Original Article

Standart Prophylactic Granulocyte Colony Stimulating Factor Usage as a Part of Autologous Stem Cell Transplantation Procedure

Otolog Kök Hücre Naklinin Bir Parçası Olarak Standart Profilaktik G-CSF Uygulanması

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ABSTRACT

Introduction: One of the major causes of morbidity and mortality of autologous hematopoietic stem cell transplantation (ASCT) is infections during prolonged neutropenia. In this study, we aimed to investigate the effect of prophylactic G-CSF use in ASCT patient on the frequency of infection, duration of neutrophil engraftment and neutropenia, length of hospital stay and transplant-related morbidity and mortality.
Methods: G-CSF has been routinely used after autologous stem cell transplantation in our unit for 3 years since February 2014. In this study, three years before and after the application consecutive auto-HSCT data were collected retrospectively. In addition to routine antimicrobial prophylaxis, In the group receiving G-CSF, 5mcg/kg/day G-CSF sc was started from fifth day and application was continued until neutrophil engraftment.
Results: A total of 226 patients (129 males, 97 females) were included in the study. In patients receiving prophylactic G-CSF, neutrophil engraftment was earlier [13 (9-23) and 12 (10-22) days], and the duration of neutropenia [11 (5-23) and 8 (5-19) days] was shorter (p <0.001). In the ASCT series prophylactic use of G-CSF showed that reduced the duration of neutropenia and decreased in neutropenic fever frequency.
Discussion and Conclusion: Transplant-related mortality (TRM) and infection-related mortality analyzes were not very significant due to the low level of event (p> 0.05).

Keywords: Auto-SCT, prophylactic G-CSF, SCT complications

ÖZET

Giriş ve Amaç: Otolog hematopoietik kök hücre transplantasyonunun (ASCT) morbidite ve mortalitesinin başlıca nedenlerinden biri, uzun süreli nötropeni sırasındaki enfeksiyonlardır. Bu çalışmada ASCT hastalarında profilaktik G-CSF kullanımının enfeksiyon sıklığı, nötrofil engraftmanı ve nötropeni süresi, hastanede kalış süresi ve nakille ilişkili morbidite ve mortalite üzerine etkisini araştırmayı amaçladık.
Yöntem ve Gereçler: G-CSF, birimimizde Şubat 2014'ten itibaren 3 yıldır otolog kök hücre nakli sonrası rutin olarak kullanılmaktadır. Bu çalışmada, uygulamadan üç yıl önce ve sonra ardışık oto-HSCT verileri geriye dönük olarak toplanmıştır. Rutin antimikrobiyal profilaksiye ek olarak, G-CSF alan grupta beşinci günden itibaren 5 mcg/kg/gün G-CSF sc başlandı ve nötrofil engraftrasyonuna kadar uygulamaya devam edildi.
Bulgular: Çalışmaya toplam 226 hasta (129 erkek, 97 kadın) dahil edildi. Profilaktik G-CSF alan hastalarda nötrofil engraftmanı daha erkendi [13 (9-23) ve 12 (10-22) gün] ve nötropeni süresi [11 (5-23) ve 8 (5-19) gün] daha kısaydı (p <0.001). ASCT serisinde profilaktik olarak G-CSF kullanımının nötropeni süresini azalttığını ve nötropenik ateş sıklığını azalttığını göstermiştir.
Tartışma ve Sonuç: Organ nakline bağlı ölüm oranı (TİM) ve enfeksiyona bağlı ölüm oranı analizleri, olay seviyesinin düşük olması nedeniyle çok anlamlı değildi (p> 0.05).

Anahtar Kelimeler: OKHN, profilaktik g-CSF, OKHN komplikasyonları

Introduction

Autologous stem cell transplantation (ASCT) is widely used in many benign and malignant hematologic diseases [1]. Infections are common complications in patients undergoing ASCT due to prolonged neutropenia,

First Received: 11.06.2021, Accepted: 13.11.2021 doi: 10.5505/aot.2022.47113

immunosuppressive treatments and catheter applications [1,2,3,4,5]. The quality and quantity of stem cell product, myeloid growth factor uses such as granulocyte colony stimulating factor (G-CSF) and patient-specific factors are effective in neutrophil engraftment [1,6,7]. Hematopoietic growth factors are multifunctional: they have a critical role for proliferation, survival and differentiation of hematopoietic stem cells [8,9]. In many centres, G-CSF is used to shorten the duration of engraftment after autologous SCT and allo-HSCT. However, there is no consensus on the standard use of G-CSF after transplantation. Infection-related morbidity and mortality can be reduced by adding to ASCT procedure prophylactic hematopoietic growth factors [8].

We aimed to investigate the effect of prophylactic G-CSF usage on autologous stem cell transplantation on the frequency of infection, neutrophil engraftment and neutropenia, length of hospital stay, transplant-related morbidity and mortality.

Materials and Methods

The approval was obtained from the Gazi Univercity Clinical Research Ethics Committee with the number 77082166-302.08.01 dated 10.02.2017. This study was conducted in accordance with the Declaration of Helsinki.

Patients received ASCT with or without G-CSF prophylaxis were included this study between 2011 and 2016. In our center, prophylactic G-CSF application in ASCT started routinely in February 2014. Tree years before and 3 years after this date were determined and the patients who underwent ASCT between these dates were included consecutively in the study. Patients who did not receive prophylactic G-CSF were used as the historical control group. Patients with haematological malignancies who had autologous peripheral stem cell transplantation were included in the study. Patients who died before prophylactic G-CSF administration (+5th day), and patients received G-CSF before +5th due to the other causes such as severe infection were excluded.

G-CSF was used in 99 patients and 127 patients did not use hematopoietic growth factor. G-CSF-related side effects and neutrophil engraftments were recorded as the first day of absolute neutrophil numbers (ANC)> 500/mm^3 for 3 consecutive days. The duration of neutropenia was taken as the number of days from the onset of neutropenia after the first day of conditioning regimen to neutrophil engraftment. In the G-CSF group, patients were treated prophylactically with filgastrim 5mcg/kg/day subcutaneously until neutrophil engraftment was achieved. Both group patients received fluconazole, levofloxacin, and acyclovir as standard antimicrobial prophylaxis.

Statistical analysis

Categorical variables were compared with chi-square test. Student-t and Mann Whitney U tests were used to compare continuous parameters. Pearson correlation test was used to investigate relationship between parameters. Survival analyses were performed by Kaplan Meier analysis and log rank test. Statistical analysis was performed using SPSS 22. All statistical tests were performed 2-sided and P value 0.05 was considered as statistically significant.

Results

A total of 226 patients (129 males, 97 females) were included in the study. 121 patients had multiple myeloma and other plasma cell diseases, 62 had non-Hodgkin's lymphoma, 23 had Hodgkin's lymphoma and 20 had acute myeloblastic leukaemia. 99 (43.8%) of the patients included in the analysis used median 9 (4-16) days of prophylactic G-CSF and 127 (56.2%) of them did not use G-CSF.

Table 1. Comparison of demographic, diagnostic and treatment characteristics of patients

	Prophylactic G-CSF		
	Absent (n=127)	Present (n=99)	P
Age (year)	54 (18-69)	55(18-70)	N.S.
Gender n(%) (Male/female)	71/56 (55.9/44.1)	58/41 (58.5/41.5)	N.S.
Diagnosis n(%)			
MM	68 (53.5)	53(53.6)	
Lymphoma	47 (37.1)	38 (38.3)	N.S.
AML	12 (9.4)	8 (8.1)	
Conditioning regimen			
Melphalan±bortezomib	68(53.5)	53(53.6)	
BEAM	39 (30.8)	22 (22.2)	N.S.
TEAM	8(6.3)	16(16.1)	
CyBu	12(9.4)	8(8.1)	
Product $CD34^+$/kg	4.8(2.5-6.9)	4.5(2.4-6.3)	N.S.

MM: Multipl myeloma
AML: Acute myeloblastic leukemia
BEAM: Karmustin,Etoposid, , Sitarabin, Melfalan
TEAM: Thiotepa, Etoposid, Sitarabin, Melfalan
CyBu: Siklofosfamid, Busulfan
N.S: No significant

Table 2. Comparison of both groups in terms of endpoints

	Prophylactic G-CSF		
	Absent (n=127)	Present (n=99)	P
Neutrophil engraftment (day)	13(9-23)	12(10-22)	<0.001
Neuthrophil>1000/mm^3 (day)	16(9-36)	12(10-22)	<0.001
Neutropenia duration (day)	11(5-23)	8 (5-19)	<0.001
Platelet engraftment (day)	13(7-27)	15(10-56)	<0.001
Duration of hospitalization (day)	18(8-54)	17(13-35)	N.S.
Neutropenic fever n(%)	109 (85.8)	69 (69.6)	<0.001
Catheter infection n(%)	35(27.5)	18(18.1)	<0.05
Pneumonia n(%)	14(11.0)	12(12.1)	N.S.

Comparison of two groups according to demographic, diagnostic and treatment characteristics of patients were shown in Table 1. Median age and infused CD34+ cells/kg of patients, distributions of gender and diagnosis were similar between two groups (p>0.05).

G-CSF related severe side effect was not documented. Neutrophil engraftment was earlier [12 (10-22 vs 13 (9-23) days] and the duration of neutropenia were shorter [8 (5-19) vs 11(5-23) days] in patients received prophylactic G-CSF (p <0.001). There was no difference neutrophil engraftment time between males and females (13.0±2.7 days vs 13.1±2.7 days, p>0.05); also between lymphoma and myeloma patients (12.9±2.8 days vs 13.2±2.7 days, p>0.05). Neutrophil engraftment day was similar between patients with and without febrile neutropenia (12.9±2.7 days vs 13.1±2.7 days, p>0.05). A negative correlation was found between the number of infused CD34 cells and the time to neutrophil engraftment (r=-0.0135, p=0.04). The frequencies of neutropenic fever attack (69.6% vs 85.8%, p<0.001) and catheter infection (18.1% vs 27.5%, p <0.05) were significantly lower in patients received G-CSF. The diagnosis of pneumonia was found with a similar frequency (p>0.05). Platelet engraftment time was earlier in patients received prophylactic G-CSF [13(7-27) vs 15(10-56), p<0.001]. Duration of hospitalization time was similar in both two groups. Transplantation related mortality (2.0% vs 3.2%, p>0.05) and overall survival (2.6% vs 3.6%, p>0.05) within first 100 days was similar statistically in patients received ASCT with and without prophylactic G-CSF.

Discussion

G-CSF reduces the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute leukaemia [10,11,12]. G-CSF is well tolerated. The most common side effects are transient fever and bone pain that responds to analgesics. Other side effects include inflammation at the injection site, elevation of LDH and ALP. Splenomegaly and splenic infarction may be seen in long-term use. [9,13,14]. In ASCT area, studies pointed that prophylactic G-CSF reduces the duration of neutropenia and febrile neutropenia frequency [1,15,16,17,18]. The recommended dose of G-CSF is 5 mcg/kg/day [9,19]. Optimal starting time of prophylactic G-CSF adapted ASCT procedure is controversial [15-20]. Few data are available regarding the ability of G-CSF to accelerate engraftment further in patients who receive adult PBSC following high-dose therapy [15,16,22-25]. Despite of the all-favourable effects, prophylactic usage of G-CSF retained controversial because of the high treatment cost [8].

In our study, we retrospectively searched the ASCT database; we composed two groups. First group-enclosed patients received prophylactic G-CSF started at day 5, and second group patients did not received prophylactic G-CSF (historical control). We documented earlier neutrophil and thrombocyte engraftment, shorter neutropenia duration, lower febrile neutropenia and catheter infection frequency in patients received prophylactic G-CSF. However duration of hospitalization, TRM and OS in first 100 days were statistically similar. The statistical significance level could not be reached due to the fact that the “event” was very low in the TRM and infection related mortality analyses.

Khwaja A et al. [22] G-CSF started on day + 8 after auto-HSCT and patients received G-CSF for an average of 10 days. They showed that the duration of neutrophil engraftment with G-CSF was significantly shortened. Linch et al. [23] had undertaken a prospective randomized study in 90 patients with relapsed or resistant lymphomas to assess the value of G-CSF in the acceleration of myeloid recovery after ASCT. This was associated with shorter duration of time in hospital post ASCT. Median days to platelet independence, platelet transfusions, and incidence of infection and red cell transfusion were the same in both arms. Gisselbrecht et al. [24] administered 163 patients G-CSF daily infusion and 152 patients received placebo daily for 28 days or until neutrophil recovery. In G-CSF treated group, time to neutrophil recovery was faster; patients had fewer infection, antibiotic usage and hospital stay. Survival was the same on days 100 and 365. Transplantation teams treat to patient's infections through modern approaches; also decreasing neutropenia and its complications are safety. Brice at all [25] reported that the average cost of autologous BMT was lower in patients receiving G-CSF. Results were largely attributable to decreased expenditure on hospitalisation and antimicrobial therapy in the G-CSF treated group. G-CSF is increasingly used to accelerate neutrophil engraftment after bone marrow transplantation [26]. Current data recommend the use of G-CSF when the risk of febrile neutropenia is greater than 20% [9].

The major limitation of this study is its retrospective character and have historical control group. However, in our study show that prophylactic G-CSF administration adapted to autologous stem cell transplantation procedure was led to shorter neutrophil engraftment, and decreased neutropenic fever frequency. G-CSF prophylaxis might be adapted to ASCT procedure as a standard, thus infection-related morbidities can further decrease.

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Doi: 10.5505/aot.2022.47113

