

Engraftment Kinetics of Neutrophils and Platelets in Peripheral Blood Stem Cells Transplant Patients in a Quaternary Care Centre

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ABSTRACT

Background: This study aimed to evaluate the rate of neutrophil and platelet engraftment in pediatric hematopoietic stem cell transplant (HSCT) patients. Additionally, it sought to assess whether engraftment kinetics were influenced by CD34+ cell dose, CD3+ cell dose in T cell-replete transplants with post-transplant cyclophosphamide (PTCy), and the type of stem cell transplantation.

Materials and Methods: The study included 60 pediatric patients undergoing hematopoietic stem cell transplantation between August 2023 and January 2024. Flow cytometry was used to quantify CD34+ cells. A peripheral smear and the haematology analyzer were used to measure the platelet count and neutrophils from day 1+ to day 28+.

Results: Among 60 patients, 3 were autologous (5%), 15 were MRD (25%), 6 were MUD (10%), 30 were T-cell-repleted transplants with PTCy (50%), and 6 were TCR α/β -depleted transplants (10%). The neutrophil and platelet engraftment were correlated with demographic characteristics (e.g., age and gender) and clinical factors (e.g., transplant, diagnosis, and CD34+ cell dosage levels). In addition, CD3+ T cell dosages of $\geq 2 \times 10^8$ cells/kg or $< 2 \times 10^8$ cells/kg were also correlated with engraftment kinetics. Both the type of peripheral blood stem cell transplant (PBSCT) and the CD3+ T cell dose showed a statistically significant association with neutrophil engraftment.

Conclusion: This study showed a poor correlation between CD34+ cell dosage and engraftment. However, maximum engraftment occurred between day 10+ and day 14+ in fully matched transplants. T cell-repleted transplants with PTCy exhibited maximum engraftment between 15–18 days, and all TCR α/β depleted transplants engrafted between day 10+ and day 14+.

Keywords: CD34+cells; Peripheral blood stem cell transplant; CD3+ T cell dosage; Engraftment

INTRODUCTION

Numerous benign and malignant haematological disorders can be cured by hematopoietic stem cell transplantation (HSCT)¹. The majority of the HSCT procedures are performed by using stem cells derived from bone marrow or Peripheral blood stem cells (PBSC). CD34+ cells include both the early uncommitted fraction and subsets of committed progenitor cells, indicating a heterogeneous population. CD34+ cell count is used to evaluate the

stem cell concentration². Graft failure and graft-versus-host-disease (GVHD) are the two dreaded complications of HSCT. Bone marrow is considered the ideal source of stem cells, as the concentration of stem cells is more than the lymphocytes, whereas PBSC has a higher concentration of both the stem cells and the lymphocytes, predisposing to GVHD. Even though bone marrow is the ideal stem cell source, many transplant centers are preferring PBSC due to the ease of collecting the stem cells, earlier

engraftment, and also due to the availability of better GVHD prophylaxis. Though earlier it was thought that more CD34+ cells could give better engraftment, it was later proven in many studies that higher CD34+ cells than the optimum level can increase the risk of GVHD³. Hence, various studies have been done to define the optimum dose of CD 34 + cell dose to get better engraftment without increasing the risk of GVHD^{4,5}. The optimum CD34+ cell dosage was usually considered to be 5×10^6 cells/kg body weight of the recipient⁶. CD34+ cell doses below the optimal level lead to delayed neutrophil and platelet recovery.

Engraftment can be established or monitored by neutrophil and platelet counts without transfusion support. Post-transplant neutrophil engraftment is defined as an absolute neutrophil count surpassing $0.5 \times 10^3/\mu\text{l}$ for 3 subsequent days. A platelet count of $>20 \times 10^3/\mu\text{l}$ without transfusion support for 7 subsequent days is considered platelet engraftment⁷.

HSCT can be broadly classified into autologous and allogeneic transplantations. Allogeneic HSCT can be either fully matched or haplo-identical. In our hospital, fully matched transplants were either fully matched related donors (MRD) or matched unrelated donors (MUD), and haploidentical transplants were managed by either TCR α/β depleted transplants or by T cell-repleted transplants with post-transplant cyclophosphamide (PTCy). The purpose of this study was to determine the rate of engraftment of neutrophils and platelets in patients undergoing transplants. It has been shown by studies that CD34+ cells play a significant role in engraftment kinetics. However, CD3+ cell count also plays a significant factor in T cell-repleted transplants with post-transplant cyclophosphamide (PTCy) as haploidentical HSCT increased. Hence, CD34+ cell count and CD3+ cell count, along with other characteristics and their role in engraftment kinetics is the heart of this study.

MATERIALS AND METHODS

This study was a prospective observational study of CD34+ cell counts received in our hospital haematology department for a period of 6 months from August 2023 to January 2024. The hospital's

ethical committee approval was obtained in August 2023. The minimal stem cell dose of 5 million cells per kilogram of the recipient's weight was infused. However, in haploidentical HSCT, particularly in TCR α/β depleted grafts, the infused stem cell quantity varied with the underlying conditions. All cases of paediatric (0–18 years old) PBSCT, including autologous PBSCT, fully matched related donor allogeneic PBSCT, matched unrelated donor allogeneic PBSCT, and haploidentical PBSCT were included in the study. Patients who had died due to various complications and graft failure were excluded from the study.

2ml of the product sample was received in the haematology laboratory for CD34+ cell quantification. CD34+ cell quantification was done through the NAVIOS EX flow cytometer (Beckman Coulter U.S.A.) and as per ISHAGE (International Society for Hemotherapy and Graft engineering) guidelines. CD3+ T cells were also quantified by the NAVIOS EX flow cytometer (Beckman Coulter U.S.A.). After quantification, the volume to be infused into the recipient was calculated per kg of the recipient and transplanted on the day of product/donor sample collection and CD34+ quantification. The next day of the transplant was taken as Day 1+. From Day 1+ to Day 28+, the neutrophils and platelet count were assessed in the haematology department by using the ADVIA haematology analyzer and by a peripheral smear. Wright Giemsa was used for staining the peripheral smear. In our institute, post-transplant neutrophil engraftment was defined as an absolute neutrophil count surpassing $0.5 \times 10^3/\mu\text{l}$ for 3 subsequent days. A platelet count of $>20 \times 10^3/\mu\text{l}$ without transfusion support for 7 subsequent days was considered platelet engraftment. Failure to engraft by Day 28+ was called graft failure.

Descriptive statistics were presented with frequency (percentage) and mean \pm SD for the categorical and continuous factors, respectively. A chi-square or Fisher's exact test was used to determine the association between two independent categorical factors. A Karl-Pearson correlation test was used to determine the relationship between CD34 and neutrophil engraftment. A P-value < 0.05 was considered statistically significant. All the statistical analysis was carried out using SPSS (IBM, 28.0).

RESULT

This study evaluated the neutrophil and platelet engraftment kinetics for 60 paediatric PBSCT patients. The mean and median age were 7.8 years and 7 years, respectively. Males occupied 58.3% (n = 35), and females occupied 41.7% (n = 25). The median day of engraftment was day 15+. The transplant type was broadly classified into autologous PBSCT which occupied 5% (n = 3) and allogeneic PBSCT which involved 95% (n = 57).

Type of Transplant

The allogeneic transplant was further categorized into the following categories: 1. Fully matched related donor (MRD) (either from a sibling or parents), 2. Fully matched unrelated donor (MUD), 3. haploidentical PBSCT with CD3+T cells repleted donor with PTCy, and haploidentical PBSCT with TCR α/β depleted donor. The earliest day of neutrophil engraftment was day 10+, and the latest was day 26+ in this study. This study didn't have any engraftment on day 27+ or day 28+. In view of only 5% (n = 3) of autologous transplants, no significant correlation was obtained with regard to autologous transplants and engraftment kinetics.

Fully matched allogeneic PBSCT

In fully matched PBSCT, MRD occupied 25% (n = 15) and MUD occupied 10% (n = 6), and all the cases had neutrophil engraftment on or before day 18+. In MRD PBSCT, 80% (n = 12) engrafted neutrophils between day 10+ and day 14+, and 20% (n = 3) engrafted neutrophils between day 15+ and day 18+. Within MUD PBSCT, 83% (n = 5) engrafted neutrophils between day 10+ and day 14+, and 16% (n = 1) engrafted neutrophils between day 15+ and day 18+.

Haploidentical PBSCT

In haploidentical PBSCT, all the cases with TCR α/β + T cells- depleted transplants, which is 10% (n = 6) of the total transplants, engrafted neutrophils in day 10+ to day 14+. While CD3+T cell-repleted transplants with PTCy occupied 50% (n = 30), 70% (n = 21) of this transplants got neutrophils engrafted between day 15+ and day 18+, 23.3% (n = 7) patients got neutrophils between day 19+ and day 22+, and

6.6% of the patients (n = 2) got neutrophils engrafted between day 23+ and day 26+.

The transplant type and its correlation with neutrophil engraftment in days are depicted in Figure 1.

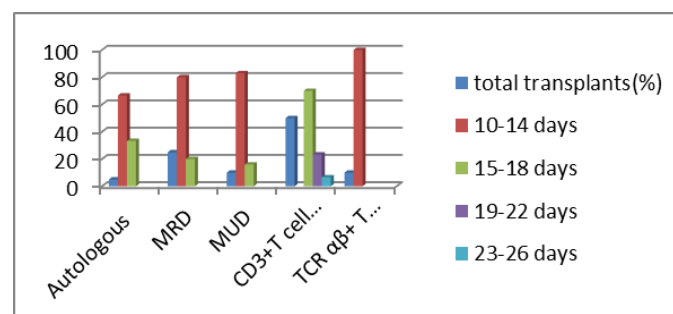


Figure 1. Transplant type and its days of engraftment

CD3+T cells repleted transplant and PTCy

We also correlated the neutrophil engraftment kinetics with the dosage of CD3+T cells infused in the PBSCT haploidentical transplant. It was further categorized depending on CD3+Tcell dosage into $\geq 2 \times 10^8$ cells/kg or $< 2 \times 10^8$ cells/kg of the recipient. Within this category, 90% (n = 27) of the patients had a CD3+T cell dosage of $\geq 2 \times 10^8$ cells/kg, of which 74.07% (n = 20) engrafted between day 15+ and day 18+, 22.22% (n = 6) engrafted between day 19+ and day 22+, and 3.7% (n = 1) engrafted between day 23+ and day 26+. 10% (n = 3) patients had CD3 dosage $< 2 \times 10^8$ cells/kg of the recipient, of which 33.3% (n = 1) patients had engraftment between day 15+ and day 18+, 33.3% (n = 1) patients had engraftment between day 19+ and day 22+, and 33.3% (n = 1) patients had engraftment between day 23+ and day 26+.

Primary illness

Based on the diagnosis, the patients were classified into the following 6 categories: 1) Hemoglobinopathies, which include thalassemia and sickle cell anemia, 2) Primary immunodeficiency, which had severe combined immunodeficiency (SCID), congenital dyserythropoietic anemia (CDA), lipopolysaccharide-responsive vesicle trafficking, beach-and-anchor-containing (LRBA) deficiency, bare lymphocyte syndrome and immune dysregulation, polyendocrinopathy, enteropathy, X-

linked (IPEX) syndrome, 3) haematological malignancies including B and T ALL, AML, MLL rearranged AML, and myelofibrosis, 4) Solid tumours include neuroblastoma, medulloblastoma, and relapsed Wilm's tumour, 5) Aplastic anaemia, and 6) Others include Mendelian susceptibility to mycobacterial disease and speech delay, X-linked adrenoleukodystrophy, glucose phosphoisomerase gene mutation with transfusion-dependent anaemia with iron overload, myelodysplastic neoplasm, and Hunter syndrome. Hemoglobinopathies were 48.3% (n = 29), primary immunodeficiency were 15% (n = 9), haematological malignancy were 21.7% (n = 13), solid tumours were 5% (n = 3), aplastic anaemia was 1.7% (n = 1), and others included % (n = 5).

Platelet engraftment

With regards to platelet engraftment, nearly all the patients had platelet transfusion before the engraftment criteria for platelets were fulfilled. However, the majority of the patients did not get platelet transfusions following platelet engraftment, despite the fact that the majority of them had moderate to severe thrombocytopenia for a prolonged time.

Engraftment and other factors

The demographic and clinical factors were enlisted, and each factor was correlated with neutrophil engraftment. A 'p' value was calculated for every factor and was listed in Tables 1 and 2. It was found that transplant type and CD3+T cell dosage levels correlated with neutrophil engraftment with a 'p' value of <0.001, which was statistically significant. In the case of a fully matched PBSCT, either MRD or MUD, the patients had maximum engraftment within day10+ to day14+, and none of the patients took more than 18 days for engraftment. In haploidentical TCR $\alpha\beta$ + T cell-depleted transplants, neutrophil engraftment occurred between day10+ and day14+. While haploidentical CD3+Tcells-repleted PBSCT patients had engraftment maximum at day15+ to day18+, few had engraftment between day19+ and day22+ days, and few patients had engraftment between day23+ and day26+.

Engraftment and CD34

The mean CD34+ cell dosage was 8.21×10^6 cells/kg, and the median dosage was 7.74×10^6 cells/kg (ranging from 2.77×10^6 cells/kg to 17×10^8 cells/kg). With regards to CD34 and neutrophil engraftment, the Pearson coefficient was used, and the results were listed in Table 3 and represented in Figure 2. The 'p' value for CD34 levels and neutrophil engraftment was 0.895 and had a poor correlation in this study.

Result summary

Table 3 shows that there was a very poor correlation between CD34 and days of Neutrophil engraftment (ρ -0.018; *P*-value 0.895). The relationship was statistically not significant.

Engraftment occurred between day 10+ and day 14+ in the majority of patients who underwent fully matched MRD and MUD PBSCT, and haploidentical TCR alpha/beta-depleted transplants. Although the highest engraftment was observed in haploidentical CD3+ T cells repleted PBSCT with PTCy at day 15+ to day 18+, there was a slight delay in engraftment as compared to the other types of allogeneic PBSCT. Also, a CD3+T cell dosage of $\geq 2 \times 10^8$ cells/kg favored engraftment before day 18+.

Table 1: Demographic factors

Parameters	Day of Neutrophil engraftment (In days)				Overall, (n=60)	P-value [^]
	10 – 14, (n=25)	15 – 18, (n=26)	19 – 22, (n=7)	23 – 26, (n=2)		
Age(In years)						
<1	2 (8)	-	-	-	2 (3.3)	0.325
1 – 5	12 (48)	4 (15.4)	2 (28.6)	-	18 (30)	
6 – 10	7 (28)	12 (46.2)	2 (28.6)	1 (50)	22 (36.7)	
11 – 15	3 (12)	8 (30.8)	3 (42.9)	1 (50)	15 (25)	
16 – 18	1 (4)	2 (7.7)	-	-	3 (5)	
Gender						
Male	15 (60)	16 (61.5)	4 (57.1)	-	35 (58.3)	0.401
Female	10 (40)	10 (38.5)	3 (42.9)	2 (100)	25 (41.7)	

[^] Chi-square/Fisher's exact test**Table 2.** Clinical factors

Parameters	Day of Neutrophil engraftment (In days)				Overall, (n=60)	P-value [^]
	10 – 14 (n=25)	15 – 18, (n=26)	19 – 22, (n=7)	23 – 26, (n=2)		
Transplant type						
Autologous	2 (8)	1 (3.8)	-	-	3 (5)	<0.001
Fully matched MRD	12 (48)	3 (11.5)	-	-	15 (25)	
Fully matched MUD	5 (20)	1 (3.8)	-	-	6 (10)	
Haploidentical with CD3+ T cells repleted	-	21 (80.8)	7 (100)	2 (100)	30 (50)	
Haploidentical with TCR α,β+ T cells depleted	6 (24)	-	-	-	6 (10)	<0.001
CD3 infused(cells/kg)						
Other cases	25 (100)	5 (19.2)	-	-	30 (50)	
CD3 <2×10 ⁸	-	1 (3.8)	1 (14.3)	1 (50)	3 (5)	
CD3 ≥2×10 ⁸		20 (76.9)	6 (85.7)	1 (50)	27 (45)	
Diagnosis Hemoglobinopathies						
Primary immunodeficiency	10 (40)	14 (53.8)	4 (57.1)	1 (50)	29 (48.3)	0.775
Hematological malignancy	6 (24)	1 (3.8)	2 (28.6)	-	9 (15)	
Solid tumours	5 (20)	7 (26.9)	-	1 (50)	13 (21.7)	
Aplastic anemia	2 (8)	1 (3.8)	-	-	3 (5)	
Others	-	1 (3.8)	-	-	1 (1.7)	
	2 (8)	2 (7.7)	1 (14.3)	-	5 (8.3)	

[^] Chi-square/Fisher's exact test; Boldface indicates statistical significance**Table 3.** Correlation between CD34 and Neutrophil engraftment

Parameters	Mean ± SD (Range)	Rho (95% CI)	P-value*
CD34	8.74 ± 3.61 (2.77 – 20)	-0.018 (-0.272 to 0.240)	0.895
Neutrophil engraftment	15.73 ± 3.22 (11 – 26)		

*- Karl-Pearson correlation test

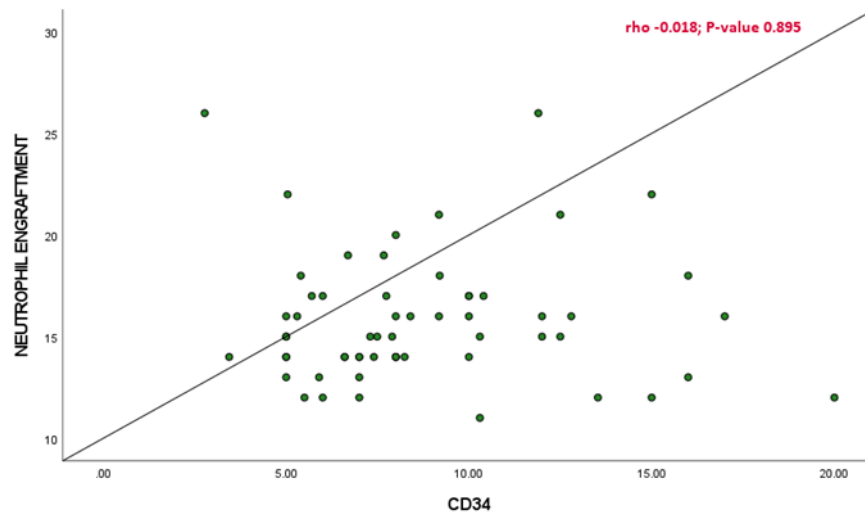


Figure 2. Scatter plot for Neutrophil engraftment and CD34

DISCUSSION

A tiny percentage of cells that express the CD34 antigen are hematopoietic stem cells. All the lymphoid and myeloid progenitors were present in the CD34 population⁸. The pre-apheresis count of circulating CD34 cells was the most reliable indicator of cell yield⁹. Sienna et al. conducted a detailed review article on CD34+ cells, their identification, the role of growth factors, and a comparative analysis of studies using varying CD34+ cell dosages⁸.

Abraham et al. demonstrated that, in general, faster engraftment was obtained with a CD34+ cell dosage of 5×10^6 cells/kg. They also emphasized that there was no benefit shown at a dose larger than 5×10^6 cells/kg⁶. In the case of autologous transplants, Benzinger et al. showed that a CD34+ cell dosage of 5×10^6 cells/kg hastens platelet recovery, still they didn't find any significant correlation between CD34+ cell dosage and neutrophil engraftment, while this study didn't show a significant correlation between CD34+ cell dosage and both neutrophil and platelet engraftment¹⁰. This may be due to the use of optimum CD34+ cell dosage levels, in addition to platelet transfusion. Similarly, Chang et al. proposed that platelet engraftment can be achieved with a CD34+ cell dosage of 2.19×10^6 cells/kg and mentioned certain factors like colony-stimulating factor dosage as their advantage, still they also didn't

have a significant correlation with neutrophil engraftment⁶. Thus, the optimal CD34+ cell dosage was found to be $\geq 5 \times 10^6$ cells/kg^{6,9,11}.

In haploidentical transplants, T cells from donors have both TCR $\alpha\beta$ + T cells and TCR $\gamma\delta$ + T cells. TCR $\alpha\beta$ + T cells are involved in GVHD, and TCR $\gamma\delta$ + T cells are involved in graft engraftment^{12,13}. Hence, a TCR $\alpha\beta$ + T cell-depleted donor sample can lead to successful engraftment due to intact TCR $\gamma\delta$ + T cells and a reduced risk of GVHD due to TCR $\alpha\beta$ + T cell depletion. On the other hand, the other method is CD3+T cell-repleted transplants with PTCy. This is the in vivo technique for T cell depletion, wherein the donor's optimal number of CD3+T cells is transplanted with the graft and, a high dose of cyclophosphamide is utilized to deplete T cells after the transplant¹⁴. The optimal engraftment rate requires a minimum CD3+T cell dosage of 1.5×10^8 /kg of recipient body weight¹⁵. In our study, we correlated engraftment with CD3+T cell dosage with a cutoff of 2×10^8 cells/kg of the recipient. We found that greater than 70% of engraftment occurs before day 18+ when $\geq 2 \times 10^8$ cells/kg is infused, which is in close agreement with the results by Kesavan et al.⁽¹⁵⁾. There are several factors involved in graft engraftment, and over the years, a number of risk factors related to graft failure have been discovered. The risk factors include the following: 1) ABO

mismatching: Olsson et al. noted that there is no longer a chance of graft failure when an ABO incompatible graft is used, yet Lowsky and Messner et al. found few PRCA complications in the few ABO mismatched transplants^{16,17}, 2) HLA disparity: HLA-mismatched unrelated grafts show an increased risk of graft failure than fully matched or haploidentical unrelated grafts¹⁸, 3) the primary illness¹⁸, 4) the origin of the graft: bone marrow transplant has a three-times greater risk than PBSCT⁽¹⁸⁾, 5) CD3+ T cells and CD34+ cells dosage: a CD3 cell dosage of $<2.4 \times 10^8/\text{kg}$ may result in primary graft failure, while CD34+ cell dosage plays an important role in secondary graft failure⁽¹⁸⁾, and 6) The major factor in transplants or graft failure is viral infections, such as parvovirus, HHV-6, and CMV, as well as medications that may cause myelosuppression¹⁸.

Abraham et al. did a retrospective study for 10 years, from November 2008 to December 2017, in their institute⁶. They included 131 patients. They demonstrated the gender distribution, age distribution, route of transplant, type of transplant, and the median time for neutrophil engraftment and platelet engraftment. According to their study, the median time for neutrophil engraftment was 11 days in autologous stem cell transplants, 15 days in allogeneic stem cell transplants, and 12 days was the median time for platelet engraftment in both autologous and allogeneic stem cell transplantations, while this study had median time for neutrophil engraftment as 15 days. Depending on the CD34+ cell dose, they divided the patients into three groups, and they found no difference in time for either neutrophil or platelet engraftment. They also found no difference in time for engraftment between autologous and allogeneic stem cell transplantation⁶. While in this study, we could not compare the engraftment between autologous and allogeneic transplants because of only 5% autologous transplants. However we could compare the engraftment kinetics within the subtypes of allogeneic transplants.

Kamel et al. did a study from 2001 to 2002 and included the patients who received allogeneic PBSCT from HLA identical siblings². In their study, they established some correlation between time, neutrophil engraftment, and the three following

parameters: CD34+ cell dose, CD34+/CD61- levels, and CD34+/CD33- levels. They had neutrophil engraftment between 8 and 26 days, while this study had engraftment between 10 and 26 days².

Chang et al. did a study for 6 years, and they included only the allogeneic HSCT with HLA-identical or unrelated donors⁷. In their study, the median time for neutrophil engraftment was 13 days, and the median time for platelet engraftment was 16 days. Of their 348 patients, 17 died without achieving platelet engraftment. They emphasized the relationship between CD34+ cell dose and platelet engraftment alone⁷. This study showed that >80% of fully matched related donors and fully matched unrelated donors may engraft within 14 days, with a median engraftment period of 15 days.

CONCLUSION

The time taken for engraftment varied by the donor source. It was earlier in fully matched HSCT, ideally between day 10+ and day 14+, whereas it is day 15+ to day 18+ in haploidentical HSCT. Also, when CD3 is $\geq 2 \times 10^8$ cells/kg, engraftment occurred in < 18 days compared to grafts with CD3 $< 2 \times 10^8$ cells/kg, where it took more than 18 days. Thereby we recommend using CD34 cut-off minimum of $\geq 5 \times 10^6$ cells/kg in fully matched HSCT and CD3 of $\geq 2 \times 10^8$ cells/kg for optimal and early engraftment. This study showed a poor correlation between neutrophil engraftment and CD34 levels, which may be due to the use of an optimum dosage of CD34+ cells, which is $\geq 5 \times 10^6$ cells/kg in our hospital.

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