DOI: 10.46765/2675-374X.2023V4N2P192

CARDIOTOXICITY AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT): LONGITUDINAL AND OBSERVATIONAL STUDY

Katia Regina Lopes Alves[1,3,5]; Kelli Borges dos Santos[1,4,6]; Ângelo Atalla[1,3,7]; Paulla Rayane Chaves Utsch[2,3,8]; Abrahao Elias Hallack Neto[1,3]

1 Professor at Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil; 2 Master's student Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil; 3 Physician at the university hospital, Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil; 4 Nurse at the university hospital, Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil; 5 Master's degree from the Federal University of Juiz de Fora; 6 PhD from the Federal University of Juiz de Fora; 7 PhD from the Federal University of Rio de Janeiro; 8 Medical residency at the University Hospital of Juiz de Fora;

Corresponding author: Kátia Regina Lopes Alves katiaalopes@yahoo.com.br - ORCID: 0000-0002-1797-6312

Received: 21 Dec 2022 • Revised: 16 May 2023 • Accepted: 24 May 2023.

ABSTRACT

Objectives: To assess incidence and extent of early cardiotoxicity after autologous hematopoietic stem cell transplantation (AHSCT). **Methods**: Study carried out in two bone marrow transplant centers, in public and private hospital, located in interior of Minas Gerais, Brazil. All patients who underwent AHSCT at centers between March 2018 and May 2019 and October 2019 were included. Altered results were classified according to Brazilian Cardio-Oncology Guidelines. **Results**: Of the 36 patients evaluated, seven (21.2%) had cardiotoxicity on echocardiography, with mean left ventricular ejection fraction decreasing from 71.53 to 64.75% before and after conditioning (p = 0.00013). Clinical cardiovascular alterations were associated with advanced staging and time of more than one year between diagnosis and AHSCT (p=0.01 in both cases). Specific clinical signs of congestion were correlated with radiotherapy to the mediastinum and a dose >400 mg of doxorubicin before AHSCT (p=0.02 and p=0.01, respectively). **Conclusions**: Thus, higher incidence of cardiac injury was observed after AHSCT, which was related to type of pre-transplant therapy. This fact reflects our limitations and leads us to seek improvements in cardiovascular assessment of patients undergoing AHSCT, in order to reduce morbidity and mortality associated with myocardial injuries in these patients.

Keywords: Cardiotoxicity. Risk factors. Hematopoietic Stem Cell Transplantation.

INTRODUCTION

We are currently experiencing longer survival of cancer patients, which is due to advances in cancer therapy and adequate clinical support for patients[1]. Despite this, complications still occur, especially in post-HSCT patients due to intensive chemotherapy[2], such as high-dose cyclophosphamide and total body irradiation, in addition to pre-HSCT therapeutic exposure, which often includes anthracyclines, alkylating agents, and cardiac radiotherapy[3,4,5]. Other risk factors for cardiac damage independent of cancer therapy include advanced age, smoking, systemic arterial hypertension (SAH), and obesity[4].

Congestive heart failure (CHF) is one of the most serious and common adverse effects following chemotherapy and may occur in the immediate post-transplant period or months later[6]. High rates of morbidity and mortality associated with this complication have been described and may even lead to the need to interrupt treatment and compromise proper disease control[6,7].

Considering that the detection of cardiovascular risk in the subclinical phase is necessary to prevent morbidity and mortality in these patients, our study aimed to evaluate the incidence and extent of cardiotoxicity in the early phase after AHSCT with echocardiographic examination and troponin I (TnI) determination. We focused on detecting clinical signs of cardiotoxicity during hospitalization and associated these signs with prior cardiovascular risk factors unrelated to chemotherapy.

MATERIAL AND METHODS

After ethics and research committee approval and patient consent to participate in the study, all patients who underwent AHSCT at two bone marrow transplant centers from March 2018 to May 2019 and October 2019 were included and evaluated. Patients with insufficient information were excluded.

Echocardiograms (Echo) were performed using the one-dimensional method corrected by the Teicholz formula, using the two-dimensional technique before the start of conditioning chemotherapy and thirty to sixty days after chemotherapy. For the definition of cardiotoxicity, a reduction in left ventricular ejection fraction (LVEF) of more than 10% was considered according to the criteria of Brazilian Guidelines on Cardio-Oncology, described below[7]:

- **Grade I:** asymptomatic reduction of LVEF between 10% and 20%.
- **Grade II:** LVEF reduction greater than 20% or below normal (LVEF: 50%).
- **Grade III:** symptomatic heart failure

Laboratory dosing of TnI was performed before conditioning chemotherapy, during the period of neutropenia (neutrophils less than 500 mm^3) and 30 days after the conditioning protocol. An increase in TnI levels above the normal range was considered a sign of cardiotoxicity. The methods used to detect TnI were immunochromatography and chemiluminescence.

To analyze the deterioration of cardiac output based on LVEF in echocardiography, the Shapiro-Wilk test was used to test normality, followed by the non-parametric Wilcoxon test and the parametric Paired T-test.

To describe the profile of the sample, frequency tables were constructed and the Fisher's test was used to assess the association between the risk factor variables and the outcome. Outcome variables included the difference between LVEF before and after AHSCT, arterial hypertension, hypotension, signs of congestion, and clinical changes in the cardiovascular system after AHSCT.

Correlation analysis was performed between the presence of grade I and II cardiotoxicity on the echocardiogram and changes on physical examination suggestive of cardiac congestion and several risk factors independent of or related to cancer therapy, including: age, obesity, smoking, concomitant cardiovascular disease, cancer diagnosis, advanced staging, previous chemotherapy with cyclophosphamide and doxorubicin, mediastinal radiotherapy, lack of complete response before AHSCT, cardiovascular complications during cancer treatment, mobilization for stem cell collection with cyclophosphamide, cellularity of progenitor cells with CD34 labeling, time between diagnosis and AHSCT, and conditioning protocol for AHSCT with high-dose cyclophosphamide.

R Core Team software (2018) was used for statistical analysis, assuming a significance level of 5% ($p \leq 0.05$).

RESULTS

Thirty-six patients who underwent AHSCT during the study period were evaluated. The mean age was 49.9 years (23 - 69 years), and most patients were female (52.7%). Some clinical characteristics of the disease and treatment are described in Table 1.

On physical examination during hospitalization for AHSCT, clinical changes related to the cardiovascular system, such as tachycardia, hypertension, hypotension, edema, and lung sounds, occurred in 86% (n = 31) of patients after conditioning chemotherapy. Thirty-one percent (n = 11) of patients had more specific signs of congestion.

A significant association was found between cardiovascular changes with advanced staging and time between diagnosis and transplantation ($p = 0.01$ and $p = 0.01$, respectively). There was a trend toward greater development of clinical changes in the cardiovascular system in patients who underwent chemotherapy protocols containing anthracyclines and/or alkylating agents prior to AHSCT ($p = 0.08$).

The clinical changes more specifically related to signs of congestion, such as third heart sound, progressive lower limb edema, pulmonary crackles and jugular turgence, showed a significant correlation with radiotherapy in an area involving the heart ($p = 0.02$) and use of doxorubicin in a dose greater than 400mg pre-AHSCT ($p = 0.01$).

Thirty-three patients underwent echo before and 30 to 60 days after AHSCT, of whom 7 (21.2%) had cardiotoxicity on examination, 4 with grade I cardiotoxicity and 3 with grade II. The corrected LVEF values observed in echocardiogram examinations before AHSCT and 30 to 60 days after this treatment were recorded and the difference between these values was then calculated. At the second examination, there was a decrease, maintenance, or increase in LVEF compared with the first examination, and the 10 patients who had an increase in LVEF were excluded from the analysis. A significant difference between the mean echo values before and after conditioning was detected by the paired t-test ($p = 0.00013$) under the normality assumption, with 71.53±6.67% and 64.75±7.65% for the echo values before and after conditioning, respectively (Figure 1).

Twenty-one patients (56.7%) underwent TnI examination before AHSCT, at nadir time after conditioning chemotherapy and 30 days after treatment. Of these, only one patient had an abnormality on examination at the time of neutropenia associated with high-grade atrial fibrillation with hemodynamic instability, and one patient had a positive test 30 days after transplantation. Neither event was associated with early change in LVEF on echo after AHSCT.

DISCUSSION

The cardiotoxicity of chemotherapeutic agents has gained importance as these treatments improve survival in cancer patients. Cardiovascular symptoms associated with alkylating agents usually occur within the first week and month of therapy[9,10]. In accordance to the literature, we found signs of early cardiotoxicity, approximately 4 to 6 weeks after AHSCT[9].

Regarding clinical findings of cardiotoxicity, we found more signs of congestion in patients who had taken doxorubicin at a dose greater than 400 mg prior to AHSCT ($p = 0.01$) and also in those who had undergone radiotherapy to an area that included the heart ($p = 0.02$). Advanced staging and a time between diagnosis and AHSCT of more than 1 year also showed a correlation with clinical signs related to the cardiovascular system ($p = 0.01$ and $p = 0.01$, respectively), probably because these patients received a greater number of cycles and lines of therapy and consequently a higher dose of treatment with cardiotoxic potential.

Although it has been described that atrial fibrillation can be caused by the use of melphalan,[11] we believe that this was not the only reason for the arrhythmia in the only patient in our series who had such an arrhythmia, since it occurred after a stem cell infusion in which dimethyl sulfoxide (DMSO) was used as a cryopreservative, which also has arrhythmogenic potential.

Echocardiography and troponin measurement are methods that can help detect cardiotoxicity in AHSCT[12]. Chung et al.[9] studied 39 patients undergoing AHSCT and observed a decrease in LVEF in 31% (n=10) of them, a value very similar to our study, in which signs of cardiotoxicity, assessed by echo, were found in 21.2% (n=7) of the sample of 36 patients. A tendency to cardiotoxicity was observed in patients who had received chemotherapy with anthracyclines or alkylating agents prior to AHSCT (p=0.09), which has also been demonstrated in previous studies[1,11].

Similar to Morandi et al., we did not find an association between the use of high-dose alkylating agents used in AHSCT and cardiac dysfunction, in contrast to studies from the 1970s and 1980s in which combined therapy regimens with cyclophosphamide resulted in an incidence of up to 43% cardiotoxicity, which was due to the use of high-dose cyclophosphamide (up to 7 g/m^2) in a non-fractionated administration regimen[11].

All patients who had grade II toxicity in echo (n=3) underwent AHSCT more than 1 year after diagnosis. This indicates that the likelihood of cardiotoxicity is related to the greater number of prior therapies (p=0.06), consistent with the literature in which left ventricular dysfunction has been associated with three or more lines of chemotherapy prior to AHSCT[13].

Chung et al. demonstrated a reduction in mean LVEF from 62% at baseline to 55% at 6 weeks after conditioning chemotherapy and transplantation,[9] which is very similar to our results regarding reduction in LVEF.

Of the 21 patients who underwent TnI testing, only two showed changes in test results within 30 days of high-dose chemotherapy. This is likely due to the lack of standardization of diagnostic tests and better determination between monitoring intervals, which is not yet well defined in the literature[8].

The occurrence of cardiotoxicity does not appear to be related to high-dose conditioning chemotherapy but rather to therapeutic exposure prior to AHSCT, with exposure to anthracyclines and alkylating agents being independent risk factors for CHF.

Therefore, identification of patients at increased cardiovascular risk through surveillance measures allows implementation of early treatment.

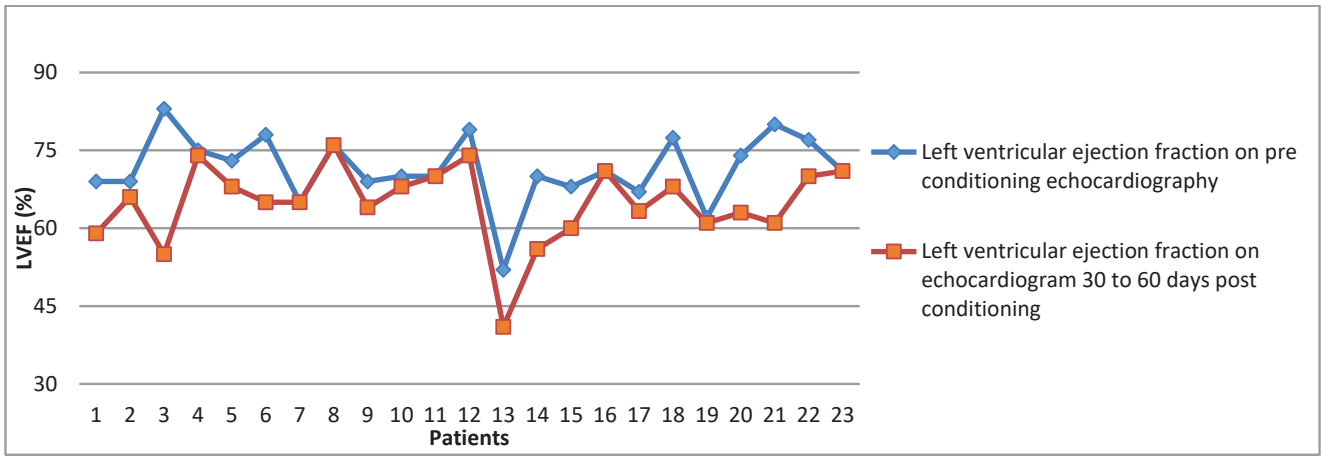
Real-life studies, such as ours, are the best way to represent the population we typically deal with in our daily clinical practice[14]. However, prospective studies with a larger number of patients and standardized tests are needed to detect signs of cardiac dysfunction that are still in the subclinical phase or when cardiac injury is not yet irreversible. The analysis of this study will allow us to propose ways to improve the cardiovascular assessment of patients undergoing AHSCT and consequently reduce cardiac toxicity in our setting.

TABLE 1. Population characteristics and clinical alterations in the cardiovascular system after autologous hematopoietic stem cell transplantation.

	Clinical changes of the cardiovascular system after conditioning chemotherapy		
	Yes N (%)	No N (%)	P value
Advanced stage of disease			
Yes	22 (71.0)	0 (0.0)	0.01366
No	9 (29.0)	4 (100.0)	
Pre-transplant chemotherapy including anthracycline or alkylating agents			
Yes	29 (93.5)	3 (60.0)	0.08429
No	2 (6.5)	2 (40.0)	
Time lapse between diagnosis and transplant			
≤365 days	6 (19.4)	4 (80.0)	0.01515
>365 days	25 (80.6)	1 (20.0)	

Chi-squared test.

FIGURE 1 Echocardiograms performed pre and post conditioning



REFERENCES

1. Alexandre J, Cautela J, Ederhy S, et al. Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. J Am Heart Assoc. 2020;9(18):e018403.

2. Gavriilaki E, Gkaliagkousi E, Sakellari I, et al. Early prediction of cardiovascular risk after hematopoietic cell transplantation: are we there yet? Biol Blood Marrow Transplant 2019;25(10):e310-6.

3. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977-1997. Bone Marrow Transplant. 2001;28(3):283-7.

4. Chow EJ, Wong K, Lee SJ, et al. Late cardiovascular complications after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2014;20(6):794-800.

5. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation. 2013;128(17):1927-95.

6. Armenian SH, Sun CL, Francisco L, et al. Late congestive heart failure after hematopoietic cell transplantation. J Clin Oncol. 2008;26(34):5537-43.

7. Kalil R Filho, Hajjar LA, Bacal F, et al. I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2011;96(suppl 2):1-52.

8. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000;36(2):517-22.

9. Chung T, Lim WC, Sy R, et al. Subacute cardiac toxicity following autologous haematopoietic stem cell transplantation in patients with normal cardiac function. Heart. 2008;94(7):911-8.

10. Ghafoor S, James M, Goldberg J, et al. Cardiac dysfunction in hematology oncology and hematopoietic cell transplant patients. In: Duncan CN, Talano JA, McArthur JA, eds. Critical Care of the Pediatric Immunocompromised Hematology/ Oncology Patient. New York: Springer; 2019:211-235.

11. Morandi P, Ruffini PA, Benvenuto GM, et al. Cardiac toxicity of high-dose chemotherapy. Bone Marrow Transplant. 2005;35(4):323-34.

12. Hajjar LA, Costa IB, Lopes MA, et al. Diretriz Brasileira de Cardio-oncologia – 2020. Arq Bras Cardiol. 2020;115(5):1006-1043

13. Murbraech K, Smeland KB, Holte H, et al. Heart failure and asymptomatic left ventricular systolic dysfunction in lymphoma survivors treated with autologous stem-cell transplantation: a national cross-sectional study. J Clin Oncol. 2015;33(24):2683-91.

14. Harari S. Randomised controlled trials and real-life studies: two answers for one question. Eur Respir Rev. 2018; 27(149):180080.