells for collection through apheresis in normal volunteer donors. G-CSF is usually administered subcutaneously at 10 μg/kg/day for a period of 4–6 days. Peripheral blood stem cell apheresis starts from day 5 forwards until seventh days following initial dose of G-CSF. Most common side effects of this procedure are bone pain, low-grade fever and headache which are generally manageable [11]. On the other hand, administration of G-CSF for 5–6 days could cause some rare complications such as thrombosis, pyogenic infections, splenic rupture and flare of autoimmune diseases [12–15].

In order to struggle with these new problems and manage them, new clinical implications have to be remedied. The aim of this paper is to share our 6 years' experience and provide in house clinical implications particularly for stem cell mobilization and collection within the series of more than 200 consecutive allogeneic HSCT at our transplant center.

2. Subjects & methods

Two hundred and seven consecutive patients who underwent allogeneic PBSC transplantation at the Sisli Florence Nightingale Hospital Stem Cell Transplantation Unit between June 2011 and December 2016 were included in this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All patient records were analyzed retrospectively. Age, sex, weight, complete blood counts, $CD34^+$ cell counts and total collected amount of $CD34^+$ cells on 4th and 5th days of G-CSF treatment, $CD34^+$ cells per 10 l processed; femoral/jugular catheter insertion, mobilization failure and adverse events were recorded. All allogeneic donors received G-CSF (Neupogen, Amgen) to mobilize stem cells into the peripheral blood for apheresis in doses ranging from 7.5 to 10 μg/kg/day. We started to check complete blood count and peripheral blood circulating CD34+ cells (pCD34) by flow-cytometry using ISHAGE platform on day 4 till collection of target stem cell amount (5×10^6/kg recipient's body weight). We started leukopheresis if the donor pCD34+ cell exceeded 40/mcl on day 4 or for the rest as a routine on day 5. The primary measure of hematopoietic recovery was the time after transplantation until a neutrophil count of $>0.5 \times 10^9$/L and platelet count of at least $>20 \times 10^9$/L was observed for consecutive 3 days.

Statistical analyses were performed using commercially available software (SAS version 9.1; SAS Institute, Inc., Cary, NC). Data with non normal distribution were expressed as median (range) for comparison using the Mann-Whitney test. The chi square test or Fisher exact test was used to compare differences between groups of categorical data. $P < 0.05$ was considered significant.

3. Results

Two hundred and seven successive donors and patients were evaluated. Median age was 40.2 ± 12.9 (21–68) years and 46.4 ± 13.4 (17–67) years for donors and patients, respectively. Slight female predominance was found among the donors (%53.6). Mean donor weight was 73.2 (40–135) kilograms. White blood cell count was $45.6\ (\pm 3.2) \times 10^3$/ and $43.5(\pm 1.0) \times 10^3$/ on 4th and 5th day of G-CSF respectively.

Median $CD34^+$ cell count at the 4th day of mobilization was 62 (11–203) cell/μL. The number of donors who had undergone adequate $CD34^+$ cell harvesting and completed the procedure on the fourth day was 67 (32.8% of all donors). On the 4th day, there were 6 donors whose cell apheresis started and continued on the 5th day. On the other hand, there were 122 donors (58.9% of all donors) who had experienced enough $CD34^+$ cells by apheresis on the fifth day. Only 12 donors required cell apheresis both on day 5 and 6. Therefore, it was shown that, target $CD34^+$ cells were collected when apheresis start on the 4th day. Apheresis was completed on day 4 and/or day 5 in 94.2% of all our donors.

The total amount of $CD34^+$ cells collected on the day 4 and day 5 from the donors was also evaluated. The quantity of collected cells on the 4th day was statistically significantly higher than the 5th day (median $CD34^+$ cells were 7.6×10^6/kg and 6.2×10^6/kg on 4th and 5th days respectively, p value = 0.003). There was no significant association between $CD34^+$ stem cell volume and age, gender and weight values of donors.

When the amount of $CD34^+$ cells per 10 liters processed was evaluated, no significant difference was observed between days 4 and 5 (4th day = 6.6 $CD34^+$ cells/10L and 5th day = 6.3 $CD34^+$ cells/10L). During the procedure, 29.9% of donors (n = 62) needed a catheter. There were no catheter-related grade 2–4 complications in any of our cases.

Mobilization failure was not seen in our series. Bone pain and myalgia were reported as the most frequent short-term adverse events. Other commonly observed short-term symptoms included headache, fatigue and fever. We did not see any serious complication of G-CSF during the mobilization.

4. Discussion

In our study, we clearly demonstrated that peripheral stem cell mobilization with G-CSF is highly effective even on the 4th day in order to collect enough number of stem cells. Traditionally, stem cell collection starts on the 5th day of G-CSF. We showed that there wouldn't be any need to extend G-CSF treatment to 5 days in some of the donors (1/3 of donors in our series) to avoid G-CSF related side effects as well as complications. Therefore, we think that peripheral stem cell collection might start on day 4th of G-CSF treatment.

Peripheral blood stem cell mobilization for allogeneic transplantation was started in the mid-1990s with the advance of G-CSF into the clinical practice [16,17] and became the most commonly method of stem cell mobilization. The classic mobilization treatment protocol consists of daily G-CSF (10 μg/kg) for a minimum of 5 days. Then peripheral blood $CD34^+$ cell counts were analyzed by flow cytometry just before beginning of apheresis. The $CD34^+$ cell number in the apheresis product was determined using standard flow cytometry analysis and cells were cryopreserved using standard procedures [18]. Although this mobilization protocol is considered sort of a "gold standard" method, the search for a better mobilization technique has not ended. Several groups are still working on different agents; dosages, combinations as well as treatment length in order to increase the $CD34^+$ yield efficiency. One of the key studies belongs to Majolino et al. [19], which is published about 2 decades ago. They administered G-CSF (filgrastim) 16 μg/kg subcutaneously for 4 days in five normal subjects. The $CD34^+$ cells peaked to (median) 147.0/μL on day 4. They concluded that G-CSF 16 μg/kg × 4 days is an efficient schedule for PBSC mobilization in healthy donors. In another study, Majolino et al. [20] reported that a schedule of 10 μg/kg for 5 days is as effective as 16 μg/kg for 4 days with a single apheresis that would be enough in 80% of cases. In our study, we used a lower dose (10 μg/kg × 4 days) than Majolino's first study [19] and more than in 1/3 of donors even a single apheresis procedure on day 4th proved similarly adequate stem cell yields when compared to 5th day. Grigg et al. [21] evaluated the kinetics of mobilization by G-CSF in normal volunteers. They detected a peak for $CD34^+$ cells between days 4 and 6 after 10 μg/kg G-CSF. Liang and Ren [22] retrospectively analyzed data from 431 healthy donors and studied the factors influencing the efficacy of mobilization. Similar to our study, they analyzed donor age, sex, weight, daily G-CSF dose and schedule of G-CSF administration. Contrary