Original Article

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Prophylactic intravenous immunoglobulin use in allogeneic stem cell transplantation; does intravenous immunoglobulin affect survival, sepsis, and engraftment time?

Ahmet Kaya, İlhami Berber, İrfan Kuku, Emin Kaya, Mehmet Ali Erkurt, Soykan Biçim[1], Süleyman Arslan, Fatma Hilal Yağin[2]

Abstract:

BACKGROUND: Stem cell transplant recipients have an increase in various infections depending on the immunosuppression. The purpose is to explore the effect of the use of proflactıc intravenous immunoglobulin (IVIG) on transplant recıpıents.

OBJECTIVE: It was aimed to examine the effect of IVIG on allogeneic stem cell transplantation.

MATERIALS AND METHODS: In this study, sepsis status, infection focus causing sepsis, neutrophil and platelet engraftment time of patients the length of stay in the hospital at the time of the stem cell transplant, if the patient died, how many days after the transplant the event developed, and the data of the bone marrow transplant unit were reviewed retrospectively. One hundred and eleven patients who were given IVIG (400 mg/kg/week IVIG intravenous was given to the patients as a weekly prophylactic up to 100 days starting on the 7th day after transplantation) and 190 patients who did not receive IVIG were included in the study.

RESULTS: There was no statistically significant difference between the IVIG groups in terms of gender, diagnosis, donor characteristics, and event ($P > 0.05$). Sepsis was observed significantly less in patients who were given IVIG compared to patients who were not given IVIG ($P < 0.001$). While it was observed that IVIG did not have a significant effect on platelet engraftment and discharge times ($P > 0.05$), neutrophil engraftment time was significantly higher in patients given IVIG compared to patients not given IVIG ($P < 0.009$). It was observed that the use of IVIG in patients with sepsis did not have a positive effect on survival. (with sepsis hazard ratio [HR]: 3.890 $P = 0.001$, IVIG given HR: 3.244 $P = 0.035$).

CONCLUSION: It was observed that the use of IVIG in allogeneic stem cell transplantation was associated with a decrease in sepsis, but the use of IVIG did not have a positive effect on survival and could prolong neutrophil engraftment.

Keywords:

Engraftment, intravenous immunoglobulin, sepsis, survival

Department of Hematology, Turgut Ozal Medical Center, Inonu University, [1]Department of Hematology, Malatya Education and Research Hospital, [2]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Inonu University, Malatya, Turkey

Address for correspondence:
Prof. İlhami Berber, Department of Hematology, Turgut Ozal Medical Center, Inonu University, Malatya, Turkey.
E-mail: ilhami.berber@inonu.edu.tr

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Introduction

Allogeneic stem cell transplantation is an effective treatment option in hematological cancers and some nonmalignant diseases. Changes in the immune system and susceptibility to infections occur as a result of transplantation in patients. Drugs used to prevent graft-versus-host disease in an allogeneic

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transplant recipient may lead to immunodeficiency in the patient.[1]

Allogeneic hematopoietic cell transplant recipients are at increased risk for various infections depending on their degree of immunosuppression and exposure. After stem cell transplantation, patients may develop various infections and these infections are an important problem of allogeneic stem cell transplantation. Infections after stem cell transplantation are an important component of patient survival and treatment problems.[2]

Therefore, the introduction of prophylactic intravenous immunoglobulin (IVIG) for the prevention of infection is the subject of discussion. Protection against infection when administered in hypogammaglobulinemia, antibody deficiency disorders, and/or other immunodeficiency states, IVIG acts by providing passive immunity, providing adequate antibody concentrations against a wide variety of pathogens. Hyperimmune globulins provide nonspecific passive immunity.[3-5]

Immunoglobulins can act by different mechanisms depending on the nature of the disease, so it is very difficult to understand the dominant role of immunoglobulins. It can interact with Fc receptors on phagocytic cells in the spleen and liver, such as spleen macrophages.[6] It can cause inhibition of dendritic cell differentiation and maturation.[7] Inflammation can be inhibited by the reduction of proinflammatory subsets from peripheral blood monocytes and suppression or neutralization of cytokines by these cells.[8] It can contribute to the prevention of infections by providing neutralizing antibodies against microbial toxins.[9] It can create differentiation in the immune system by causing changes in regulatory T-cells.[10] In previous publications in the literature, the use of immunoglobulin in stem cell transplantation was supported.[11,12]

However, recent studies have shown that the use of IVIG has no survival benefit and increases the risk of veno-occlusive disease (VOD).[13]

In this study, we aimed to investigate the use of prophylactic immunoglobulin in stem cell transplantation. For this purpose, prophylactic IVIG use was evaluated in terms of survival, sepsis, and engraftment using the data of our hospital.

Materials and Methods

Study design

Informed consent was obtained from all patients participating in this study. Patients who underwent stem cell transplantation in the adult bone marrow transplant unit of Turgut Özal Medical Center between February 10, 2011, and August 15, 2022, were retrospectively scanned through the hospital automation system. A total of 962 patients were found to have undergone stem cell transplantation. It was observed that 661 autologous transplants and 301 allogeneic transplants were performed in the patients (245 within relatives fully matched, 42 perfectly matched outside relatives, and 14 haploidentic). The data of 301 patients over the age of 18 who underwent allogeneic stem cell transplantation were included in the study. A total of 301 patients, 111 (36.9%) IVIG given and 190 (63.1%) IVIG not given, were included in the study. Sepsis status of the patients (Sequential Organ Failure Assessment patients with two or more criteria were considered sepsis). The focus of infection causing sepsis, neutrophil and platelet engraftment time (days), duration of hospitalization at the time of stem cell transplantation (days), and if the patient died, how many days after transplantation the event developed were collected. Patients were divided into groups: those who received prophylactic IVIG and those who did not (patients who received IVIG were between 2011 and 2016 and those who did not receive IVIG were between 2016 and 2022).

Ethical approval

The study was approved by the Inönü University Clinical Research Ethics Committee with 15 sessions and 2022/3763 decision on September 20, 2022. The study complied with the Helsinki Declaration, human research ethics. The data of the study are available in the electronic data archive of the Turgut Özal Medical Center and the file archives of the bone marrow transplantation unit. Ethical consent was obtained from all the patients participating in the study and it is available in the patient files.

Intravenous immunoglobulin application

One hundred and eleven patients were given IVIG (400 mg/kg/week IVIG intravenous was given to the patients as a weekly prophylactic up to 100 days starting on the 7th day after transplantation) and 190 patients who did not receive IVIG were included in the study.

Engraftment

The first of three consecutive days on which a continuous peripheral blood neutrophil count of >500 × 10^6/L was obtained, as the neutrophil engraftment time was included in the study.[14] Platelet engraftment platelet count was accepted on the 1st day that it was more than >20 × 10^9/L, and there was no need for platelet transfusion for at least 7 days.[15]

Statistical analysis

The number of patients in the study was determined by the whole count method (all patients who received a stem cell transplant). The data of patients without neutrophil

and platelet engraftment (19 IVIG given and 40 IVIG not given) were calculated in statistical analysis using mean values. Qualitative variables are written as percentages. Groups were analyzed for variables using Pearson's Chi-square test, Chi-square test, and Fisher's exact tests (when appropriate). The normal distribution range of the variables was determined using the Shapiro–Wilk test. While quantitative variables were specified because they did not show a normal distribution, they were specified with minimum maximum and median scaling.

Survival analysis

Groups were analyzed using the Mann–Whitney U-test. Kaplan–Meier test was used for survival analysis of patients. Hazard ratio (HR) estimates were determined using multivariate Cox regression analysis. The follow-up period of the patients was determined as the time until the death of the patient for any reason after stem cell transplantation. In statistical tests, the $P < 5\%$ was considered to be statistically significant. American Psychological Association style was used to report statistical differences. All statistical analyses were performed using SPSS statistics for Windows version 26.0 (IBM Corp., Armonk, NY, United States).

Results

Descriptive statistics for the groups IVIG given and not given according to the qualitative variables in the data set are given in Table 1. There was no statistical difference between the groups that received and did not receive prophylactic IVIG in terms of gender, diagnosis, donor, and exsitus event, so the effect of IVIG was insignificant ($P > 0.05$). However, sepsis was observed significantly less in patients who were given IVIG compared to patients who were not given IVIG ($P < 0.05$) [Table 1].

While it was shown that IVIG had no statistically significant effect on platelet engraftment, discharge times, and patient age ($P > 0.05$), neutrophil engraftment time was significantly higher in patients who received IVIG than in patients who did not receive IVIG ($P < 0.05$) [Table 2].

For survival analysis, patients were divided into two groups, living ($n = 190$) and deceased ($n = 111$) (total =301). The mean survival time of the patients was 65.33 ± 6.38 days [Figure 1].

Sepsis developed after stem cell transplantation in 31 patients who received prophylactic IVIG and 52 patients who did not receive prophylactic IVIG. Pneumonia was the most common cause (35.48%–34.62%) in the groups of patients who developed sepsis and were given and not given IVIG. Catheter infection is the second, and mucormycosis infection is the third.

Based on the results of Cox regression analysis, those with sepsis had a 3,890-fold greater risk of death than those without (HR: 3.890 [95% confidence interval (CI) [1.687–8.968]; $P = 0.001$]). Furthermore, those who were given IVIG had a 3244 times greater risk of death than those who did not (HR: 3.244) (95% CI [1.084–9.705]; $P = 0.035$) [Table 3].

Kaplan–Meier (KM) survival was performed for variables that were significant in the multivariate Cox regression analysis. According to KM results, it was analyzed that patients without sepsis lived significantly longer than patients with sepsis. It was also observed that patients who were not given IVIG had significantly longer survival than patients who were given IVIG [Table 4].

Discussions

Infections in the early engraftment period of allogeneic stem cell transplantation are the most important conditions that the clinician and patient deal with the most and increase patient mortality. Neutropenia and mucositis developing before or after transplantation are the most important risk factors. After bone marrow recovery, there is an increased risk of infection associated with catheter and graft-versus-host disease. In the late stage, when the immune system recovers, varicella zoster and capsule bacterial infections are common with pathogens seen in the early period after engraftment. Following cessation of posttransplant immunosuppressive therapy, an appropriate vaccination schedule, prophylactic IVIG, and administration of antibiotics during immunosuppressive therapy for vaccine versus host disease may reduce the risk of infection. Elderly patients, with severe mucositis, prolonged deep neutropenia, transplanters with low human leucocyte antigen (HLA) compatibility, patients who have undergone transplantation with cord blood, and patients who develop graft-versus-host disease have an increased risk of opportunistic fungal infection. Complications associated with stem cell transplantation can be avoided with appropriate prophylactic measures.[16] In the study of Ido *et al*., in which they investigated the therapeutic effect of IVIG, 400 mg/kg IVIG was used for 5 consecutive days in allogeneic transplant patients with refractory disease. About 57.1% of the patients had complete recovery from the disease. It was concluded that IVIG was more effective in exogenous viruses.[17] In this study, the rate of sepsis was lower in the group of patients who received 400 mg/kg weekly IVIG after transplantation ($P < 0.001$), while a shorter survival rate was observed in these patients (HR: 3.244). Sepsis due to pneumonia was the most common in patients (%35, 48). It was not investigated whether sepsis was exogenous or endogenous. It is approved for use in IVIG allogeneic stem cell transplantation to prevent

Table 1: Statistical analysis on age, diagnosis, transplant parameters, sepsis, and exsitus status

Variable	Group		*P*
	IVIG given, *n* (%)	IVIG not given, *n* (%)	
Gender			
Female	47 (39.17)	73 (60.83)	0.50
Male	64 (35.36)	117 (64.64)	
Diagnosis			
AML	62 (41.89)	86 (58.11)	0.55
ALL	25 (32.89)	51 (67.11)	
NHL	4 (36.36)	7 (63.64)	
HL	3 (37.50)	5 (62.50)	
AA	4 (17.39)	19 (82.61)	
Myelofibrosis	2 (22.22)	7 (77.78)	
MM	0	1 (100.00)	
CML	4 (44.44)	5 (55.56)	
MDS	4 (50.00)	4 (50.00)	
CLL	1 (50.00)	1 (50.00)	
Thalassemia	2 (50.00)	2 (50.00)	
PNH	0	2 (100.00)	
Donor feature			
Fully compatible with relatives	91 (37.14)	154 (62.86)	0.43
Nonrelative fully compatible	13 (30.95)	29 (69.05)	
Haploidentical	7 (50.00)	7 (50.00)	
Sepsis			
Do not have sepsis	80 (36.70)	138 (63.30)	<0.001
Have sepsis	31 (37.35)	52 (62.65)	
Event			
Alive	85 (44.74)	105 (55.26)	0.91
Exsitus	26 (23.42)	85 (76.58)	

IVIG=İntravenous immunoglobulin, PNH=Paroksismal noktürnal hemoglobinüri, CLL=Chronic lymphocytic leukemia, MDS=Myelodysplastic syndrome, CML=Chronic myelocytic leukemia, MM=Multiple myeloma, AA=Aplastic anemia, HL=Hodgin lymphoma, NHL=Non hodgin lymphoma, ALL=Acute lymphocytic leukemia, AML=Acute myelocytic leukemia

Table 2: Statistical analysis of engraftment times, age, and discharge time

Variable	Group		*P*
	IVIG given, median (minimum–maximum)	IVIG not given, median (minimum–maximum)	
Neutrophil engraftment	17 (5–56)	15 (10–44)	0.009
Platelet engraftment	18 (6–56)	16 (0–44)	0.191
Age	41 (18–66)	37 (18–74)	0.266
Discharge time	20 (5–65)	20 (1–60)	0.798

IVIG=İntravenous immunoglobulin

Table 3: Results of the Cox regression model based on risk factors

Risk factor	*B*	SE	Wald	*P*	HR	95.0% CI for HR	
						Lower	Upper
Gender-male	0.052	0.355	0.021	0.884	1.053	0.525	2.112
Donor unrelated fully compatible	0.197	0.445	0.196	0.658	1.218	0.509	2.910
Donor haploidentical	−0.600	0.829	0.525	0.469	0.549	0.108	2.784
Neutrophil engraftment	0.027	0.061	0.192	0.661	1.027	0.911	1.158
Platelet engraftment	−0.017	0.056	0.089	0.766	0.983	0.881	1.098
Discharge time	−0.004	0.028	0.020	0.887	0.996	0.944	1.051
Have sepsis	1.358	0.426	10.160	0.001	3.890	1.687	8.968
IVIG given	1.177	0.559	4.431	0.035	3.244	1.084	9.705

B=Coefficient, SE=Standard error, HR=Hazard ratio, CI=Confidence interval, IVIG=İntravenous immunoglobulin

opportunist infections and prevent the development of graft-versus-host disease, but the effective concentration dose is unknown. In a randomized IVIG dose study, transplant patients received IVIG at doses of 100, 250,

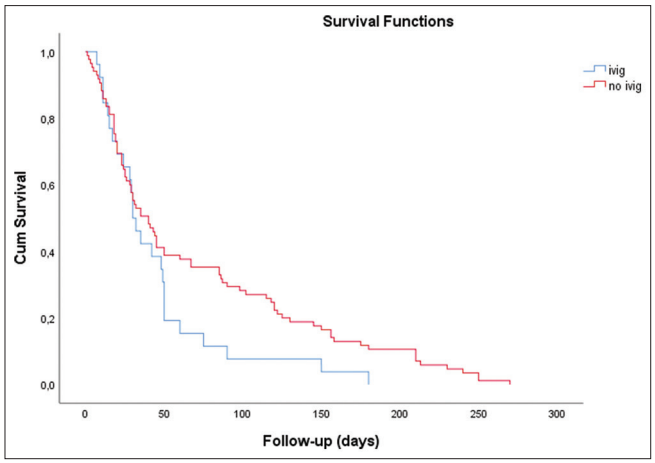

Figure 1: The survival curve by intravenous immunoglobulin groups

Table 4: Survival results in the multivariate Cox regression analysis

	KM analysis	
	Survival time (days), mean±SE	Log-rank (*P*)
Have sepsis	103.17±10.98	<0.001
Do not have sepsis	31.98±3.29	
IVIG given	71.71±7.85	0.048
IVIG not given	44.46±8.09	

SE=Standard error, IVIG=İntravenous immunoglobulin, KM=Kaplan–Meier

and 500 mg/kg/week after transplantation. Acute graft-versus-host disease was seen in 39%, 42%, and 35% of patients given 100, 250, and 500 mg/kg/week, respectively (P = 0344). In patients with allogeneic stem cell transplants with mismatch donors, higher doses of IVIG were associated with less acute graft-versus-host disease (P = 0.07). Similar chronic graft-versus-host disease and infection were observed in all three IVIG doses given, and IVIG doses were unrelated to survival and infection subtypes.[18] In this study, the development of sepsis in patients using 400 mg/kg IVIG weekly after stem cell transplantation was examined and the rate of sepsis was observed less in patients who received IVIG. However, this reduction in sepsis was not associated with survival. The relationship between IVIG and relapse was not examined in the study. In addition, neutrophil engraftment was observed longer in patients who received IVIG. In a randomized study by Abdel-Mageed *et al*., the effect of IVIG dose on infection and acute graft versus disease was examined. Patients were given IVIG at doses of 200 and 500 mg/kg/week, starting from the 1st week and up to 100 days after transplantation. The results of the study were that both doses used had similar survival and infection effects. Only high-dose use caused less acute graft-versus-host disease development (P = 0.03).[19] In this study, patients who received a dose of 400 mg/kg IVIG were examined and it was seen that it caused a decrease in the rate of sepsis. However, it was seen that the use of IVIG did not have a positive effect on survival. The effect of IVIG use on graft-versus-host disease was not evaluated. It has no correlation with platelet engraftment and hospital stay. In the study of Cordonnier *et al*., starting the 1st week after transplantation, 50, 250, and 500 mg/kg/week doses of IVIG and placebo were given to the patients until 100 days after transplantation. The incidence of infection was 92% and 90% in IVIG and placebo groups, respectively. Graft-versus-host disease, survival was similar in both groups. IVIG dose was found to have no effect. The incidence of VOD was increased in patients given high IVIG doses (P = 0.01).[13] In this study, the rate of sepsis was observed less in patients who received IVIG. Pneumonia was the most common cause in the group that received and did not receive IVIG. While platelet engraftment was not affected in the patient group receiving IVIG, it was observed that neutrophil engraftment was prolonged. It was observed that donor characteristics were unrelated to the effects of IVIG use. The frequency of infection in allogeneic stem cell transplantation may increase due to the decrease in the level of immunoglobulin. In the study of Howell JE colleagues, similar rates of infection, except for parainfluenza, were seen in patients who received prophylactic 200 mg/kg/week IVIG (patients with serum immunoglobulin levels <400 mg and whose serum levels were not studied) (P = 0.003).[20] In this study, sepsis was examined as a result of serious infection and was detected to a lesser extent in the patient group receiving IVIG. In this study, it was determined that prophylactic 400 mg/kg/week IVIG dose caused a decrease in sepsis in patients with allogeneic stem cell transplantation. The most common cause of sepsis was pneumonia. The causative agent of pneumonia was not examined in the study.

Limitation

When the sepsis status of the patients could not be clarified in the hospital automation system, the intania and chest diseases consultations, and intensive care observation forms were reviewed to clarify the sepsis status. Patient observation forms were reviewed necessarily to clarify the IVIG doses that the patient received.

Conclusion

It is thought that the use of IVIG in allogeneic stem cell transplantation is associated with a decrease in sepsis but the use of IVIG does not have a positive effect on survival and may prolong neutrophil engraftment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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