The Relationship between Conditioning Regimen with Viral and Fungal Infections in Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract: *Background:* Infections are one of the most important factors that adversely affect the transplantation process at hematopoietic stem cell transplantation (HSCT). Quality of life and even the loss of patients due to infection may result in the failure of the HSCT. While the studies in the literature were mostly related to bacterial infections in HSCT, the viral and fungal infections were evaluated. The relationship between viral and fungal infections and the types of conditioning regimens used in HSCT was investigated.

Methods: Three hundred fifthy one (351) patients who had allogeneic HSCT were performed. The viral and / or fungal infections and conditioning regimens were determined from the medical records. The conditioning regimens were evaluated in two groups as myeloablative and non-myeloablative. We aimed to determine the statistical relationship between viral and fungal infections and type of conditioning regimen.

Results: Of the 351 patients, 104 had CMV infection, 4 had parvovirus infection, and 87 had fungal infection. Myeloablative regimen was used in 226 of 351 patients and non-myeloablative regimen was used in 125 patients. There was no significant relationship between the type of conditioning regimen and CMV, parvovirus and fungal infections.

Conclusion: The lack of a significant relationship between the type of conditioning regimen and the viral and fungal infections during HSCT provides the clinician with the choice of the conditioning regimen. However; we need to do more studies with larger case series and also relationship between the type of conditioning regimen and viral and fungal infections should be more clearly demonstrated.

Keyworlds: Viral infection, Fungal infection, Allogeneic hematopoetic stem cell transplantation.

INTRODUCTİON

Hematopoietic Stem Cell Transplantation (HSCT) is used in the treatment of malign and non-malign diseases. One of the most important factors affecting the success in the HSCT and in the post-transplant period is the infections that the patient has during the HSCT [1]. It is known that viral and fungal infections can be seen frequently in addition to bacterial infections among transplant-related infections [2, 3]. All or each of the bacterial, viral or fungal infections impair the quality of life during the HSCT. Therefore, it is necessary to minimize infection rates by minimizing the factors that may cause infection, at that case HSCT process will be managed more successfully.

It is a question of interest whether there is a relation between the type of conditioning regimen and infections that develop during the HSCT, and it has been emphasized in the literature that it is necessary to be careful in terms of viral and / or fungal infections that may develop in the case of using some of the conditioning regimens [4,5]. In this retrospective review are presented the relation between the type of conditioning regimen and viral and fungal infections that developed during the HSCT.

MATERİAL AND METHOD

Three hundred and fifty-one (351) patients who underwent ASCT were reviewed retrospectively. Two main group were determined according to the conditioning regimen: non-myeloablative conditioning regimen and myeloablative conditioning regimen . It was evaluated whether there was a significant relations between the type conditioning regimen and post-transplant viral and fungal infections.

STATİSTİCAL ANALYSİS

MEDCALC software SPPS-16 version (MedCalc Software bvba, Ostend, Belgium) was used for analysis of the data. Categorical values were calculated by Chi-square test, and non-categorical values were calculated by Mann-Whitney U test. P value <0.05 was considered significant.

RESULTS

The median age of the patients was 34.40/year (minimum – maximum: 15-64/year). Two hundred and twenty-seven (64.7%) patients were male and 124

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(35.3%) patients were female. One hundred sixteen (33%) patients had Acute Myeloid Leukemia (AML), 80 (22.8%) patients had Acute Lymphoblastic Leukemia (ALL), 30 (8.5%) patients had Aplastic Anemia (AA), and 26 (7.4%) patients had Multple Myeloma (MM), 16 (4.6%) patients had Hodking's Disease (HH), 22 (6.3%) patients had non-Hodking's Disease (N-HH), 18 (5.1%) patients had Myelodysplastic Syndrome (MDS), 3 (0.9%) patients had Fanconi Aplastic Anemia (FAA), 6 (1.7%) patients had Paroxysmal Nocturnal Hemoglobinuria (PNH), 2 (0.6%) patients had AML transforming from MDS, 5 (1%) patients had Myeloproliferative Disease (MPH), 3 (0.9%) patients had Granulocytic Sarcoma, 2 (0.6%) patients had Burkitt's Lymphoma, 12 (3.4%) patients had Chronic Myeloid Leukemia (CML), 1 (%0.3) patient had Thalassemia, 3 (0.9%) patients had Chronic Lymphocytic Leukemia (CLL), 2 (0.6%) patients had Chronic Myelomonocytic Leukemia (CMML), 1 (0.3%) patient had Large Granular Lymphocyte (LGL) syndrome, 1 (0.3%) patient had Congenital Hypoplastic Anemia (CHA), and 2 (0.6%) patients had Plasma Cell Leukemia (PHL). The risk classification of the patients were done according to the “Hematopoeitic Cell Transplantation- Comorbidity Index (HCT-CI/SORROR). The risk score evaluated to 2 group: low risk (SORROR 0-1-2), high risk (SORROR 3-4-5-6). There were 302 (86.1%) patients with low risk score, 49 (14%) patients with high risk score in this retrospective review . Considering the recipient and donor blood group and gender compatibility, 196 (55.8%) recipients had ABO blood group compatible, 152 (44.2%) recipients had not had ABO blood group compatible; 192 (54.7%) recipients had sex-matched donor and 159 (45.3%) recipients had not had sex-matched donor. There were 309 (88%) recipient who had a full matched (HLA matched:10/10) donor. Three hundred and forty-one (97.2%) patients received peripheral blood stem cell transplantation. Considering the recipient and donor Cytomegaly virus (CMV) serotype; 325 (92.6%) recipient and donor CMV was positive-positive, 4 (1.1%), recipient and donor CMV was negative-negative, 17 (4.8%) recipient-donor CMV was positive-negative and 5 (1.4%) recipient-donor CMV was negative-positive. While 26 (7.4%) of 351 patients had CMV infection at the remission-induction treatments , fungal infection was observed in 62 (17.7%) patients at the remission-induction treatments. At the post-transplant period, CMV infection was seen in 104 (29.6%) patients, parvovirus infection was seen in 4 (1.1%) patients, and fungal infection was seen in 87 (24.8%) patients.

Myeloablative conditioning regimen was used in 226 (64.4%) of 350 patients, and non-myeloablative conditioning regimen was used in 125 (35.6%) patients. Table **1** show patients’ conditioning regimens. Myeloablative conditioning regimen was included; fludarabine - TBI (total body irradiation), Velcade - melphalan, Endoxan - busulfex, TBI – cyclosporine - busulfan, TBI – melphalan, BEAM (included:carmustine -etoposide-anthracycline-melphalan), cyclophosphamide - busulfan, TBI - cyclophosphamide, Tiotepa - TBI, Tiotepa-melphalan. Non -myeloablative conditioning regimen was included: Zevalin-fludarabine-melphalan, busulfan-cyclophosphamide-fludarabine, fludarabine-melphalan, fludarabine-cyclophosphamide-ATG (anti-thymocyteglobulin),f ludarabine- cyclophosphamide- ATGAM (lenfosit immunoglobulin/antitimosit globulin), cyclophosphamide-ATG, ETO-melfalan, cyclophosphamide-fludarabine-busulfan-ATG, fludarabine-ATG, fludarabine, fludarabine-busulfan-cyclophosphamide-ATG (Table **1**).

When the conditioning regimen type was evaluated in two groups as myeloablative and non-myeloablative, no significant correlation was found between the conditioning regimen type and post-transplant CMV, parvovirus and fungal infections (CMV infection p=0.814, parvovirus infection p=0.546, fungal infection p=0.305).

DİCUSSİON

Viral infections, especially CMV infections, cause serious problems in the HSCT and cause to reduce the success of HSCT due to its negative effect on survival [6]. Fungal infections developing during the HSCT are also life-threatening, quality of life is also affected due to anti-fungal treatment and/or antifungal prophylaxis using in a long-term [7]. In this retrospective evaluation, it was investigated whether there was a relation between the type of conditioning regimen and post-transplant viral and fungal infections. No relation was found in this retrospective review. There is no study in the literature showing a relation between the type of conditioning regimen and post-transplant viral or fungal infections. However, Ustun *et al*. were showed that myeloablative conditioning regimen increased the risk of infection (bacterial/viral/fungal) compared to non-myeloablative or reduced-intensity conditioning regimens [8]. According to Ustun *et al*. myeloablative conditioning regimen in the first 100 days after HCST in AML patients, caused bacterial infections more frequently than other conditioning regimens’. However; this significant finding has not been demonstrated for viral or fungal infections [8]. Kim *et al*. stated that

Table 1: Conditioning Regimen in Allogeneic Stem Cell Transplantation

Conditioning Regimen	N of Patients	%.
Fludarabin -TBI	7	2,0
Velcade – melphalan	1	0,3
Cyclophosphamide –busulfex	1	0,3
TBI-cyclophosphamide-busulfan.	2	0,6
TBI-melphalan	1	0,3
Zevalin-fludarabin-melphalan.	2	0,6
BEAM	3	0,9
Busulfan-cyclophosphamide-fludarabin	14	4
Fludarabin- melphalan	58	16,5
Cyclophosphamide-busulfan	144	41
TBI- cyclophosphamide	61	17,4
Fludarabine- cyclophosphamide -ATG.	12	3,4
Fludarabine- cyclophosphamide –ATGAM	4	1,1
Cyclophosphamide –ATG	10	2,8
ETO-melphalan	2	0,6
Cyclophosphamide	5	1,4
Fludarabin-busulfan-ATG.	8.	2,3
Fludarabin-ATG.	1	0,3
Tiotepa- cyclophosphamide -busulfan.	1	0,3
Tiotepa- cyclophosphamide -TBI.	7	2,0
Fludarabin	4	1,1
Fludarabin-busulfan- cyclophosphamide -ATG	2	0,6
Tiotepa-busulfan	1	0,3
Total	351	100

ATG: anti-timosit globulin, ATGAM: lenfosit immunoglobulin/antitimosit globulin, BEAM: carmustin, etoposide, cytarabin, melphalan, ETO: etoposit, TBI: total body irridation.

bacterial infection were higher in myeloablative conditioning regimens, but the same finding was not observed for viral and fungal infections [9]. In both studies, it was emphasized that the rate of bacterial infection was associated with neutropenia and that bacterial infection rates decreased during the period when patients recovered from neutropenia [8, 9]. At the same time, it was emphasized that the rate of bacterial infection may have increased with myeloablative conditioning regimens caused a more damage to the gastrointestinal mucosa [8, 9]. However, these findings are not seen in viral and fungal infections. Because viral and/or fungal infections may occur independently of neutrophil count, they cannot only be associated with damage to the gastrointestinal mucosa. In the other words, as long as the immunosuppressive treatment was continued, there might be increase the rate of viral and fungal infections, which is independent of neutropenia and damage to the gastrointestinal mucosa. While the rate of viral and fungal infections is expected to be high in myeloablative conditioning regimens because to severe immunosuppression by myeloablative conditioning regimens, however, no statistically significant differences were found between myeloablative and non-myeloablative conditioning regimens in terms of fungal and/or viral infections in this evaluation.

Considering only CMV infection, it has been reported in the literature that CMV infection is more common in myeloablative conditioning regimens than in reduced-intensity conditioning regimens [10]. For fungal infections, it is known that less common in the first 3 months of HSCT [8]. İn contrast to CMV infections; the relationship of fungal infections to the conditioning regimen could not be demonstrated [11, 12]. However, Yong *et al*., were considered that previous CMV infection may increase the risk of fungal infection [13]. Ustun *et al*., were emphasized that a past infection type may increase other types of

infections sequentially [8], Consecutive infections or any previous infection type may cause to trigger the next new infection. Therefore, "Should we taken into account previous infections during the previous chemotherapy for choosing the conditioning regimen ?" . This question is coming to physicians mind for preventing the infections during HSCT.

It is known that the type of conditioning regimen (myeloablative or non-myeloablative) should be determined according to the patient's disease status, co-morbid factors and the patient's performance. The ideal conditioning regimen should be effective with low toxicity . It should also cause a low rate of bacterial and/or viral and/or fungal infection. The relationship between the conditioning regimen type and viral and fungal infections should be revealed more clearly with studies which are included large case series, and it should not be forgotten that previous infections should also be taken into account when determining the conditioning regimen.

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