Cardiologic evaluation of bone marrow transplantation patients

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Bone marrow transplantation procedure may produce cardiologie adverse effects on recipients. Most of them are related to the conditioning regimens. The infusion of the graft, especially when it is mixed with some preservative agents, can induce some cardiopulmonary disturbances. Infections and immunologic events seen during the posttransplant period may also cause a heart injury. We monitored cardiac findings of 24 patients who underwent bone marrow transplantation (22 allogeneic, two autologous). Besides routine physical and laboratory examination, telecardiograms, electrocardiograms were obtained and two-dimensional and M-mode echocardiography examinations were done before and after the transplantation. Continuous cardiac monitoring was also done by the Hotter technique before and during stem cell infusion. Low voltage was observed in one patient (4%), hypokinesia in two patients (8%), and minimal pericardial effusion in three patients (13%). Supraventricular extrasystoles were seen more during infusion (p>0.05) and bradyarrhythmias were not seen. Deaths related to cardiac disturbances were not observed in our patients. These results suggested that; (1) patients who undergo BMT should be examined and monitorized for the cardiac disorders, (2) if these measures are taken, cardiac complications of BM T will not limit the success of the procedure. [Turk J Med Res 1995; 13(2): 50-54]

Key **Words:** Bone marrow transplantation, Cardiac complications

The existence of various effects to the heart poses a threat to the patient who is a candidate for bone marrow transplantation (BMT). First of all, antracycline antibiotics which are given to the patient before transplantation have significant cardiotoxic effect. Cyclophosphamide, which is a component of many conditioning regimens and used at higher doses, is another potentiating agent for cardiotoxicity (1,2). Total body irradiation has also adverse effects on heart. Infusion of cryopreserved Bone marrow (BM), which contains donor buffy coat or mononuclear cells (MNC) with dimenthylsulphoxide (DMSO) and human serum, may be also accompanied with some cardiopulmonary and circulatory complications (3,4). Infusion of BM may cause severe arrhytmias (5). The infections, especially seen in the febrile neutropenic period may produce an injury on different sites of the heart. Incidence of non-bacterial thrombotic endocarditis (NBTE) has also been found to be increased in BMT patients (6).

Received: Dec. 24,1994 **Accepted:** Feb. 4,1995

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However, it is controversial whether cardiac complications are among the important factors which limit the success of BMT. We examined and monitored the patients who underwent BMT to evaluate cardiac complications of BMT.

PATIENTS AND METHODS

Patients

Twenty-four patients who underwent BMT at Ankara University Ibn-i Sina Hospital between December 1993 and November 1994 were included in the study. There were 13 men and 11 women. Their mean age was 27.1 (17-48) years. Fourteen of them were myeloid leukemia (AML), two were acute lymphoblastic leukemia (ALL), five were chronic myeloid leukemia (CfyiL), one was Hodgkin's disease, one was multiple myeloma and one was adrenoleukodystrophia patient. All the patients with both AML and all were in first complete remission before transplant. Eight patients received daunorubicin containing (total dose of 400-720 mg), six patients received mitoxantrone (MTX) containing (total dose of 80-120 mg), one patient received idarubicine containing (total dose of 100 mg) chemotherapeutic regimens. Total 150 mg

Table 1. Characteristics of the patients

Patient Number	Age	Sex	Diagnosis	Interca. Agents* (mg)	CY* (mg)	Cond. Regimen	Type of Transpl.
1	18	M	AML	100 (MITOX)		BU+CY	AlloBMT
2	26	F	ALL	150 (DAU)	2000	BU+CY	AlloBMT
3	20	M	AML	100 (MITOX)		BU+CY	AlloBMT
4	26	F	AML	480 (DAU)		BU+CY	AlloBMT
5	40	F	AML	80 (MITOX)		BU+CY	AlloBMT
6	22	M	AML	400 (DAU)		BU+CY	AlloBMT
7	18	M	HD		12600	MEL+CY	APBCST
8	23	M	AML	720 (DAU)		BU+CY	AlloBMT
9	17	F	AML	100 (IDA)		BU+CY	AlloBMT
10	36	M	CML			BU+CY	AlloBMT
11	22	M	ALD			BU+CY	AlloBMT
12	17	F	ALL			BU+CY	AlloBMT
13	25	F	CML			BU+CY	AlloBMT
14	29	F	CML			BU+CY	AlloBMT
15	19	M	AML	540 (DAU)		BU+CY	AlloBMT
16	24	F	AML	400 (DAU)		BU+CY	AlloBMT
17	24	M	AML	420 (DAU)		BU+CY	AlloBMT
18	23	F	CML			BU+CY	AlloBMT
19	21	M	CML			BU+CY	AlloBMT
20	35	F	AML	100 (MITOX)		BU+CY	AlloBMT
21	39	M	AML	120 (MITOX)		BU+CY	AlloBMT
22	38	M	AML	600 (DAU)		BU+CY	AlloBMT
23	48	F	MM			HDM	APBSCT
24	41	M	AML	120 (MITOX)		BU+CY	AlloBMT

INTERCA: intercalating, CY: cyclophosphamide, COND: conditioning, TRANSPL.: transplantation, AML: acute myeloblasts leukemia, ALL: acute lymphoblastic leukemia, HD: Hodgkin's disease, CML: chronic myeloid leukemia, ALD: adrenoleukodystrophia, MM: multiple myeloma, MITOX: mitoxantrone, DAU: daunorubicin, IDA: idarubicin, BU: busulfan, MEL: melphalan, HDM: high dose melphalan, AlloBMT: allogeneic bone marrow transplantation, APBSCT: autologous peripheral blood stem cell uansplantation,
*: pretransplant medication

daunorubicin plus 2000 mg cyclophosphamide (CY) were given to one patient. Another patient with Hodgkin's disease received 12.600 mg CY. Eight patients received neither chemotherapeutic regimens containing anthracyclin nor CY (Table 1).

Transplant Procedure

Busulfan (BU) plus CY (BU: 4 mg/kg/d, po, four days, CY: 60 mg/kg/d, iv, two days) conditioning regimen was applied to 22 patients. One patient received CVB (CY: 1500 mg/m^2/d, iv, four days, etoposide: 125 mg/m^2/d, iv, four days, BCNU: 600 mg/m^2/d, iv, one day) and one patient received BU plus melphalan (BU: 4 mg/kg/d, po, 4 days, melphalan: 120 mg/kg total, iv) regimens for conditioning. Cyclosporin-A plus short course methotrexate were used for graft versus host disease (GVHD) prophylaxis.

Allogeneic bone marrow transplantation (alloBMT) from a HLA-identical sibling donor was performed for 22 patients and two patients underwent autologous peripheral blood stem cell transplantation (PBSCT).

Cardiovascular follow-up

Before starting the transplant procedure, routine physical, laboratory and radiologic examinations were done for all patients. Twelve-lead ECG's of the patients were examined for arrhythmias, axis deviations, ischemia findings, ST segment and T wave changes and QT interval changes. Two-dimensional and M-mode echocardiography examinations were done for evaluating cardiac valves, ventricular movements and function and pericardium. Twenty-four-hour Holter monitoring was done before transplant and during stem cell infusion. In addition to daily physical examinations, the above mentioned cardiovascular examinations were repeated aproximately 45 days after the transplantation.

Statistical Analysis

The results were given as meantstandart deviation. Paired t test was used for the statistical analysis of echocardiographic findings, and Wilcoxon test was used for Holter results.

Table 2. Pre- and posttransplant ECG changes

	Disrythmia (n)	Voltage Changes (n)	Infarction (n)	ST segment Changes (n)	QT Prolong (n)	T wave Changes (n)
Pretrans.	1 (VT)	1 (VLH)	—	1 (V1 -3 elevation)	—	7
Posttrans.	1(VE)	1 (VLH)	—	1 (V1-3 depression)	—	7

Pretrans: pretransplant, Posttrans: posttransplant, VT: ventricular tachycardia,
VLH: voltage criteria of left ventricular hypertrophy, DEC: decreasing of voltage

Table 3. Holter monitoring at pretransplant period and during graft infusion

	Before BMT			During Graft Infusion		
Patient Number	SVE (n/h)	VE (n/h)	VT	SVE (n/h)	VE (n/h)	VT
1				0.50	—	
2	0.50	—	—	0.50	—	—
o						
o	1.20	3.00	+	—	—	+
4			(SHORT)			(LONG)
e						
6	0.50	6.00	+	2.00	14.10	+
7	2.12	88.00	—	2.10	51.30	—
8	0.90	—	—	—	—	—
9	10.00	25.60	—	—	47.30	+
10	3.00	—	—	8.10	2.05	—
11	3.00	1.50	—	3.00	1.00	—
12	1.00	—	—	3.10	—	—

SVE: supraventricular extrasystoles, VE: ventricular extrasystoles, n/h: number per hour, VT: ventricular tachycardia

RESULTS

Clinical Evaluation

Except for one patient with AML, there were no history or physical examination findings related to cardiovascular disorders for the patients in pretransplant period. This patient described an unconscious period lasting about 15 minutes; resembling syncope.

In the period beginning from the conditioning of the patients and lasting average 45 days in BMT unit, one patient had short term palpitation, one patient had hypotension (70/50 mmHg) and syncope attack, seven patients had hypertensive attacks (ma. 180/120 mmHg). The above mentioned patient with pretransplant syncope history, had also palpitation lasting 10 minutes with hypertension.

Roentgenologic Changes

Telecardiograms taken before transplantation had no findings indicating cardiovascular pathology. One patient was suspected to have pericardial effusion in his telecardicgram in postransplant period.

Electrocardiographic Changes

Pretransplant examinations of the patients' ECGs revealed nonsustained ventricular tachycardia in one patient (Table 2), voltage criteria for left ventricular hypertrophy and ST segment change in one patient, precordial T wave negativity in seven patients. There was no myocardial infarction findings or prolongation of QT interval in the patients' pre and posttransplant ECGs. Ventricular premature systoles occured in one patient's ECG, which was normal before transplantation, in posttransplant period. Left ventricular hypertrophy criteria and T wave negativity mentioned above persisted in posttransplant period. Low voltage and ST segment depression occured in one patient's ECG in posttransplant period.

Evaluation of Holter ECG

Holter ECG could be administered only to 12 patients. The significant findings were supraventricular extrasystoles (SVE), ventricular extrasystoles (VE) and ventricular tachycardia (VT). The Holter ECG findings are shown in Table 3. The mean number of SVE was 1.6±1.1/hour before transplantation and 3.1±2.6/h during marrow infusion ($p>0.05$). VE were not recorded in six patients. One patient's Holter records revealed 3 VE/h before transplantation and none during infusion. Another patient had no VE before transplantation and 2.05/h during transfusion. Four patients had mean 30.2±37.8 VE before transplantation and 28.4±24.7 during infusion ($p>0.05$). VT attacks lasting very short

periods of time were seen in two patients' records before and during infusion. One patient's records showed short VT attacks only before transplantation.

Echocardiographic Findings

Left ventricular wall movements, valve functions and pericardium were evaluated as normal for all patients before transplantation. After transplantation, three patients had minimal pericardial effusion, one patient had hypokinesia of anterior, inferior wall and interventricular septum and one patient had interventricular septal hypokinesia. Left ventricular fractional shortening was mean 35.56±2.83% before transplantation and 34.35±4.90% after transplantation ($p>0.05$).

DISCUSSION

The cardiac histopathologic examination of 29 cases who had been treated with BMT (24 allogeneic, two syngeneic, two autologous, one maternal) revealed similar changes to those that seen in patients with hematologic diseases not treated with BMT. They consisted of cardiomegaly, cardiac atrophy, hemorrhage, foci of necrosis due to shock associated with sepsis or hepatic failure, myocardial abscesses secondary to systemic candidiasis or staphylococcal infection, fibrinous pericarditis, and hemosiderosis (7). Some of these patients had more specific cardiac changes which might be attributable to the transplant procedure; interstitial reactive changes which were probably mediated by immune mechanisms and myocardial damage with features of acute severe injury which might be induced by high dose cyclophosphamide. The cardiac effects of high dose CY have been investigated in many studies. In one of them two patients whose ECGs were normal prior to receiving CY at a total dose of 168 mg/kg and 144 mg/kg respectively for alloBMT, developed decreasing of voltage and ST-T changes (1). In the clinical setting, one patient died of congestive heart failure, the other patient developed tamponade. Histopathological examination revealed thickened left ventricles and intramyocardial hemorrhage. Another study which examined 32 patients with hematologic malignities who were given 180 mg/kg CY over four days showed declining left ventricular systolic function, decreasing of ECG volage with or without pericardial effusion, congestive heart failure (28%; 19% died) and pericardial tamponade (19%) (2). Pathologic examination showed endothelial injury and a hemorrhagic myopericarditis.

In Cazin et al study, 63 patients who underwent BMT (57 autologous, 6 allogeneic), were investigated for cardiac complications (8). Cardiomyopathies, pericarditis, arrhythmias and heart failure were found and the mortality was 9%. Especially the regimens which contained CY were accused for the cardiac toxicity and it was concluded that radiotherapy and anthracyclines play a secondary role. In the same study, reversible subclinic cardiac abnormalities were seen in routine echocardiographic examinations. Clinically significant cardiac involvement found in 5-10% of 45 patients who underwent alloBMT after conditioning with CY and TBI in Kupari et al's study (9). Clinical and laboratory examinations of these patients revealed ST-T changes in 15 patients with or without arrhythmias (two patients with VE, one with paroxysmal atrial fibrillation, one with repeated supraventricular tachycardia and one with QT prolongation with ventricular tachyarrhythmias), decreasing of the total QRS voltage sum (12 patients) and congestive heart failure. Autopsy (15 of the 20 patients who died during the first posttransplant year) findings were myocardial edema, fibrosis, cellular hypertrophy and in two patients marantic endocarditis of the aortic valve. Retrospective analysis of 30 pediatric patients who underwent BMT (20 allogeneic, 10 autologous) after conditioning with different regimens revealed that acute and late cardiotoxicity may occur after BMT (10). Irradiation, CY and melphalan containing regimens seemed particularly cardiotoxic while high-dose Ara-C was well tolerated. Cardiac tamponade was seen after alloBMT in an 11-year-old boy with thalassemia major (11). In that case, conditioning regimen consisted of busulfan and CY. In our patients, hypertension was more common than hypotension (29% and 4% respectively). Low voltage occured in only one patient after transplantation (4%). Hypokinesia which might be accepted as a sign of myocardial injury was seen in two patients (8%). Pericardial effusion which is an expected side effect of high dose CY was seen minimally in three patients (13%).

Most of the autologous transplants were performed with cyropreservation of hematopoietic stem cell containing material (buffy-coat cells of BM, peripheral blood stem cells, cord blood, etc.) in 10% dimethylsulfoxide (DMSO) with or without other cryoprotectants and storing them in liquid nitrogen. Ex vivo BM processing like erythrocyte depletion, T-cell depletion, and purging may apply sometimes. Intravenous infusion of this cryopreserved material after thawing may be accompanied with different adverse effects which were attributable to hypothermia, cell lysis, preservative material, remnants of prior BM processing, in vivo leukoagglutination of leukocytes present in the graft, etc. In addition to symptoms like nausea, abdominal cramping, flushing, renal failure, different allergic reactions, hemolytic reactions and respiratory changes; cardiac symptoms have also been reported. Arrhythmias (especially bradycardias), heart blocks, and increased or decreased blood pressure are the most common (4,5). Styler et al found that there was an increased incidence of heart blocks in the patients who faced the exposure of CY and vinca alkaloids much more (5). Bradyarrhythmias have been attributed to the stimulation of carotic or aortic baroreceptors or atrial stretch receptors by bolus mar-

row infusion, effects of cell lysis products, negative chronotropic and histamine releasing effects of DMSO, local hypothermia. Although all these complications related to the infusion of cryopreserved bone marrow are rarely life-threatening, severe events like cardiac arrest have been reported (3). In a recent study, it was concluded that, increasing infusion time of cryopreserved material, using a standart transfusion filter and diureticts, might reduce toxicities associated with the infusion of cryopreserved grafts (12). They observed ventricular ectopic beats more than atrial ectopic beats in autologous BMT patients after graft infusion. In our patients, SVE was seen more during infusion (although it was not statistically significant). Bradyarrhythmias were not seen and this may be related to the fact that majority of our patients underwent alloBMT. Deaths connected with cardiotoxicity of transplant procedure were not observed in these patients.

We experienced an endocarditis with large vegetation on the mitral valve and peripheral embolism in the posttransplant period of the acute myeloblastic leukemia patient who underwent alloBMT (13). Although she had serious clinical problems except this, she improved completely after mitral valve replacement Patchell et al reported nonbacterial thrombotic endocarditis whose antemortem diagnosis is very difficult in many cases, with higher prevalence (7.7%) in BMT patients comparing with other autopsies (1.9%) (6). Isolated relapse in pericardium of the AML patient who underwent alloBMT was seen 11 months after the transplant (14).

Broad spectrum of cardiologic complications may be seen after BMT. Many of them may be life-threatening, although we did not face such events. Cardiac examination and monitorization should be done seriously in BMT patients. Besides well known effects of cytotoxic agents, infections, and some cytoprotective chemicals, the effects of the features which are more specific to the transplant procedure (such as tissue invasiveness of the graft and immunologic interaction between the graft and the host) should particularly be investigated.

Kemik iliği transplantasyonu uygulanan hastaların kardiyolojîk değerlendirilmesi

Kemik iliği transplantasyonu (KİT) işlemi kardiyolojîk yan etkiler oluşturabilir. Bunların çoğu hazırlama rejimleri ile ilişkilidir. Graft infüzyonu, özellikle bazı koruyucu ajanlarla karışım halinde olması durumunda, bazı kardiyopulmoner bozukluklara yol açabilir. Transplant sonrası dönemde görülen infeksiyonlar ve immünolojik olaylar da kalpte zedelenmeye sebep olabilirler. Bu çalışmada, kemik iliği transplantasyonu uygulanan 24 hastanın (22 allojeneik, iki otolog) kardiyak bulguları izlenmiştir. Rutin fizik ve laboratuvar incelemeler dışında, transplantasyon öncesi ve sonrası telekardiyogramlar, elektrokardiyogramlar ile iki boyutlu ve M-mode ekokardiyografik incelemeler yapılmıştır. Stem hücre infüzyonu öncesinde ve infüzyon sırasında Holter tekniğiyle sürekli kardiyak monitorizasyon gerçekleştirilmiştir. Bir hastada (%4) düşük voltaj, iki hastada (%8) hipokinezi ve üç hastada (%13) minimal perikardiyal effüzyon gözlenmiştir. Graft infüzyonu sırasında supraventriküler ekstrasıstoller daha sık iken (p>0.05) bradiaritmiler görülmemiştir. Hastalarımızda kardiyak komplikasyonlara bağlı ölüm görülmemiştir. Bu sonuçlar; (1) KİT uygulanacak hastaların kardiyak hastalıklar yönünden incelenmesi ve izlenmesi gerekliliğini, (2) bu tedbirler alındığında KİT'na bağlı kardiyak komplikasyonların işlemin başarısını sınırlandırmayacağını vurgulamaktadır. [TurkJ Med Res 1995; 13(2): 50-54]

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