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Research Article

Investigation of the Effect of Pre-Transplantation Iron Overload on Posttransplantation Complications and Survival in Patients with Hematopoietic Stem Cell Transplantation

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Abstract

Objectives: Many studies have shown that ferritin values that are used as an indicator of iron overload are associated with adverse outcomes after bone marrov transplantation. The aim of this study was to evaluate the effect of ferritin on development of complications after transplantation.

Methods: The data of the patients who underwent HSCT (Hematopoietic Stem Cell Transplantation) in Hacettepe University Faculty of Medicine, June 2001 - March 2012 were retrospectively reviewed. The study cohort was divided into 2 groups as low ferritin group (ferritin <500 ng/ml) and high ferritin group (ferritin ≥500 ng/ml).

Results: The median age was 43 (17-69) in whole group, 51 (19-69) in the autologous SCT group, and 33 (17-58) in the allogeneic SCT group. There was a statistically significant relationship between the levels of ferritin concentrations and mucositis, fungal infection, BCI (blood circulation infections) development in some groups. There was no statistically significant relationship between high ferritin values and transplant related mortality and overall survival in both autologous and allogeneic SCT patients (p=1 and p=0.17).

Conclusion: It was observed that high ferritin concentrations before SCT were associated with post-transplantation toxic and infectious complications such as mucositis, fungal infection, BCI.

Keywords: Ferritin, hematopoietic stem cell, posttransplantation

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Hematopoietic stem cell transplantation (HSCT) is the introduction of hematopoietic precursor cells from any source (such as bone marrow, peripheral blood, umbilical cord blood) and donor (allogeneic, autologous) to regenerate bone marrow.[1] In recent years, many studies have reported that iron overload increases the posttransplantation morbidity and mortality in HSCT recipients. Many studies have shown that ferritin values that are used as an indicator of iron overload are associated with adverse outcomes after bone marrov transplantation (BMT),[2–7] particularly associated with an increased risk of infection[3–6, 8–10] and non-relapse mortality, and even in some studies it has been shown to be associated with acute Graft Versus Host disease (GVHD)[2, 6, 11] and liver veno-occlusive disease (VOD).[3, 12–14] The aim of this study was to evaluate the effect of ferritin elevation before transplantation on development of mucositis after transplantation, development of fungal infection, risk of blood circulation infections (BCI), development of pneumonia, acute and chronic GVHD, veno-occlusive disease (VOD)/Sinusoidal Obstruction Syndrome (SOS) development, transplant related mortality (TRM) development and overall survival (OS) in patients who underwent stem cell transplantation (SCT).

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Methods

The data of the patients who underwent HSCT (autologous and allogeneic) in Hacettepe University Faculty of Medicine, Department of Internal Medicine, Hematology unit between June 2001-March 2012 were retrospectively reviewed. Patients' demographic characteristics, ferritin averages before transplantation, and posttransplant mucositis, BCI (blood and catheter), fungal infection and pneumonia development, GVHD, SOS/VOD conditions, TRM, OS were recorded by examining the patient files. Data were recorded in the SPSS version 18 database (SPSS version 18: SPSS inc.Chiago, Illinois). The study cohort was divided into 2 groups as low ferritin group (ferritin <500 ng/ml) and high ferritin group (ferritin ≥500 ng/ml) by accepting mean 500 ng/ml value as cut-off value for pre-SCT ferritin.

Statistical analyzes were performed in 3 categories as whole group (allogeneic+autologous), allogeneic group and autologous HSCT group. Mucosit status was examined according to NCI/CTC criteria. Fungal infections were defined according to EORTC/MSG[15] criteria. Blood circulation infections were considered to be significant if there were 2 blood and/or catheter culture samples with the same microorganism. Seattle criteria[16] were used to identify SOS/VOD. GVHD was evaluated separately as acute and chronic aGVHD was classi-fied according to degree of involvement (grade 0-4) and kGVHD was classified according to status of involvement (limited, widespread).

Categorical variables in 2 groups were compared using x^2 test and Fisher's test when necessary. Data are shown as mean-SD (standard deviation), median-range and % (percentage). OS and TRM were assessed by Kaplan-Meier method. Log-Rank test was used for comparison. p<0.05 was accepted as statistically significant. This study was approved by the Hacettepe University Non-invasive Clinical Research Ethics Committee. During the study, the principles of the Helsinki Declaration have been adhered to and attention has been given to the confidentiality of patient information.

Results

The median age of 142 patients was 43 (17-69), of which 81 (57%) were male and 61 (43%) were female. The median age was 51 (19-69) in the autologous SCT group, and 33 (17-58) in the allogeneic SCT group. Median follow-up period was 732 (14-3782) days. Mean (SD) ferritin concentrations of the patients before HSCT were 1306.6 ng/ml (1763.1) in the whole group, 624.3 ng/ml (787.7) in the autologous SCT group, and 1750.9 (2061.2) ng/ml in the allogeneic SCT group. 21 patients (37.5%) in the autologous group and 63 patients (73.3%) in the allogeneic group had high ferritin values (ferritin ≥500 ng/ml). The characteristics of the patients and the findings related to transplantation are given in Table 1.

Transplantation Results

Mucositis: Mucositis (grade 1-4) was detected in 49 (87.5%) of 56 patients who underwent autologous SCT and in 77 (89.5%) of 86 patients who underwent allogeneic SCT. There was a statistically significant relationship between the levels of mucositis and high ferritin concentrations in both groups (In the autologous SCT group, p=0.038 and in the allogeneic group p<0.001). Grade 3 and 4 mucositis were found in 17 (17.8%) patients in the autologous group and 15 (26.8%) in the allogeneic group. There was no statistically significant relations-hip between high ferritin values and grade 3 and 4 mucositis in both groups (p=0.39 ve p=1; respectively).

Fungal Infections: Fungal infections were detected in 12 of 56 patients (21.4%) who underwent autologous SCT and in 35 (40.7%) of 86 patients who underwent allogeneic SCT. There was a significant association between fungal infection and high ferritin values (ferritin ≥500 ng/ml) in the whole group (p=0.009). However, there was no statistically significant association between high ferritin values and fungal infection in the autologous SCT group and allogeneic SCT group (p=0.33 in the autologous SCT group, p=0.1 in the allogeneic SCT group)

Blood Circulation Infections (BCI): BCI was detected in 66 patients (46.5%) in the whole group and there was a statisti-

Table 1. Demographic and clinical characteristics of patients

Variable	Autologous SCT (n=56)	Allogeneic SCT (n=86)	Total (n=142)
Age, Median	51 (19-69)	33 (17-58)	43 (17-69)
Sex, n (%)			
Male	33 (58.9)	48 (55.8)	81 (57)
Female	23 (41.1)	38 (44.2)	61 (43)
Diagnosis, n (%)			
AA	N/A	14 (16.3)	14 (9.9)
ALL	N/A	25 (29.1)	25 (17.6)
AML	N/A	30 (34.9)	30 (21.1)
HD	1 (1.8)	4 (4.7)	5 (3.5)
NHL	5 (8.9)	4 (4.7)	9 (6.3)
CML	N/A	7 (8.1)	7 (4.9)
MDS	N/A	1 (1.2)	1 (0.7)
MM	50 (89.3)	N/A	50 (35.2)
PNH	N/A	1 (1.2)	1 (0.7)

AA: Aplastic Anemia; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloblastic Leukemia; HD: Hodgkin Disease; NHL: Non-Hodgkin Lymphoma; CML: Chronic Myeloid Leukemia; MDS: Myelodysplastic Syndrome; MM: Multiple Myeloma; PNH: Paroxysmal Nocturnal Hemoglobinuria.

cally significant relationship between high ferritin values and BCI (blood and catheter infection) development (p<0.001). A statistically significant correla-tion was found between high ferritin values and BCI development in autologous SCT (p<0.001). In contrast to autologous SCT; no statistically significant correlation was found between high ferritin values and BCI development in allogeneic SCT (p=0.61).

Pneumonia: Pneumonia was detected in 51 patients (36%) in the whole group and there was no statistically significant relationship between high ferritin values and pneumonia development (p=0.09). There was no statistically significant correlation between high ferritin values and pneumonia development in both autologous and allogeneic SCT (p=0.07 and p=0.86).

GVHD: Acute GVHD (aGVHD) was seen in 7% of all SCT recipients and 12% of allogeneic stem cell transplant recipients (10 patients). No aGVHD was detected in autologous SCT recipients. There was no statistically significant relationship between high ferritin values and aGVHD in allogeneic SCT patients (p=1). Chronic GVHD was seen in 28% of allogeneic SCT patients, there was no significant relationship between high ferritin values and chronic GVHD (p=0.44).

Sinusoidal Obstruction Syndrome/Veno-occlusive Disease: SOS/VOD was detected in 10 patients (7%) (2 patients in autologous and 8 patients in allogeneic group). Of these, 7 (70%) were in high ferritin and 3 (30%) in the low ferritin group. There was no statistically significant relationship between high ferritin values and SOS development in the whole group, autologous and allogenic groups (p=0.53, p=0.53 and p=0.67).

Transplant and Relapse-Related Mortality Cases: TRM was detected in 2 patients (3.5%) who underwent autologous SCT in the first 100 days and in 3 (3.5%) patients with allogeneic SCT. There was no statistically significant relationship between high ferritin values and TRM development in both autologous and allogeneic SCT patients (p=1 and p=0.17).

Of the 142 patients, 36 died within the total follow-up period (25.3%). In these patients, mortality was divided into two groups as non-relapse related and relapse-related. Non-relapse mortality was detected in 2 patients (3.5%) who underwent autologous SCT and 6 patients (9.3%) who underwent allogeneic SCT. No statistically significant correlation was found between high ferritin and non-relapse mortality in autologous and allogenic groups (p=1 and p=0.17, respectively).

Relapse-related mortality was detected in 7 patients (12.5%) who underwent autologous SCT and in 21 patients (24.4%) who underwent allogeneic SCT. There was no correlation between high ferritin levels and relapse-related mortality in autologous and allogenic groups (p=0.7 and p=0.7).

Effect of Ferritin Concentration on Overall Survival: The predicted survival time was over 2000 days in the autologous SCT group, but it was over 3000 days in the allogenic SCT group. There were 35 patients in the low-ferritin group (ferritin <500 ng/ml) in autologous SCT, and among these 35 patients; 6 mortality cases were seen during the total follow-up period (%17.1). In the high ferritin group (ferritin ≥500 ng/ml), there were 21 patients and 3 mortalities (14.3%). There were 23 patients in the low-ferritin group in the allogeneic SCT group, there were 10 mortality cases (%43,5). In the high ferritin group there were 63 patients, and there were 17 mortality cases (%27). According to the log rank test, there was no statisti-cally significant correlation between high ferritin values and survival in autologous and allo-geneic SCT (p=0.78 and 0.14, respectively) (Figs. 1, 2).

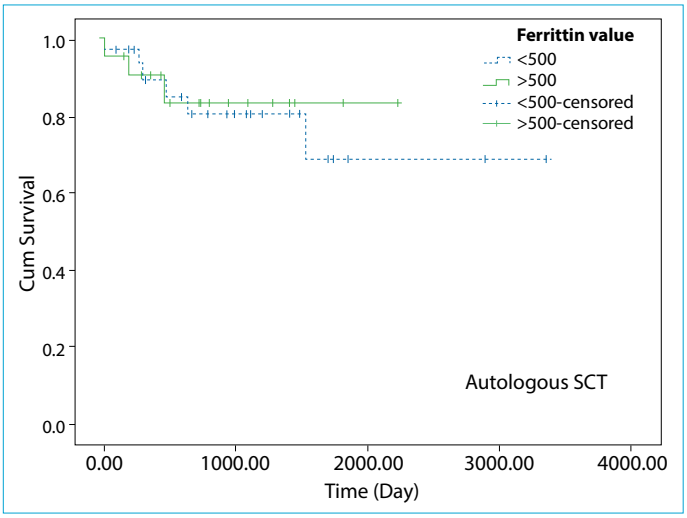

Figure 1. Survival curve according to ferritin values in the autologous group.

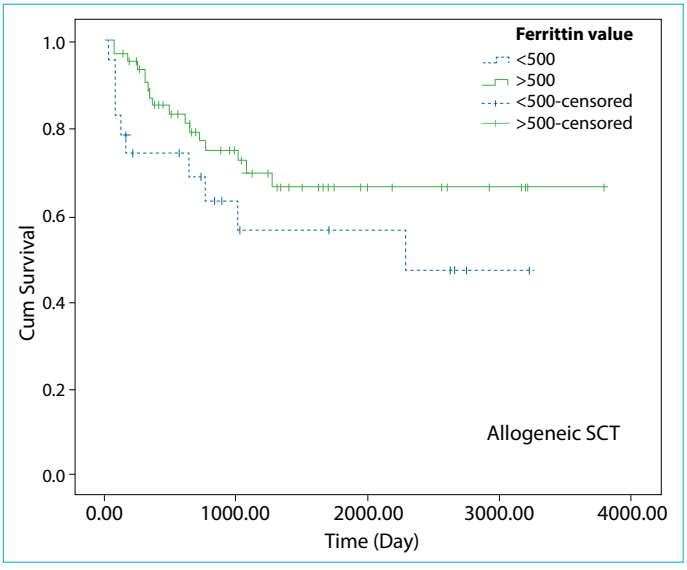

Figure 2. Survival curve according to ferritin values in allogeneic group.

Among the whole patient group, 72.4% (n=42) of the high ferritin group and 76.2% (n=64) of the low ferritin group were alive. Statistically, there was no statistical relationship between survival and high ferritin values in the whole group (p=0.46) (Fig. 3).

Discussion

In this study, it was observed that high ferritin concentrations before SCT were associated with post-transplantion toxic and infectious complications such as mucositis, fungal infection, BCI. However, ferritin elevation before SCT did not have a significant effect on overall survival, transplant-related mortality and complications such as GVHD and SOS. Many studies have been conducted on the effects of ferritin elevation on post-HSCT condition in patients without thalassemia in previous years and elevated iron overload before SCT is found to be related with increased complication rates and reduced mean survival after HSCT especially in MDS and acute leukemia patients.[4–6, 11, 17, 18]

As in a previous study, the cut-off value for ferritin was accepted as 500 ng/ml.[3] Thus, it was shown that toxic and infectious complications may be increased in HSCT even in low iron loads. Iron overload increases the relapse rate of the underlying disease as well as leading to an increase in treatment-related mortality.[19, 20]

Although the ferritin concentration is not a direct indicator of total iron storage in the body, it is the most practical and economic evaluation method for the measurement of iron overload. In general, ferritin values of 300 microgram (mcg)/L

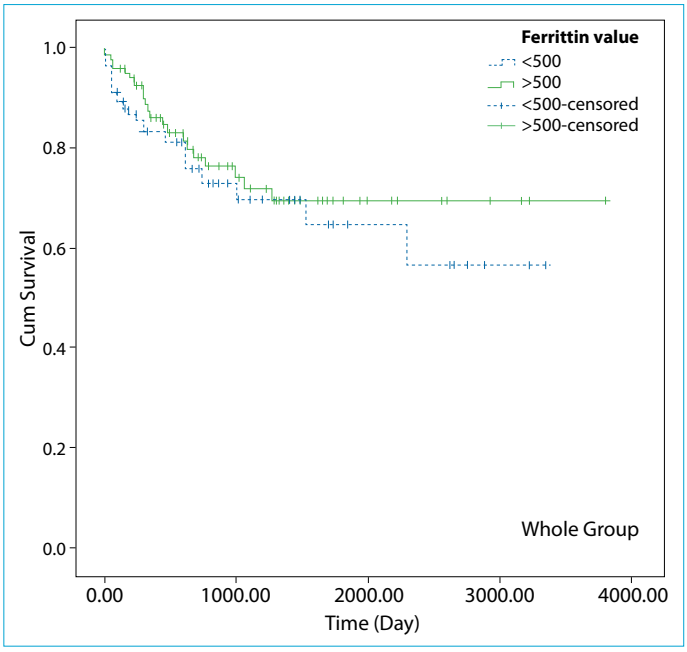

Figure 3. Survival curve according to ferritin values in the whole group.

in males and above 200 mcg/L in females correspond to increased values.[21] This continues to be used as an indicator of iron overload in patients undergoing HSCT.[19]

Past studies have shown a direct relationship between iron overload and toxic and infectious complications such as mucositis, fever and bacteremia in the first 3 months after HSCT in allogenic SCT patients.[22] Consistent with previous studies, this study showed a significant association between the elevated levels of ferritin before SCT and any degree of mucositis in patients with autologous and allogeneic SCT, However, there was no statistically significant relationship between grade 3 and 4 mucositis development and high ferritin values in both autologous and allogenic SCT recipients.

In this study, it was shown that there was a statistically significant relationship between BCI and high ferritin values before SCT application in the whole group and in the group with auto-logous SCT. The reason for a more clear relationship in allogenic SCT recipients than in autologous SCT recipients can be explained by the masking potential of more important variables such as disease-related factors, immunosuppression, intensive treatment regimens, GVHD, and steroid therapy in allogeneic SCT recipients.[6, 22]

There was a close relationship between pneumonia development and high ferritin levels before SCT in the whole group and in the autologous SCT group that was close to the statistical significance limit, but there was no statistically significant relationship between these two variables in the allogeneic SCT group. In our study, a statistically significant relationship was found between the high ferritin concentrations before SCT and the development of fungal infection in the whole group (n=142). This relationship was close to the statistical significance level in allogenic SCT recipients. In allogenic SCT recipients; an association between fungal infection and iron overload has been previously shown.[23, 24] Elevated ferritin level before SCT is also a risk factor for acute GVHD development.[6, 11] In this study, no statistically significant correlation was found between both acute and chronic GVHD and high ferritin values. The small number of patients may be the reason of inadequate clinical significance.

SOS/VOD is a condition that has a significant mortality which can be seen with a rate of app-roximately 1% to 54% in patients with HSCT.[25] It has been reported in several studies that iron overload contributes to the pathogenesis of SOS and that ferritin elevation before SCT increases the risk of SOS development.[12, 26–28] However, in our study, the number of cases with SOS was limited, so that this relationship could not be shown statistically.

In this study, no statistically significant correlation between

high ferritin concentrations and TRM and OS was found in patients with autologous and allogeneic SCT. In a study, the presence of a ferritin concentration above 685 ng/ml was shown to be related with decreased OS and relapse-free survival, increased relapse ratio and relapse-related mortality.[20] Majhail et al.[26] showed that ferritin elevation significantly increased the risk of early relapse-free mortality after autologous and allogeneic SCT. Similarly, Sucak et al.[3] have also shown that ferritin elevation in allogenic SCT recipients is associated with a 30-day and 100-day mortality after transplantation.

Conclusion

This study aims to shed light on the role of iron overload in the development of toxic and infectious complications in HSCT patients after transplantation. It is obvious that more randomized controlled studies with large patient groups are needed in order to determine the role of ferritin in HSCT patients.

Disclosures

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Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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