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The Timing of Granulocyte Colony-Stimulating Factor in Hematopoietic Stem Cell Transplant in the Pandemic

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ABSTRACT

Granulocyte-colony stimulating factors (G-CSF) are used to shorten the duration of neutropenia after hematopoietic cell transplantation (HCT). However, there is no consensus on which days treatment should be started post-transplantation during the COVID-19 pandemic. In this study, we looked at the influence of G-CSF on clinical outcomes on the fifth (G-CSFd5) and tenth (G-CSFd10) days following allo-HCT. Our study includes the data of 60 patients (G-CSFd5, n=28 vs G-CSFd10, n=32) who underwent HCT with the diagnosis of acute lymphoblastic leukemia (ALL) between 2015 and 2022. Primary outcome is the effect of G-CSF on hospital stay. Secondary outcomes are the development and duration of febrile neutropenia (FEN), neutrophil engraftment (NE), platelet engraftment (PE), engraftment syndrome (ES), acute graft versus host disease (aGVHD), cytomegalovirus (CMV) viremia, and effects on antimicrobial use. Length of hospital stay, 34.5 days vs. 30 days (p=0.19); median NE, 13.85 vs 15.03 days (p=0.007); median PE, 15.5 vs 12 days (p=0.12); ES, 28.5% vs 12.5% (p=0.12); FEN, 85.7% vs 84.3% (p=0.88); aGVHD, 39.2% vs 40.6% (p=0.92); were observed for G-CSFd5 and G-CSFd10, respectively. Although starting G-CSF in the early period after allo-HCT shortened the duration of NE, positive effects on clinical outcomes were not observed. On the contrary, the frequency of ES increased in the group that received GCSF early.

Keywords: Length of Hospital Stay, COVID-19, Febrile Neutropenia, Acute Lymphoblastic Leukemia

Introduction

Hematopoietic cell transplantation (HCT) has been increasingly used in hematological and non-hematological malignancies over the last 25 years (1). For this reason, complications of HCT that cause morbidity and mortality in the acute and chronic periods have started to be encountered more frequently. Despite improved healthcare settings and treatments, infections, acute graft versus host disease (aGVHD), and drug toxicities remain the leading causes of morbidity and mortality in the early stages following a transplant (2). Prolonged severe neutropenia is the most important factor in the development of infection after a transplant, but other factors such as primary disease and remission status, type of conditioning regimen, infections, antiviral-antimicrobial regimens, and the development of aGVHD are all associated with neutropenia and affect infection development (3). The use of granulocyte colony-stimulating factor (G-CSF) has been shown to accelerate neutrophil engraftment to shorten the prolonged neutropenia period after HCT (4). However, although the advantage of neutrophil engraftment for 1-6 days with CSF is obtained, the debate continues its positive effect on clinical outcomes (5). For example, in the meta-analysis of Dekker et al., it was found that although there was a decrease in the risk of infection and antibiotic use, there was no decrease in infection-related mortality (6). Another controversial point regarding the use of post-transplant G-CSF is the conflicting results on aGVHD. Although most research implies that using CSF does not raise the incidence of aGVHD, there are those that suggest the opposite (6,7).

At the end of 2019, a new coronavirus called SARS-CoV-2 emerged, and the Coronavirus

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disease 2019 (COVID-19) began to spread rapidly over the world (8). The World Health Organization (WHO) declared COVID-19 a pandemic as of March 2020. During the pandemic period, health authorities have had recommendations for public health, patients, and health workers. Considering the recommendations of the European Bone Marrow Transplantation (EBMT) association in the field of HCT, it has been suggested that transplantations cannot be postponed during the pandemic in hematological malignancies, attention should be paid to preventive measures, and SARS-CoV-2 infected donors, patients, and healthcare personnel are recommended. However, no additional recommendations were found during transplantation (9). In this regard, there is a lack of information to guide clinicians.

The goal of our study is to see how G-CSF, which we began providing early in the pandemic to minimize the duration of neutropenia, influences clinical outcomes in patients who received allo-HCT throughout the pandemic.

Material and Methods

Patients: This study was designed as a retrospective observational cross-sectional study. It contains data of patients who underwent HCT in the Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Bone Marrow Transplant Unit between 2015 and 2022 with the diagnosis of Acute Lymphoblastic Leukemia (ALL). The data of the patients were collected from electronic media and archive files. Over 18 years of age, first complete remission, from related or unrelated donors, fully matched (10/10) or single mismatched (9/10), graft source peripheral stem cell transplant based on HLA-A, B, C, DRB1, DQ allele match transplant are all included. The study excluded transplants from haploidentical and cord blood origin, bone marrow stem cell-derived, and using a regimen other than Fludarabine (Flu)-AntiThymocyte Globulin (ATG)-Total Body Irradiation (TBI)-Post-Transplant Cyclophosphamide (FluATGTBI+PTCy).

This study was carried out in accordance with the Declaration of Helsinki's ethical principles. Ankara Dr. Abdurrahman Yurtaslan Training and Research Hospital local ethics committee approval was obtained (Number: 2022-01/40).

Selection of Study Groups: In our center, before the COVID-19 pandemic, G-CSF administration in allo-HCT patients was started on the 10th post-transplant day. After the COVID-19 pandemic, GCS-F administration was started on the 5th post-transplant day. According to these procedures, the G-CSFd10 group (n:32) includes patients who received transplants between 2015 and 2020, and the G-CSFd5 group (n:28) includes patients who received transplants between 2020 and 2022.

Conditioning Regimens and GVHD Prophylaxis: FluATGTBI+PTCy; Flu 4 days (on the -9^{th} -8^{th} -7^{th} -6^{th} days, 30 mg/m2), ATG 2 days (Grafalon, on the -5^{th} -4^{th} days, 2.5 mg/kg), and TBI for 3 days (on the -3^{th} -2^{th} -1^{th} days, 2x2 Gy/day, total 12 Gy) conditioning regimen were used in fully match patients who received allo-HCT. The conditioning regimens are the same in mismatch transplants, but the dosage of ATG is raised to 10 mg/kg.

All patients received cyclophosphamide 2 days (post-transplant +3^{rd} +4^{th} days, 50 mg/kg) and cyclosporine (Csa) for GVHD prevention. On the +5. day after transplantation, Csa was begun intravenously at a dose of 2x1.5 mg/kg and maintained orally at a dose of 2x3 mg/kg depending on the suitability of oral intake after engraftment. The goal was to keep the Csa level between 200 and 400 ng/ml, and the average use duration was four months.

Anti-infective prophylaxis: All patients were given oral levofloxacin (500 mg daily), fluconazole (400 mg daily), metronidazole (500 mg three times a day), nystatin (200 000 IU four times a day), and valacyclovir (500 mg two times a day) in addition to the conditioning regimen. The medications levofloxacin, nystatin, and metronidazole were continued until engraftment occurred. Fluconazole was given for as long as immunosuppressive medication was sustained. Valaciclovir was given for a year. Trimethoprim-sulfamethoxazole (800/160 mg three times a week, twice a day) was started after engraftment and continued for six months.

Outcomes: Our study groups were divided into two groups, one that started post-transplant G-CSF at day fifth (G-CSFd5) and one that started at day tenth (G-CSFd10). The primary outcome is the effect of G-CSF on hospital stay. The length of hospital stay was calculated according to the first discharge from the start of the conditioning regimen. Secondary outcomes are febrile neutropenia (FEN) and duration, neutrophil engraftment (NE), platelet engraftment (PE), engraftment syndrome (ES), aGVHD, cytomegalovirus (CMV) viremia, and effects on antimicrobial use. A neutrophil count of 500/mm3 over the next three days was defined as

NE, and a platelet count of 20.000/mm3 during a seven-day transfusion-free period was defined as PE. Spitzer's 2001 criteria were used in the diagnosis of ES (10). CMV viremia was taken as the basis for the CMV PCR level to be higher than 500 IU/mL in 2 consecutive measurements or above 1000 IU/mL in a single measurement.

Statistical Analysis: Analyzes were performed with SPSS Software (Version 26.0 Armonk, NY). Descriptive statistics were used to summarize the data. Categorical data were expressed as ratios, and numerical data as median and mean ± standard deviation. Numerical data were compared with Mann Whitney U, and categorical data were compared with a chi-square test to detect differences between groups. $P<0.05$ was considered statistically significant.

Results

A total of 60 ALL patients were included in the study, and 49 (81.7%) patients were in the B-ALL subtype. 46 (76.7%) of the transplants were from related donors, and 44 (73.3%) of the transplants were performed in full HLA match. The median CD34 (10^6/kg cells) infusion amount was 7.46 (range 4.05-8.44) 10^6/kg/cell. Age, demographic, and descriptive information of the patients are available in Table-1.

There were 28 (46.6%) patients in the G-CSFd5 group and 32 (53.4%) in the G-CSFd10 group. Similar characteristics were found in terms of age, gender, ALL subtype, performance status, transplant co-morbidity indices, donor characteristics, and amount of CD 34 infused. The characteristics of the groups are available in Table-2.

The G-CSFd5 group stayed in the hospital for 34.5 days, while the G-CSFd10 group stayed for 30 days (p=0.19). Median NE was seen as 13.85 (range 11-20) and 15.03 (range 13-22) days, G-CSFd5 and G-CSFd10, respectively (p=0.007). Median PE was seen at 15.5 (range 9-40) and 12 (range 10-26) days, G-CSFd5 and G-CSFd10, respectively (p=0.12). ES was found in a total of 12 (20%) patients, 8 (28.5%) in the G-CSFd5 group and 4 (12.5%) in the G-CSFd10 group (p=0.12). FEN was seen in 24 (85.7%) patients in the G-CSFd5 group and 27 (84.3%) patients in the G-CSFd10 group (p=0.88) and remained for a median of 3 days in both groups (p=0.40). Similar characteristics were found between the groups in terms of gram-positive antibiotic and antifungal use. aGVHD was found in 11 (39.2%) patients in the G-CSFd5 group, 13 (40.6%) patients in the G-CSFd10 group (p=0.92), CMV viremia was found in 15 (53.5%) patients in the G-CSFd5 group and 17 (53.1%) in the G-CSFd10 group (p=0.28). Detailed results of starting G-CSF on the fifth and tenth days are available in Table-3.

Discussion

In the study, we found that the duration of NE was significantly shortened, and the duration of PE tended to be prolonged in the G-CSFd5 group. Despite early NE in the G-CSFd5 group, no difference was found between the groups in terms of length of hospital stay, number and duration of FEN, and antimicrobial use. We also found a trend in the occurrence of ES in the G-CSFd5 group. Similarly, no difference was found between the two groups in terms of aGVHD and CMV viremia.

There are quite conflicting results regarding the effect of prophylactic G-CSF use on the length of hospital stay after allo-HCT. In a 2006 study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), G-CSF was found to shorten the duration of NE but had no influence on the length of hospital stay. Again, in the 2020 CIBMTR study, it was observed that, in addition to decreasing the NE duration, G-CSF significantly shortened the length of hospital stay in transplants with fully matched unrelated donors (11,12). Also, a meta-analysis showed that using prophylactic G-CSF reduced the length of hospital stay, the duration of NE, the incidence of infection, and antibiotic use (6). In our study, although the duration of NE was observed earlier in the G-CSFd5 group (p=0.007), no significant difference was found between the two groups in terms of length of hospital stay and infection rates. Unlike these studies, in our study, a tendency to prolong hospital stay was found in the G-CSFd5 group. Based on the findings of Schmid et al., who discovered that the use of G-CSF is a risk factor for the development of ES, we believe that higher G-CSF exposure in our G-CSFd5 group increased the frequency of ES formation and hence caused a longer hospital stay (13). In a separate study on the occurrence of ES in allo-HCT patients, the rate of ES development was observed to be 10% (14). Similarly, whereas the ES rate in the G-CSFd10 group was 12.5 percent, the rise in the ES ratio to 28.5 percent in the G-CSFd5 group supports our idea that early-onset G-CSF induces the development of ES.

Although many studies show that prophylactic G-CSF decreases the development of FEN in patients after myelosuppressive chemotherapy, the effects of prophylactic G-CSF on FEN after auto and allo-HCT are contradictory (15-18). In the study conducted by Özcan et al., it was found that the number of FEN attacks decreased in those who received prophylactic G-CSF after allo-HCT, but there was no difference in terms of the number of days with fever and antimicrobial use (19). In two different trials, one of

Table 1. Clinical Features of the Cohort

Parameters	n=60, %
Age (median, min-max)	34 (17-59)
Gender (M/F)	34 (56.7) / 26 (43.3)
ECOG Score (median, min-max)	0 (0-2)
ALL subtype (B vs T)	49(81.7) / 11 (18.3)
HCT-CI Score (0 vs1-2)	42 (70) / 18 (30)
EBMT Score (0-2 vs ≥3)	41(68.3) / 19 (31.7)
HLA Compatibility (Matched vs One Mismatched)	44 (73.3) / 16 (26.7)
Donor (R vs UNR)	46 (76.7) / 14 (23.3)
Gender mismatch (Male patient female donor)	15 (25%)
Conditioning Regimen (FLU-ATG-TBI-CY)	60 (100%)
CD 34 infused (106/kg/cell)	7,46 (4,05-8,44)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ALL, Acute lymphoblastic leukemia; HCT-CI, Hematopoietic cell transplantation comorbidity index; EBMT, The European Group for Blood and Marrow Transplantation; HLA, Human leukocyte antigen; R, Related; UNR, Unrelated; FLU, Fludarabine; ATG, Anti-thymocyte globulin; TBI, Total body irradiation; CY, Cyclophosphamide; CD, Cluster of differentiation.

Table 2. The G-CSF Groups

Parameters	G-CSFd5 group (n=28)	G-CSFd10 group (n=32)	P value
Age (median)	37,6	32,6	0.13
Gender (M/F)	11/17	14/18	0,65
ECOG Score	0 (0-2)	0 (0-2)	1
ALL subtypes (B vs T)	21/7	28/4	0.22
HCT-CI Score (0 vs1-2)	8/20	22/10	0.82
EBMT Score (0-2 vs ≥3)	21/7	20/12	0.30
HLA Compatibility (Matched vs One Mismatched)	21/7	23/9	0.79
Donor (R vs UNR)	22/6	24/8	0.74
Gender mismatch (Male patient female donor)	7	8	1
CD 34 infused (106/kg cells) (median)	7	7,2	1

*p<0.05 was regarded as statistically significant.

Abbreviations: G-CSFd5, Patients who received granulocyte colony stimulating factor on the fifth day post-transplantation; G-CSFd10, Patients who received granulocyte colony stimulating factor on the tenth day post-transplantation; ECOG, Eastern Cooperative Oncology Group; ALL, Acute lymphoblastic leukemia; HCT-CI, Hematopoietic cell transplantation comorbidity index; EBMT, The European Group for Blood and Marrow Transplantation; HLA, Human leukocyte antigen; R, Related; UNR, Unrelated; CD, Cluster of differentiation.

which was a randomized prospective controlled trial, the administration of prophylactic G-CSF following allo-HCT was shown to have no effect on FEN or antibiotic use (20,21). Three other studies, designed similarly to ours, reported no differences in terms of NE, PE, FEN, or antimicrobial needs when G-CSF was administered in the early and late periods following allo-HCT (22-24). In our study, although there was no difference in FEN or antimicrobial requirements, there were differences in NE and PE durations. We think that one of the reasons for the differences in our study's results is that the patient groups we chose have a more homogeneous distribution than in other studies.

One of the results that caught our attention in our study was the prolongation of PE duration in the G-CFSd5 group. Despite the fact that most studies including the use of G-CSF after transplantation reported no difference in PE durations, two previous studies found that PE duration was prolonged, which is consistent with our findings (7,21). We think that this situation emerges as a consequence of platelet consumption or the role of G-CSF in myeloid mass production.

One question is whether the use of G-CSF after allo-HCT increases the development of aGVHD. The influence of G-CSF administration after transplantation on the development of aGVHD was not found in many studies and meta-analyses (11,21,25,26), but two studies reported a significant development of aGVHD in the post-transplant use of G-CSF (27,28). In our study, there was no difference in the occurrence of aGVHD between the groups.

Our study's main limitations are its retrospective design and small number of patients. One of the study's other limitations is that it included related and unrelated donors who were HLA compatible in both full match and mismatch settings. Another limitation,

Table 3. G-CSF Related Outcomes

Parameters	G-CSFd5 group (n=28), %	G-CSFd10 group (n=32), %	P value
CMV viremia	15 (53.5)	17 (53.1)	0.28
Neutrophil Engraftment (min-max)	13,85 (11-20)	15.03 (13-22)	0.007*
Platelet Engraftment (min-max)	15,5 (9-40)	12 (10-26)	0.12
FEN observed	24 (85.7)	27 (84.3)	0.88
FEN duration (days)	3	3	0.40
Gram positive antibiotherapy initiation	20 (71.4)	23 (71.8)	0.97
Antifungal initiation	5 (17.8)	6 (18.7)	0.56
Acute GVHD	11 (39.2)	13 (40.6)	0.92
Engraftment syndrome observed	8 (28.5)	4 (12.5)	0.12
Hospitalization duration (days)	34,5	30	0.19

*p<0.05 was regarded as statistically significant.
Abbreviations: G-CSFd5, Patients who received granulocyte colony stimulating factor on the fifth day post-transplantation; G-CSFd10, Patients who received granulocyte colony stimulating factor on the tenth day post-transplantation; CMV, Cytomegalovirus; FEN, Febrile neutropenia; GVHD, Graft versus host disease.

due to the fact that all of the patients in our study were G-CSF users, is insufficient in terms of providing information about GM-CSF. The positive aspects or strong sides of our study are that the groups were made up entirely of ALL patients, that the graft source was peripheral stem cells, and that they all received the same conditioning regimen and immunosuppressive treatment made our groups very homogeneous, allowing us to obtain more reliable results.

In conclusion, we observed that initiating G-CSF prophylactically on day 5 after allo-HCT had no benefit other than early NE compared to starting on day 10. On the contrary, it seems to be disadvantageous because it tends to increase ES frequency and prolongs hospital stay.

Declarations

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Conflict of interest: None.

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