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PRE-TRANSPLANT DEPRESSION FOUND TO BE RELEATED TO DELAY OF NEUTROPHIL ENGRAFTMENT IN MULTIPLE MYELOMA PATIENTS WHO UNDERGO AUTOLOGOUS PERIPHERAL STEM CELL TRANSPLANTATION

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August 28, 2024

Abstract

Objectives: Malignancy diagnosis and treatments, such as chemotherapy and transplantation processes, cause psychological stress for most of the patients. During the diagnosis and transplantation period, the possibility of an unfavorable outcome and the anticipated adverse effects of treatment are the major sources of stress and negatively affect the psychological status of the patients. It has been shown that physical and psychological status and stress prior to HSCT are closely related to treatment success. The present study was designed to investigate the possible negative effects of depression and anxiety on neutrophil and platelet engraftments in multiple myeloma patients who underwent autologous peripheral stem cell transplantation. **Materials and Methods:** Fifty-two patients completed the Hospital Anxiety and Depression Scale (HADS) before HSCT. Patients were divided into two groups according to the presence of depression or not. The neutrophil and platelet engraftment days of the patients with and without significant depressive symptoms were compared with Mann-Whitney U test. **Results:** The neutrophil engraftment was significantly delayed in patients with significant depressive symptoms (p=0.043). There was no difference in terms of the sociodemographic characteristics and treatment variables between the patients with or without significant depressive symptoms. **Conclusion:** The results of this study may support the presence of the effect of the prior psychological status on HSCT outcomes and also support the widely held belief that the central nervous system (CNS) is effective on the immune system.

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ABSTRACT

Objectives: Malignancy diagnosis and treatments, such as chemotherapy and transplantation processes, cause psychological stress for most of the patients. During the diagnosis and transplantation period, the possibility of an unfavorable outcome and the anticipated adverse effects of treatment are the major sources of stress and negatively affect the psychological status of the patients. It has been shown that physical and psychological status and stress prior to HSCT are closely related to treatment success. The present study was designed to investigate the possible negative effects of depression and anxiety on neutrophil and platelet engraftments in multiple myeloma patients who underwent autologous peripheral stem cell transplantation.

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Results: The neutrophil engraftment was significantly delayed in patients with significant depressive symptoms (p=0.043). There was no difference in terms of the sociodemographic characteristics and treatment variables between the patients with or without significant depressive symptoms.

Conclusion: The results of this study may support the presence of the effect of the prior psychological status on HSCT outcomes and also support the widely held belief that the central nervous system (CNS) is effective on the immune system.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a frequently used treatment modality in hematological malignancies like leukemia and lymphoma, and in non-malignant diseases such as aplastic anemia.

Autologous HSCT has become the standard treatment regimen in the symptomatic form of multiple myeloma (MM) following high dose chemotherapy (HDC) in patients younger than 65 years as well as those between 65 and 75 years (Kumar et al., 2003; Bird et al., 2011).

HSCT is mandatory for repopulating the damaged bone marrow with stem cells following HDC. Autologous (patient's own) hematopoietic stem cells (HSCs) are most frequently used for this purpose. These cells are collected from the patient prior to HDC and transfused intravenously following HDC. Engraftment is the process of relocation of transplanted HSCs in the bone marrow and which become productive again within 10- and 21-days following transplantation. Patients remain neutropenic and are highly vulnerable to infections until engraftment, and full recovery of the immune system usually takes 3 to 6 months (Peggs and Mackinnon, 2004). Time of engraftment is important for transplantation outcomes, because it's known that rapid neutrophil engraftment correlates strongly with overall survival and nonrelapse mortality (Kim et al., 2006).

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Recent research by Hoodin et al. highlights the impact of pre-transplant emotional status on HSCT outcomes. They found that negative emotions correlate with poor long-term survival, while optimism boosts short-term survival. Notably, depression was the most significant risk factor, heavily influencing early post-HSCT mortality. These findings emphasize the importance of psychological well-being in pre-transplant care (Hoodin et al., 2006).

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The possibility of an unfavorable outcome, and the anticipated adverse effects of treatment are only a few of the issues that may cause a high level of stress and negatively affect the psychological status of patients with hematological malignancies. Research findings indicate that depressive symptoms are evident in 20% to 35% of patients undergoing HSCT (Illescas-Rico et al., 2002; Loberiza et al., 2002). The psychosocial status of the patients has long been thought to affect the outcome of treatment and has been the subject of many studies (Constanzo et al., 2013). Research has demonstrated a correlation between treatment results and physical and psychological functionality prior to the HSCT (Sorror et al., 2005; Andorsky et al., 2006; Rosenberg et al., 2015). Furthermore, it has also been shown that pre-HSCT psychological status has an effect on patients' survival, the mechanism of which has not been clarified yet (Andrykowski et al., 1994; Loberiza et al., 2002; Prieto et al., 2005). In a recent meta-analysis, it was discovered that during the post-transplant period, depressed patients experience a 7% reduction in survival rates (Guillaume et al., 2023). Immunological mechanisms are usually thought to be responsible for these results, but none of the studies mentioned above measured a direct immunological parameter.

The exact mechanism by which depression impacts post-HSCT outcomes remains unclear. However, it is assumed that depressed patients tend to neglect their care, adhere poorly to treatment regimens, have reduced access to health services, and engage in unhealthy behaviors such as poor diet, inadequate sleep, lack of physical activity, drug abuse, and smoking (Loberiza et al., 2002; Kiecolt-Glaser et al., 1988). Additionally, there is evidence that psychological factors, including depression, negatively affect immune recovery and overall clinical outcomes (Kiecolt-Glaser et al., 2002; Burns et al., 1990; Costanzo et al., 2011).

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In their study, McGregor et al. (2013) conducted the initial investigation, monitoring white blood cell count post-autologous HSCT as a direct measure of immunological reconstitution. They then correlated these findings with the pre-HSCT emotional distress levels of the patients diagnosed with various hematological malignancies. Their findings indicated that anxiety and depression had a negative effect on white blood cell counts. Another study investigated the relationship between engraftment and pre-HSCT anxiety, along with the level of optimism among patients with various hematologic malignancies (Knight et al., 2014). Their findings revealed a delayed neutrophil engraftment among patients exhibiting lower levels of optimism and higher levels of anxiety. Likewise, Tavakoli-Ardakani et al. (2019) observed a significant association between depression and delayed time to engraftment, as well as mortality within the first-year post-transplantation period in the patients undergoing HSCT.

In this study we examined a group of multiple myeloma patients prospectively to investigate a possible association between their pre-HSCT emotional status and post-HSCT neutrophil and platelet engraftments. We hypothesized that both depression and anxiety would delay neutrophil and platelet engraftment.

MATERIAL AND METHODS

Participants

The study included all patients with MM who were hospitalized in the Transplantation Unit of the Hematology Department at a university hospital between June 2014 and July 2015 for autologous peripheral stem cell transplantation were included in the study. All patients had symptomatic MM and did not have any

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other hematological or immunological diseases. They were undergoing high-dose chemotherapy with the same chemotherapeutic agent (43 patients received 200 mg/m^2, 8 patients received 140 mg/$m^2$and 1 patient received 100 mg/m^2 melphalan. The reasons for receiving lower doses of melphalan were kidney dysfunction, age, and the performance status of the patients). All patients underwent a psychiatric evaluation by a clinician to exclude major neuropsychiatric disorders. The study protocol was approved by the Ethical Committee of the Ankara University Medical School Hospital (Approval No: 11-463-14, Approval Date: 23 June 2014). All participants provided written informed consent before enrollment in the study.

Psychological Measures

All enrolled patients underwent assessment using the Hospital Anxiety and Depression Scale (HADS) and completed the Sociodemographic Data Form within the window of 0 to 7 days before the day of transplantation. The Hospital Anxiety and Depression Scale is a 4-point Likert-type scale including 14 questions; 7 of which measure anxiety symptoms, while the other 7 questions measure depression symptoms (Zigmond and Snaith,1983). The Turkish version of the HADS was found to be a valid and reliable tool for detecting anxiety and depression in medically ill patients. The cut off points are 10 for the anxiety subscale and 7 for the depression subscale (Aydemir and Köroğlu, 2012).

Engraftment Days

The day of engraftment was determined by using the post-transplant daily complete blood count results. The day of neutrophil engraftment was the first day of the first consecutive 3 days that the absolute neutrophil count was $> 0.5x10^9$/L. The day of platelet engraftment was the first day of the first consecutive 7 days that the platelet count was $>20x10^9$/L without transfusion.

Statistical Analysis

The data analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS), version 17.0. The patients were divided into two groups according to the presence of significant depressive symptoms, indicated by HADS depression subscale score greater than 7. Due to the limited number of patients with high anxiety ratings, it was not possible to categorize the patients into two separate groups based on their anxiety levels. Continuous variables were analysed with independent sample t-test. Categorical variables were compared using the chi-square test. The Mann-Whitney U test was used for the statistical comparison of platelet and neutrophil engraftment days between the groups.

RESULTS

A total of 52 participants were included in the study. Seventeen of the patients had scores greater than 7 in HADS and included in the group "patients with depression". Thirty-five of the patients were included in the patients without depression group according to HADS scores.

There were no differences in the sociodemographic characteristics and treatment variables between the two groups. All patients were either in complete remission or very good partial remission in order to eliminate the impact of disease load on the outcome. Similarly, all patients received same induction treatment, conditioning regimen and growth factors after the infusion of stem cells. The amount of stem cells infused were also similar in patients with and without depression. The neutrophil engraftment occurred significantly earlier in patients without depression. Neutrophil engraftment was significantly delayed in patients with depressive symptoms compared to those without. The mean neutrophil engraftment day was 12.6 ± 1.7 days for the depressed group, compared to 11.8 ± 1.1 days for the non-depressed group (p= 0.04). There was no difference between the two groups in terms of platelet engraftment days. The mean platelet engraftment day was 12.2 ± 3.4 days for patients with depression and 12.1 ± 3.3 days for those without depression (p=0.87). (Table-1)

Table-1: The comparison of the sociodemographic characteristics and treatment variables and outcomes between the groups.

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	Patients with depression (N=17)	

	Patients with depression (N=17)	
Age, Mean ± SD	56.1 ± 8.3	5
Gender, N (%) Female Male	4 13	
Education (years), Mean ± SD	7.8±3.8	8
Number of CD34+ stem cells/kg, Mean ± SD	5.2±1.6	4
Melphalan dose, N (%) Lower dose (100 and 140mg/ m^2) Normal dose (200 mg/ m^2)	3 14	6
Amount of platelet concentrates transfused until the engraftment, Mean ± SD	3.0±2.7	2
Amount of erithrocyte concentrates transfused until the engraftment, Mean ± SD	1.3±1.4	
Neutrophil engraftment day, Mean ± SD	12.6±1.7	
Platelet engraftment day, Mean ± SD	12.2±3.4	

Note: [a] Student-t Test; [b] Chi-square test; [c] Mann-Whitney U test; SD, standard deviation.

DISCUSSION

This study aimed to examine the impact of pre-transplant depressive status on the successful engraftment of neutrophils and platelets in MM patients who had autologous HSCT. The findings demonstrated a notable delay in the establishment of neutrophil engraftment among individuals with depression. The exact clinical implications of a one-day delay in neutrophil engraftment are uncertain; nevertheless, it might be quite significant for some patients who develop an infection during the predicted engraftment period.

The results of our study align with previous findings, confirming the connection between emotional status and immune system restoration in HSCT patients. Studies by Hoodin et al. (2006), McGregor et al. (2013), Knight et al. (2014), El-Jawahri et al. (2017), and Tavakoli-Ardakani et al. (2019) have similarly indicated that pre-transplant depression negatively impacts HSCT outcomes. For instance, El-Jawahri et al. (2017) found that allogeneic HSCT patients with depression showed lower survival rates, more acute GVHD, and fewer days out of the hospital, while autologous HSCT patients with depression had reduced days out of the hospital. Additionally, Grulke et al. (2008) reported that HSCT patients with depression had over 2.5 times higher relative risk for mortality compared to non-depressed patients.

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McGregor et al. (2013) examined the association between psychological distress and immune reconstitution. The researchers found that higher levels of anxiety and depression were associated with slower white blood cell recovery in 70 patients following autologous stem cell transplantation. The patients exhibited diverse hematologic malignancies, resulting in significant variations in their underlying immunological and hematological impairments as well as treatment protocols. This variation may have complicated the comparisons between the groups. Furthermore, there was a lack of information about engraftment days, which is a more conclusive clinical parameter than the increase in white blood cells, since post-transplantation morbidity and mortality risks essentially depend on engraftment days. Tavakoli-Ardakani et al. (2019) conducted a study to compare the time it takes for engraftment to occur in patients who underwent hematopoietic stem cell transplantation (HCST), with a specific emphasis on differentiating between patients with depression and those without depression. The findings indicated a statistically significant prolongation in the process of engraftment for patients diagnosed with depression. The difference between the mean durations was 1.9 days, which lines up with our own results. The main difference between the present study and the previous ones is the constitution of the patient groups. The present study included only patients with MM who underwent a standardized treatment regimen. All patients were evaluated by the same psychiatrist. The patients' ages did not differ widely reflecting the nature of their disease.

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The mechanisms by which depression affects post-HSCT outcomes remain unclear but likely involve behavioral and psychosocial factors. Depressed patients tend to neglect their care, adhere poorly to treatment regimens, and engage in unhealthy behaviors, such as poor diet, inadequate sleep, and lack of physical activity. Additionally, psychological factors, including depression, may negatively affect immune recovery and overall clinical outcomes by influencing the release of catecholamines, glucocorticoids, and affecting inflammation, angiogenesis, and immune function (Knight et al., 2013). Behavioral and psychosocial factors likely influence immune, angiogenic, and inflammatory pathways in tumor development and progression through neuroendocrine transmitter activation, despite unclear mechanisms (Costanzo et al., 2011). Depression impairs immune system function, playing a crucial role in recovery following HSCT (Costanzo et al., 2013). The mechanisms by which psychosocial factors affect clinical outcomes after transplantation are unclear, but factors like depression and anxiety may influence the release of catecholamines and glucocorticoids, as well as inflammaion, angiogenesis, and immune function (Knight et al., 2013). The results of the present study support the widely held belief that brain has a significant effect on the immune system. Psychological stress may affect hematopoiesis and lymphopoiesis via sympathetic regulation. This type of mind-body interaction is explicated through the production of certain molecules, such as cytokines, hormones, and peptides from the central nervous system and through the activation of afferent and efferent neurological pathways in lymphoid organs, with both immunosuppressive and immunostimulating effects (Procaccini and Pucino et al., 2014). It has been suggested that there is anatomical evidence for sympathetic regulation of hematopoiesis and lymphopoiesis in bone (Bellinger et al., 2008).

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To our knowledge, the present study is the first one to*investigate* the effect of pre-transplant psychological symptoms on hematological and immunological reconstitution in a homogeneous group of patients. All of the patients had multiple myeloma and underwent autologous transplantation. All patients were either in CR or VGPR to exclude the disease burden effect on outcome. The groups were similar in terms of their age, gender, sociodemographic characteristics, amount of erythrocyte and platelet concentrate transfused, chemotherapeutic agent, and the amount of CD34+ stem cells they received which might all have an effect on the engraftment day.

Additionally, this study had certain limitations. Due to the small size of the group with higher anxiety subscale scores, further analyses were not possible. Another limitation of the study is the use of the Hospital Anxiety and Depression Scale (HADS), a self-rating scale used to assess the depression and anxiety levels of the patients. Future research should explore the mechanisms underlying the influence of depression on HSCT outcomes in greater detail. Studies involving larger patient populations and examining the effects of targeted psychological interventions on immune recovery and engraftment times are warranted. Investigating the impact of treating depression on post-transplant immunological reconstitution may provide valuable insights for improving patient outcomes.

CONCLUSIONS

Our study findings confirm the prevailing notion that the brain exerts a substantial influence on the immune system. Conclusive conclusions can only be drawn from studies involving a substantial number of patients. Furthermore, the impact of depression treatment on immunological reconstitution may require additional research to determine its positive effects.

The findings from this study underscore the importance of addressing psychological well-being in pre-transplant care. Depression's impact on engraftment suggests that interventions to improve mental health before transplantation may improve HSCT outcomes. This has clinical implications for the management of HSCT patients, suggesting that psychological assessments and interventions should be integrated into standard pre-transplant care protocols.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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