Transfusion and Apheresis Science 50 (2014) 46–52

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Assessment and comparison of acute cardiac toxicity during high-dose cyclophosphamide and high-dose etoposide stem cell mobilization regimens with N-terminal pro-B-type natriuretic peptide

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 19 November 2013
Accepted 2 December 2013

Keywords:
Cardiac toxicity
Natriuretic peptide
Cyclophosphamide
Etoposide
Mobilization chemotherapy

ABSTRACT

This study was undertaken to prospectively evaluate and compare the acute effect of high-dose (HD), cyclophosphamide (CY) and HD etoposide (ET) on cardiac function assessed by plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients undergoing stem-cell mobilization. NT-proBNP was measured at baseline and 6 h after completion of mobilization chemotherapy (MC) in 58 patients. Of 58 patients, 33 received HD CY, and 25 received HD ET. The mean baseline NT-proBNP values were similar between the CY and ET group (119.5 vs 149, respectively, $p > 0.05$). NT-proBNP levels were increased in almost all patients, except 2 from CY group. A significant difference between NT-proBNP concentrations at baseline and 6 h after completion of MC was observed in both groups ($p < 0.001$). The value of changes in NT-proBNP was more significant in the ET group. The changes in NT-proBNP according to the MC regimens were analyzed and a cut-off value of 422 pg/ml was determined. Based on this cut-off value, only the type of MC was significantly correlated with the chances in NT-proBNP concentrations. Receiving HD ET as a MC was found to be 5.25 times more cardiotoxic compared to the HD CY. Congestive heart failure was seen in 3 (5.2%) patients. Our results suggest that stem cell mobilization with HD CY and HD ET cause acute cardiac toxicity mediated by neurohumoral activation, which was detected by the increases in cardiac biomarker NT-proBNP, and as a matter of fact cardiotoxicity of HD ET seems to be more potent than those exhibited by HD CY.

1. Introduction

Despite the development of new and effective agents, high-dose (HD) chemotherapy supported by autologous hematopoietic stem-cell transplantation (HSCT) remains an important treatment modality for the management of patients with plasma cell myeloma (PCM) and lymphoma (non-Hodgkin's lymphoma and Hodgkin's lymphoma) [1–3]. Treatment intensification, however, inevitably leads to higher rates of treatment-related side effects. The incidence of clinically significant cardiotoxicity has been estimated between 5% and 10% of patients undergoing autologous or allogeneic HSCT (4). Cardiovascular events after HSCT are primarily associated with the use of HD cyclophosphamide (CY) in the mobilization and/or conditioning regimen [5–8].

Etoposide (ET) is another effective mobilizing agent getting more popular in recent years in autologous HSCT era with a few potential side effects like the development of therapy-related myelodysplasia and acute myeloid

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http://dx.doi.org/10.1016/j.transci.2013.12.001

leukemia [9,10]. Although, ET is generally not regarded as drugs frequently causing heart damage, unlike the well-known cardiotoxicity of HD CY, the potential for HD ET-induced cardiotoxicity remains obscure.

Left ventricular ejection fraction (LVEF), assessed by echocardiogram, is the most commonly used parameter to evaluate LV function in cancer patients undergoing chemotherapy. However, LVEF measurements are not sensitive enough for the early detection of pre-clinical cardiac disease [11]. Brain natriuretic peptide (BNP) is a natriuretic hormone initially identified in the brain but subsequently found to be a predominantly a cardiac hormone [12–13]. Cleavage of the prohormone proBNP produces biologically active 32 aminoacid BNP as well as biologically inert 76 aminoacid N-terminal pro-BNP (NT-proBNP). Natriuretic peptides have diuretic, natriuretic and hypotensive effects. They also inhibit the renin-angiotensin system, endothelin secretion, and systemic and renal sympathetic activity [14]. They are predictors of the development of the heart failure, as well as other cardiovascular events, in asymptomatic patients without congestive heart failure (CHF) [15]. Natriuretic peptide measurements have been used to monitor cardiotoxicity during and after HSCT [16–19]. This approach is minimally invasive, cheaper than echocardiogram and easily repeated. So far, there are no studies using NT-proBNP to evaluate ET – related acute cardiotoxicity given as a mobilization regimen for autologous HSCT in the literature.

This study was undertaken to prospectively evaluate and compare the acute effect of HD CY and HD ET on cardiac function assessed by plasma NT-proBNP in patients with lymphoma and MM undergoing stem-cell mobilization for autologous HSCT.

2. Materials and methods

2.1. Patients

This prospective single center study involved 75 consecutive adult patients with hematological malignancies who underwent mobilization chemotherapy (MC) either with HD CY or HD ET for HD conditioning chemotherapy with autologous HSCT.

Study eligibility criteria were Eastern Cooperative Oncology Group performance status score <2, left ventricular ejection fraction >45%, adequate hepatic function (serum bilirubin <2 mg/ml and transaminases <3 times normal) and adequate pulmonary function (vital capacity or carbon monoxide diffusing capacity >50% of predicted). Patients were required to have glomerular filtration rate >30 ml/min. All patients underwent pretransplant cardiac evaluation including echocardiogram and electrocardiogram. No case with cardiac or cardiovascular disease was observed except for two patients with heart valve disease and one patient with cardiac amyloidosis. All patients had LVEF >45%. The cumulative dose of anthracyclines (idarubucine, dounarubucin, mitoxantrone and epirubicin) was calculated as the equivalent dose of doxorubucine. Patients had earlier received anthracyclines with a median cumulative dose 40.5 mg/m^2 (range, 0–600 mg/m^2). None of the MM or lymphoma patients had extramedullary plasmocytoma involving chest or mediastinal mass that would require treatment by thoracic irradiation of the chest. At the time of the MC, none of the patients had suffered from infections. Post-mobilization cardiac failure was diagnosed based on clinical symptoms (fluid retention, dyspnea and orthopnea), and findings (peripheral edema, increased jugular venous pressure, sinus tachycardia) and supported by chest X-ray or a beneficial response to therapy for heart failure.

A total of 17 patients were excluded from the study, due to inappropriate blood draw for measuring NT-proBNP levels (not on time or lack of blood draw) after the first or second blood draw in 13 patients and the low glomerular filtration rate in 4 patients. Therefore, the statistical analyses in this study were restricted to 58 patients. The diagnosis was PCM in 38 patients and lymphomas (non-Hodgkin's and Hodgkin's lymphoma) in 20 patients. The patients consisted of 40 males and 18 females with a median age of 54 years (range, 19–72 years). Median previous treatment number is 2 (range, 1–5), consists of different chemotherapy regimens for the treatment of underlying malignancies. Clinical characteristics of the patients are shown in Table 1.

The study protocol was approved by the ethics committee of the local hospital, and written informed consent according to institution rules was obtained from each patient before the study.

2.2. Mobilization chemotherapy

Of 58 patients, 33 received HD CY and 25 received HD ET as MC for auto-HSCT. The CY was given as 2 h infusion with a dose 2 g/m^2 on 2 consecutive days in combination with mesna with a dose 2 g/m^2. The ET was given as 24 h infusion with a dose of 1.6 g/m^2. Intensive hydration therapy (>4 l/day) with diuretics was administered on 2 consecutive days together with MC in both group of patients. G-CSF was commenced 24 h after the last dose of chemotherapy and continued to the end of peripheral stem cell collection.

2.3. Measurement of N-terminal proBNP values

Plasma NT-proBNP values (normal range, <125 pg/ml) was measured once just before high dose MC administration and at 6 h after completion of MC. Blood samples were taken from peripheral vein after a 10-min bed rest. NT-proBNP concentrations were measured immediately by electrochemiluminescence immunoassay on Pathfast analyzer (Mitsubishi, Japan). Physicians in charge of patients were not blinded for the results.

2.4. Statistical analysis

Statistical analyses were performed with the statistical package SPSS for Windows version 20.0 and Medcalc 11.1.0.0. The distribution of variables was checked initially by Shapiro Wilk's test. Parametric tests were applied to data having normal distribution, whereas non-parametric tests were applied to data having non-normal distribution. Independent samples t test, Mann–Whitney U test and Kolmogorov Smirnov test were applied to determine the