

Benefits of Pre-harvest Peripheral Blood CD34 Counts Guided Single Dose Therapy with PLERIXAFOR in Autologous Hematopoietic Stem Cell Transplantation: A Retrospective Study at a Tertiary Care Institute in India

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Abstract Peripheral blood is a convenient source of stem cells for hematopoietic stem cell transplantation. However, in autologous transplants, the harvest failure rates are high because of inadequate mobilization using G-CSF alone. Plerixafor is a potent mobilizer when used with G-CSF. However, its routine use is limited by high cost. This is a retrospective study done at a tertiary care oncology centre in India. All the harvest records were analyzed between Jan 2015 and Nov 2017. May 2016 onwards pre-harvest peripheral blood CD34 count was done in all cases of autologous transplants on day 4 of G-CSF therapy and they were given a single dose of Plerixafor if counts were < 20 cells per cumm. The results were compared amongst various

groups. A total of 321 cases were analyzed. 172/321 were allogeneic transplant cases of which 5% (n = 7) failed to achieve a target live stem cell dose of > 2 million per kg of the recipient. The overall failure rate in autologous group (n = 149) was 27% (n = 41) ($p \leq 0.001$ auto vs. allo). The failure rate was higher (36%, n = 28/77) when no intervention with Plerixafor was done. The overall failure rate in the group treated with pre-harvest 34 count based single dose therapy of Plerixafor was 18% (n = 13/72, $p = 0.01$). However, within this intervention group, the patients who had pre-harvest peripheral blood CD34 above the desired cutoff had a higher failure rate of 21% ($p = 0.13$). Pre-harvest CD34 count based intervention with Plerixafor help optimizing the cost.

Disclaimers: The identity of the patient is not disclosed here in this case.

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Introduction

Autologous stem cell transplant (ASCT) is now seen as a standard of care consolidation therapy in a variety of hematopoietic and non-hematopoietic neoplasm [1, 2]. The successful engraftment after conditioning regime requires a minimum CD34+ cell dose of 2 million per kg body weight of the recipient [3]. This dose cannot be achieved if peripheral blood harvest is done under resting conditions as in normal physiological states every individual has a very low number of stem cells in peripheral blood (0.01–0.05% of the nucleated cells) [4]. Thus prior to harvest, it is essential to mobilize the stem cells from marrow pools into the peripheral blood. A number of mobilization agents have been introduced, of which most common is G-CSF [5].

The issue with ASCT is exposure of the donor (patient in these cases) to multiple cycles of chemotherapy which is

toxic to the stem cell pool. Thus, it is often observed that in ASCT it is often difficult to achieve the desired dose in the first harvest sitting and repeated procedures are exhaustive for the already morbid individual [6].

Plerixafor is a CXCR4 antagonist which has shown to be useful for stem cell mobilization. When used alone Plerixafor is a very poor mobilizer however when used with G-CSF its effect is substantially potentiated. Several studies have shown that the use of Plerixafor for stem cells mobilization significantly increases the success rate of stem cell harvest [2, 3, 7]. However, using preemptive Plerixafor in all cases significantly increases the procedure cost. In addition to mobilizing the resting stem cells, Plerixafor mobilizes the dormant leukemic stem cells from their protective niche and sensitize them to chemotherapy [3].

At our institute, we had high harvest failures in cases of autologous transplants. Published literature has shown that pre-harvest CD34 based guided therapy with Plerixafor significantly reduces the failure rates. The best cutoff below which Plerixafor has to be given was < 20 CD34+ cells in one of the published study [3]. In accordance with this study, we started single-dose therapy with Plerixafor in all patients with autologous transplants who had pre-harvest peripheral blood CD34 counts < 20 cells per cumm. In the current study, we evaluate the benefits of this approach.

Materials and Methods

This is a retrospective analysis of the patient's data at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India. All the cases coming for first harvest procedure were included in the study and those who were coming for prior failure (insufficient CD34 dose in first harvest) were excluded from study.

- All allogenic donors (Jan 2015 to Nov 2017) and autologous patients (Jan 2015 till May 2016) were given G-CSF at a dose of 10–15 mcg per kg per day and harvest was done on day 5. No CD34 guided Plerixafor therapy was given to these cases.
- May 2016 onwards pre-harvest CD34 was done on day 4 in all cases of ASCT and based on the results of CD34 counts two groups were formed:
 - < 20 CD34+ cells per cumm: single dose of Plerixafor 0.24 µg per kg body weight of donor was given.
 - > 20 CD34+ cells per cumm: no change
- Harvest was done on day 5 in all patient after final G-CSF dose

- Failure was defined as the inability to achieve > 2 million live stem cell/kg/dose in first harvest sitting.
- Failure rates were compared between:
 - Allogenic and autologous group
 - Those who were taken for pre-harvest CD34 based therapy (after May 2016) versus non-intervention group (before May 2016) within autologous cases
 - Those who were given Plerixafor versus those who were not given (autologous cases within the intervention group i.e. after May 2016)
 - Fischer exact test was used to compute the significance of the difference in failure rates.
- CD34 cell analysis was done using ISHAGE protocol with single platform bead-based assay (BD stem kit reagent) on CANTO-II 3 laser 8 colour flow cytometer with 7-AAD used for viability testing.

Results

A total of 324 new patients/donors taken up for stem cell harvests were evaluated. Three of these were excluded, as the harvest failure in these cases was due to machine or procedure related errors. The final results are described in 321 cases.

Patient Demography Profile

The patient's characteristics are described in Table 1.

Table 1 Demography details of 321 patient enrolled in the study after applying exclusion criteria

Characteristic	Autologous	Allogenic
Number	149	172
Age range (median) years	2–67 (52)	1–64(30)
Sex ratio (male:female)	2.1	2.44
<i>Disease profile</i>		
Acute leukemia	0	105
Multiple myeloma	94	0
DLBCL	10	2
Other NHL	20	10
Hodgkin lymphoma	17	0
Thalassemia	0	24
Aplastic anemia	0	12
Non hematopoietic neoplasm	8	0
MDS, MPN, MDS/MPN, HLH	0	19

Pre Harvest CD34 Results and Failure Rates

There were a total of 321 harvests were finally analyzed (Table 1, first arrow). A total of 172 harvests were done for allogenic transplants over this period of time (Table 1, second arrow) with a total of 7 (5%) failures. There were 149 cases in the autologous group (Table 1, third arrow) with a total 41 (27%) failures. 77 of these did not receive any CD34 guided Plerixafor therapy (prior to May 2016, Table 1: 4th arrow left half). Remaining 72 cases (Table 1: 4th arrow right half) were analyzed for preharvest CD34 levels and single dose Plerixafor was given if counts were less than 20 cells per cumm (Table 1, first short arrow) and no intervention if counts were more than 20 cells per cumm (Table 1, last arrow). Failure rates amongst various groups along with *p* value are described in Fig. 1.

Benefits of Approach

Failure rates were also compared within the intervention group (ASCT May 2016 onwards) and the failure rates

were compared between those who received and those who didn't receive Plerixafor. The results are summarized in Fig. 1.

Discussion

The present study, studies the benefits of peripheral blood CD34+ cell guided therapy with Plerixafor.

Failure Rates (Autologous vs. Allogenic)

Inability to achieve the adequate dose of stem cells (> 2 million cells per kg of the recipient) for transplant is a frustrating issue both for patients and the clinicians. Previously numerous studies have shown that failure rates in autologous transplants are much higher in comparison to allogenic transplant. The main reason for this phenomenon is the toxicity to the stem cell pool exerted by the chemotherapy used in autologous transplants. In current series also it was seen that the failure rates in allogenic

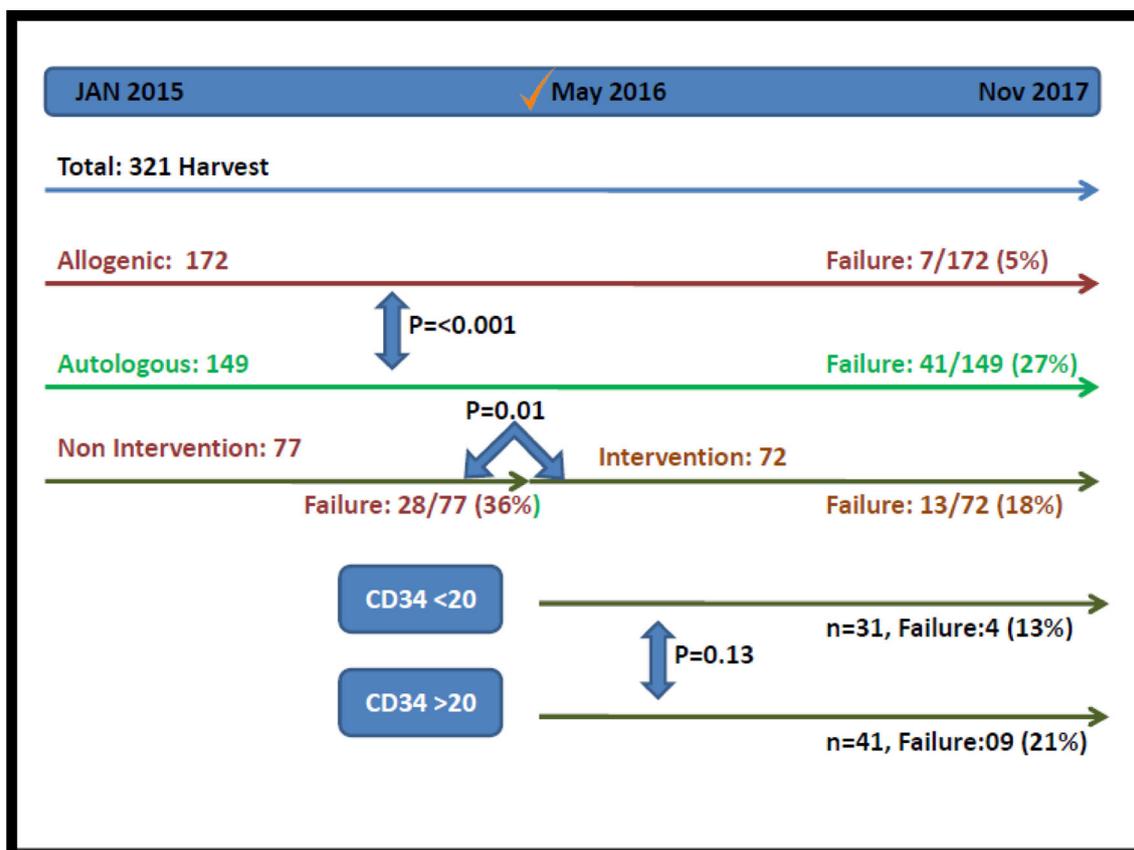


Fig. 1 The figure summarizes the results of the study. Each extended arrow here denotes a group with the name mentioned on the left end of each arrow and failure rates or right end. The failure rate significance is mentioned as *p* value with the comparison groups being marked with solid arrows. 2016 is the time point where pre-

harvest peripheral blood stem cells stem cell guided single-dose therapy with Plerixafor was introduced. The results of autologous group are further divided into non intervention (before May 2016) and intervention (after May 2016)

transplant were just 5% in comparison to 27% in autologous (overall failure) cases ($p \leq 0.001$). This failure rate was even higher (36%) when no intervention with Plerixafor was done. Failure rates up to 40% have been described in autologous transplants as per the published literature [8].

Benefits of Guided Plerixafor Therapy

The overall failure rate in the autologous group was 27%. It was observed that when pre-harvest peripheral blood CD34 guided therapy was used, the failure rates were reduced to 18 versus 36% when given G-CSF alone ($p = 0.01$). Similar failure rates of 6–12.5% have been described previously when Plerixafor + G-CSF based mobilization was used in all patients [9]. The study published on Indian myeloma patients shows failure rates of 16% when Plerixafor + G-CSF based mobilization was used as a preemptive method in all autologous myeloma transplants [9]. The failure rate of 18% in the current study is almost similar to 16% obtained by the preemptive approach. Thus it appears that the benefits of preemptive approach can be obtained by restricted use of Plerixafor in a selected group of patients. This approach can help optimizing the cost in economically constrained settings. Giralt et al. [8] have also concluded that pre-harvest CD34 guided mobilization method can prevent unnecessary Plerixafor use.

Is Pre-emptive Plerixafor Required?

We have observed that the benefits of preemptive approach can be obtained by pre-harvest CD34 guided therapy. However, it was observed that failure rate in the patients with pre-harvest CD34 count > 20 , who were not given any Plerixafor was higher as compared to those who were given Plerixafor (21 vs. 13%). This difference, however, was not significant statistically ($p = 0.13$). Thus, this question is left unanswered as it can only be answered when a prospective comparison trial is made between guided and preemptive therapy. However, it can be hypothesized that if all benefits of preemptive therapy are obtained with guided approach itself than it is unlikely that the patients who failed harvest in spite of having > 20 CD34+ cells per cumm will show benefits with Plerixafor. The study by Villa et al. [3] has shown in a prospective trial that best benefits are obtained when a cutoff of < 20 CD34+ cells per cumm is taken to guide Plerixafor therapy.

Conclusions

- Harvest failure rates in peripheral blood autologous transplants are much higher as compared to allogenic transplants (27 vs. 5%, $p \leq 0.001$).

- Using pre-harvest peripheral blood CD34 counts on day 4 of G-CSF as a guide to Plerixafor therapy can significantly bring down this failure rate (18 vs. 36%, $p = 0.01$). The benefits are similar to what is obtained by preemptive Plerixafor in all patients (comparison to published literature).
- However, the failure rates remain high in the subgroup that was not given any Plerixafor (21%) ($p = 0.13$).

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study involves a retrospective analysis of data and no animal subjects were involved.

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