

Ventricular Dysfunction and Heart Failure in Patients Undergoing Hematopoietic Stem Cell Transplant

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It has been known for a long time that Cyclophosphamide (Cy) for conditioning regimens in hematopoietic stem cell transplant (HSCT) can induce cardiotoxicity.¹ We have been learning in cardio-oncology that the best practice is to identify the risks of cardiotoxicity and, when possible, minimize them before the exposure. Several factors contribute to define cardiovascular toxicity risks including the type of transplant, age at transplant, hypertension, diabetes mellitus, dyslipidemia, and current smoking. Multiple uncontrolled preexisting cardiovascular conditions such as atrial fibrillation or atrial flutter, node sinus disease, ventricular arrhythmias, coronary artery disease, valve diseases and heart failure with reduced ejection fraction may also contribute to cardiotoxicity. So, it is important to know about the disease severity at the time of transplantation and probability of relapse, which may be correlated with increased exposure to other cardiotoxic chemotherapy drugs and radiotherapy before HSCT.

There are mainly two types of HSCT: (1) autologous transplantation, in which the patient receives his/her own progenitor cells, and the cardiotoxicity is mainly attributed to the direct toxic effects of the conditioning regimen; and (2) allogeneic transplantation in which the patient receives cells from another individual who may be fully or partially compatible. The allogeneic transplantation is known to have a higher risk of cardiotoxicity because in addition to the conditioning toxic effects, there are indirect effects of cytokines released in graft-versus-host disease and a possible direct cardiotoxicity through donor T-cell infiltration into the myocardium with subsequent inflammation leading to cardiac dysfunction.² The HSCT has six stages as presented in Figure 1: pre-transplant, conditioning phase (when the patient receives chemotherapy and often radiotherapy to eliminate the recipient's bone marrow, infusion, aplasia, recovery and post-transplant stage. In pre-transplant, the cardio-oncologist must perform a comprehensive assessment of the risk factors for cardiotoxicity. Clinical history and physical examination,

electrocardiogram, laboratory tests including T troponin and brain natriuretic peptide (BNP) (or N-terminal-proBNP NTproBNP), X-ray or, preferably, chest computed tomography, strain echocardiogram and spirometry test are essentials for a good evaluation.³ Rhythm and hemodynamic changes are described in the infusion stage, usually quick and benign as sinus tachycardia or bradycardia, hypotension or hypertension, but also serious ones as a total AV block. These changes seem to be caused by dimethyl sulfoxide, a cryoprotectant, but there is still not enough data to support this hypothesis.⁴ Many infectious complications may occur in the aplasia phase, such as myocarditis due to viral reactivation and sepsis-induced cardiomyopathy. The differential diagnosis between these conditions and cardiotoxicity can be challenging.

Cardiovascular risk factors, exposure to cardiotoxic agents, high cumulative dose (anthracyclines $\geq 250\text{mg/m}^2$) chemotherapy administered during conditioning (which is rare), with or without radiation, contribute synergistically to cardiovascular morbidity and mortality. Oxidative stress, cycling by iron complexes and genetic variants have been suggested as mechanisms. Women are twice as likely as men to develop heart failure. Cardiac adverse events have been attributed to different components of HSCT itself such as total body ablative radiation therapy combined with a multi-drug conditioning regimen.⁵

Congestive heart failure is generally considered a long-term complication of HSCT, but a new onset left ventricular dysfunction can also occur in the short term. Early-onset heart failure occurs in approximately 0.4% to 2.2% of patients, occurring within 100 days after allogeneic HSCT and as early as four days after Cy infusion.^{2,6} It was defined as a decrease in left ventricular function a reduction $\geq 10\%$ from baseline left ventricular function and of $\leq 53\%$ after HSCT, irrespective of baseline left ventricular function, which was assessed before the first chemotherapy session.

The five-year incidence of congestive heart failure was reported to be 4.8%, rising to 9.1% at 15 years. The transplant is usually contraindicated in patients with a pre-transplant left ventricular ejection fraction less than 35%, especially because of the association between pre-transplant ejection fraction and short-term outcomes.⁷ Cardiovascular disease, unless very severe, should not be a specific barrier to indicate HSCT and can often be managed by a multidisciplinary team before the procedure. Periodic monitoring of cardiac function using global longitudinal strain or left ventricular ejection fraction in echocardiography and serum biomarkers is recommended to detect early changes in cardiac status before irreversible cardiac complications develop.⁸

Keywords

Insuficiência Cardíaca; Cardiotoxicidade; Transplante; Medula Óssea

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Manuscript received November 21, 2022; revised manuscript December 20, 2022; accepted January 19, 2023

DOI: <https://doi.org/10.36660/abchf.20220090>

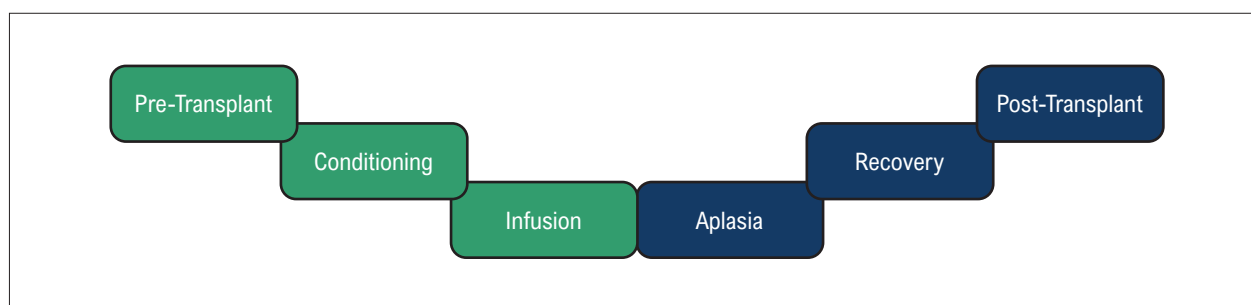


Figure 1 – Stages of hematopoietic stem cell transplantation.

Clinical benefits with prophylactic usage of beta-blockers or angiotensin-converting enzyme inhibitors have not been fully established in preventing cardiotoxicity in HSCT.

In summary, patients who are candidates for HSCT must be evaluated in advance by a cardio-oncologist or an expert cardiologist, have their cardiovascular and metabolic status optimized and followed up during the various stages of the transplant, and during a mid- and long-term follow-up plan.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Luz KRM, Cortizo B, Moreira MCR.

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Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.



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