



Successful Allogeneic Hematopoietic Stem Cells Transplantation with Treosulfan-based Conditioning Despite Advanced Heart Insufficiency

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Abstract

We report a case of a 47-year old patient with intermediate risk Acute Myeloblastic Leukemia (AML) in first remission with positive minimal residual disease and heart insufficiency due to dilated cardiomyopathy with low (35% to 38%) Left Ventricular Ejection Fraction (LVEF), who was treated with allogeneic Hematopoietic Stem Cells Transplantation (HSCT) from HLA-matched sibling-donor following treosulfan-based myeloablative conditioning. Heart function did not worsen following conditioning and transplantation. Patient is alive over 8 years post-transplant, with stable full donor's chimerism, no evidence of GVHD and slightly improved heart function. Our report proves that HSCT can be successfully performed in patients with low LVEF.

Keywords: Allogeneic; Hematopoietic stem cells transplantation; Heart insufficiency; Left ventricular ejection fraction; Treosulfan

Introduction

Patients with poor cardiac contractility usually are not regarded as candidates for intensive chemotherapy and allogeneic Hematopoietic Stem Cells Transplantation (HSCT), as it may adversely impact cardiac function. Risks related to heart disease should be carefully weighed against benefits of transplantation in patients with acute leukemia and increased risk of relapse. Despite the growing number of elderly and co-morbid patients undergoing HSCT, a lack of data regarding the safety and effectiveness of HSCT in patients with poor cardiac function remains.

Material and Methods

We report allogeneic HSCT performed in 47 years old male patient with AML with normal karyotype in first Complete Remission (CR) with positive Minimal Residual Disease (MRD) and advanced cardiomyopathy. Time from diagnosis to HSCT was 10 months. Initial induction chemotherapy with Daunorubicin and Ara-C (3+7) was not effective, CR was achieved after CLAM reinduction therapy and was followed by 2 consolidation courses of HD Ara-C +/ Cladribine. Pre-transplant patient had CR with positive MRD (0.119%). Echocardiography revealed low (30% to 38%) Left Ventricular Ejection Fraction (LVEF), hypokinesis of apical, interventricular septum, bottom and front walls segments, mitral valve grade 3 and tricuspid valve grade 1 regurgitation. Consulting cardiologist advised to prolong all intravenous infusions of iv fluids (500 ml given at least during 3 hr to 4 hr, equaling 30 to 40 drops per minute). Although the European Group for Blood and Marrow Transplantation (EBMT) transplantation-related risk score was low (2), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) and age-adjusted HCT-CI scores were high (8 and 9, respectively).

The donor was 41 years old brother compatible in HLA-A, B, C, DR antigens in low resolution typing and in major blood groups and Rh antigens. The myeloablative conditioning was individually tailored and consisted of treosulfan 10 mg/m²/d in days -6 to -3 and fludarabine 25 mg/m²/d in days -5 to -2. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A 3 mg/kg/d from day -1 and methotrexate 15 mg/m² in day +1 and 10 mg/m² in days +3 and +13. Transplanted bone marrow in the total volume of 1995 ml contained 2.38 x 10⁸ nucleated cells/kg, 1.87 x 10⁶ CD34⁺ cells/kg and 1.13 x 10⁷ CD3⁺ cells/kg.

Results

During the transplantation patient experienced elevated arterial blood pressure (with maximum

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146/100 mmHg) and complained on fatigue. Severe chest pain in the retrosternal region and palpitations were observed during apnea, control electrocardiogram examinations did not reveal any changes. Agranulocytosis lasted for 19 days, granulocytes 1.0 G/l and absolute neutrophils count 0.5 G/l have been achieved on day +22, platelets counts 20 and 50 G/l on days +14 and +19. CR with positive MRD (0.413%) and mixed 98% donor's chimerism (by short tandem repeat method) were assessed in the bone marrow on day +24 following HSCT. During tapering of CsA due to MRD positivity, discrete symptoms of acute GVHD grade 1 were transiently present in skin. At 3 months following HSCT donor's chimerism increased to 99%, MRD was still positive (0.2%), thus the immunosuppression was withdrawn completely and patient received three Donor Lymphocyte Infusions, at 5, 6 and 7 months following HSCT, each with 1×10^7 CD3⁺ cells/kg, what led to achievement of full donor's chimerism at 1 year. At 5 years, LVEF was 46%, left atrium and left ventricle distention and mild mitral regurgitation were present, and NYHA was assessed as III due to cardiomyopathy. In the recent examination performed at 7.5 years posttransplant LVEF was 50% and ultrasonographic abnormalities were same as previously. Currently, over 8 years from HSCT, patient has full donor's chimerism, no symptoms of GVHD, without need of hematological treatment and with stable cardiac function.

Discussion

An ejection fraction <50%, as measured by two-dimensional echocardiography, and prior history of congestive heart failure, are significant independent correlates of clinical cardiotoxicities [1]. Although a high risk of HSCT regimen-related toxicity limits this potentially curative treatment to patients with LVEF of $\geq 50\%$, few reports indicate, that selected patients with a LVEF of $\leq 45\%$ can safely receive HSCT without a significant increase of cardiac toxicity or non-relapse mortality [2]. Evaluation of patients with significantly lower LVEF before transplantation due to previous use of anthracyclines (with minimum 39%), showed no increased risk of decline in cardiac function, what led to the conclusion, that HSCT procedure did not seem to affect myocardial function 1-7 months after transplantation [3]. Autologous transplants were performed without cardiac adverse events in patients with mucopolysaccharidosis and severe left ventricular dysfunction (LVEF 25%) at diagnosis, which improved after enzyme replacement therapy prior to HSCT, but their LVEF at transplant was still decreased (39% to 45%) [4]. The systolic function may even increase in patients with a reduced pre-HSCT EF <47% [5]. The presence of at least 1 of the 7 pre-transplant cardiac risk factors (past history of smoking, hypertension, hyperlipidemia, coronary artery disease, arrhythmia, prior myocardial infarction, and congestive heart failure) was associated with a higher cardiac complication rate in patients with a reduced LVEF [2]. Reduced EF may predispose patients to cardiotoxic events, however, this was

restricted to minor cardiac events, while life-threatening cardiac toxicity was not significantly increased in patients with pathologic results before HSCT. Moreover, none of the patients with an EF less than 50% developed cardiac toxicity [6].

The design of conditioning treatment was considered after the following factors were taken into account: 1.) reduced renal clearance of treosulfan and higher systemic exposure due to cardiac deficit, as about 30% of treosulfan dose is eliminated via kidneys within 12 hrs of administration, 2.) the need to control the infusion volumes used for solution of treosulfan, and 3.) appropriate dosing level required for treatment of AML with positive MRD. In the presented case low initial LVEF not only did not worsen during or after the conditioning treatment, but it gradually improved posttransplant.

Our report shows, that successful allogeneic hematopoietic cells transplantation can be safely performed with treosulfan-based myeloablative conditioning in patient with heart insufficiency. Decision whether to transplant and conditioning treatment modification in patient not fulfilling generally accepted qualification criteria due to low LVEF should be individually considered and balanced against potential risks of the disease [7].

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