# Early Hepatic Complication in First Year after Bone Marrow Transplantation in Major Beta Thalassemic Patients

**Iravani M.[1], Arshy M.[2], Toutounchi M.[2], Nedaeifard L.[3,*], Ghavamzadeh A.[4]**
Hematology- Oncology and BMT Research Center
*Shariati Hospital, Tehran University of Medical Sciences, Iran*
*[1]Assistant professor of hematology- oncology, [2]General practitioner, [3] Pediatrician, [4]Professor of hematology- oncology*
*[*]Corresponding author:+98 21 88029390*

## Abstract

**Introduction:** Bone marrow transplantation is a good therapeutic modality for beta thalassemia. Liver complications are one of the major causes of morbidity and mortality following BMT. Determination of the factors of liver injury leads to earlier diagnosis after BMT and improves prognosis.

**Method:** We studied 113 major Beta thalassemic patients who have been transplanted from 1990- 2000 in bone marrow transplantation center of Shariati Hospital. 62 were male and 51 were female. 27 patients were class one, 56 were class two and 30 were class three. The median age of each class were 6.5, 6.3 and 8.7. Conditioning regimen consisted of busulfan (3.5-4mg/Kg) and cyclophophamide (40-50mg/Kg).For GVHD prophylaxis we gave cyclosporine ± metothoroxate. Grade of liver fibrosis defined by biopsy in all patients before BMT. All patients and their donors tested for HBSAg, HBSAb, HCVAb, CMVAb with RIA method. We assessed causes of liver dysfunction before and after transplantation and effect of high ferritin level on liver function.

**Results:** Hepatic dysfunction in first year after transplantation was seen in 86 (76%) patients**.** Causes of liver dysfunction were consisted of 53.1% GVHD, 15.93% cyclosporine hepatotoxicity, 7.07% conditioning regimen hepatotoxicity and VOD. In all three classes hepatic GVHD, cyclosporine toxicity, death and normal liver function post BMT had significant relation with hepatic dysfunction before BMT (P=0.001). In patients with ferritin level more than 1000, there were significant hepatotoxicity with conditioning regimen (P=0.001)**.** 17 (15.04%) of patients have been died.

**Discussion:** According to our study hepatic GVHD (%53.1) is the most common cause of hepatic dysfunction in all three classes**.**

**Key words:** BMT, Thalassemia, Hepatic complications

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## Introduction

Beta thalassemia is one of the most common hereditary diseases in Iran which can be presented from mild morphological changes to fetal disease. BMT is a good therapeutic modality for thalassemia. Liver complications are a major cause of morbidity and mortality following BMT. Determination of the pretransplantation factors that are likely to lead to liver injury may allow earlier diagnosis after BMT and may possibly improve prognosis.

In this study, we assessed early hepatic complications during the first year after BMT in three classes of major Beta thalassemic patients to determined the most common cause of early hepatic failure in each class and the relationship between disturbance of hepatic function before and after transplantation .We also assessed the relationship between hepatic disease in the first year following transplantation in each class of patients with a ferritin level of more than 1000 pretransplantation.

## Method

We studied 113 Beta thalassemic patients who have been transplanted from 1990- 2000. At least one year has passed from their transplantation and they were followed in BMT clinic. They have been classified according to Mr. Lucarelli, et al criteria: liver size, liver biopsy and deferoxamine therapy. Conditioning regimen consisted of busulfan and cyclophophamide in all patients. For GVHD prophylaxis in most patients with class I and II we gave cyclosporine and in class III patients we gave cyclosporine and metothoroxate.

Grade of liver fibrosis was defined by biopsy in all patients before BMT. All patients and their donors tested for HBSAg, HBSAb, HCVAb, and CMVAb with RIA. All of them were

HBSAg negative. We measured ALT (alanin amino transpherase), Alk (alkaline phosphates), total bilirubin, direct bilirubin and ferritin level pretransplantation

Liver function tests have been assessed two times a week in the first month, weekly in the second month, monthly from 2-6 months and every two months from 6-12 months after transplantation. Then we assessed results according diagnostic criteria of liver function disturbance as mentioned below:

1-**Hepatic GVHD:** increasing of bilirubin and Alk in100 days after BMT is acute and more than that period is chronic.

2-**Drug hepatotoxicity:** conditioning regimen, cyclosporin and other drugs.

3-**Viral hepatitis:** positive serology of viral hepatitis with liver dysfunction.

4-**Sepsis:** bacterial or fungal infection with liver dysfunction.

5-**VOD:** (venocclussive disease) clinical criteria consisting of icter (total bilirubin >1.2mg/dl) with two signs of hepatomegaly, acaitis or increasing of weight more than 5% (almost before 30 days after BMT).

6-**Disease relapsation:** liver dysfunction with clinical sign of relapse.

7-**Unknown cause:** liver dysfunction which can not be related to any known cause.

## Results

We studied 113 major Beta thalassemic patients who have been transplanted between 1990- 2000 in BMT center of Shariati hospital.

27 (23.9%) patients were class one, 56 (49.5%) were class two and 30 (26.6%) were class three.62 patients were male and 51 were female. The age distribution of each class has been shown in table-1.

Pretransplantation 36 patients were HBSAb positive, one was Anti HCV positive, 43 patients were CMV Ab positive and all were HBSAg negative.

All grafts were allogen. Sources of stem cells were 65.49% from BM, 23.89% from peripheral blood and 1.77% from cord blood. Engraftment occured 92.59% in class one, 87.5% in class two and 87.67% in class three.In total 100 patients (88.5%) have been engrafted and 13 patients (11.5%) have not engrafted.

**Table-1; The age distribution of each class**

| | Class one | Class two | Class three |
|---|---|---|---|
| Number of patients | 27(23.9%) | 56(49.5%) | 30(26.6%) |
| Mean age (y) | 5.6 | 6.3 | 8.7 |
| Minimum age(y) | 2.8 | 3 | 4 |
| Maximum age (y) | 9.5 | 14 | 17 |

Hepatic dysfunction in the first year after transplantation was seen in 86 (76%) patients. In class one 48.15%, in class two 76.79% and in class three 100% had hepatic dysfunction.

Causes of liver dysfunction consisted of 53.1% hepatic GVHD, 15.93% cyclosporine hepatotoxicity, 5.3% conditioning regimen hepatotoxicity and 1.77%VOD (Table-2)(Chart 1&2).

Hepatic GVHD was the most common cause of hepatic dysfunction (53%). Acute hepatic GVHD was seen in 46(40.7%) patients, chronic hepatic GVHD in 27(23.89%) and chronic hepatic GVHD after acute hepatic GVHD in 13(11.5%).We used t-student test in order to assess the effect of hepatic dysfunction before transplantation on hepatic function post BMT.

Patients of class one there was relation between hepatic GVHD and normal liver function test post BMT and hepatic dysfunction before transplantation. There was little relation between cyclosporin toxicity, and death and hepatic dysfunction before BMT. There were not any significant relations between conditioning regimen and VOD with hepatic dysfunction before transplantation.

In patients of class two there was little relation between hepatic GVHD, cyclosporin toxicity, death, normal liver function post BMT, conditioning regimen and VOD with hepatic dysfunction before transplantation.

In patients of class three there was a relationship between hepatic GVHD, cyclosporine toxicity and hepatic dysfunction before transplantation. There was little relation between conditioning regimen, death and hepatic dysfunction before transplantation. There was no significant relation between VOD with hepatic dysfunction before transplantation.

Totally in all three classes hepatic GVHD (p=0.001), cyclosporine toxicity (p=0.001), death (p=0.001) and normal liver function post BMT (p=0.001) had a significant relationship with hepatic dysfunction before BMT. This was not seen in VOD (p=0.345) and conditioning regimen (p=0.009) (Table-4).

Between the three classes, 45 patients had ferritin level > 1000, 27 patients <1000 or normal level before transplantation and 41 had no exact data and were deleted.

**Table 2- Causes of hepatic dysfunction in each class**

| | Class one | Class two | Class three | Total |
|---|---|---|---|---|
| Normal LFT posttransplant | 14(51.85%) | 13(23.21%) | 0 | 27(23.9%) |
| Abnormal LFT posttransplant | 13(48.15%) | 43(76.79%) | 30(100%) | 86(76%) |
| Hepatic GVHD | 11(40.74%) | 28(50%) | 21(70%) | 60(53%) |
| Cyclosporin hepatotoxisity | 2(7.41%) | 10(17.85%) | 6(20%) | 18(15.93%) |
| Conditioning regimen hepatotoxicity | 0 | 4(7.15%) | 2(6.67%) | 6(5.3%) |
| VOD | 0 | 1(1.79%) | 1(3.33%) | 2(1.77%) |

**Table 3- Hepatic GVHD after BMT in each class**

| | Class one | Class two | Class three | Total |
|---|---|---|---|---|
| Acute hepatic GVHD | 9(33.33%) | 22(39.28%) | 25(83.33%) | 46(40.7%) |
| Chronic hepatic GVHD | 6(22.2%) | 9(16%) | 12(40%) | 27(23.9%) |
| Chronic after acute hepatic GVHD | 4(14.81%) | 3(5.35%) | 6(20%) | 13(11.50%) |
| Total hepatic GVHD | 11(40.74%) | 28(50%) | 21(70%) | 60(53%) |

**Table 4 -Relation of hepatic dysfunction before BMT**

| | Abnormal liver function | Normal liver function | P value |
|---|---|---|---|
| Hpatic GVHD | 1(%100) | 54(%53) | 0.001 |
| Cylosporin toxicity | 0(%0) | 18( | 0.001 |
| Conditioning regime hepatotoxicity | 0(%0) | 6(%5.9) | 0.009 |
| Hepatic VOD | 0(%0) | 1(%0.98) | 0.345 |
| Normal LFT post BMT | 0(%0) | 26(%25.5) | 0.001 |
| Death | 0(%0) | 13(%12.7) | 0.001 |

In patients with ferritin level more than 1000, there were significant hepatotoxicity with conditioning regimen (p=0.001), but there was no more hepatic GVHD (p=0.317), cyclosporin toxicity (p=0.211) and hepatic VOD (p=0.373).

two on days 31-60, six on days 61-180 and three on days 181-365 have been dead.

Seventeen (15.04%) patients died in first year post BMT and most common causes of death were bacterial infection, hepatic GVHD and CMV infection.

In patients of class one only three died in the-first month. In patients of class two 8 have been dead, mostly in days 61-180.In patients of class three 6 died, mostly between days 60-365.

One year overall survival post BMT was 84.96%. One year overall survival in class one was 88.89%, in class two 85.71% and class three 80%. In first month post BMT 6 patients,

## Discussion

According to our study the most common complication in the first year post BMT is hepatic dysfunction (%76.1), which is similar to the result of other study [1,8].

In our study hepatic GVHD (%53.1) is the greatest common cause of hepatic dysfunction in all three classes. Cyclosporin toxicity (%15.93), VOD and conditioning regimen hepatotoxicity (<%10) had other causes, this is compatible with other studies.

In one study in Korea, hepatic dysfunction was seen in 84.2% of post BMT patients and hepatic GVHD and drug hepatotoxicity were the greatest causes. In a similar study in Australia and Turkey same results have been reached [1,2,6].

In our study hepatic GVHD was %53.1 (40.7% acute and 23.9%chronic). In a simillar study in Italy 61.8% was reported (25.8% acute and 36% chronic).[3]

In Egypt, after allogeneic BMT in 103 patients, 48% patients have died because of liver disease, mostly from hepatic GVHD (%22.3).[5]

All patients and donor were HBSAg negative and only one patient was HCVAb positive and we did not assess the effect of viral hepatitis on liver function post BMT.

Hepatic dysfunction before BMT and hepatic GVHD, cyclosporin hepatotoxicity and death were related but the number of patients were few and the relations were not significant. In a similar study in Korea, there was no increased risk of liver dysfunction, GVHD and death in patients who had liver dysfunction before BMT.[1]

In one study in Taiwan, abnormal liver dysfunction pretransplantation had relationship to post BMT liver dysfunction.[4]

Ferritin level more than 1000 before BMT and conditioning regimen hepatotoxicity had significant relationship (p=0.001), although for more exact results we must study a greater number of patients.

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