Original Article

Evaluation of the Relationship Between Cytomegalovirus Replication and Acute Graft-Versus-Host Disease in Patients with Allogeneic Hematopoietic Stem Cell Transplantation

Allojenik Hematopoietik Kök Hücre Transplantasyonlu Hastalarda Sitomegalovirüs Replikasyonu ve Akut Graft-Versus-Host Hastalığı Arasındaki İlişkinin Değerlendirilmesi

Duygu Mert[1], Alparslan Merdin[2], Bahar Uncu Ulu[3], Mehmet Sinan Dal[3], Merih Kızıl Çakar[3], Gülşen İskender[1], Sabahat Çeken[1], Tuğçe Nur Yiğenoğlu[3], Fevzi Altuntaş[3], Mustafa Ertek[1]

[1]University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey.
[2]University of Health Sciences Gülhane Education and Research Hospital, Hematology Clinic and Stem Cell Transplantation Unit, Ankara, Turkey.
[3]University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Hematology Clinic and Bone Marrow Transplantation Unit, Ankara, Turkey.

ABSTRACT

Introduction: It is controversial that cytomegalovirus (CMV) replication is a cause of graft-versus-host disease (GVHD). The aim of this study is to evaluate whether CMV replication causes acute GVHD development or not.

Materials and methods: The study is retrospective. Patients diagnosed with acute GVHD with a prior history of allogeneic hematopoietic cell transplantation (allo-HCT) were included in the study. All the included patients were followed-up in the bone marrow transplantation unit between 01/01/2013-10/31/2019. As the control group, patients without a history of acute GVHD after allo-HCT were included. The data of patients with acute GVHD after allo-HCT and patients with out known acute GVHD were compared.

Results: Fifty nine patients with acute GVHD and 178 patients without acute GVHD after allo-HCT were included in the study. Sixteen of the patients with acute GVHD were female and 43 were male. Sixty two of the patients without acute GVHD were female and 116 were male. The average CMV-DNA level was found as 1871.0 [821.0-16720.0] copies/ml in patients who had CMV replication in the acute GVHD group. On the other hand, the average of CMV-DNA level was found as 1607.5 [601.0-119181.0] copies/ml in the non-acute GVHD group. There was no statistically significant difference between the two groups.

Discussion: CMV replication does not seem to contribute to acute GVHD development after allo-HCT. Suppression of CMV replication may not prevent acute GVHD development.

Keywords: CMV replication, acute GVHD, allo-HCT

ÖZET

Giriş: Sitomegalovirus (CMV) replikasyonunun, graft-versus-host hastalığının (GVHH) bir nedeni olduğu tartışmalıdır. Bu çalışmanın amacı CMV replikasyonunun akut GVHH gelişimine neden olup olmadığını değerlendirmektir.

Gereç ve yöntemler: Çalışma, geriye dönüktür. Daha önceden allojenik hematopoietik hücre nakli (allo-HHN) öyküsü olan akut GVHH tanısı alan hastalar çalışmaya dahil edilmiştir. Dahil edilen tüm hastalar 01/01/2013-31/10/2019 tarihleri arasında kemik iliği nakil ünitesinde takip edilmiştir. Kontrol grubu olarak, allo-HHN sonrası akut GVHH öyküsü olmayan hastalar alınmıştır. Allojenik

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hematopoietik hücre naklinden sonra akut GVHH'si olan hastalar ile nakil sonrası bilinen akut GVHH'si olmayan hastaların verileri karşılaştırılmıştır.
Bulgular: Allojenik hematopoietik hücre naklinden sonra akut GVHH'li 59 hasta ve akut GVHH'si olmayan 178 hasta çalışmaya dahil edilmiştir. Akut GVHH'li hastaların 16'sı kadın, 43'ü erkektir. Akut GVHH olmayan hastaların 62'si kadın, 116'sı erkektir. Akut GVHH grubunda CMV replikasyonu olan hastalarda ortalama CMV-DNA düzeyi 1871,0 [821,0-16720,0] kopya/ml bulunmuştur. Akut olmayan GVHH grubunda ise CMV-DNA düzeyi ortalaması 1607,5 [601,0-119181,0] kopya/ml bulunmuştur. İki grup arasında istatistiksel olarak anlamlı bir fark saptanmamıştır.
Tartışma: CMV replikasyonunun, allo-HHN sonrası akut GVHD gelişimine katkıda bulunmadığı görülmektedir. CMV replikasyonunun baskılanması akut GVHH gelişimini engellemeyebilir.

Anahtar kelimeler: CMV replikasyonu, akut GVHH, allo-HHN

Introduction

Hematopoietic cell transplantation is accepted as a part of the treatment for many serious congenital or acquired diseases of the bone marrow [1]. Despite the progress in immunosuppressive and antiviral treatments, acute graft-versus-host disease (GVHD) and cytomegalovirus (CMV) infection remain major complications after allogeneic hematopoietic cell transplantation (allo-HCT) [2].

Multiple studies have shown that GVHD and its treatment put patients at risk for CMV replication [3-5]. In contrast, it is controversial that CMV replication might be a cause of GVHD. Data directly associating CMV replication and GVHD development are missing [6]. In a recent study reported by Wang LR et al, the presence of CMV replication was shown in the development of acute GVHD [7].

Hereby in this study, we aimed to evaluate whether CMV replication causes acute GVHD development or not.

Materials and method

The study is retrospective. Approval was obtained from the Ethics Committee of Tertiary Hospital (Approval date: 01/22/2020 and decision no: 2020-01/510).

Patients diagnosed with acute GVHD with a prior allo-HCT were included in the study. All the patients included in the study were followed-up in the bone marrow transplantation unit of tertiary hospital between 01/01/2013-10/31/2019. As the control group, patients without a history of acute GVHD after allo-HCT were included.

The present study was included data that were obtained from patients with acute GVHD and patients without acute GVHD after allo-HCT in tertiary hospital bone marrow transplantation unit.

Records of the patients were obtained electronically as a retrospective file scan. Demographic data and other information of the patients were recorded in a previously prepared form. The patients' gender, age during allo-HCT, underlying disease [Acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), Hodgkin's lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), myelodysplastic syndrome (MDS), other diseases], CMV replication status, measured CMV-DNA level in the patient file, status of acute GVHD presence, acute GVHD type [skin GVHD, liver GVHD, gastrointestinal tract (GIS) GVHD, lung GVHD, other GVHD] were recorded.

After allo-HCT, patients were monitored for CMV-DNA levels once a week.

In patients with CMV replication, initial values of CMV-DNA level above 1000 copies/ml or close to 1000 copies/ml were recorded. The data of patients with acute GVHD after allo-HCT and patients without known acute GVHD after allo-HCT were compared. Fifty nine patients with acute GVHD and 178 patients without acute GVHD (as a control group) were included in the study.

Table 1. Evaluation of the effect of age, gender, donor match status, CMV replication status and disease type on GVHD.

Variable	Acute GVHD (n=59)	No GVHD (n=178)	Total (N=237)	Statistical analysis* Possibility
Gender				
Female	16 (27.1%)	62 (34.8%)	78 (32.9%)	χ^2=1.194 p=0.275
Male	43 (72.9%)	116 (65.2%)	159 (67.1%)	
Underlying disease				
AML	20 (33.9%)	86 (48.3%)	106 (44.8%)	χ^2=14.581 p=0.029
ALL	21 (35.6%)	45 (25.3%)	66 (27.8%)	
CML	1 (1.7%)	8 (4.4%)	9 (3.8%)	
HL	9 (15.2%)	11 (6.2%)	20 (8.4%)	
NHL	1 (1.7%)	14 (7.9%)	15 (6.4%)	
MM	-	2 (1.1%)	2 (0,8%)	
MDS	3 (5.1%)	3 (1.7%)	6 (2.5%)	
Other diseases	4 (6.8%)	9 (5.1%)	13 (5.5%)	
CMV replication				
Yes	27 (47.4%)	95 (54.0%)	122 (52.4%)	χ^2=0.754 p=0.385
No	30 (52.6%)	81 (46.0%)	111 (47.6%)	

*"Pearson-χ2 cross tables" were used to analyze the relations of two qualitative variables.
GVHD: Graft-versus-host disease, AML: Acute myeloid leukemia, ALL: Acute lymphoid leukemia, CML: Chronic myeloid leukemia, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin lymphoma, MM: Multiple myeloma, MDS: Myelodysplastic syndrome.

Patients aged 15 years or older, patients who had allo-HCT with or without acute GVHD were included in the study.

Statistical analysis

SPSS (IBM SPSS Statistics 24) was used to analyze the data. Frequency tables and descriptive statistics were used to interpret the findings. "Pearson-χ2 cross tables" was used to analyze the relationship between the qualitative variables. In the data without normal distribution, "Mann-Whitney U" test (Z-table value) statistics were used to compare the two independent groups with the measured values. P <0.05 was considered statistically significant.

Results

Fifty nine patients with acute GVHD and 178 patients without acute GVHD after allo-HCT were included in the study. Sixteen (27.1%) of the patients with acute GVHD were female and 43 (72.9%) were male. Sixty two (34.8%) of the patients without acute GVHD were female and 116 (65.2%) were male. There was no significant difference between the two groups in terms of gender (Table 1). The age at the time of transplantation was 35.0 [15.0-63.0] years in patients with acute GVHD and 36.5 [15.0-64.0] years in patients without acute GVHD. There was no statistically significant difference between the two groups in terms of the age at the time of transplantation (Z = -0.943, p = 0.346) (Table 2).

A statistically significant difference was found between the groups in terms of underlying disease type ($\chi2$ = 14.581; p = 0.029).

The incidence of acute GVHD was the highest among patients with ALL, on the other hand, the incidence of acute GVHD was the least among patients with AML (Table 1).

There was no statistically significant difference between the groups regarding CMV replication status (p> 0.05). In acute GVHD group, CMV replication occured in 27 (47.4%) patients wheras 95 (54.0%) patients had CMV replication in the non-acute GVHD group (Table 1).

The average CMV-DNA level in patients who had CMV replication in the acute GVHD

Table 2.The effects of transplantation age, CMV-DNA level on GVHD development.

Variable	Acute GVHD (n=59)	No GVHD (n=178)	Statistical analysis* Possibility
Transplantation age (years)	35.0 [15.0-63.0]	36.5 [15.0-64.0]	Z=-0.943 p=0.346
CMV-DNA level (copies/ml)	1871.0 [821.0-16720.0]	1607.5 [601.0-119181.0]	Z=-0.890 p=0.373

*In the data without normal distribution, "Mann-Whitney U" test (Z-table value) statistics were used to compare the two independent groups with the measured values.
GVHD: Graft-versus-host disease.

Table 3. Distribution of acute GVHD types

Distribution of acute GVHD types	Acute GVHD	
	n	%
Skin	23	39.0
Skin and liver	4	6.8
Skin and gastrointestinal tract	7	11.9
Liver	12	20.3
Liver and gastrointestinal tract	1	1.7
Gastrointestinal tract	12	20.3

GVHD: Graft-versus-host disease.

group was found as 1871.0 [821.0-16720.0] copies/ml. Besides, the average CMV-DNA level was found as 1607.5 [601.0-119181.0] copies/ml in non-acute GVHD group. There was no statistically significant difference between the two groups in terms of CMV-DNA level (Z= -0.890, p = 0.337) (Table 2).

Acute skin GVHD which was detected in 23 (39%) of the patients, was the most common form of acute GVHD in patients. Gastrointestinal system acute GVHD and liver acute GVHD were nearly equally detected in patients (Table 3).

Discussion

Acute GVHD, which is one of the most important complications of allo-HCT [8]. Acute graft-versus-host disease remains a major cause of morbidity and mortality following allo-HCT [9]. Despite prophylactic treatment, acute GVHD affects 30%–70% of recipients depending on the type of transplant, patient characteristics and GVHD prophylaxis regimen [10].

The National Institutes of Health consensus criteria use clinical findings to distinguish between acute and chronic [11]. Therefore, patients presenting with typical acute GVHD findings before the 100th day are considered to be "classical acute GVHD", whereas patients presenting with the same findings after the 100th day are typically categorized as "late-onset acute GVHD" upon reduction of immunosuppression [11].

In a study, it has been reported that skin, GIS and liver are the main target organs in patients with acute GVHD [12]. In the study of Martin et al, they found that 81% of patients had skin involvement, 54% had GIS involvement, and 50% had liver involvement at the onset of acute GVHD [13].

In this study, we found that skin, GIS and liver GVHDs were observed more frequently in patients with acute GVHD.

Risk-bearing allo-HCT recipients should be screened at least once a week from the 10th day to the 100th day after transplant, regardless of the treatment method chosen for the presence of CMV viremia or antigenemia [14].

In this study, CMV replication before acute GVHD was detected in 27 (47.4%) of 59 patients with acute GVHD. On the other hand, CMV replication was detected in 95 (54.0%) of 178 patients in the non-acute GVHD group.

There was no statistically significant difference found between the two groups in terms of the frequency of patients with CMV replication status.

Endothelial cells infected with CMV might produce inflammatory cytokines, such as interleukin 6, which play an important role in the initial phase of GVHD [15].

In patients with CMV replication after allo-HCT, the inflammatory response can thus contribute to the initiation of acute GVHD [16]. However, data directly linking CMV replication with acute GVHD development are not yet available [17,18]. In the study of Meyers et al, it was reported that the frequency of acute GVHD increased in relation to the CMV replication [19].

In the study of Cantoni et al, they reported that acute GVHD incidence and transplant-related mortality increased in patients with CMV replication after allo-HCT [20]. On the other hand, we did not find any statistically significant difference between the two groups in terms of the frequency of patients with CMV replication.

CMV-DNA levels should be monitored from days of engraftment started to at least 100 days in the recipients after allo-HCT [21].

In conclusion, this study shows that CMV replication may not contribute to acute GVHD development after allo-HCT. When CMV replication is detected in patients, preemptive treatment is generally started. However, it should be kept in mind that suppression of CMV replication would not prevent acute GVHD development.

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Corresponding author e-mail: drduygumert@hotmail.com

Orcid ID:
Duygu Mert 0000-0002-6810-2199
Alparslan Merdin 0000-0003-1689-630X
Bahar Uncu Ulu 0000-0002-6230-9519
Mehmet Sinan Dal 0000-0002-5994-2735
Merih Kızıl Çakar 0000-0003-0978-0923
Gülşen İskender 0000-0001-7619-1366
Sabahat Çeken 0000-0002-3679-0978
Tuğçe Nur Yiğenoğlu 0000-0001-9962-8882
Fevzi Altuntaş 0000-0001-6872-3780
Mustafa Ertek 0000-0002-9397-8432

Doi:

