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Effect of Mannose-Binding Lectin Gene Polymorphism on Infection in Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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ABSTRACT

Introduction: The aim of this study was to investigate the association of mannose-binding lectin (MBL), which is involved in the classical complement pathway in innate immunity, with infections in the autologous hematopoietic stem cell transplantation (AHSCT) process and the frequency of *MBL* gene polymorphism.

Methods: Single gene nucleotide polymorphisms of codons 52 and 54 in exon 1 of the *MBL-2* gene were investigated in 30 patients who had received AHSCT with a diagnosis of multiple myeloma in the Adult Bone Marrow Transplant Unit between January 2020 and December 2020. Demographic characteristics, engraftment times, and infectious processes of the patients were recorded.

Results: Neutropenic fever developed at least once in 28 (93.3%) patients during AHSCT. During hospitalization pneumonia developed in 6 (20%), urinary tract infection in 4 (13.3%), and catheter infection in 4 (13.3%) patients. *MBL* gene polymorphism at codon 54 was found in 4 (13.3%) of the patients included in the study. Among the 4 patients with *MBL* gene polymorphism, 2 had pneumonia and 2 had urinary tract infection ($p=0.16$ and $p=0.07$, respectively). There was no difference between the patients with *MBL* gene polymorphism and those without *MBL* gene polymorphism in terms of age, gender, and infection type ($p>0.05$).

Conclusion: Bacterial infection was observed in all patients with *MBL* gene polymorphism during AHSCT. This may be related to the increased susceptibility to infection caused by *MBL* gene polymorphism. However, in this study no relationship was found between *MBL* gene polymorphism and infection frequency and type in AHSCT.

Keywords: Mannose-binding lectin, autologous, transplantation

Introduction

Mannose-binding lectin (MBL) is involved in the lectin pathway of capillary activation and functions as a part of innate immunity (1,2). When MBL binds to carbohydrates on the surface of microorganisms, serine proteases of the lectin pathway are activated. Then, the lectin pathway and the classic complement pathway together from a membrane attack complex and microorganisms are lysed (3).

MBL gene polymorphisms increase the susceptibility to infection by decreasing MBL serum levels. A single gene nucleotide polymorphism is defined in exon 1 of the *MBL-2* gene. In Eurasia, codon 54 polymorphism is observed at a rate of 25%, and this is the most common MBL variant (4).

It is known that patients with MBL deficiency have increased susceptibility to infections such as *Pseudomonas* and *Meningococci* (5).

Multiple myeloma (MM) is a malignant disease characterized by an uncontrolled, clonal increase in plasma cells in the bone marrow. High-dose melphalan followed by autologous hematopoietic stem cell transplantation (AHSCT) is the standard treatment for MM in appropriate patients after induction therapy (6).

The aim of this study was to investigate the frequency of *MBL-2* gene polymorphism and its relationship with infections in the process of AHSCT.

Methods

Our study was prospectively planned. The study was carried out with the permission of the İstinye University Hospital Clinical Research Ethics Committee (approval number: 2/2019.K-019, date: 04.12.2019). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

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Between January 2020 and December 2020, 30 patients who were planned to undergo AHSCT with a diagnosis of MM at our hospital were included in the study after their consent was obtained. In this prospective study, 5 mL peripheral blood samples were obtained from 30 patients before transplantation to investigate single gene nucleotide polymorphisms of codons 52 and 54 in exon 1 of the *MBL-2* gene. *MBL-2* gene rs1800450 C>T, rs7095891 G>A polymorphisms were analyzed by sequencing using sequencing kits (GML, Switzerland). All patients received VCD (bortezomib, dexamethasone, cyclophosphamide) or PAD (bortezomib, adriamycin, dexamethasone) as standard induction therapy followed by AHSCT for consolidation. Ciprofloxacin 500 mg 1x1, fluconazole 200 mg 1x1, acyclovir 200 mg 3x1 and trimethoprim sulfamethoxazole 800/160 mg 2x1, 2 days a week were administered prophylactically to all patients. All patients received melphalan 200 mg/m^2 IV on day -2 before AHSCT. All patients received at least $2x10^6$/kg CD34+ AHSCT, and granulocyte colony-stimulating factor 300 µg/day IV was initiated on day 4 after stem cell infusion. Neutropenic fever was defined as an absolute neutrophil count $<0.5x10^9$/L and a temperature of 38.3 degrees Celsius or higher on tympanic measurement. Blood, catheter and urine cultures of the patients who developed neutropenic fever were taken, ciprofloxacin 500 mg 1x1 was stopped and IV broad spectrum antibiotics vancomycin and meropenem were initiated. Engraftment time was defined as a neutrophil count $\geq 0.5x10^9$/L for 3 consecutive days. Demographic characteristics of the patients, neutropenic fever status during the transplantation process, treatments received, infection type, blood culture, catheter culture, and urine culture results, and engraftment times were recorded.

Statistical Analysis

SPSS (version 20) Windows software was used for statistical analysis. Confidence interval at 95% level and $p<0.05$ were considered statistically significant. Chi-square test or if applicable Fischer's exact test was used for comparison of the groups.

Results

Among the 30 patients included in the study, 11 were female (36.7%) and 19 were male (63.3%) and the age range was 50-70 years with a mean age of 60 years. Neutropenic fever developed at least once in 28 (93.3%) patients during AHSCT. During hospitalization pneumonia developed in 6 (20%), urinary tract infection in 4 (13.3%), and catheter infection in 4 (13.3%) patients. Among the 6 patients who developed pneumonia, 2 of them developed pseudomonas and 1 of them developed haemophilus influensa in sputum culture, and prophylactic antifungal treatment was extended in 3 (10%) patients because of fungal pneumonia. *E. coli* was grown in urine culture in all patients with urinary tract infection. Serratia marcescens were grown in 2 patients and *Staphylococcus aureus* was grown in 2 patients in the catheter tip culture of patients with a catheter infection.

Neutrophil engraftment time was 10 days in 11 (36.7%), 11 days in 7 (23.3%), 12 days in 9 (30%), and 13 days in 3 (10%) patients.

CC, CT, TT for MBL rs1800450 C>T and GG, GA, AA genotypes for MBL rs7095891 G>A were analyzed. MBL rs1800450 C>T was found in the CC normal genotype in all patients, MBL rs7095891 G>A was found in GA heterozygous in 4 (13.3%) patients, and in the GG normal genotype in 26 (86.7%) patients. Among the 4 patients with *MBL* gene polymorphism, 2 had pneumonia and 2 had urinary tract infection ($p=0.16$ and $p=0.07$, respectively). No difference was found between the patients with *MBL* gene polymorphism and those without *MBL* gene polymorphism in terms of age, gender and infection type ($p>0.05$) (Table 1).

Discussion

MBL is part of innate immunity and is involved in the lectin pathway (7). In previous studies (4), *MBL* gene polymorphism was defined as around 25%. In our study, MBL codon 54 polymorphism was found with a rate of 13.3%, whereas MBL codon 52 polymorphism was not found in any patient. 4 (13.3%) patients with MBL rs7095891 G>A polymorphism was in the heterozygous (GA) genotype.

Table 1. Descriptive and clinical characteristics of the groups

Parameter	G54D (+), (n=4)	G54D (-) and R52C (-), (n=26)	p-value
Age	59±9	62±8	0.24
Gender			
Female	2 (50%)	9 (34.6%)	0.61
Male	2 (50%)	17 (65.4%)	
Infection type			
Pneumonia	2 (50%)	4 (15.4%)	0.16
Bacterial	2 (50%)	1 (3.8%)	
Pseudomonas	2 (50%)	0	
Haemophilus influensa	0	1 (3.8%)	
Fungal	0	3 (11.6%)	
Urinary tract infection	2 (50%)	2 (7.7%)	0.07
E. coli	2 (50%)	2 (7.7%)	
Catheter infection	0	4 (15.4%)	
Serratia marcescens	0	2 (7.7%)	
Cytaphylococcus aureus	0	2 (7.7%)	

In previous studies (8,9), *MBL* gene polymorphism increases susceptibility to some infections in the process of stem cell transplantation. In our study, pneumonia or urinary tract infection was observed in all patients with *MBL* gene polymorphism during AHSCT. In addition, pneumonia was observed in 15.4% and urinary tract infection in 7.7% of patients without *MBL* gene polymorphism. This difference between groups was not statistically significant. This may be related to the detection of *MBL* gene polymorphism in only 4 patients in our study.

Unlike our study, a previous study (10) showed that *MBL* gene polymorphism was associated with an increased risk of fungal infection during stem cell transplantation. Although *MBL* gene polymorphism was found in 2 patients with fungal pneumonia in our study, the increased risk of fungal infection with *MBL* gene polymorphism could not be demonstrated in this study because *MBL* gene polymorphism was not found in 2 patients with fungal pneumonia. This may be related to the small number of patients.

Previous studies (11) have found an increased risk of bacterial infection during the process of stem cell transplantation in patients with *MBL* gene polymorphism. Similarly, the bacterial infection was observed in all patients with *MBL* gene polymorphism in our study. Similar to previous studies (12), *MBL* gene polymorphism was in 2 patients with pseudomonas infection. This supports the increased frequency of pseudomonas infection, especially with *MBL* gene polymorphism.

Serratia marcescens and *Staphylococcus aureus* were grown in catheter cultures of 2 patients without *MBL* gene polymorphism.

E. coli growth was detected in the urine culture of 2 patients with *MBL* gene polymorphism and no resistant microorganisms were grown in the urine culture of any of the patients.

All patients were administered prophylactic oral acyclovir 600 mg/day during AHSCT. Unlike a previous study (13), in our study, no difference was found in terms of viral infections in patients with or without *MBL* gene polymorphism. This may be related to the small number of patients.

No difference was found between patients with or without *MBL* gene polymorphism in terms of infections and response to treatments. Mortality was not detected in any patient.

Although increased infections are known to prolong engraftment time, engraftment time was not different from that expected in patients with or without *MBL* gene polymorphism.

MBL gene polymorphisms increase the susceptibility to infection by decreasing MBL serum levels (14). In our study, a heterozygous mutation in codon 54 of the *MBL-2* gene was detected in 4 (13%) patients. Since MBL serum levels of the patients were not analyzed, no comparison could be made regarding MBL serum levels.

Study Limitations

The most important limitation of this study is the small number of patients. In addition, the lack of comparison with MBL serum levels and the absence of a control group are other limitations.

Conclusion

In this study, bacterial infection was observed in all patients with *MBL* gene polymorphism during AHSCT. This may be related to the increased susceptibility to infection caused by *MBL* gene polymorphism. However, in this study no relationship was found between *MBL* gene polymorphism and infection frequency and type in AHSCT. Considering the number of patients in this study, in patients who are planned to receive intensive immunosuppressive treatment such as stem cell transplantation, it may be an appropriate approach to investigate *MBL* gene polymorphisms in patients with low MBL serum levels. In this way, close follow-up of infections, differentiation of prophylactic agents to be used, and effective treatment of infections may be possible in this group of patients during the processes requiring intensive immunosuppressive treatment. The results of this study need to be supported by randomized prospective, clinical, laboratory, and histopathological studies with a larger number of patients.

Ethics Committee Approval: The study was carried out with the permission of the İstinye University Hospital Clinical Research Ethics Committee (approval number: 2/2019.K-019, date: 04.12.2019).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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