

Non-malignant late effects in lymphoma patients treated with autologous hematopoietic stem cell transplantation

Otolog hematopoietik kök hücre nakli yapılan lenfomalı hastalarda malign olmayan geç etkiler

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ABSTRACT

Objective: Developments in transplantation procedures have led to an increase in the number of long-term survivors after hematopoietic stem cell transplantation (HSCT). In this study, we investigated non-malignant late side effects after autologous HSCT (AHSCT) in lymphoma patients.

Methods: Patients were evaluated for immune system, eye, lung, heart, liver, kidney, and endocrine function tests.

Results: Nine (26%) patients had absolute lymphopenia. Cataract was the only eye complication. Four (11.4%) patients had obstructive- and 8 (22.9%) had restrictive-type pulmonary function abnormalities. Only one patient had symptomatic heart failure. One patient developed renal failure. Fifty-three percent of male patients described impotence. The most frequent endocrine disorder was hypothyroidism. Five (14.2%) patients had osteoporosis.

Conclusion: There is not enough data on the non-malignant late effects after AHSCT. Although the lack of a control group is a limitation of our study, our results emphasize the importance of following AHSCT patients for non-malignant late effects of transplantation.

Keywords: Lymphoma, autologous hematopoietic stem cell transplantation, non-malignant, late effect

ÖZ

Amaç: Nakil işlemlerindeki gelişmeler hematopoietik kök hücre nakli (HKHN) sonrası uzun süre yaşayan hasta sayısında artışa neden olmuştur. Biz bu çalışmada lenfomalı hastalarda otolog HKHN sonrası malign olmayan geç yan etkileri araştırdık.

Yöntemler: Hastalar immün sistem, göz, akciğer, kalp, karaciğer ve böbrek fonksiyon testleri ile değerlendirildi.

Bulgular: Dokuz (%26) hastada lenfopeni saptandı. Katarakt tek göz komplikasyonuydu. Dört (%11,4) hastada obstrüktif ve 8 (%22,9) hastada restriktif tip akciğer fonksiyon anormalliği mevcuttu. Yalnızca 1 hastada semptomatik kalp yetmezliği vardı. Bir hastada renal yetmezlik gelişmişti. Erkek hastaların %53'ü impotans tarifledi. En sık endokrin anormallik hipotiroidi idi. Beş (%14,2) hastada osteoporoz saptandı.

Sonuç: Otolog HKHN sonrası malign olmayan geç etkilere ilişkin yeterli veri yoktur. Kontrol grubunun olmaması bir kısıtlılık olmakla birlikte, sonuçlarımız otology HKHN yapılan hastaların malign olmayan nakil geç yan etkileri açısından takip edilmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Lenfoma, otolog hematopoietic kök hücre nakli, malign olmayan, geç etki

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a widely used curative treatment option for various malignant and non-malignant hematological diseases. Developments in the field of transplantation procedures and supportive care have led to an increase in the number of long-term survivors after transplantation. Knowledge regarding the late side effects after transplantation is increasing due to longer post-transplantation follow-up period.

Despite the fact that post-transplant late side effects can arise after three months, they generally emerge after many years. Organ

or tissue dysfunction, changes in quality of life, and delayed or abnormal immune reconstitution associated with infections, and secondary cancers are the main late side effects. Many of these events occur as a result of the accompanying chronic graft versus host disease (GVHD).

The type and risk of developing late side effects after transplantation depend on previous treatments, conditioning regimen, age at transplantation, donor type, source of stem cells, accompanying problems (especially GVHD, infection, etc.), follow-up period after transplantation, and use of steroids or other immu-

nosuppressive treatments. The actual frequency and prognostic impact of the non-malignant late effects after autologous HSCT (AHSCT) are not very well known and can be more easily overlooked. In this study, our aim was to evaluate these overlooked non-malignant effects.

METHODS

In our study, lymphoma patients who underwent transplantation between February 2004 and February 2015 were evaluated at least one year after transplantation. Thirty-five patients were included in the study. The study protocol received institutional review board approval, and the participants provided informed consent.

The diagnoses were Hodgkin lymphoma (HL) in 19 (54.3%) patients and non-Hodgkin lymphoma (NHL) in 16 (45.7%) patients. Twenty-six (74.3%) patients were males and 9 (25.7%) were females. Patients had received a median of 8 (4-11) courses of chemotherapy before transplantation. Three (8.6%) patients were treated for post-transplant recurrence. Only one (2.9%) patient received both chemotherapy and radiotherapy (RT). Thirty-one (88.5%) patients received steroids in the treatment protocol. As a pre-transplant conditioning regimen, 16 (45.7%) patients had received carmustine, etoposide, and cyclophosphamide (CBV) and 19 (54.3%) had received carmustine, melphalan, etoposide, and cytarabine (BEAM) regimens. The age of the patients at the time of transplantation was 43.5 ± 11.7 years. Physical examination and laboratory tests were performed for the late side effects directed at the immune system, eyes, lungs, heart, liver, kidneys, endocrine system, and fertility.

Absolute lymphocyte count, CD4+ lymphocyte count, CD8+ lymphocyte count, T helper/suppressor cell ratio, total immunoglobulin (Ig) G, IgG1, IgG2, IgG3, IgG4, IgA, and IgM were evaluated for the assessment of immune reconstitution.

Microvascular retinopathy, optic disc edema, hemorrhage, infectious retinitis, cataracts, and keratoconjunctivitis sicca were investigated with regard to eye complications.

The respiratory system was evaluated through physical examination, posterior-anterior (PA) chest X-ray, and pulmonary function tests (PFT). If forced expiratory volume in 1 second (FEV_1) was $\geq 80\%$, PFT was considered normal, or FEV_1 /forced vital capacity (FVC) ratio was evaluated. $FEV_1/FVC < 70\%$ was considered obstructive, and $FEV_1 \geq 70\%$ was considered restrictive abnormality. The patients with the ratio of $FEV_1/FVC < 70\%$ and $FVC \leq 80\%$ were considered to have a mixed-type abnormality.

The cardiovascular system was assessed with physical examination, pro-brain natriuretic peptide (BNP), 12-lead electrocardiogram (ECG), and echocardiography (ECHO).

The renal side effects were evaluated in terms of blood-urine nitrogen (BUN), creatinine, creatinine clearance (Modification of Diet in Renal Disease [MDRD] = $186 \times [\text{plasma creatinine}]^{-1.154} \times [\text{age}] - 0.203 \times [0.742 \text{ if female}] \times 25$), Ca, P, Na, K, Cl, urine microscopy, and spot urine protein/creatinine ratio.

The menopausal status, impotence, and fertility have been questioned in terms of endocrine late effects. Total testosterone, free testosterone, thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, adrenocorticotrophic hormone (ACTH), growth hormone, and parathyroid hormone (PTH) measurements were also conducted. Bone mineral density was measured using the Dual-energy X-ray absorptiometry (DEXA) method in the Nuclear Medicine Department.

The outcomes were also compared in terms of other factors that may influence the development of late side effects (sex, primary diagnosis, stage, presence of concomitant diseases, previous therapies, RT, steroid use, conditioning regimen, stem cell count, time period between diagnosis and transplantation, time period between transplantation and assessment, smoking and alcohol use, Eastern Cooperative Oncology Group (ECOG) performance status, remission status and concomitant medications).

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) 21 (IBM Corp. Released 2012; IBM SPSS statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The summary values of continuous variables were expressed as mean \pm standard deviation or median (Q1-Q3), and categorical variables were expressed as frequency and percentage. The compliance of continuous data with the normal distribution was investigated using the Shapiro-Wilk test. The groups conforming to the normal distribution were compared using independent samples t-test (2 groups), or by one-way analysis of variance (for 3 groups and above). The differences of those that do not meet the normal distribution were investigated using Mann-Whitney test (for 2 groups) or the Kruskal-Wallis test (for 3 groups and above). The relationship between categorical variables was analyzed using chi-square test. A $p < 0.05$ was considered significant in the results of analysis.

RESULTS

Absolute lymphopenia was detected in 9 (26%) patients, CD4 lymphopenia was detected in 12 (34.3%), and CD8 lymphopenia was detected in one (2.9%) patient. Thelper/Tsuppressor (Th/Ts) ratio was low in 7 (20%) patients. Total IgG was low in 17.1%, IgA was low in 14.3%, and IgM was low in 51.4% patients. Total IgG reduction was detected most frequently in patients receiving cisplatin, cytarabine, dexamethasone (DHAP) followed by adriamycin (doxorubicin), bleomycin, and vinblastine (ABVD) before transplantation ($p = 0.024$). A decrease in IgM was detected more frequently in NHL than HL (66.7% vs 33.3%; $p = 0.026$).

The only eye complication was cataract and was detected in 6 of the 35 patients.

Chest radiography revealed interstitial involvement in 2 (5.7%) patients, bronchovascular involvement in one (2.9%) patient, and effusion and air trapping in one (2.9%) patient. Obstructive abnormality was detected in 4 (11.4%) patients, restrictive abnormality was detected in 8 (22.9%), and mixed-type abnormality was detected in 3 (8.6%) patients through PFT.

From the viewpoint of the cardiovascular system, T-wave negativity was observed in the ECG of 2 patients. Ejection fraction (EF) was low only in one patient; pro hormone B-type Natriuretic Peptide (pro-BNP) was high (≥ 300 pg/mL) in 4 patients.

When the late effects associated with kidneys were evaluated, creatinine clearance was low in 6 (17.1%) patients. Spot urine protein/creatinine ratio was high in 8 (22.9%) patients.

Seven of 9 women were postmenopausal. The estradiol, progesterone, FSH, and LH levels of all women were in the normal range. Fourteen (53%) of 26 male patients described impotency. Total testosterone was low in 14 (46.2%) patients and free testosterone in 10 (38.5%) patients. Thyroid-stimulating hormone (TSH) was high (>4.2 pg/mL) in 5 (4.2%), free T3 was high in one (2.9%) patient, and free T4 was high (>1.7 ng/dL) in 2 (5.7%) patients. TSH was low (<0.27 pg/mL) in 4 (11.4%) patients and free T3 was low (<2 pg/mL) in 4 (11.4%) patients. Nine patients (25.71%) had osteopenia and 5 (14.28%) had osteoporosis.

DISCUSSION

It is well-known that allogeneic HSCT has a long-lasting effect on the immune system. Although we could not find a similar study on the late effects of AHSCT on the immune system, absolute lymphopenia, CD4 lymphopenia, CD8 lymphopenia, low Th/Ts ratio, and low Ig levels were the detected abnormalities with regard to the immune system in our study. However, there were no clinical findings suggesting immunosuppression. These findings suggest that the effects of AHSCT on the immune system may also last long but cause few clinical problems.

Majhail et al. (1) compared patients who underwent AHSCT due to HL and NHL with their healthy siblings at a median follow-up of 6 years and found an increased incidence of cataract. Cataract was observed more frequently in the group receiving total body irradiation (TBI) as a conditioning regimen. Cataract was the only eye complication detected in our study. In one patient, cataract was observed despite the absence of steroid use, and none of our patients had a history of TBI. Since our patients had no routine eye examination in the pre-transplant period, the effect of aging and/or steroid use could not be assessed.

The reduction in lung functions after HSCT is generally associated with carmustine used as a conditioning regimen and relapsed malignancy (2, 3). Carlson et al. (4) reported the interstitial pneumonitis frequency as 11% and TBI as the major risk factor at a median follow-up of 12 months in 102 patients surviving 6 months after autologous transplantation. Lane et al. (5) reported the frequency of pneumonitis as 22% in 222 patients receiving CBV as a conditioning regimen. Mediastinal radiotherapy, carmustine dose over 1000 mg, and age <54 years were reported as risk factors. Interstitial pneumonitis was present in 5.7% of patients in our study. Since all the patients received carmustine at equal doses, the effect of carmustine on pneumonitis frequency could not be evaluated in our study. TBI had not been applied to any of our patients. Thus, we concluded that caution should also be taken in terms of pneumonitis in patients not receiving TBI.

Cervera et al. (6) determined PFT as normal in 62% of 52 pediatric patients after 3-11 years of autologous and allogeneic transplantation, and they observed a restrictive loss in 23% patients. Multiple remissions, allogeneic transplantation, and pulmonary infections have been found effective on results. Although our patients consisted of only adult group and were limited with the patients undergoing autologous transplantation, obstructive and restrictive losses were found to be similar.

Clinically evident cardiac complications after HSCT are rare. Previously, age and cardiac dysfunction were accepted as more restrictive, but today, the transplantation applied to older patients may lead to an increased incidence of impaired cardiac function (7-9). Ruiz-Soto et al. (10) reported the rate of patients developing left ventricular dysfunction as 6% in their study, wherein they evaluated 493 patients with aggressive NHL who underwent AHSCT. Only 2% of these patients were reported as symptomatic. In our study, symptomatic heart failure was found to be less frequent possibly due to younger age and better cardiac performance at the pre-transplant period.

We could not find any study evaluating cardiac complications after AHSCT in terms of pro-BNP. The pro-BNP level was detected as high in 4 of our patients. All of the patients were males. Three of the patients were asymptomatic and had normal ECG and EF. The symptomatic one patient had T-wave negativity on ECG and low EF. Although the cumulative anthracycline dose, mediastinal radiotherapy, cardiac function before transplantation, and the type and intensity of conditioning regimen have been defined responsible for late cardiovascular events after HSCT (7), we could not find a relationship with these factors.

There is less information regarding the extent of late renal dysfunction after HSCT. The use of various nephrotoxic agents shows a strong relationship with renal dysfunction (11). Other risk factors reported for developing chronic renal failure (CRF) are advanced age at transplantation, post-transplant hypertension, a low glomerular filtration rate before transplantation, single-dose TBI regimen and fludarabine, and the presence of GVHD (12). In our study, only one patient met the criteria for CRF. This patient had uncontrolled hypertension as a risk factor in the pre-transplant period, but the use of nephrotoxic drugs given for post-transplant relapse may also have contributed to CRF.

Moser et al. (13) calculated the 15-year cumulative incidence of renal failure as 11% in their study, wherein they evaluated 757 NHL patients with a ≥ 2 -year survival after AHSCT. Ruiz-Soto et al. (10) followed 439 aggressive NHL patients who underwent AHSCT for a median of 3 years after transplantation in terms of late complications. The number of the patients with late complications was 68, and renal failure was identified only in one patient. The CRF frequency in our study was found to be 2.85%. However, patient characteristics and the differences in the conditioning regimen and supportive care make the comparison difficult. Our study suggests that AHSCT does not have a significant negative effect on renal functions, but the patients with risk factors of the general population should be considered more carefully.

Mertens et al. (14) evaluated 270 pediatric and adult lymphoma patients, who underwent bone marrow transplantation and determined the rate of gonadal dysfunction as 92% in males and as 99% in females. In our study, most of our female patients (5/9) were post-menopausal in the transplantation period. Two patients became post-menopausal after transplantation. Seven patients had a history of birth in the pre-transplant period. Two patients gave birth after transplantation. Our data suggest that AHSCT has no significant negative effect on female gonadal functions but larger prospective studies are needed to make definitive results.

Schimmer et al. (15) evaluated sexual functions in 16 male patients ≤ 50 years of age, surviving for at least 6 months of remission in their post-transplant period and having the diagnosis of HL (n=9), acute myeloid leukemia (AML; n=4), and NHL (n=3). Four of the 16 patients described moderate sexual desire and two of them described frequent erectile dysfunction. In our study, when 26 male patients were evaluated in terms of the gonadal functions, 14 (53%) patients described impotence. Unfortunately, the results were obtained from a subjective evaluation.

Thomas et al. (16) evaluated 186 autologous and allogeneic HSCT patients remaining under complete remission for ≥ 1 year. The diagnosis was lymphoma in 50% of patients and the conditioning regimen was TBI. No clinical thyroid symptoms were detected in patients. Biological dysfunction was observed in 10%, hypothyroidism in 6.5%, thyroiditis in 3%, and Basedow's disease in 0.5% patients. All the patients in our study group were euthyroid before transplantation. Subclinical hypothyroidism was detected in 2 (5.8%) patients, sick euthyroid syndrome in one (2.9%) patient, overt hypothyroidism in 3 (8.7%) patients, and hyperthyroidism in 2 (5.8%) patients under Levothyroxine (LT4) in the post-transplant evaluation. The reason for different rates can be associated with a heterogeneous group of patients, the variability of evaluation methods, and the evaluation period.

Majhail et al. (17) evaluated HL (n=92) and NHL (n=184) patients in terms of the late complications compared with their siblings. Osteoporosis (4.3% vs 2.2%) and avascular necrosis (3.3 vs 0.3%) was more common in patients undergoing AHSCT at a median 6-year follow-up. Osteoporosis was more common in women. Since, our study was designed to be without a control group we were not able to make similar comparisons. The reason for higher frequencies in our study (10.5% in HL and 18.75% in NHL) is thought to be related with the lower number and the higher mean age of our patients. We could not evaluate the effect of gender to the osteoporosis due to the limited number of our female patients.

CONCLUSION

Since some of our patients received chemotherapy for recurrence after transplantation, our data may not be interpreted solely as an effect of AHSCT. However, despite other limitations of study, such as the low number of patients, heterogeneity of the patient group, and the lack of control group, our results emphasize the importance of also following AHSCT patients for non-malignant late effects of transplantation. Follow-up guidelines specific for AHSCT recipients can be useful and will probably become necessary in the future.

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