Original Article

Non-Infectious Complications in Patients with Allogeneic Hematopoietic Stem Cell Transplantation- Single Center Experience from Eastern Anatolia

Doğu Anadolu'dan Tek Merkez Deneyimi- Allojenik Hematopoietik Kök Hücre Nakli Yapılan Hastalarda Enfeksiyöz Olmayan Komplikasyonlar

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ABSTRACT

Introduction: The aim of this study was to investigate late non-infectious complications in patients with allogeneic hematopoietic stem cell transplantation (HSCT).

Materials and Methods: The records of 143 patients who underwent allogeneic HSCT between 01.02.2011 and 31.12.2018 in Inonu University Turgut Özal Medical Center Department of Hematology were retrospectively reviewed.

Results: In our study, late non-infectious complications were seen in 68 % of the patients. Graft Versus Host Disease (GVHD) was observed in 43 patients (33%) %. The most common GVHD involvement sites were skin and liver.

It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD (p=0,01) and late stage complications (p=0,016). Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count.

When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group (p=0.005).

It was observed that the rate of recurrence of the primary disease, renal complications and neurological complications was higher in the 90-120th days after transplantation. Ocular and GVHD complications were more likely to develop later. It was observed that endocrine complications were encountered equally in both early and late periods.

Discussion: It was seen that, late complications were common in patients who underwent allogeneic HSCT and these complications were mostly related to GVHD and GVHD treatment.

Keywords: Hematopoietic stem cell transplantation, Late complications, non-infectious complications, GVHD

ÖZET

Giriş: Bu çalışmanın amacı, allojenik hematopoietik kök hücre transplantasyonu (HSCT) olan hastalarda geç enfeksiyon dışı komplikasyonları araştırmaktı.

Gereç ve Yöntemler: İnönü Üniversitesi Turgut Özal Tıp Merkezi Hematoloji Anabilim Dalı'nda 01.02.2011-31.12.2018 tarihleri arasında allojenik HKHT yapılan 143 hastanın kayıtları retrospektif olarak incelendi.

Bulgular: Çalışmamızda hastaların %68'inde geç enfeksiyon dışı komplikasyonlar görüldü. Graft Versus Host Hastalığı (GVHD) 43 hastada (%33) gözlendi. En yaygın GVHD tutulum bölgeleri cilt ve karaciğerdi.

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CD 34 (+) hücre sayısının kronik GVHD gelişimi (p=0,01) ve geç dönem komplikasyonları (p=0,016) üzerinde anlamlı etkisi olduğu belirlendi. Yüksek CD 34 (+) hücre sayısı verilen grupta kronik GVHD ve geç komplikasyon oranları daha düşük bulundu.
Hastalar hazırlık rejimlerine göre gruplandırıldığında miyeloablatif rejim grubundaki hastalarda %78,8 oranında istatistiksel olarak anlamlı derecede daha fazla komplikasyon gözlendi (p=0,005).
Nakil sonrası 90-120. günlerde primer hastalık, böbrek komplikasyonları ve nörolojik komplikasyonların tekrarlama oranlarının daha yüksek olduğu gözlendi. Oküler ve GVHD komplikasyonlarının daha sonra gelişmesi daha olasıydı. Endokrin komplikasyonların hem erken hem de geç dönemlerde eşit oranda görüldüğü gözlendi.
Tartışma: Allojenik HKHT yapılan hastalarda geç komplikasyonların sık görüldüğü ve bu komplikasyonların daha çok GVHD ve GVHD tedavisi ile ilişkili olduğu görüldü.

Anahtar kelimeler: Hematopoetik kök hücre nakli, Geç komplikasyonlar, non-infeksiyöz komplikasyonlar, GVHD

Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment method that is being used more and more in the curative treatment of many malignant and non-malignant diseases. In allogeneic HSCT, donors are classified as fully matched, haploidentic (semi-matched) and incompatible according to their HLA compatibility with the recipient. Regimens in which the patient's bone marrow is suppressed with high-dose cytotoxic chemoradiotherapy are myeloablative regimens, and regimens in which bone marrow is suppressed with minimal immunosuppression are non-myeloablative regimens [1]. Non-myeloablative regimens are generally applied to people over 55 years of age with comorbidities [2].

Early and late complications of treatment are more common [3]. Early and late complications have a great impact on mortality and morbidity [4]. The main complications that occur in the late period are; chronic Graft Versus Host Disease (GVHD), secondary malignancies, infections, pulmonary complications, cardiac toxicity, endocrine complications. In addition to these, complications of some other organ systems related to treatment may also be seen [5].

GVHD, which is one of the late complications, can also be seen in HLA-matched transplants and affects many organs and systems. Standard prophylaxis regimens given to prevent the development of GVHD and drugs used in its treatment may also lead to various complications in the late period. Late complications were attributed to the primary disease, donor compliance, preparation regimen, steroid use, various drugs used, and many other factors.

The important thing is to anticipate these complications and manage them successfully. Successful treatment of early and late complications will contribute to prolonging survival and improving quality of life. Non-infectious complications in patients wıth allogeneic hematopoietic stem cell transplantation is may be important in these population.

It is aimed to investigate late stage non infectious complications and the factors affecting it.

Materials and Methods

Between 01.02.2011-31.12.2018, 143 patients who had allogeneic HSCT at İnönü University Turgut Özal Medical Center adult stem cell and bone marrow transplant center were fol-

lowed up in our center for at least 3 months were included in the study. Approval was obtained from the Inonu University Malatya Clinical Research Ethics Committee with the date of 02.07.2019 and the approval number

2019/277. The study was conducted in accordance with the Helsinki declaration.

Age, gender, disease subtype, preparation regimen, late complications of our patients were determined through the hospital automation system. Late complications of the patients were considered as complications occurring 100 days after transplantation. Our study was retrospective and no invasive procedure was performed on the patients.

Statistical analyses

Research data was uploaded to the computer environment via "SPSS (Statistical Package for SocialSciences) for Windows 22. Descriptive statistics were presented as mean±standard deviation, median (minimum-maximum), and percentage. Pearson Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables.

The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov Test. The Mann-Whitney U Test was used as a statistical method for the statistical significance between two independent groups for the variables that were not found to fit the normal distribution. Statistical significance level was accepted as $p<0.05$.

Results

Of the 143 patients included in the study, 60 (42%) were female and 83 (58%) were male. The median age was 41 (18-65) years. In our study, 7 different preparation regimens were used before hematopoietic stem cell transplantation. Peripheral-derived stem cell transplantation was performed in all patients. The demographic and clinical characteristics of 143 patients are given in Table 1.

The distribution of the patients included in the study according to the chemotherapy preparation regimen they received before HSCT is given in Table 2.

When the amount of CD34 (+) cells given to the patients was examined, the minimum amount of CD34 (+) cells was 4.76 x 10^6/kg, the maximum was 15.75 x 10^6/kg, and the median value was 7.45 x 10^6/kg.

When the donors of 143 patients who underwent allogeneic HSCT were examined, 57 were female and 86 were male. The age range was 12-67 years and the median value was 40.

In total, 123 patients underwent relative and 20 patients underwent unrelated transplants, and nine patients underwent haploidentic transplants.

One hundred and twenty five of the patients were transplanted in the first complete remission and 18 in the second complete remission.

When the development of chronic GVHD of the patients was examined, it was seen that chronic GVHD developed in 43 patients (33%). The distribution of GVHD developed in patients who underwent allogeneic HSCT according to the site of involvement is given in Table 3.

There was no effect of patient age, donor age, blood group compatibility, gender, gender match, engraftment time on the development of chronic GVHD. It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD (p=0,01) and late stage complications (p=0,016). Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count.

The development rates and times of hepatic complications in the patients were examined. Liver function tests elevation was detected for

Table 1. Demographic and clinical characteristics of our patients

	Patients with complication(n=99)	Patients without complication (n=44)	P value
Age,median (range)	41 (18-65)	38 (18-65)	0,4
Gender (male:female)	58:41	25:19	0,8
Gender Compatibility			0,5
Present, n	52 (%52,5)	21(47,7%)	
Absent, n	47(%47,5)	23(52,2%)	
Diagnosis			
Acute myeloid leukemia, n	57 (57,5%)	26 (59,9%)	
Acute lymphoblastic leukemia, n	25 (25,2%)	7 (15,9%)	
Myelodisplastıc syndrome, n	5 (5,05%)	1 (2,27%)	
Non-hodgın lymphoma, n	4 (4,04%)	1 (2,27%)	
Others, n	8 (8,08%)	9 (20,4%)	
Blood Group Compatibility			0,6
concordant, n	61 (61,6%)	22 (50%)	
major mismatch, n	16 (16,1%)	9 (20,4%)	
minor mismatch, n	11 (11,1%)	7 (15,9%)	
mix mixmatch, n	11(11,1%)	6 (13,6%)	
Donor age, median (range)	40 (12-65)	37 (15-67)	0,899
Relationship			0,1
Matched sibling donor, n	87 (87,8%)	42 (95,4%)	
Matched unrelated donor, n	12 (12,1%)	2 (4,5%)	
Cd34 (+) x 10^6 cell, median(range)	7 (4,7-15,7)	8 (5-13)	0,016
Engraftment time, median (range)	20 (12-35)	18 (11-35)	0,970

Table 2. Distribution of patients according to the preparation regimen

Conditioining chemotherapy regimen	n	%
Busulfan-Cyclophosphamide (Bu-Cy)	89	62.3
Busulfan-Fludarabin-Anti-thymocyte globulin (Bu-Flu-ATG)	26	18.2
Fludarabine–Amsacrin–Cytarabine (Flu-Ams-Siter)	10	6.9
Treosulfan-Flu-ATG	8	5.6
Fludarabine, Anti-thymocyte globulin, Thiotepa (Flu-ATG-Tio)	4	2.8
Busulfan, Cyclophosphamide, Etoposide (Bu-Cy-Eto)	4	2.8
Fludarabine, Anti-thymocyte globulin, Cyclophosphamide (Flu-ATG-Cy)	2	1.4

Table 3. Distribution of GVHD by site of involvement

Site of involvement	n	%
Skin	10	23
Skin and liver	6	16
Gastrointestinal system (GIS)	2	3
GIS and skin	2	3
Gıs and liver	1	2
Kidney	1	2
Lung	1	2

unknown reasons in five patients, due to drug toxicity in 12 patients, iron overload in six patients, associated with GVHD in 19 patients, cholecystitis in one patient, cholestasis in three patients, viral hepatitis in two patients, and pancreatitis in two patients.

Type 2 diabetes mellitus in 11 patients, hypothyroidism in two patients, subclinical hyperthyroidism in two patients, infertility in two patients, early menopause in two patients, euthyroid sick syndrome in one patient, and inappropriate antidiuretic hormone syndrome in one patient were detected.

HSV infection in any region was seen in five of the patients, zona zoster in 16, xerosis in three, paraneoplastic ichthyosis in one and seborrheic dermatitis in one of the patients.

Ocular complications were seen in 18 patients, including conjunctivitis in six patients, dry eye in five patients, blepharitis in two patients, keratitis in one patient, uveitis in one patient, preseptal cellulitis in one patient, subretinal hemorrhage in one patient, and papilledema in one patient.

When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group (p=0.005).

It was observed that the rate of recurrence of the primary disease, renal complications and neurological complications was higher in the 90-120th days after transplantation. Ocular and GVHD complications were more likely to develop later. It was observed that endocrine complications were encountered equally in both early and late periods.

Discussion

Being able to predict and manage complications that may develop in the early and late period after transplantation has become one of the most important factors affecting the success of transplantation.

Similarly, the prevalence of AML and ALL diagnoses in our study and other studies reviewed confirms that transplantation is mostly performed with leukemia indications and that stem cell transplantation is an effective treatment option in acute leukemia [6,7].

It was determined that the preparatory regimes applied in each center differed, and it was observed that each center applied a preparatory regime in line with its own experience and possibilities [8,9].

In a study involving 121 patients between 2003 and 2009, the mean duration of neutrophil engraftment was found to be 15 (8-41) and when analyzed according to blood group compatibility, it was seen that blood group compatibility had no effect on engraftment duration [10].

In our study, the median value of the mean neutrophil engraftment time was determined as 19 (11-35) days.

In our study, it was observed that blood group compatibility had no effect on the development of any late complications, the development of chronic GVHD, and the engraftment times in line with the literature. In the study published by Nina Worel in 2015, Klump et al.'s study on 240 patients found that ABO mismatch had no effect on the development and severity of chronic GVHD [11,12].

In the studies, it was found that the amount of stem cells given was effective on the success of transplantation and the ideal CD34 (+) amount was determined as $4x10^6$/kg, and the lower limit value was determined as $2x10^6$/kg.

In our study, a statistically significant relationship was found between CD34 (+) cell count and chronic GVHD. It was found that chronic GVHD developed more in the group with low CD34 (+) number. In the study of Przepiorka et al. on 116 patients, CD34 (+) count was $8.3x\ 10^6$. There was no difference in terms of the development of chronic GVHD in patients with and above / kg [13]. In the study of Jose et al., it was observed that the incidence of grade 2-4 chronic GVHD

increased as the number of infused CD34 (+) cells increased [14]. In the literature, there are publications claiming that the number of CD34 (+) cells has an effect on engraftment, as well as publications saying that it has no effect.

In the study of Klump et al. on 240 patients, it was observed that blood group compatibility had no effect on the development of chronic GVHD [12]. In the study, the development of chronic GVHD was observed in the median 6 months [3-17]. In the same study, it was determined that the diagnosis of gender and blood group compatibility, and the preparation regimen had no effect on the development of cGVHD [15]. Since the distribution of disease diagnoses was not proportional in our study, analysis was not performed in terms of the development of GVHD according to the diagnoses. It was determined that more chronic GVHD was seen in the 12-month period, and age, donor age, and gender compatibility had no effect on chronic GVHD, in line with the literature.

It was observed that significantly more complications developed in the group given myeloablative regimen, one of the preparatory regimens. It was observed that there were patients who were given Treosulfan-Flu-ATG and Cyclo-Flu-ATG with the least late complications.

In our literature review, there is no publication on the analysis of patients with and without any late system complications, and our study is original in this regard. The fact that the development of GVHD was mostly observed in patients with any system complication in our study showed us that the development of complications is closely related to GVHD itself and its treatment.

The major limitation of our study was that it was retrospective. The relatively small number of patients was also a limiting factor. Multicenter studies with more patients are needed.

Conclusion

In our study, patients who were followed up for at least three months after HSCT were included in the study. It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD and late stage complications. Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count. When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group.

In order to evaluate the complication analysis more objectively, there is a need for prospective, multicenter studies in which these tests are examined at regular intervals in all patients.

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