Organ Failure Following Allogeneic Hematopoietic Stem Cell Transplantation and Transplant Outcome Organ Failure

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Abstract- Organ failure, including; liver toxicity, renal failure, and neurotoxicity, are frequent complications following HSCT which can affect the transplant outcome, morbidity, and mortality of allo-HSCT recipients: A retrospective study of 206 allo-HSCT patients was conducted to determine the frequency of organ failure and overall survival in patients receiving allo-HSCT. Liver toxicity, renal failure, and neurotoxicity were diagnosed according to clinical and laboratory records pre and post-allo-HSCT. A total of 33 patients (16%) developed organ failure within 200 days after allo-HSCT. Liver toxicity was diagnosed in 12% of patients, and the median time of its occurrence was 22 days (range: 0-207 days) post-allo-HSCT. Two percent (6 of 206) of allo-HSCT recipients presented renal failure. Renal failure was developed within the median time of 33 days (range: 5-88 days). Neurological involvement occurred in 0.9% of patients. Among 206 patients, the frequency of complications such as veno-occlusive disease (VOD) and graft-versus-host disease (GVHD) was 1.4% and 16.01%, respectively. One-year overall survival of patients who had organ failure was 24%, and the mean survival determined 329±99.58 days. Three-month overall survival of patients who developed liver injury and renal failure were 78% and 33%, respectively. Organ failure remains a common complication in patients who received allo-HSCT. Patients with GVHD and two or multi-organ involvement seem to have lower overall survival.

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Keywords: Allogeneic hematopoietic stem cell transplantation (Allo-HSCT); Liver toxicity; Renal failure; Neurotoxicity; Transplant outcomes

Introduction

Allogeneic hematopoietic stem cell transplantation is a promising therapeutic procedure to treat a wide range of malignant and non-malignant hematological disorders, immunological disorders and solid tumors. The number of patients undergoing allo-HCT is increasing (1). In 2017, 41100 patients underwent 45418 transplants; of whom, 18,281 HCT (40%) were allogeneic (2). Although allo-HSCT improved remission and survival in transplanted patients, it can be associated with early or late complications. Transplantation-related complications include acute and chronic GVHD, organ failure, and disease relapse, which affects the outcome of transplantation and survival in patients (3,4). Comorbidities, GVHD, infections as well as conditioning regimens, and GVHD prophylaxis are the main causes of post-transplantation complications (5). Various organs can be affected by transplantation-related complications such as skin, eyes (6), gastrointestinal, liver (7),

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endocrine system (8), kidney (9), cardiovascular system (10), lung (11), and neurological system (12). Liver injury, renal failure, and Neurologic complications are known as prevalent organ-toxicity complications following allo-HSCT. These complications are considerable causes of transplantation-related morbidity and mortality.

Liver complications are common in recipients of allo-HSCT, which are seen in approximately 80% of adult patients and account for up to 15% transplantation-related mortality (TRM) (13,14). The liver injury could result from various processes such as drug-induced injury, toxic injury to hepatic sinusoids (i.e., sinusoidal obstruction syndrome [SOS], also known as a veno-occlusive disease [VOD]), septicemia-related cholestasis (cholangitis lenta), GVHD, infection-mediated hepatocellular necrosis and ischemia. SOS/VOD syndrome is one of the most common liver complications following allo-HSCT (15). Severe SOS/VOD lead to multi-organ failure (MOF), which is associated with renal, pulmonary, and/or central nervous system dysfunction. A systematic review has reported that the overall mean incidence of VOD is 13.5% with a range of 0 to 40% and the mortality rate of severe VOD (MOF) was reported 84.3% (16).

Another frequent allo-HSCT complication which seems to influence patients survival in the first year after transplantation is renal failure. Acute kidney injury (AKI) is defined as 2-fold increase of serum creatinine (Cr) or at least 50% decrease of GFR from baseline, within the first 100 days after allo-HSCT (17). The incidence of acute renal failure (ARF) is reported 27-66% in allo-HSCT. AKI occurs in several conditions comprising sinusoidal obstruction syndrome, inflammation, cytomegalovirus (CMV) reactivation, diarrhea with severe dehydration, conditioning regimen for allo-HSCT, GVHD and use of nephrotoxic drugs to prevent or treatment of GVHD and infection (18). Studies have shown that acute renal failure is associated with all-cause mortality (ACM), nonrelapse mortality (NRM), and survival (19,20).

Neurological complications are also of the frequent and life-threatening allo-HSCT consequences having an extended ranges according the incidence rate and severity. The etiologies of neurological complications include neurotoxic drugs (e.g., calcineurin inhibitors), infectious pathogens, metabolic complications and immune-mediated diseases. Seizures and impaired consciousness were reported as the main neurologic symptoms in patients (21,22).

The aims of this retrospective study were to 1) determinate the frequency of liver injury, renal failure and neurological complications in patient underwent allo-HSCT 2) determinate the mortality rate and overall survival in patients suffered from liver injury, renal failure and neurological complications.

Materials and Methods

Patient

A retrospective study was performed on 206 patients with malignant and non-malignant hematological disorders who underwent allo-HSCT between 2009 and 2018 at Taleghani Hematopoietic Stem Cell Transplantation Center in Tehran, Iran. Patients' clinical and laboratory data were collected from the clinical records. The study was confirmed by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Procedure of transplantation

All patients received myeloablative conditioning regimen intravenously (IV) consisting of busulfan (BU) 0.8 mg/kg every 6 hours for 4 days followed by either two days of cyclophosphamide (CY) 60 mg/kg/day or fludarabine (Flu) 30 mg/m^2 of body surface area once a day for 5 days. Reduced Intensity Conditioning (RIC) regimen used for patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) comprised of fludarabine 30 mg/m^2 of body surface area IV for 5 days, CCNU 100 mg/m^2, P.O for 2 days and melphalan 40 mg/m^2 IV for 1 day.

All patients received GVHD prophylaxis with cyclosporine A (CsA) 3 mg/kg/day IV from day -2 until +5 (the day of allo-HSCT considered as day zero) and 12.5 mg/kg/day P.O. until day +180 in combination with methotrexate (MTX) from day +1 with dose of 10 mg/kg IV and in days +3, +6 and +11 with the dose of 6 mg/kg IV. In some patients, 2.5 mg/kg of anti-thymocyte globulin (ATG) for 2 days (-1 and -2) was added to this combination. The stem cell source was mobilized peripheral blood. Donors received granulocyte-colony stimulating factor (G-CSF) subcutaneously at a dosage of 5-10 µg/kg/day for 4-5 consecutive days. The enumeration of donor peripheral blood CD34+ cell was performed by flow cytometry (Attune NxT, Country) on day 5 post-G-CSF administration using PE-conjugated human anti-CD34 (EXBIO, Czech Republic) to determine the optimal day for apheresis. Plasma reduction for ABO minor-mismatched and RBC depletion for major and bidirectional mismatched grafts were performed on the apheresis product. RBC depletion was performed using hydroxyl ethyl starch (HES) 6% (GRIFOLS, Spain). The number of CD34+ cells and

CD3+ (FITC-conjugated, human, Beckman Colter, Miami, FL, US) cells in apheresis product were counted, and viability tests on all apheresis yields were performed using Trypan Blue viability dye (Biowest, France) before transplantation.

GvHD was diagnosed according to National Institutes of Health (NIH) criteria (23) and treated with adjusting cyclosporine A dose and methylprednisolone as the first line of treatment. All patients who received infection prophylaxis consisted of acyclovir (antiviral), ciprofloxacin (antibacterial), and fluconazole (antifungal).

Organ failure definition and assessment

In general, organ failure patients are selected based on the clinical manifestation and diagnosis of the specialists. The classification of the organ failure into liver injury and renal complication was performed based on the following laboratory factors. Liver injury was defined as serum total bilirubin >1.95 mg/dL, which is equivalent to the grade 2 hyperbilirubinemia. (the normal range of total bilirubin in our laboratory is 0.3 mg/dL to 2.0 mg/dL). Furthermore, the presence of serum total bilirubin >2 mg/dL with at least two associated clinical manifestations, including ascites, weight gain >5% from baseline, hepatomegaly, or right upper quadrant pain in the first 35 days post allo-HSCT were considered as VOD. In all patients, serum total bilirubin, direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), ALP and LDH were measured 3-4 times per week in the inpatient unit from pre-transplantation days to at least 30 days post transplantation. Patients are categorized according to the serum bilirubin concentration into three groups; group 1 Hyperbilirubinemia=2-4 mg/dL; group 2 Hyperbilirubinemia>4 mg/dL; and group 3 Hyperbilirubinemia>10 mg/dL.

Renal failure was defined as founding at least 1.5 fold increase in serum creatinine concentration, compared to baseline value. In addition, serum levels of urea, BUN, uric acid, and albumin were measured in all patients at time of admission and at least 30 days after allo-HSCT.

Diagnose of neurologic complications was made by notes from neurology consults and clinical presentations; such as: headache, confusion, seizures, nausea, vomiting and delirium. Moreover, patients with failure in more than one organ considered as MOF.

Statistical analyses

The selected dataset were cleaned and revised for the analysis. The mean, median and SD for numerical data, frequencies, and percentages for non-numerical data were reported. The comparison of the means was also performed for the risk factors. The overall survival for all the patients, by their gender and their organ failure, was conducted through the Kaplan Meier curve. All these descriptive statistics were carried out using IBM SPSS 19.

Results

Patient characteristics

There were 206 patients who underwent allo-HSCT from 2009 to 2018, of which 44 patients (21.3%) developed organ failure (Table 1), and their demographic and clinical characteristics are listed in table 2. Among transplant patients who developed organ failure, there were 22 (50%) women and 22 (50%) men with the median age of 29.16±8.86 years. Organ failure developed in 36 (17.5%) of all the patients within 100 days after allo-HSCT. Among these patients, liver-related complications developed in 32 patients (15.5%), which mostly occurred within 1 month after transplantation with the median time of 22 days (range: 0-207). The frequency of renal failure was 2.9% (6 patients) mainly occurred within the first 1 month with the median time of 33 days (range: 5-88) after allo-HSCT. Five patients (2.4%) developed neurotoxicity, and MOF progressed in 7 (3.4%) patients (Table 1). In all patients with organ failure, 6-month and one-year overall survivals were 33% and 24%, respectively (Figure 1A). The mean survival time for all the patients with organ failure was 329±99.58 days, among which the men possessed a high mean survival time (494.70±241.62 days), in comparison with women (220.07±62.96 days) (Figure 2B). Eight patients (3.9%) have been diagnosed clinically with organ failure by the clinicians, but the laboratory factors related to the renal and liver complications were missed or in the normal range, so they have been considered as non-classified organ failure patients (Table 1).

Liver-related complications

The mean serum concentration of total bilirubin, direct bilirubin, ALT, AST, LDH, and ALP was analyzed among patients who had liver-related complications (Table 3). The mean serum total bilirubin was 0.97±0.42 mg/dL and 13.30±13.31 mg/dL before and after HSCT, separately. The maximum value of serum total bilirubin was 78.50 mg/dL and the median time of hyperbilirubinemia onset was 22 days after allo-HSCT. We categorized hyperbilirubinemia into three groups based on the serum bilirubin concentration. Three percent of the patients had bilirubin between 2-4 mg/dL, 61% had bilirubin higher than 4 mg/dL, and 36% had bilirubin

higher than 10 mg/dL. The pre-transplantation mean of direct serum bilirubin, ALT, AST, LDH, and ALP was 0.37±0.21 mg/dL, 46.37±69.49 IU/L, 27.98±31.48 IU/L, 566.36±429.47 IU/L, 176.47±103.59 IU/L, Respectively. Following allo-HSCT, the mean serum direct bilirubin, ALT, AST, LDH, and ALP was 7.82±7.98 mg/dL, 99.28±114.92 IU/L, 85.73±112.37 IU/L, 868.99±674.71 IU/L, 584.86±576.95 IU/L, respectively.

Table 1. Frequency of HSCT complications (n=206)

Type of complication	Frequency (%)
Renal failure	6(2.9%)
Liver failure	32(15.5%)
Neurotoxicity	5(2.4%)
MOF	7(3.4%)
VOD	4(1.9%)
Non-classified	8(3.9%)

MOF, multi-organ failure; VOD, Veno-occlusive disease;

Table 2. Characteristics of patients who developed organ failure following allo-HSCT

Variables	Subgroup	Frequency (%)/mean±SD
Age	-	29.16±8.86
Gender	Male	22(50%)
	Female	22(50%)
Diagnosis	N.H.L	2(4.5%)
	H.D	2(4.5%)
	AML	22(50%)
	ALL	13(29.5%)
	AA	2(4.5%)
	FA	1(2.3%)
	MDS	1(2.3%)
	ALD	1(2.3%)
Conditioning Regimen	MAC *(Bu + CY or Bu + Fu)*	40 (90.91%)
	RIC *(Fu/CCNU/Mel)*	4 (9.09%)
GVHD Prophylaxis	Cys A + MTX	41(93.2%)
	Cys A + ATG	3 (6.8%)
GVHD	Yes	33(75%)
	No	11(15%)

Demographic and clinical data of the patients with organ failure is demonstrated. Data of age are illustrated as mean±SD, and the other data was shown as frequency and percentage. SD, Standard deviation; NHL, non-Hodgkin's Lymphoma; HD, Hodgkin's Disease; ALL, Acute Lymphocytic Leukemia; AML, Acute Myeloid Leukemia; ALL, Acute Lymphocytic Leukemia; AA, Aplastic Anemia; FA, Fanconi Anemia; MDS, Myelodysplastic Syndrome; ALD, Adrenoleukodystrophy; MAC, Myeloablative Conditioning Regimen; RIC, Reduced-Intensity Conditioning; Bu, Busulfan; CY, Cyclophosphamide; Fu, Fludarabine; CCNU, Cyclonexyl-Chloroethyl-Nitrosourea; Mel, Melphalan; CysA, Cyclosporine A; MTX, Methotrexate; ATG, Anti-thymocyte globulin; mPS, Methylprednisolone; GVHD, Graft-versus-host disease

Table 3. Characteristics of liver injury patients before and after allo-HSCT

Variable	Before transplantation	After transplantation*
Total bilirubin	0.97±0.42	13.30±13.31
Direct bilirubin	0.37±0.21	7.82±7.98
ALT	46.37±69.49	99.28±114.92
AST	27.98±31.48	85.73±112.37
LDH	566.36±429.47	868.99±674.71
ALP	176.47±103.59	584.86±576.95

22 (50%) patients showed an increase in serum transaminases, ALP and bilirubin levels which the median duration of the first change in levels of aminotransferase enzymes was 26.5 days after HSCT. This median time was 10 and 52.5 days for LDH and ALP levels. Four of 32 patients (12.5%) who had a liver complication met the diagnostic criteria for VOD. Two of these VOD patients presented other organs involvement (renal toxicity). The one-month survival for VOD patients is 75%, and the 3-month survival was 25%. The GVHD occurred in 50% of them.

GVHD happened in 20 (62.5%) of the liver toxicity patients, of which 9 (28.1%) patients developed acute GVHD (aGVHD) before the occurrence of liver-related complications and 11 (34.3%) presented aGVHD after liver-related complications. Three-month, 6-month and one-year overall survival of patients with liver-related complications were 78%, 35%, and 23%, respectively. The mean survival time of these patients was 401.51±172.62 days (Figure 1C). Generally, overall survival in liver injury patients with or without aGVHD was 12% and 30%, respectively.

Renal failure

Serum creatinine, BUN, uric acid, and albumin were measured before and after allo-HSCT (Table 4). Among 6 patients who initiated renal failure, there was a significant rise in the mean serum creatinine from the baseline value of 0.91±0.19 mg/dL to 3.1±1.91 mg/dL within 100 days post-HSCT. The median time for the occurrence of renal failure was 33 days (range: 5-88 days). The mean pre-HSCT serum albumin, BUN, and uric acid were 4.40±19.27, 17.92±10.62, and 3.70±1.51 mg/dL, respectively. The mean serum albumin concentration was reduced to 3.14±0.53 mg/dL after transplantation. Conversely, mean serum BUN and uric acid levels rose to 55.33±29.45 mg/dL and 6.05±1.78 mg/dL within 100 days post-HSCT.

Table4. Characteristics of renal failure patients before and after allo-HSCT

Variable	Before transplantation	After transplantation*
Creatinine	0.91±0.19	3.1±1.91
BUN	17.92±10.62	55.33±29.45
Albumin	4.40±19.27	3.14±0.53
Uric acid	3.70±1.51	6.05±1.78

The values are reported as mean±SD and the unit of all values in mg/dL. * The time for measurement of factors after transplantation is within 100 days post-HSCT. BUN, blood urea nitrogen;

Among the patients who developed renal failure, VOD was diagnosed in 2 (33.3%) patients, and GVHD happened in 4 (66.6%) patients, but none of them required dialysis. Data showed one patient developed GVHD before renal failure, and in 3 of them, the renal failure began to manifest after GVHD. Overall survival of renal failure patients was 33% at 3 months, and the mean survival time was 99.20±13.50 days (Figure 1C).

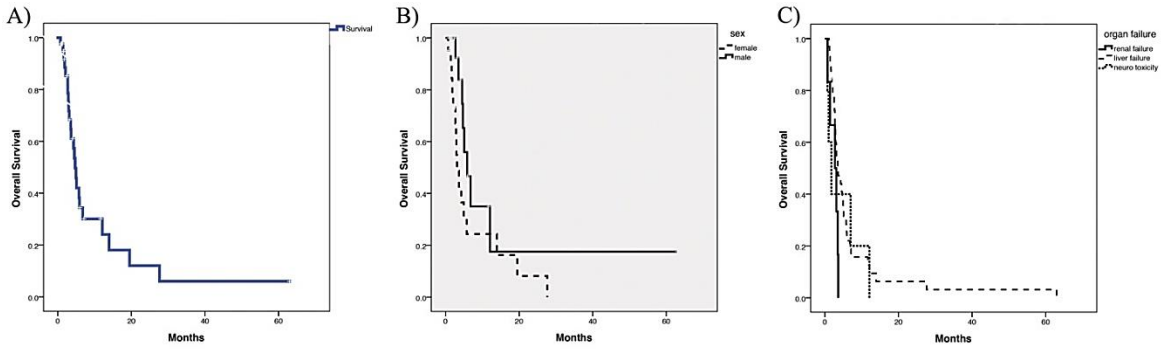

Figure 1. Overall survival of patients with organ failure. The Kaplan-Meier curves of overall survival in all patients with organ failure are demonstrated in figure (A), and the categorized overall survival curves by sex and organ failure are demonstrated in figure (B) and (C), respectively

Neurotoxicity

The one-month survival for neurotoxicity patients was 60%, and the 7-month survival was 30% (Figure 1C). Sixty percent of these patients had GVHD. The neurotoxicity occurred in one of the patients before GVHD.

Multi-organ failure

The one-month survival for MOF patients is 85%, and the 3-month survival is 42%. The overall survival curve for the MOF group is overlapped with that of the renal failure group and hence was not illustrated. In patients with MOF, 71% of them had GVHD. Five of these patients had both liver and renal complications. One of them had both neuro and liver, and the other one had neuro and renal complications.

Discussion

We designed a retrospective study to report the frequency of organ toxicity in patients receiving allo-HSCT at Taleghani Bone Marrow Transplantation Center. The frequency of organ failure was 21.3% of 206 patients who underwent allo-HSCT. In our patients, renal failure frequency was 2.9%, the frequency of liver injury was 15.5%, and neurologic complications had 2.4% frequency. There are variable reports based on frequency and incidence of organ failure or organ toxicity in different studies. Various frequency of organ failure in different studies may be due to the patient population heterogeneity, variation in conditioning regimens, diverse definition of organ failure, differential procedure of transplantation setting and etc. In present study, we described liver injury frequency, and changing serum levels of total bilirubin, direct bilirubin, and liver enzymes including ALT, AST and ALP in patients who underwent allogenic transplantation. ALT is a transaminase enzyme and more specific than AST to detect liver injury because of predominant presenting in the liver cytosol (24,25). Transaminases (ALT and AST) as well as bilirubin are the most reliable indicators for routine determination of liver injury. A study has shown that liver enzymes elevation is occurred in 71.5% of patient within the first year after HSCT (26). Our data showed that 50% of patients defined as liver injury had elevated levels of liver enzymes, including ALT, AST, and ALP as well as bilirubin. Elevated levels of total bilirubin as well as ALT levels above upper limit normal have been reported in 26% and 58% of patients at 3 months after HSCT, respectively (27). Hogan *et al*., found that of 196 patients received nonmyeloablative conditioning regimen before transplantation, 84% had total serum bilirubin levels >1.2 mg/dl and showed different grades of hyperbilirubinemia. The frequency of patients with total serum bilirubin level range between 1.3-3.9 mg/dL have been reported 58% and 26% of patients had bilirubin levels above 4.0 mg/dL. They noted hyperbilirubinemia >4.0 mg/dL is associated with poor prognosis in patients (28). In the current study, total bilirubin serum levels >4.0 mg/dL were detected in 61% of patients and 36% had hyperbilirubinemia >10.0 mg/dL. VOD frequency was 1.9% in our study. This complication had a higher frequency (12.5%) in hyperbilirubinemia patients. P Barba *et al.*, showed that 4% of patients with hyperbilirubinemia met diagnostic criteria of VOD (29).

Multivariate analyses of risk factors correlation with liver injury have been carried out by different studies. Drug hepatotoxicity, GVHD- or sepsis-related cholestasis, iron overload, and age are some risk factors associated with the occurrence of liver injury and elevation of bilirubin and liver enzymes following HSCT (15,30,31). Similar to previous studies, we confirmed hyperbilirubinemia is a frequent complication after HSCT. In our patients, the maximum bilirubin level was 78.5 mg/dL, which was higher than the report of Hogan *et al*., (39 mg/dl) (28). Our data showed that 62.5% of liver injury patients presented GVHD, as well. It is suggested GVHD and drug toxicity are major causes of liver dysfunction following HSCT (26). We also found mortality rate in liver injury patients with GVHD is higher than in patients without GVHD.

Renal failure is known as a common organ complication after HSCT. Studies have reported different frequencies and incidences of renal failure among HSCT recipients (32,33). In a study of 378 HSCT recipients, Saddadi *et al.*, reported 37.8% of patients developed AKI and all of them occurred within the first month after transplantation (34). Hingorani and colleagues also showed renal injury occurred in 36% of myeloablative hematopoietic cell recipients (35). Renal failure had only 2.9% frequency in our patients. The contradiction in various studies likely resulted from differences in baseline disease, renal failure definition, conditioning regimens, transplantation type, and comorbidities (36,). In most studies, the median time of renal failure development has been reported within the first month after transplantation (35,37). Similarly, the median time of renal failure development was 33 days after transplantation in our patients. Also, an assessment of

changes in renal function showed that the mean serum creatinine concentration rose from the baseline of 0.91±0.19 mg/dL to 3.1±1.91mg/dL post-transplantation. Y Caliskan revealed allo-HSCT patients had a high mean serum creatinine concentration in comparison with autologous patients within 100 days after HSCT. They also reported that the mean serum creatinine concentration elevated from baseline 0.75±0.15 to 2.4971.91 mg/dL on day 51±22 in allo-HSCT patients (9). Tokgoz *et al*., showed ARF patients had a mean serum creatinine level 0.71±0.18 mg/dL before transplantation and it significantly began to rise from second weeks after transplantation. The mean serum creatinine concentration of their patients was 1.62±0.65, 1.46±0.70 and 0.94±0.38 mg/dL on the first, second, and third months after HSCT, respectively (38).

Four of 6 (66.6%) patients with renal failure manifested hepatic VOD or liver toxicity, and the rest (33.3%) had no liver toxicity. In order to investigate the correlation of liver complications with renal failure, Parikh *et al*., showed that 93% of renal patients presented hepatotoxicity, and renal failure without liver toxicity were reported in only 7% (6 of 88) of patients. They reported that there is a significant correlation between liver toxicity and renal failure development. Moreover, it has been indicated that 51% of patients with grade 3 renal failure had liver toxicity and hepatic VOD and overall mortality rate in renal patient was 56% (39). We however, found 33% overall survival in renal failure patients 3 months after HSCT. In our study, neurotoxicity had 2.4% frequency after HSCT while several studies reported a wide range of frequency in neurotoxicity from 7.8% to 18%. This considerable difference may be due to the heterogeneity of patients population, variety of neurotoxicity definition and transplantation type (22,40,41). The frequency of patients with more than one organ failure was 3.4% of total and 16% of organ failure patients with the most involvement in liver and kidney. Carreras was reported MOF developed in 26 patients who all of them met VOD criteria. In these patient renal, pulmonary, and neurologic involvement occurred in 16, 20 and, 5 patients, respectively (42). We found that some organ failures happened before the incidence of GVHD. It is know that the onset of GVHD process might be far long before its manifestation, because of host tissue damage-induced conditioning regimens, produced pro-inflammatory cytokines, increased the expressions of MHC, and activated APC (42). Therefore, it could be concluded that the organ failure is likely the consequence of GVHD.

Our study has some limitations including: this is a single-center retrospective study and we only reported characteristic of patients with organ failure because we had no sufficient data of hepatic- and renal-related laboratory factors for all patients. It would be more conclusive in case we had enough data of patients without organ failure to compare with those with organ complication. In conclusion, we have indicated that organs toxicity are frequent and common problems following allo-HSCT and it seems necessary to follow up both the clinical and laboratory parameters of organ failure in all to achieve an early diagnosis and prevent their progression.

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