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Multiple Myelom Hastalarında Otolog Kök Hücre Nakli Kardiyotoksik Mi, Kardiyoprotektif Mi?

Is The Autologous Stem Cell Transplantation Cardiotoxic or Cardioprotective in Patients With Multiple Myeloma?

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ÖZ

GİRİŞ ve AMAÇ: *Multiple myelom (MM) hastalarında otolog kök hücre nakli (OKHN) etkili bir tedavi seçeneğidir. Kullanılan kemoterapötikler nedeniyle OKHN sonrası kardiyak yan etkilerin gelişebileceğine dair endişeler mevcuttur. Bu çalışmada MM hastalarında OKHN sonrası geç kardiyak etkilerin değerlendirilmesini amaçladık.*

YÖNTEM ve GEREÇLER: *Kurumumuza MM tanısı ile başvuran ve OKHN yapılmış olan hastalar retrospektif olarak incelendi. Rutin pretransplant ve nakil sonrası birinci yıl ekokardiyografik değerlendirmeleri olan 30 hasta çalışmaya alındı. Sol ventrikül diastol sonu çapı (LVEDD), sol ventrikül sistol sonu çapı (LVESD), sol ventrikül ejeksiyon fraksiyonu (LVEF), E dalgası, A dalgası ve E/A indeksine ait veriler toplandı.*

BULGULAR: *Sol ventrikül sistolik fonksiyonunun göstergesi olarak nakil sonrası LVEF'deki (ortalama±SD, 66.66±8.5 %) artış, nakil öncesi LVEF (62.46±4.51 %) ile karşılaştırıldığında istatistiksel olarak anlamlıydı (p=.013). Alt grup analizlerinde LVEF'deki artış tandem nakil olan grupta (5.25±5.2 %), tek nakil olan gruba (4.72±8.68 %) göre daha yüksekti ancak istatistiksel anlamlılık sağlanamadı (p=.872). Sol ventrikül diyastolik disfonksiyonundaki düzelmenin kanıtı olarak nakil sonrası LVEDD (45.4±5.8 mm) ve LVESD (27.3±4.9 mm) değerlerinde nakil öncesi LVEDD (48.9±4.1 mm) ve LVESD (31.1±4.1 mm) değerlerine göre istatistiksel olarak anlamlı düşüş tespit edildi (p=.044, p=.041, sırasıyla).*

TARTIŞMA ve SONUÇ: *Bu çalışma literatürde MM'li hastalarda OKHN sonrası geç dönemde artmış kardiyak sistolik ve diyastolik fonksiyonları gösteren ilk çalışmadır. Bu sonuçlar OKHN sürecinde kök hücrenin sistemik etkilerini göstermesi açısından önemlidir*

Anahtar Kelimeler: *kök hücre tedavisi, granülosit koloni stimülan faktör, kardiyotoksisite, sol ventrikül sistolik fonksiyonu, sol ventrikül diyastolik fonksiyonu*

ABSTRACT

INTRODUCTION: *Autologous stem cell transplantation (ASCT) is an effective treatment option in patients with Multiple Myeloma (MM). There is a concern about development of cardiac complications following ASCT because of the chemotherapeutics which are used. In this study we aimed to evaluate late cardiac effects of ASCT in patients with MM.*

METHODS: *The patients who presented to the our institution with diagnosis of MM and underwent ASCT were studied retrospectively. Thirty cases who had routine pretransplant and posttransplant first year echocardiographic examinations were examined. The data of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), E wave, A wave and E/A index were collected.*

RESULTS: *The increase in posttransplant LVEF (mean±SD, 66.66±8.5 %) as a marker of left ventricular systolic function compared with pretransplant LVEF (62.46±4.51 %) was statistically significant (p=.013). In subgroup analyses, the increase in LVEF was greater in patients who underwent tandem ASCT (5.25±5.2 %) compared with did not (4.72±8.68 %), but the difference was not statistically significant (p=.872). There were significant decreases in posttransplant LVEDD (45.4±5.8 mm) and LVESD (27.3±4.9 mm) which was evidence of the amelioration of left ventricular diastolic dysfunction, compared with pretransplant LVEDD (48.9±4.1 mm) and LVESD (31.1±4.1 mm) (p=.044, p=.041, respectively).*

DISCUSSION AND CONCLUSION: *This is the first study in literature that demonstrated improved systolic and diastolic cardiac functions at late-term of ASCT in patients with MM. These results are important in terms of showing the systemic effect of stem cell during the course of ASCT.*

Keywords: *stem cell therapy, granulocyte-colony stimulating factor, cardiotoxicity, left ventricular systolic function, left ventricular diastolic function*

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INTRODUCTION

Multiple myeloma (MM) is an incurable disease that originates from the proliferation of malignant plasma cells. MM comprises 10% of hematologic malignancies and affects elderly population with the median age at diagnosis is 70 years. The long-term survival has improved significantly after the introduction of modern drugs and more than 25% of patients have 10 years of life expectancy. (1-3)

Although novel agents has sparked a re-examination of the role of autologous stem cell transplantation (ASCT), it remains the standard of care for eligible patients with MM. (4) A cyclophosphamide (CY) based mobilization regimen (1.5-4g/m²) with weight adjusted granulocyte-colony stimulating factor (G-CSF) is commonly used for stem cell harvest. (5) The most widely used conditioning regimen is a single dose of high-dose melphalan (HDM, 200mg/m²) since the report of the Intergroupe Francophone du Myélome in 2002. (6) One of the dose-limiting side effect of CY is cardiotoxicity which has been observed after the doses higher than 120 mg/kg . The pathogenesis of myocardial damage consists of oxidative stress, altered calcium homeostasis, nitrative stess, alteration in signaling pathways, cardiomyocyte inflammation and apoptosis. These mechanisms lead to cardiyomyopathy and heart failure. (7) Although arrhythmogenic effects have been well described with HDM, its negative effect on left ventricular function as a single agent has not been confirmed yet. (8,9)

There are reports in literature about the early cardiac toxicity in patients with MM treated with ASCT. (10,11) However, in our clinical practise cardiac side effects are almost never seen at late-term. Based on this observation we performed a retrospective study evaluating late cardiac effects of ASCT by echocardiographic parameters in patients with MM.

MATERIAL AND METHODS

The patients who presented to the our institution with diagnosis of MM and underwent ASCT between 2014-2017 were studied retrospectively. The records of the patients were evaluated. The diagnoses were based on the updated diagnostic criteria of International Myeloma Working Group.

Patients who received maintenance therapy or relapsed/refractory after the ASCT were excluded. In addition the patients who had thoracic irradiation history or signs of concomitant AL amyloidosis were excluded. The remained thirty cases who had routine echocardiographic examinations in the pretransplantation period and one year after the transplant, were enrolled in this study. The systolic function of left ventricle was assessed by left ventricular ejection fraction (LVEF). The left ventricular diastolic function was assessed by diastolic mitral inflow velocities; E wave, A wave and E/A index. The data of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) were collected. The study protocol was approved by the Faculty Research Ethical Committee.

IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses. Kolmogorov-Smirnov tests were used to test the normality of data distribution. Numerical variables were expressed as mean ± standard deviation, median (minimum-maximum range) and categorical variables were given as frequencies (percentages). Time dependent changes in variables were examined by paired t test and Wilcoxon signed rank test. Time-dependent changes of two-category variables were determined by Mc Nemar test. Spearman correlation analysis was used when normal distribution assumption was not provided in the analysis of relationships between variables. A 2-sided P value <.05 was considered statistically significant.

RESULTS

Thirty cases were enrolled the study. Seventy percent (n:21) of the cases were male and the median age was 60 years (range, 48-75 years). Characteristics of the patients are shown in Table 1.

Table 1. Characteristics of the Patients

Feature	n (%)
Median Age (range) year	60 (48-75)
Gender (female/male)	9/21 (30/70)
Stage (ISS)	
I	12 (40)
II	11 (36.7)
III	7 (23.3)
Type of MM	
IgA kappa	7 (23.3)
IgA lambda	2 (6.7)
IgG kappa	9 (30)
IgG lambda	4 (13.3)
Lambda light chain disease	1 (3.3)
Kappa light chain disease	6 (20)
Non-secretory	1 (3.3)
Comorbidity (+/-)	10/20 (33.3/66.7)
CAD	1 (3.3)
HT	3 (10)
DM+HT	1 (3.3)
DM+HT+CAD	1 (3.3)
COPD	3(10)
CKD+HT	1(3.3)
Previous lines of therapy	
1	9 (30)
2	17 (56.7)
3	4 (13.3)
Pretransplant response	
PR	5 (16,7)
VGPR	14 (46.7)
CR	11 (36.7)
Posttransplant response	
PR	1 (3.3)
VGPR	6 (20)
CR	23 (76.7)
Mobilization regimen	
Cyclophosphamide 4 g/m²	30 (100)
G-CSF 5-10mcg/kg/day	30 (100)
Conditioning regimen	
Melphalan 140 mg/m²	2 (6.7)
Melphalan 200 mg/m²	28 (93.3)

Abbreviations: ISS, International Staging System; CAD, coronary artery disease; HT, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PR, partial response; VGPR, very good partial response; CR, complete response; G-CSF, granulocyte-colony stimulating factor

Median time from diagnosis to ASCT was 9 months (5-34 months). Patients received median 6 courses therapy (4-11) before ASCT. Seventeen patients (56,7%) received 2 cycles of VAD regimen (vincristine 0.4 mg/day, doxorubicin 9mg/m²/day, dexamethasone 40mg/day) as initial therapy since the reimbursement grounds. All of the patients received bortezomib median 4 cycles (2-10). Lenalidomide was used median 2 cycles (1-4) on seven patients. Eight patients (26.7%) underwent tandem ASCT. Three of the patients (10%) had undergone ASCT previously as part of first line therapy and the data of second transplantation was used in this study.

The mean pretransplant LVESD was 31.1±4.1 millimeter (mm), which decreased to a mean of 27.3±4.9 mm at the first year of ASCT (p=.041). A statistically significant decrease was also observed between pretransplant LVEDD (mean±SD, 48.9±4.1 mm) and posttransplant LVEDD (45.4±5.8 mm) (p=.044). The E/A ratio was higher in the posttransplant echocardiograms (0.77±0.23) compared with the pretransplant echocardiograms (0.74±0.14) but the difference was not statistically significant (p=.116). A statistically significant increase was determined in posttransplant LVEF (66.66±8.5 %) in comparison with pretransplant LVEF (62.46±4.51 %) (p=.013).

In subgroup analyses, the increases in LVEF and E/A ratio were greater in patients who underwent tandem ASCT (5.25±5.2 %, 0.19±0.04) compared with did not (4.72±8.68 %, 0.05±0.15), but the differences were not statistically significant (p=.872, p=.429, respectively). Also the decreases in LVESD and LVEDD were greater in tandem ASCT group (7.5±2.1 mm, 5.6±4 mm) compared with single ASCT group (2.1±5.3 mm, 2.3±6.4 mm), but the differences were not statistically significant (p=.078, p=.356, respectively).

The increase in LVEF was greater in patients with comorbidity (5.4±7.64 %) compared with no comorbidity (4.6±8.08 %), but the difference was not statistically significant (p=.948). The decreases in LVESD and LVEDD were greater in comorbidity positive group (4.1±4.6 mm, 4.5±5.5 mm) compared with comorbidity negative group (2.08±5.6 mm, 1.9±6.4 mm), but the differences were not statistically significant (p=.553, p=.447, respectively).

There was no statistically significant difference between pretransplant (35.46±19.54 mg/dl, 0.94±0.91 mg/dl) and posttransplant (34.85±14.22 mg/dl, 0.91±0.59mg/dl) serum urea and creatinine levels (p=.895, p=.795, respectively). A statistically significant difference was observed between pretransplant (12.25±1.79 g/dl) and posttransplant (12.76±1.19 g/dl) plasma hemoglobin levels (p=.028).

A negative correlation was detected between pretransplant E/A ratio and age (p<.05; Table 2). However, there was no correlation between left ventricular ejection fraction values and clinical parameters (p>.05; Table 2).

Table 2. The Association Between Echocardiographic Variables and Clinical Parameters

Feature	Pretransplant				Posttransplant			
	E/A	LVEF	LVESD	LVEDD	E/A	LVEF	LVESD	LVEDD
Age	-.008*	.406	.921	.201	.370	.637	.690	.993
ISS	.791	.803	.666	.747	.536	.974	.895	.907
Previous lines of therapy	.184	.597	.428	.499	.454	.291	.327	.210
Prior VAD	.066	.536	.427	.374	.913	.157	.467	.680
Prior lenalidomide	.955	.848	.685	.823	.078	.924	.559	.189
The number of bortezomib cycles	.904	.610	.844	.459	.578	.254	.043*	.364
Pretransplant								
Urea	.153	.757	.685	.033*	.569	.635	.531	.862
Cre	.379	.727	.828	.358	.813	.616	.734	.997
Hg	.296	.723	.804	.913	.994	.349	.561	.476
Posttransplant								
Urea	N/A	N/A	N/A	N/A	.315	.933	.221	.438
Cre	N/A	N/A	N/A	N/A	.481	.835	.695	.632
Hg	N/A	N/A	N/A	N/A	.994	.731	.278	.115

Abbreviations: ISS, International Staging System; Cre, creatinine; Hg, hemoglobin
*p<0.5; statistically significant

DISCUSSION

In this study we compared pretransplant and posttransplant first year cardiac functions with echocardiographic parameters. In the literature there are a few studies on the cardiac effects of ASCT specifically in MM patients. Zver et al first studied cardiac toxicity of high-dose CY (4 g/m²) on 23 patients with MM who underwent ASCT, in 2007. They demonstrated neurohumoral activation of heart failure by an increase in brain natriuretic peptide and endothelin 1 levels. However, there were no significant change in cardiac output and doppler parameters of left ventricular diastolic function by echocardiography after 8 weeks of CY administration. (10) In 2008, they reported the data of 30 patients with MM who underwent tandem ASCT. This study showed left ventricular diastolic dysfunction indicated by the duration of pulmonary vein atrial reversal velocity (a-wave) and early mitral annulus diastolic tissue velocity (Em) at follow up 3 months after tandem ASCT. (11) Clinically meaningful cardiac dysfunction was not described in both studies. Bleeker et al focused on cardiac dysfunction and revealed the rate was 1.6%

(17/1050) in MM patients undergoing ASCT, yet only 0.7% (8/1050) were probably due to HDM. (12)

The reversal of the E/A ratio (E<A) is a standart parameter of left ventricular diastolic dysfunction. In our study the E/A ratio was higher in the posttransplant echocardiograms compared with the pretransplant echocardiograms but the difference was not statistically significant. However, significant decreases of LVESD and LVEDD which can be accepted another convincing evidence of the improvement of left ventricular diastolic dysfunction, were detected. The increase in posttransplant LVEF as a marker of left ventricular systolic function compared with pretransplant values was also significant. Although the amelioration in cardiac functions was more pronounced in patients underwent tandem ASCT, the comparation with single ASCT was not statistically significant. We attribute this result to the small number of tandem ASCT cases. There was not an association between improved cardiac functions and clinical parameters even with increased posttransplant plasma hemoglobin levels. Through these findings we speculate that ASCT has a positive effect on cardiac functions in patients with MM.

In consistency with our results, Kozelj et al followed 12 patients with myeloma after tandem ASCT and exclude late cardiac complications by conventional echocardiography at the end of 6 years

follow up. (13) The discrepancy between early and late cardiac effects of ASCT can be arised from clinical variables potentially associated with cardiac functions especially important in short-term like as status of disease, sepsis, engraftment syndrome, exacerbation of comorbidities and alteration in hemoglobin levels. Since the complexity of the patients undergoing ASCT, it is difficult to attribute the acute cardiac toxicity to only chemotherapy exposure. Additionally in the setting of ASCT, circulating stem cells not only provide bone marrow recovery but also show protection on other organs.

It is known that human pluripotent stem cells have the ability to proliferate indefinitely and differentiate into any cell type of the body including cardiomyocytes. (14,15) There are many reports in literature demonstrated the impressive effects of cell therapy in experimental doxorubicin induced cardiomyopathy models. (16-18) Recently in a study conducted by Silva Dos Santos et al. revealed that the transplantation of cardiomyocytes derived from embryonic stem cells improves cardiac function by reduction in the percentage of apoptotic cardiomyocytes in the hearts of mice with doxorubicin induced cardiomyopathy. (19) The action mechanisms of stem cell therapy includes paracrine secretion, antioxidant and antiinflammatory effects. (20) Its translation to our clinical practise was examined by a meta-analysis of eight randomized controlled trials which involved 531 participants. The results suggested that stem cell therapy improves LVEF and reduces left ventricular end-systolic volume and left ventricular end-diastolic chamber size in patients with dilated cardiomyopathy. (21) Also there are studies in literature showing the beneficial effects of G-CSF on cardiac repair and remodeling prevention through either stem cell mobilization or direct angiogenesis promotion. (22,23) Based on these data we hypothesize that during the ASCT, patients do not exposed only cardiotoxic chemotherapeutics and complications associated with cardiac dysfunction, but also received cardioprotective therapy with stem cell and G-CSF. We are seeing this cardioprotective effects more clear in late-term of ASCT with the integration of stem cells into the damaged heart tissue and recover cardiac functions.

Study Limitations

The major limitation of present study is the small numbers of patients who enrolled, which was caused by the difficulty of finding patients who did not received maintenance therapy or relapsed/refractory after the ASCT. And the second was retrospective design of the study.

Conclusion

Stem cell therapy is a new effective therapeutic approach for treatment of a variety of diseases such as neurological, cardiovascular and gastrointestinal disorders. To our knowledge, present study is the first study in literature that demonstrated improved cardiac functions by echocardiographic parameters, after ASCT in patients with MM. These results are important in terms of showing the systemic effect of stem cell during the course of ASCT.

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