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Is neutropenic fever an obstacle to effective stem cell harvesting?

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Abstract:

INTRODUCTION: Autologous stem cell transplantation (ASCT) is a well-established consolidation treatment for many hematologic cancers which delivers prolonged survival. A subset of patients' adequate stem cell harvest is not achievable with a solitary use of granulocyte colony-stimulating agents (G-CSF). Generally, chemomobilization is employed for patients failing G-CSF and its most feared complication febrile neutropenia (FN).

MATERIALS AND METHODS: Here, we aimed to investigate the impact of the FN in chemomobilization on apheresis outcomes and engraftment. One hundred and eighty-three patients with the diagnosis of lymphoma or myeloma who underwent chemomobilization between 2015 and 2020 were included in the study.

RESULTS: Forty-three patients experienced FN. All patients received G-CSF. All myeloma patients were mobilized with 4 g/m^2 cyclophosphamide, but it was heterogeneous for lymphoma patients. The precollection blood counts, harvested CD34+ hematopoietic stem cells (HSCs)/kg, apheresis count, and engraftment durations were recorded. Preapheresis leukocyte and platelet were lower in the FN group (P = 0,004 and P = 0,001). Peripheral CD34 HSCs and total harvested CD34 HSCs were similar among groups (P = 0.25 and P = 0.9). More apheresis was needed in the FN group, but it was not significant (P = 0.07). Undergoing ASCT was similar (P = 0.7); however, platelet and neutrophil engraftment durations were slower in the FN group (P = 0.05 and P = 0.001).

CONCLUSION: Harvesting sufficient CD34+ HSCs from patients with FN is still feasible; however, FN treatment should begin promptly, and further apheresis sessions may be required.

Keywords:

Autologous stem cell transplantation, chemomobilization, febrile neutropenia, neutropenic fever, stem cell mobilization

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Introduction

Autologous stem cell transplantation (ASCT) is a well-established consolidation treatment for many hematologic cancers which delivers prolonged survival.[1,2] The ideal peripheral stem cell mobilization (PBSC) method has not been yet established, and it varies broadly among centers.[3] For ASCT, minimum collected CD34+ hematopoietic stem cells (HSCs/kg) was regarded as 2×10^6 and optimal collected CD34+ HSCs/kg defined as 4×10^6 by previous reports.[4]

The use of granulocyte colony-stimulating agents (G-CSF) alone for PBSC has resulted in decreased risks linked to morbidity, death, and hospitalization. However, for a subset of patients' adequate stem cell harvest is not achievable with a solitary use of G-CSF. Chemomobilization has its own advantages and limitations. It is appropriate to initiate stem cell mobilization after most chemotherapy regimens that are primarily used to treat the underlying disease. Compared with

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G-CSF alone, the extra advantages of chemomobilization include fewer apheresis processes and yields greater CD34+ HSCs.[5,6] In addition, particularly in lymphoma, it reduces tumor burden and diminishes the risk of tumor cell contamination in the apheresis product. Indeed, chemomobilization takes place frequently as a part of the induction or salvage treatment cycle for patients with lymphoma, therefore, reducing increased costs and complications involved in using additional mobilization chemotherapy.[6] For *multiple myeloma* (MM), it is generally used cyclophosphamide for chemomobilization. High-dose cyclophosphamide has an increased risk of adverse events such as febrile neutropenia (FN), prolonged antibiotic therapy, need for transfusions, and prolonged hospitalization with no additional benefit to tumor burden.[7] Another issue regarding chemomobilization is the increased variability among patients to figure out the precise timing of mobilization and it requires close follow-up for blood counts and peripheral CD34+ HSCs counts to determine the commencement of the apheresis process.[5] Chemomobilization is associated with increased stem cell harvest but also with severe toxicities such as FN, which must be weighed against the benefits.[3,8,9]

The development of neutropenia is a frequent complication observed in cancer patients. Neutrophils are essential for warranting host defense against infections, particularly for bacterial and fungal agents. The prevalence of infections increases with the severity and duration of neutropenia.[10] Avoidance of FN and prompt intervention with antibiotics and supportive care is crucial since the frequency of severe conditions such as end-organ failure is high, and mortality can be observed up to 11% and in cases of sepsis, mortality may rise to 50%.[11-13]

Predisposing aspects of FN and its effect on the stem cell harvest and the capacity to undergo ASCT have not been well defined. Here, we aimed to investigate the impact of the FN in chemomobilization on apheresis outcomes and engraftment.

Materials and Methods

Patients

Patients aged 18 years and older with the diagnosis of lymphoma or myeloma who underwent chemomobilization between 2015 and 2020 were included in the study. One hundred and eighty-three patients enrolled in the study, with 43 patients who experienced FN and 140 patients with no FN during chemomobilization. Treatment details before mobilization were recorded. After mobilization, patients were followed up to ASCT and engraftment durations were recorded. Patients who failed second mobilization and patients who had successfully mobilized with a solitary use of G-CSF were excluded from the study.

The study was carried out under the principles outlined in the Helsinki declaration. All patients signed informed consent and local institutional ethical approval was obtained.

Mobilization regimens and stem cell mobilization

Chemomobilization was utilized for myeloma patients failing to mobilize with only G-CSF and for relapsed/refractory lymphoma patients during their salvage treatments.

All patients were admitted and followed up in the in-patient setting from initiation of mobilization regimen to the achievement of stem cell collection. All myeloma patients (n = 38, 100%) were mobilized with 4 g/m^2 cyclophosphamide, but it was very heterogeneous for lymphoma patients. Lymphoma patients were mobilized mostly with their induction or salvage treatment regimen. The most prevalent regimens utilized were GDP ± R (n = 63, 43.4%), DHAP ± R (n = 18, 12.4%), and cyclophosphamide (n = 17, 11.7%). Plerixafor was used in a few patients with the on-demand strategy.

After the mobilization, regimen was initiated, patients were followed up to the white blood count nadir and then G-CSF was initiated. All patients received G-CSF, mostly filgrastim or lenograstim, and their biosimilar equivalents were given subcutaneously as a total dose of 10 μg/kg/day for 4–6 days until the apheresis procedure is completed. Leukocyte count was monitored and when it is above 1 × 10^9/L, flow cytometry peripheral blood CD34+ HSCs count was performed. Leukapheresis was started after confirming flow cytometry peripheral blood CD34+ HSCs count is on target (>20/μL was used as institutional practice). If peripheral CD34+ HSCs count is not on target, G-CSF was carried on, and the leukapheresis was commenced again on the following day. The apheresis procedure was performed mostly by peripheral venous access (61.7%). Leukapheresis was implemented over a continuous flow cell separator (Fresenius Kabi, COM. TEC, Germany). For each leukapheresis, the processed blood volume was two- and three-fold of patients' blood volume.

Neutropenic fever and treatment

Neutropenia was described as an absolute neutrophil count (ANC) <1000/μL (<1.0 × 10^9/L), severe neutropenia as ANC <500/μL (<0.5 × 10^9/L), and profound neutropenia as < 100/μL (<0.1 × 10^9/L). FN is identified by the above-defined neutropenia accompanying a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) continued over 1 h.[14] Cefoperazone/sulbactam or piperacillin/tazobactam

was administered initially for patients with FN and no focus on infection. Patients with persistent fever for >3 days were switched to meropenem. For patients with persistent fever for >5 days, amphotericin B was administered additionally as empirical antifungal treatment. Patients with identified infection focus and patients with identified pathogens in cultures were treated accordingly.

Treatment response and autologous stem cell transplantation

All patients had treatment response evaluation before ASCT, patients with progressive disease did not advance to ASCT. Bone marrow biopsy, serum, urinary protein electrophoresis, and immunofixation tests are employed for MM patients, whereas positron emission tomography–computed tomography is employed for lymphoma patients. Upfront ASCT after induction therapy was performed for MM patients. For Hodgkin's lymphoma (HL) patients, ASCT was performed for relapsed/refractory patients with chemosensitive responses to the salvage therapy. For non-HL, it was heterogeneous, for patients with mantle cell lymphoma, primary central nervous system lymphoma, and peripheral T-cell lymphoma (except anaplastic lymphoma kinase-positive) received ASCT as in upfront strategy but other non-HLs such as diffuse large B-cell lymphoma, follicular lymphoma received ASCT in relapsed/refractory setting.

Engraftment durations

The engraftment definition for neutrophils was defined as the 1st day when the ANC was ≥500/μL for 3 consecutive days, and for platelets, it was defined as the 1st day when platelet count was ≥20,000/μL without transfusion for 7 consecutive days.[15]

Statistical analyses

Analyses were processed with IBM SPSS Statistics for Windows (Version 26.0. Armonk, NY, USA) software. Demographical and clinical data were summarized with descriptive statistics. Categorical variables were displayed as a ratio; numerical variables were displayed as median (minimum–maximum). Differences between FN groups for continuous variables were analyzed with Mann–Whitney *U* and for categorical variables with the Chi-square test. $P < 0.05$ were considered statistically significant.

Results

Patients

The study included a total of 183 patients with 43 (23.5%) developing FN and 140 (77.5%) having no FN. The median age of the FN group was 53 (19–71) and for the non-FN group, it was 43 (17–72), which was similar between groups ($P = 0.1$). The distribution of gender and body mass index among groups were comparable ($P = 0.8$ and $P = 0.9$). The diagnosis of patients between groups was nonhomogenous with more myeloma patients and fewer HL patients observed in the FN group ($P = 0.001$). The rate of radiotherapy implementation and premobilization disease status were similar among groups ($P = 0.1$ and $P = 0.5$, respectively). Bone marrow infiltration was more frequent in the FN group ($P = 0.001$). Characteristics of the patients were displayed in Table 1.

Febrile neutropenia group

The median day of hospitalization for the FN group was 19.5 (13–36). Fever occurred on the median 11th day (3–17) after initiation of mobilizing regimen. Pathogen identification was possible in 13 cases and the focus of infection was evident in four cases. The details of the FN group are given in Table 2.

Mobilization and transplant outcomes

Peripheral venous access was used for most procedures (61.7%). The rate of usage for central venous access was similar among groups ($P = 0.6$). Chemomobilization was applied to all cohorts, but for some patients, there was a need for plerixafor, plerixafor usage among groups was homogenous ($P = 0.9$). Peripheral CD34+ HSCs/μL count and total harvested CD34+ HSCs/kg were comparable in groups ($P = 0.25$, $P = 0.9$). In the FN group, more apheresis procedures

Table 1: Patient characteristics

Parameters	Patients with febrile neutropenia (*n*=43), *n* (%)	Patients without febrile neutropenia (*n*=140), *n* (%)	*P*
Age	53 (19-71)	43 (17-72)	0.1
Gender (male/female)	27/16	91/49	0.8
Body mass index (kg/m²)	25.3 (15.2-38.7)	25.7 (16.9-38.6)	0.9
Diagnosis			
HL	4 (9.3)	45 (32.1)	0.001*
NHL	22 (51.2)	74 (52.9)	
MM	17 (39.5)	21 (15)	
Line chemotherapy			
1-2	35 (81.4)	103 (73.6)	0.3
≥3	8 (18.6)	37 (26.4)	
Radiotherapy	11 (25.6)	21 (15)	0.1
Disease status			
CR	15 (34.9)	57 (40.7)	0.5
PR-VGPR	22 (51.1)	58 (41.4)	
Stable/refractory	6 (14)	25 (17.9)	
BM involvement in diagnosis	25 (58.1)	42 (30)	0.001*

*$P<0.05$ statistically significant. BM=Bone marrow, CR=Complete remission, HL=Hodgkin's lymphoma, MM=Multiple myeloma, NHL=Non-Hodgkin's lymphoma, PR=Partial remission, VGPR=Very good partial response for multiple myeloma

were needed to reach adequate stem cell harvest, but it was not statistically significant ($P = 0.07$).

ASCT was not feasible for some of the cohorts due to various reasons. ASCT treatment frequency was similar between groups ($P = 0.7$). Both platelet and neutrophil engraftment were slower in the FN group ($P = 0.05$ and $P = 0.001$). The details of the mobilization and transplant outcomes are demonstrated in Table 3.

Discussion

We have observed peripheral blood CD34+ HSCs/kg and total harvested CD34+ HSCs/kg was comparable among groups. The apheresis count to reach adequate harvest was higher in the FN group; however, this did not reflect statistical significance. Precollection white blood count, hemoglobin, and platelet were lower in the FN group.

Occasionally, stem cell mobilization with G-CSF does not yield sufficient CD34+ HSCs for a group of patients. Although G-CSF alone has advantages such as less toxicity and no requirement of hospitalization. G-CSF with chemotherapy – chemomobilization – has unique aspects. It is demonstrated that chemomobilization yields greater CD34+ HSCs and ensures fewer apheresis procedures.[5,6] Furthermore, debulking tumor load is feasible with chemomobilization.[6] The risk of prolonged hospitalization, transfusion need, and serious infections such as FN are arising with chemomobilization.[3,7-9,16,17] The timing of apheresis procedure in solitary use of G-CSF is almost definite and clear, but it is not anywhere near chemomobilization with various protocols and patient-related factors make the operation very indecisive, raising a need for close follow-up.[5]

In earlier studies, poor mobilization was described as the yield of $<4 \times 10^6$ CD34+ HSCs/kg over 5 apheresis days, or the requirement of >two mobilization cycles to reach the target.[18-20] There are several unfavorable risk factors for the lessened yield after stem cell mobilization such as advanced age, multiple line chemotherapies, radiotherapy, prolonged lenalidomide therapy, thrombocytopenia, and bone marrow involvement.[4,16,21,22] Poor mobilization is regarded as an adverse factor and poor mobilizers were reported to have reduced survival.[20,23]

Khouri *et al*. observed occurrence of FN in chemomobilization was related to reduced CD34+ HSCs harvest and greater need for apheresis processes.[3] Similarly, another study revealed patients who experienced FN in mobilization were associated with lessened stem cell yield with more frequent apheresis needs.[24] Conversely, Topcuoglu and Ozcan observed no effect of FN on total harvested CD34+ and the number of apheresis processes.[25] We found no difference between groups regarding total harvested CD34+ HSCs. The requirement of >1 apheresis process was observed more frequently in the FN group, but it was not statistically significant.

FN occurrence in chemomobilization was suggested as could be related to a lessened chance of advancing to ASCT. However, earlier studies have conflicting results.[3,25] We observed no effect of FN on advancing to ASCT. Engraftment durations might be affected as patients with FN in chemomobilization are suggested to have poor bone marrow reserve. Although another

Table 2: Febrile neutropenia patients' details

Parameters	*n* (percentage/ minimum-maximum)
Median hospitalization (days)	19.5 (13-36)
Fever occurrence (days)	11 (3-17)
Identification of pathogen	13 (30.2)
Focus of infection identification	4 (9.3)
Drugs utilized for infection therapy	
Cefoperazone/sulbactam	39
Piperacillin/tazobactam	2
Meropenem	3
Vancomycin	4
Trimethoprim/sulfamethoxazole	1
Amphotericin B	1
N/A	3

N/A=Not available

Table 3: Mobilization details

Parameters	Patients with febrile neutropenia (*n*=43)	Patients without febrile neutropenia (*n*=140)	*P*
Precollection blood counts (median)			
White blood count (10^9/L)	6.5 (1.3-51.7)	10.24 (0.9-66)	0.004*
Hemoglobin (g/dl)	9.27 (7.4-12.6)	10.5 (7.57-15.8)	0.001*
Platelet (10^9/L)	50 (13-307)	68 (6-641)	0.06
Central venous access, *n* (%)	15 (34.9)	55 (39.3)	0.6
Plerixafor need	3 (7)	11 (7.9)	0.9
Peripheral blood CD34 + (median)	30.2 (1.6-478.8)	36.6 (2.1-467.1)	0.25
Harvested CD34+cell/kg (median)	9.17 (4.4-33.3)	8.15 (2.4-41.5)	0.9
Apheresis count, *n* (%)			
1	18 (41.9)	75 (53.6)	0.07
2	14 (32.6)	49 (35)	
≥3	11 (25.6)	16 (11.4)	
Undergo ASCT, *n* (%)	33 (76.7)	111 (79.3)	0.72
Platelet engraftment (median)	12 (9-19)	11 (6-27)	0.05*
Neutrophil engraftment (median)	11 (8-12)	10 (6-18)	0.001*

*$P<0.05$ statistically significant. ASCT=Autologous stem cell transplantation

study revealed no effect of FN on engraftment durations, our findings were contradictory with longer neutrophil and platelet engraftment durations in the FN group.[25] However, in our FN cohort, there were proportionally more myeloma patients and more patients with bone marrow involvement which might be the cause of longer engraftment durations.

Blood counts might be predictive of poor mobilization or FN. As Khouri *et al*. found that premobilization blood counts revealed lower hemoglobin and platelet counts.[3] Another study reported leukocyte and peripheral CD34+ HSCs count were not affected by FN.[25] We detected significantly lower white blood count and hemoglobin in preapheresis in the FN group compared with the non-FN group, although platelet counts were lower in the FN group, it was not statistically significant.

Jillella *et al*. observed 14/54 (26%) frequency of FN attack in their research, it was similar in our cohort 43/183 (23.5%).[9] However, in their cohort, there were 32% of solid cancer patients and mobilizing regimens were different from our cohort.

Our study has some limitations. Our cohort was heterogeneous regarding mobilizing regimen and patient and disease characteristics.

Conclusion

Chemomobilization is a common practice for stem cell mobilization, and it has unique pros and cons. FN is the most feared complication of chemomobilization. Harvesting sufficient CD34+ HSCs from patients with FN is still feasible; however, FN treatment should begin promptly, and further apheresis sessions may be required.

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Conflicts of interest
There are no conflicts of interest.

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