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Evaluation of Risk Factors for Hepatic Complications after Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

***Background*:** Hepatic dysfunction in patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) is a major cause of morbidity and mortality. The aim of this study is to evaluate the incidence of post-transplantation hepatic complications in these patients.
***Methods*:** A total of 121 patients (age above 15 with no abnormality in their hepatic tests) enrolled in the study. The influence of a variety of risk factors on the incidence, type, and pattern of hepatic dysfunction as well as the length of hospital stay related to these complications were studied.
Results: As a whole, 76 patients (62%)—44 males and 32 females—were diagnosed with hepatic dysfunction after transplantation. As many as 31(25%) of the patients showed increased measures in their hepatic enzyme, while 45(37%) of them ended up with both abnormal enzyme measure and clinical symptoms including diarrhoea, skin rash, jaundice, and anorexia. The hepatic dysfunction rates owing to drug toxicity and graft versus host disease (GVHD) (21.5% and 16.5%, respectively) proved to be the highest in our study. We found that there is a significant relationship between the immunosuppressive regimen and the type of hepatic dysfunction—i.e., less patients with GVHD were found in the group who received anti-thymocyte globulin (ATG) in their regimen (p =0.034). Possible risk factors for the type of hepatic dysfunction are its pattern and clinical symptoms.
Conclusion: According to these findings, the immunosuppressive regimen can play a role in preventing the incidence of GVHD. Less occurrence of hepatic complications, especially GVHD, may lead to less clinical symptoms and time of hospital stay.

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Introduction

Hematopoietic stem cell transplantation (HSCT) is the transplantation of stem cells derived from bone marrow, peripheral blood, or the umbilical cord, which is performed frequently for treatment of malignant or non-malignant diseases. In this procedure, hematopoietic progenitor cells are derived either from the patient (autologous HSCT) or from a donor (allogenic HSCT)(1).

Patients who undergo allogenic HSCT may experience

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different complications including infections, graft-versus-host disease (GVHD), neutropenia, pulmonary toxicity, liver toxicity, and gastrointestinal (GI) toxicity (2). Hepatic enzymes disturbance is one of the most common complications in HSCT recipients and may involve more than 80% of patients (3,4). Leading causes of post-transplant complications are drug toxicity, GVHD, and sepsis (3).

GVHD occurs as donor immune cells attack normal host tissues. It is still the leading obstacle for successful stem cell transplantation. It comes in two forms- acute and chronic. The onset of acute GVHD is before day +100, while the chronic form occurs beyond this time (5). The clinical symptoms include skin rash, diarrhoea, and vomiting, among others. Although the definite diagnosis is through biopsy, the conditions for biopsy may limit the diagnosis to only clinical symptoms (6).

Hepatic complications would increase morbidity and mortality rates in early post-transplantation. Liver-related mortality in post-transplantation period is as high as 4% to 15% (4). Because of high morbidity and mortality rates, immediate diagnosis and treatment of HSCT-induced liver injury is essential (3). Multiple factors including the type of immunosuppressant regimen, conditioning regimen, sex, and engraftment time may affect the incidence of hepatic complications following HSCT (4).

This study intends to evaluate the incidence, patterns, and risk factors of hepatic complications within one month of allogeneic HSCT in Iran's Bone Marrow Transplantation Centre at Shariati Hospital.

Patients and Methods

Design of the study:

This prospective cross-sectional study was designed to evaluate the incidence of hepatic dysfunction in patients who underwent allogeneic HSCT during one month after transplantation. Furthermore, it was aimed to evaluate the effect of different conditioning regimens, immunosuppressant therapy, being of the same sex with donor, primary disease and other risk factors on incidence, type and pattern of liver dysfunction. The effect of these risk factors on length of hospital stay was also assessed.

Patients:

Data was collected from those who were admitted for allogeneic HSCT from August 2015 to September 2016. The inclusion criteria were admission in the hospital and age above 15. The exclusion criterion was abnormal hepatic test (above the normal range at baseline) including bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). According to these criteria, 121 patients (77 male and 44 female) diagnosed with different diseases like AML (acute myeloid lymphoma), ALL(acute lymphoblastic leukaemia), and MM (multiple myeloma) etc. were recruited to the study. After transplantation, the patients were monitored daily for hepatic dysfunction (Hepatic enzyme tests including ALT, AST, ALP, total bilirubin, and direct bilirubin and clinical findings associated with hepatic dysfunction including diarrhoea, anorexia, and jaundice), adverse reactions to medication (such as cyclosporine nephropathy), and management of any clinical problems. All medical data of the patients were recorded in a datasheet by a pharmacy student.

Conditioning regimens:

Different conditioning regimens were prepared for the patients before HSCT in accordance with their types of disease. All the information is provided in Table 2.

Immunosuppressive regimen:

Prevention of GVHD was performed by using the immunosuppressive regimen. The medicines that were mainly used are cyclosporine and methotrexate. The indications may differ based on diagnosis. For all the patients, except the haploidentical ones, cyclosporine was used intravenously (1.5 mg/kg from Day -3 to +5). Then, it changed to the oral form with a dose of 8 mg/kg, which was adjusted until it reached 102-307 mg/dL level in blood, otherwise adverse reactions could occur. For haploidentical patients, cyclosporine was used intravenously (1.5 mg/kg from Day -2 to -6 and then 3mg/kg) until the patients could take the oral form. Monitoring the dose of cyclosporine was performed according to a trough concentration that had been taken in the morning, right before the next dose, and the HPLC method was used for determination of the concentration. Methotrexate was used intravenously (10 mg/m2 on Day +1 and then 6 mg/m2 on Day +3, +6 and +11). For patients with thalassemia, Class III and aplastic anaemia, ATG was used at a dose of 1.25 to 2.5 mg/kg for two to four days. For haploidentical patients, ATG was used at a dose of 2.5 mg/kg for three days. The number of patients who took different regimens is shown in Table 2.

Pretransplantation care:

Allogenic HSCT has many side effects owing to conditioning regimens and immunosuppressive medications. That is the reason which patients should be closely monitored for toxicity of drugs and receive supportive care in accordance with protocols. Granisetrone for prevention of nausea and vomiting, phenytoin for busulphan-induced seizures, Mesna for prevention of haemorrhagic cystitis, blood transfusion in low haemoglobin, and platelet for thrombocytopenic patients are part of these protocols. Prevention of infections is also performed by showing compliance to protocols. For prophylaxis of VOD (veno-occlusive disease), weight and waist size are measured at the baseline and frequently after transplantation. If there happens to be a big difference,

Table 1. Demographic information and patients' primary disease.

Variables	N
Average age (years)	33.6
Average length of hospital stay (days)	26.3
Gender	
Male	77
Female	44
Type of disease	
AML	64
ALL	32
MM	8
AA	5
Major thalassemia	4
CML	2
Lymphoma	2
CGD	1
Neimann-Pick	1
MDS	1
PNH	1

AA: aplastic anemia, **ALL**:acute lymphoblastic leukemia, **AML**:acute myeloid lymphoma, **MM**:multiple myeloma, **PNH**:paroxysmal nocturnal hemoglobinuria, **CGD**:chronic granulomatous disease, **CMD**: Chronic Myelogenous Leukemia, **MDS**:myelodysplastic syndromes.

fluid restriction or even enoxaparine may be needed.

Assessment of liver dysfunction:

All the admitted patients were evaluated about liver dysfunction by physical examination, laboratory tests, and any history of liver diseases before transplantation. Abnormal AST, ALT, ALP, total bilirubin, and direct bilirubin measures (above the normal range) were criteria to exclude patients from the study. After transplantation, the patients were monitored routinely for any sign or symptoms of liver disease including jaundice, anorexia, change in the colour of stool or urine, weakness, stomach-ache, and encephalopathy. Besides, laboratory tests and physical examinations were performed daily during patients' hospital stay.

Statistical analysis

Descrpitive statistics were reported by mean (SD) for quantitative variables and frequency (Percentage) for qualitative ones. Occurrence of hepatic dysfunction, type and pattern of the dysfunction was tested to detect any relationship to categorical variables using Chi square test. T-test and ANOVA (or their non-parametric equivalents tests, Mann-Whitney and Kruskal-wallis in cases of non-normal distributions) were used to compare between incident cases of hepatic dysfunction and also their patterns and types regarding quantitave variables., in all tests, p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 121 patients enrolled in the study. Patients' demographic and primary diseases data are shown in Table 1. The average time of hospital stay was 26.3±8.7: for 102 patients, it was 20–28 days; for 19 patients, it was more than 28 days. A total of 76 patients (62%) were diagnosed with hepatic disease consisting 44 (57%) men and 32 (72%) women with the mean age of 32.7 ± 11.7 (in the range of 15-52). While all patients with hepatic injury showed hepatic enzymes rising (the average rise in ALT and total bilirubin were 82.3±9.7% and 98.1±8.6%, respectively), 45 (59.2%) patients experienced clinical symptoms including diarrhea (23 patients), skin rash (11 patients), anorexia (8 patients), jaundice (2 patients) and edema (1 patient). It should be considered that most of the patients had more than one symptom. Regarding types of hepatic injury, 28 (36.8) patients developed hepatocellular dysfunction, 1 (1.3%) patient developed cholestatic dysfunction and 47 (61.9%) patients developed mixed hepatic dysfunction. Number of patients who developed hepatic injury related to different reasons is shown in Table 3.

In patients who developed hepatic injury, 31 (25%) had only showed increases in the level of hepatic enzymes and no clinical symptoms, while 45 (37%) experienced both clinical symptoms associated hepatic injury and increases

Table 2. The number of patients in different group of conditioning and immunosuppressive regimen.

Conditioning regimen	N
Bu/Cy*	102
Flu/Bu¥	4
Flu/Mel$^{\delta}$	10
Cyclophosphamide plus ATG§	5
Immunosuppressive regimen	
Cyclosporine and MTX	39
Cyclosporine and MTX and ATG	68
Cyclosporine and ATG**	14

*Busulfan 3.5-4 mg/kg orally for 4 days (day -6 to -3), Cyclophosphamide 50-60 mg/kg IV for 2 days (-2 to -1), haploidentical patients also received ATG and the whole dose of ATG must be below 2.5 mg/kg. ¥Busulfan 3.5 mg/kg for 4 days (day -6 to -3) Fludarabine 30 mg/m2 for 5 days (day -7 to -3). $^{\delta}$Melphalan 70 mg/m2 for 2 days (day -3 to -2), Fludarabine 30 mg/m2 for 5 days (day -6 to -2). §Cyclophosphamide 50 mg/kg IV for 4 days. ATG: Anti Thymocyte Globuline.

in the level of hepatic enzymes. These symptoms include diarrhoea (23 patients), skin rash (11 patients), anorexia (eight patients), jaundice (two patients), and edema (one patient). It should be considered that most of the patients (73.3%) had more than one symptom. The types of hepatic injury were different, and the number of patients who developed such injury because of different reasons is shown in Table 3. As a whole, 28 patients developed hepatocellular dysfunction, one patient developed cholestatic dysfunction, and 47 patients developed mixed hepatic dysfunction. These constitute 23.1%, 0.8%, and 38.8%, respectively, of all the patients who entered the study.

Incidence of GVHD:

Among all patients who were diagnosed with hepatic disease, 20 of them developed GVHD. Patients with GVHD were categorized, according to GVHD grading by previous studies (5,6). Detailed information is manifested in Table 3.

Analytical assessment of risk factors:

The distribution of liver dysfunction in the potential risk factors including sex, being of the same sex with donor, type of primary disease, immunosuppressive regimen and conditioning regimen are summarized in Table 4. None of these factors could predict the incidence of liver

Table 3. Reasons for hepatic injury in patients.

Causes of hepatic injury	No. of patients	Percentage of incidence*
GVHD	20	26.31
Grade 1	10	13.15
Grade 2	4	5.26
Grade 3	6	7.89
Grade 4	0	0
Drugs	26	34.21
Conditioning regimen	20	26.31
Voriconazole	4	5.26
Cyclosporine	2	2.63
Sepsis	4	5.26
VOD	1	1.32
Idiopathic	12	15.79
Multifactorial¥	13	17.11
Total	76	100

GVHD: Graft-versus-host disease, **VOD**: Veno-occlusive disease

*percentage of incidence is calculated at the base of the patients who were diagnosed with hepatic dysfunction.

¥more than one reason

Table 4. Liver dysfunction and the potential risk factors.

Variables	Liver dysfunction (n=76)	Normal liver (n=45)	P value
Gender			
Male	44	33	0.06
Female	32	12	
Donor matched sex	28	16	0.52
Donor Unmatched sex	39	21	
Type of primary disease			
AML	37	27	0.28
ALL	20	12	
Other disease	19	6	
Immunosuppressive regimen			
CSA/MTX	21	18	0.34
CSA/MTX/ATG	45	23	
CSA/ATG	10	4	
Conditioning regimen			
BUSULFAN+CYCLOPHOSPHAMIDE	61	41	0.46
BUSULFAN+FLUDARABIN	3	1	
FLUDARABIN+MELFALAN	8	2	
CYCLOPHOSPHAMIDE+ATG	4	1	

ALL:acute lymphoblastic leukemia, **AML**:acute myeloid lymphoma, **ATG**:Anti-thymocyte globulin, **CSA**: cyclosporine, **MTX**: methotrexate.

dysfunction, because there was no significant difference between experimental groups (P>0.05).

The risk factors for the types of hepatic dysfunction were also considered and are shown in table 5. There was a significant correlation between immunosuppressive regimen and the type of hepatic complication. Patients who took ATG beside cyclosporine and methotrexate significantly developed less GVHD. From 23 patients who took this regimen, only 5 patients developed GVHD. The pattern of hepatic dysfunction had significant correlation with type of hepatic complication, too (P: 0.03). The clinical symptoms also showed significant correlations with types of hepatic complication, which means that 17 patients with drug-induced hepatic injury (out of 26 or 65%) were almost free of any symptoms and displayed only a slight rise of the level of enzymes. On the other side, 60% of patients with GVHD and 92% of patients with multifactorial hepatic dysfunction had clinical symptoms.

Duration of hospital stay was shown to be related to type of hepatic injury. The longest time is for patients with GVHD (27.7±6.6 days) and multifactorial hepatic dysfunction (28.1±8.4 days)(P: 0.04).

Discussion

Liver dysfunction is one of the most complicated issues after HSCT. Such dysfunction increase morbidity and mortality of the procedure. Drug toxicity (conditioning regimen, voriconazole and cyclosporine) and graft-versus-host disease (GVHD) are the most common hepatic complications early after transplantation (9). Among these complications, GVHD is more substantial, because it happens at a frequency of 40–60% after HLA-identical transplants. GVHD diagnosis involves hepatic, skin, and gastrointestinal signs and symptoms, and both clinical and laboratory findings are used for definite diagnosis (1).

The rate of hepatic injury in our study was 62.8 %. This rate was 65% and 71.5 % in two independent studies that are similar to the findings of our study (10, 11). The slight differences can be related to types of stem cell transplantation, preconditioning regimen, and sample size.

The mean time of hospital stay in our study was 26.5 days, and the patients were only monitored during their admission time and were not followed after they left the hospital. According to Ozdogan et al., the probability of hepatic injury like VOD and drug-induced hepatic complications is the highest during the first 30 days, which is almost similar to the time that we monitored patients in hospital-i.e., one month(11). The best rationale for these findings is drug-induced hepatic toxicity that mostly happens two weeks after administration.

Determining the main reason of hepatic dysfunction was one of the main components of our study, although

Table 5. The risk factors, Patterns and duration of hospitalization for different types of hepatic dysfunction.

		Normal (n)	GVHD(n)	Drug(n)	Multifactorial(n)	*p*-value
Immunosuppressive regimen	CSA/MTX	18	0	10	1	0.04
	CSA/MTX/ATG	23	18	11	11	
	CSA/ATG	4	2	5	1	
Conditioning regimen	BU/CTX	41	17	19	10	0.11
	BU/FLU	1	1	1	1	
	FLU/MEL	2	0	6	1	
	CTX/ATG	1	2	0	1	
Pattern of hepatotoxicity	Hepatucelluar	-	4	14	3	0.034
	Cholestatic	-	0	0	0	
	MIX	-	16	12	10	
Duration of hospitalization	Mean	25.96	27.70	25.15	28.15	0.05

ATG:anti-thymocyte globulin, **BU**: busulfan, **CTX**: cyclophosphamide, **CSA**: cyclosporine, **FLU**: fludarabine,**GVHD**: Graft versus host disease, **MEL**: melphalan, **MTX**: methotrexate

finding the exact rational was difficult in most of the cases and two or more etiologies were considered. Diagnosis of drug-induced liver toxicity was even more difficult, since many medications in pre-transplantation care would lead to liver toxicity including methotrexate, prednisolone, cyclosporine, cotrimoxazole, and voriconazole, among others. In our study, the rate of drug-induced hepatic injury was 24.1%, while another study reported this number to be 18.7% in allogeneic HSCT during 30 days after transplantation (11). We utilized naranjo scale for determining the likelihood of whether hepatic dysfunction was due to drug or other factors. Sepsis was another cause of liver dysfunction that the rate of it was 3.3% in our study and other investigations reported a rate below 10 % (12). Incidence of multifactorial hepatic dysfunction was 10.7 % and idiopathic liver injury was 5.7% in our study, which is similar to other reports (11). Veno-Occlusive Disease (VOD) is another serious hepatic dysfunction after transplantation with the rate of incidence of ranging rhetorically between 1% and 64 % (13). In our study, only one patient was diagnosed with VOD, which confirms the report of other research studies (11).

Although our study revealed a higher percentage of hepatic complications in females, statistical analysis showed no signs that gender would be accounted as a significant risk factor for hepatic dysfunction. This claim was proved in other research studies as well (11).

The relationship between the cause of liver dysfunction and the pattern of liver dysfunction was significant in our study. Dramatic increase in conjugated bilirubin and alkaline phosphatase, and slight increase in AST and ALT, are the common manifestations of GVHD. On the other side, hepatocellular hepatitis, which is the increase in ALT (more than three-folded) and normal or slight increase in ALP, is a common pattern of drug–induced hepatic disease. This discrimination was significant in our study.

This study represents that there is no significant relationship between different immunosuppressive therapy and incidence of liver dysfunction. The basic medications in immunosuppressive therapy are cyclosporine and methotrexate. Though many changes have been made in doses of these medications, no study has reported any effectiveness of the modified therapy (14). But another finding was the relationship between less GVHD with the use of ATG. ATG is a part of immunosuppression, and it has no benefits for survival and makes no significant differences in incidence of GVHD, but it decreases the incidence of GVHD Grade 2 to 4 (15). In our research, the role of ATG has been proved for less incidence of GVHD.

Although conditioning or preparative regimen has some advantages, like inducing remission in tumours and ablating immune responses in host, the toxicity of the agents is always a complicating issue (16). Some studies have shown that different conditioning regimens can predict the incidence of GVHD. Shimoni et al., reported that although the incidence of GVHD is not different among different conditioning regimens, the rate of GVHD Grade III/IV is higher in patients who had taken Bu/Cy compared with F-B (fludarabine and busulfan) (17). Another recent research evaluated the results of non-myeloablative regimen in patients with advanced age or comorbid diseases and reported the effect of primary aggressive malignancy and inclusion of fludarabine in the preparative regimen as indicators of inferior survival (18). But there was no significant difference between various conditioning regimens in our research. The total number of patients who had taken the Bu/Cy regimen was 102, and only 19 patients were in the other three groups. The

latter number is too small to be compared and the results may not reflect a true concept.

A relationship between clinical symptoms and the cause of liver injury was proved in this report. Clinical symptoms were observed in 70% of patients with GVHD and 92% of patients with multifactorial hepatic dysfunction, while in the drug-induced type there was mostly a rise in hepatic enzymes and clinical symptoms were seen in only 34.6% of patients. This may lead to a lengthened time of staying in hospital due to complications of GVHD or sepsis.

Another finding in our research indicates that there was no significant correlation between clinical symptoms and the grade of GVHD. This is because the number of patients with GVHD in our study was only 20 and the small sample size can lead to misinterpretation.

Conclusion

The goal of this study was to evaluate hepatic complication after allogeneic HSCT. Among various reasons, drug-induced hepatic disease and GVHD are the leading causes. Some risk factors may influence the variables in our study. Use of ATG in the immunosuppression regimen can decrease the incidence of GVHD, while it does not essentially decrease the rate of overall occurrence of hepatic dysfunction. Drug-induced liver complications occurred mostly without clinical symptoms, while GVHD and multifactorial hepatic can accompany clinical symptoms like skin rash and diarrhoea. GVHD complications can lead to a longer time of hospital stay and extra burden on the healthcare system.

The role of the conditioning regimen in prevention of hepatic complications was not significant and this may be a consequence of variance in number of patients who were placed in different groups of regimen. The time of observing patients was limited to their hospital stay and it was about one month. Further studies may be needed to evaluate patients for a longer time (for instance, three or six months) and to consider a bigger sample size especially for the condition regimen other than Bu/Cy.

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