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Indian Journal of Physiology and Pharmacology

Original Article

Effect of CD34+ cell dose on neutrophil and platelet engraftment kinetics in haematopoietic stem cell transplantation – A single-centre experience

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Received : 29 June 2020
Accepted : 05 October 2021
Published : 08 December 2021

DOI
10.25259/IJPP_138_2020

Quick Response Code:

ABSTRACT

Objectives: Haematopoietic stem cell transplantation (SCT) is curative for a number of benign and malignant hematological disorders. CD34 expression on haematopoietic progenitor cells is used to assess stem cell content in peripheral blood stem cell and bone marrow grafts. This study evaluated the relationship between numbers of CD34+ cells infused per kg and the timing of neutrophil and platelet engraftment.

Materials and Methods: The effect of cell dose was studied in consecutive HSCT patients transplanted between November 2008 and December 2017. Neutrophil engraftment was defined as the first of 2 consecutive days with an absolute neutrophil count >0.5 × 10^9/L and platelet engraftment as unsupported platelet count >20 × 10^9/L for 7 days.

Results: Of a total of 131 patients, 26 (19.8%) underwent an autologous SCT, while 105 (80.2%) underwent an allogeneic SCT. The median CD34 dose infused in the auto-SCT group was 5.29 × 10^6 $CD34^+$cells/kg (IQR = 2.95–10.98) and 6.42 × 10^6 $CD34^+$cells/kg (IQR = 4.20–9.20) in the allo-SCT group ($P = 0.773$). The median time to neutrophil engraftment in the auto-SCT group was 11 days (range 9.5–12) and in the allo-SCT group was 15 days (range 13–17), $P \leq 0.001$. The median time to platelet engraftment in both groups was similar (12 days). When patients were divided into three groups based on CD34 dose (<5, 5–8 and >8), no difference was observed in the time to ANC or platelet engraftment. Similarly, no differences in time to engraftment were noted in each quartile of CD34 dosage in auto- and allo-SCT.

Conclusion: Thus, it was concluded that a cell dose of approximately 5 × 10^6/kg provides reasonably rapid engraftment, with no advantage seen for a higher cell dose of >5.

Keywords: Haematopoietic stem cell transplantation, Stem cell transplantation, CD34

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is curative for a number of benign and malignant hematological disorders.[1] CD34 expression on haematopoietic progenitor cells is used to assess stem cell content in peripheral blood stem cell and bone marrow grafts. It can be assumed therefore that higher CD34 expression would mean higher stem cell content and therefore better engraftment and outcomes. While it is true that an adequate number of CD34 expressing cells are important for better outcomes,[2] leading to the 'more is better' practice in many centres, studies have shown that a higher cell count could lead to an increase the incidence of graft-versus-host disease (GVHD).[3] Thus, there have been various studies that evaluate the optimal cell dose range for an HSCT.[4,5]

It is thus important to establish which cell dose is optimal for every HSCT centre as a reference point for treatment protocols. Through this study, we aimed to establish just that. From the inception of the transplant program in 2008 to the conclusion of this study in 2017, all transplant cases irrespective of indication or method were analyzed to determine a correlation between cell dose and engraftment outcomes.

MATERIALS AND METHODS

This was a retrospective study of the effect of cell dose which was studied in consecutive HSCT patients transplanted between November 2008 and December 2017. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Christian Medical College and Hospital, Ludhiana) and study protocol was approved by the same.

Informed consent was obtained from the participants before proceeding with the study. All patients were included irrespective of type of disease, whether benign or malignant. Indications for transplant included acute and chronic myeloid leukaemia, acute and chronic lymphoid leukaemia, thalassemia, aplastic anaemia, multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, myeloproliferative neoplasms, sickle cell anaemia and other hematological diseases.

Following HLA typing, conditioning regimens and GVHD prophylaxis, patients were posted for the procedure. Stem cells were harvested through bone marrow or peripheral blood and were analyzed by flow cytometry at our local stem cell laboratory before transplantation. Following transplant, the following end points were pre-determined. Neutrophil engraftment was defined as the first of 2 consecutive days with an absolute neutrophil count >0.5 × 10^9/L and platelet engraftment as unsupported platelet count >20 × 10^9/L for 7 days.

Frequencies, proportions, means and standard deviations were calculated. Chi-square and *t*-test were done using SPSS version 21.

RESULTS

Out of 131 patients, 94 (72%) were male and 37 (28%) were female. [Figure 1] shows the sex distribution of patients. [Figure 2] shows the age-wise distribution of the patients where the largest group consisted of the age group of 1–9 years and the smallest group was 40–49 years.

[Figure 3] shows the age and sex distribution of all the patients which shows that in all age groups, the majority were male except in the age group of 50–59 years which had equal number of males and females.

Most patients received peripheral blood stem cells (92.4%) while 6.1% received bone marrow transplant and a small subset of patients (1.5%) received both [Figure 4] [BM = Bone marrow/PBSC = Peripheral blood stem cells]. In 131 patients, 26 (19.8%) underwent an autologous SCT, while 105 (80.2%) underwent an allogeneic SCT [Figure 5].

[Figure 6] shows the sex distribution among the two groups where there is a predominance of females in the

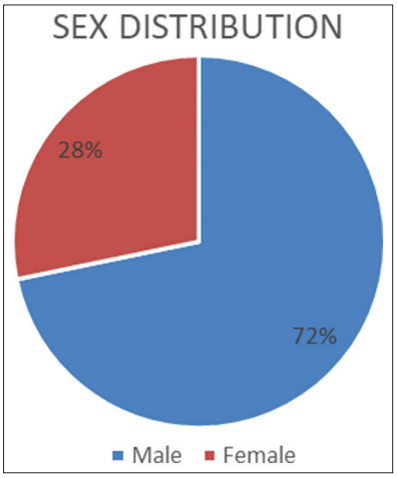

Figure 1: Sex distribution.

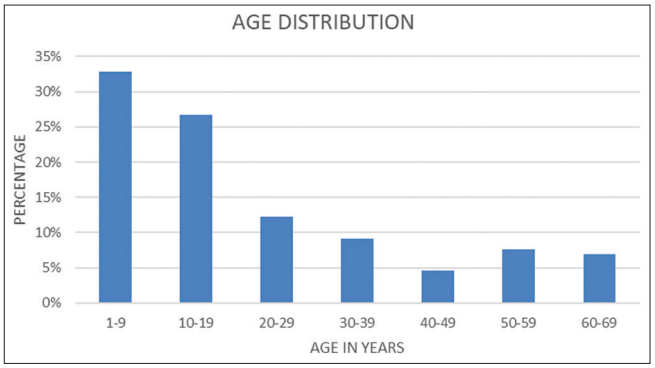

Figure 2: Age distribution.

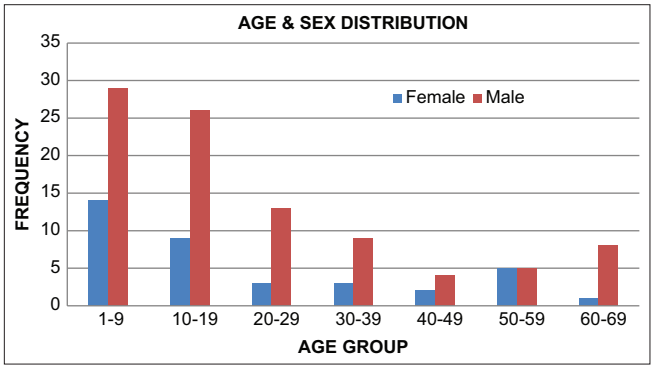

Figure 3: Age and sex distribution.

autologous group but a predominance of males in the allogeneic group.

[Figure 7] shows the distribution of age groups between the two groups where the patients receiving allogeneic transplants were mainly in the younger age group of 1–9 years whereas the patients receiving autologous transplants were in the older age group of 50–59 years.

Median CD34 dose infused in the auto-SCT group was 5.29 × 10^6 $CD34^+$cells/kg (IQR = 2.95–10.98) and 6.42 ×

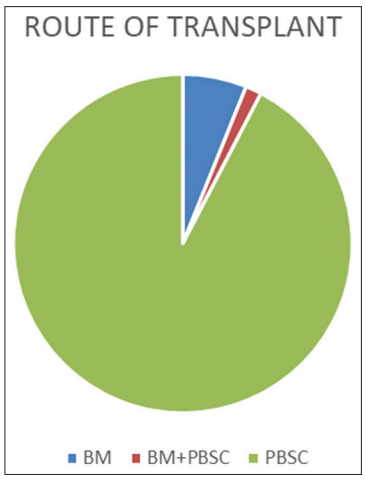

Figure 4: Route of transplant

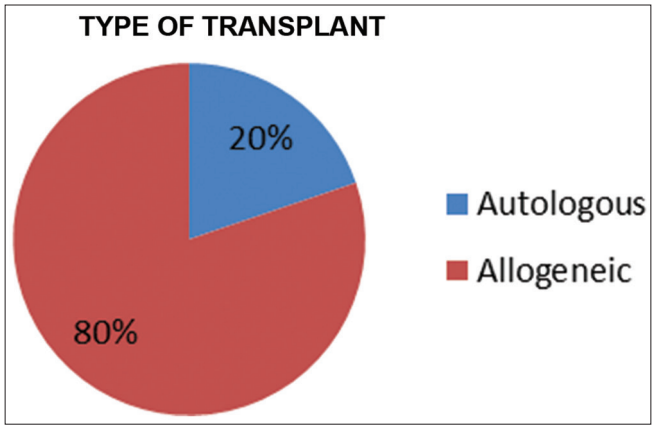

Figure 5: Type of transplant

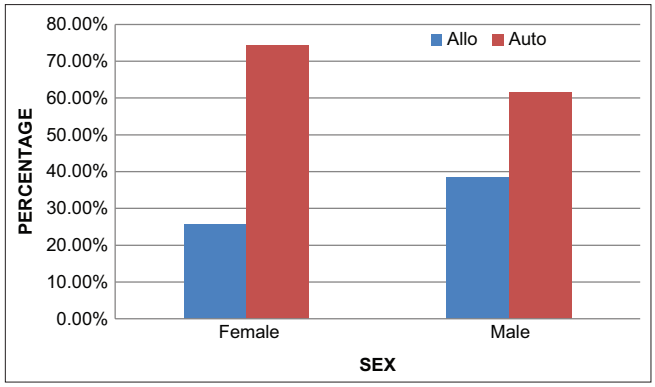

Figure 6: Sex vs type of transplant

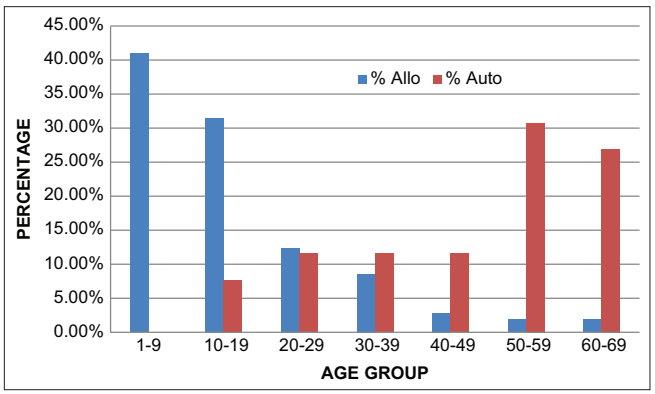

Figure 7: Age vs type of transplant

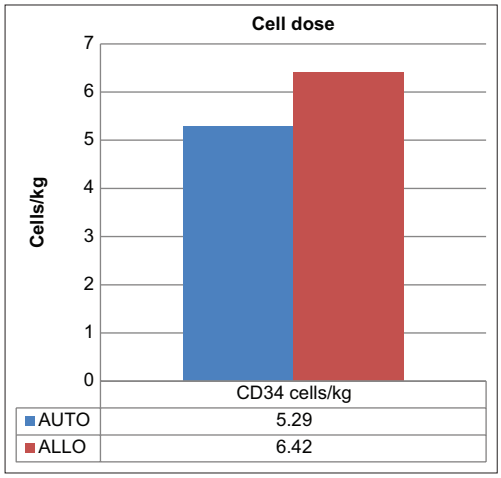

Figure 8: Cell dose vs type of transplant

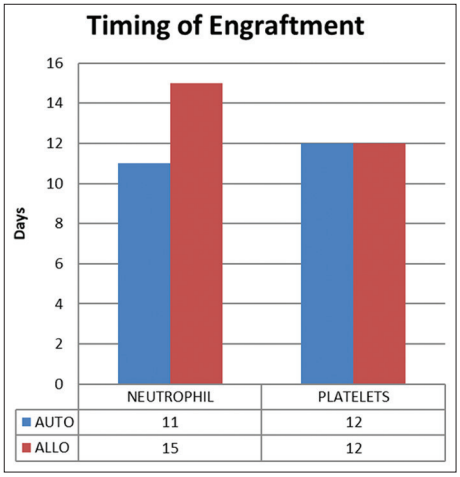

Figure 9: Timing of engraftment

10^6 $CD34^+$cells/kg (IQR = 4.20–9.20) in the allo-SCT group ($P = 0.773$) [Figure 8].

The median time to neutrophil engraftment in the auto-SCT group was 11 days (range 9.5–12) and in the allo-SCT group was 15 days (range 13–17), $P \leq 0.001$ [Figure 9]. The median time to platelet engraftment in both groups was similar (12 days).

When patients were divided into three groups based on CD34 dose (<5, 5–8 and >8 × 10^6 $CD34^+$cells/kg), no difference was observed in the time to ANC or platelet engraftment [Figure 10]. Similarly, no differences in time to engraftment were noted in each quartile of CD34 dosage in auto- and allo-SCT.

DISCUSSION

Stem cells are defined as undifferentiated cells capable of indefinite self-renewal and generation of a functional progeny of highly specialised cells. Stem cells have different properties and functions depending on their location. HSCs are characterised by the ability to self-renew and differentiate into all mature blood lineages.[6] The differentiation and proliferation of haematopoietic cells are regulated by various cellular mechanisms such as cytokines. The most primitive HSCs express the cell surface antigen CD34 and receptors for other growth factors.[7]

Different studies define different cell doses for stable engraftment. A nucleated cell dose of 5 × 10^6/kg is generally considered adequate, although cell doses of 3 × 10^6/kg can be used.[8] A study done in 2015 found that a higher $CD34^+$ cell dose was associated with a faster neutrophil engraftment in bone marrow patients and faster platelet engraftment in peripheral blood stem cell recipients.[9] A poor or inadequate harvest would require a repeat procedure and further hospitalisation of the donor. A single-centre analysis done in Oslo which studied 189 PBSC recipients from sibling donors concluded that a CD34 cell dose of 6–7 × 10^6/kg showed better survival and lesser mortality while a dose of <5 × 10^6/kg had increased relapse but lower GVHD and higher than 6.5 × 10^6/kg had lower acute GVHD.[10] Another study done in 2015 done in 205 patients from a single institution concluded that there is no ideal cell dose at transplant within a range of 10^4–10^5.[11] Thus, it becomes very important to define the minimum cell dose required to give the best engraftment.

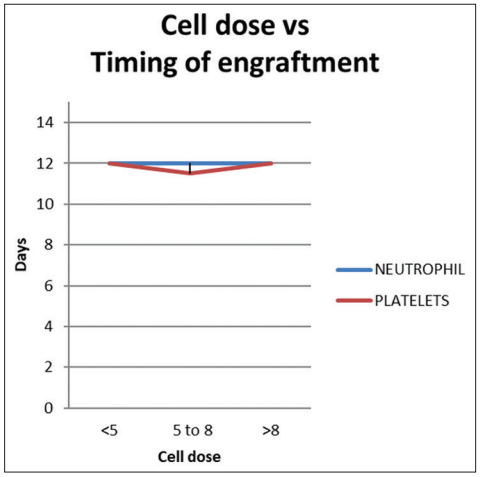

Figure 10: Cell dose vs timing of engraftment

CONCLUSION

Our study showed that a cell dose of approximately 5 × 10^6/kg provides reasonably rapid engraftment, with no advantage seen for a higher cell dose of >5. However, engraftment is not purely a function of stem cell content in the graft and can be influenced by other factors including the underlying disease, pre-HSCT therapy, conditioning regimen, use of cytokines post-HSCT, graft quality and post-HSCT complications/events (e.g., GVHD, medications and infections). This study was limited in this wherein we included all HSCT cases irrespective of all other factors. Thus, further studies are required which explore these variables and define cell doses as per the case.

Data availability

The data that support the findings of this study are available on request from the corresponding author LA. The data are not publicly available due to institutional restrictions.

Acknowledgement

I thank Dr. Joseph John, Dr. Chepsy Philip, Dr. Suvir Singh, Mr. Sohan Singh and others of the Department of Haematology, Christian Medical College and Hospital, Ludhiana, for graciously opening their department to us and their ever-present expertise and assistance throughout all aspects of our study.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Abraham L, Pramod J. Effect of CD34+ cell dose on neutrophil and platelet engraftment kinetics in haematopoietic stem cell transplantation – A single-centre experience. Indian J Physiol Pharmacol 2021;65:188-92.