Case Report

Heart Transplantation in Patients with Chemotherapy-Induced Cardiotoxicity

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Abstract

We report 3 cases of heart transplantation in adults due to chemotherapy-induced cardiotoxicity in a transplant center in Rio de Janeiro, Brazil. All patients received anthracyclines during cancer treatment. We reviewed and discussed the cases with data from the literature, addressing the importance of early diagnosis and treatment of heart failure in cancer survivors.

Introduction

The survival rates of adults and children with cancer have improved significantly due to advances in treatment and diagnosis. Therefore, many long-term survivors have been exposed to anticancer treatment (ACT). Certain chemotherapy drugs induce an increased risk of developing cardiovascular complications. Lesion incidence and severity depend on the chemotherapy drug, cumulative dose, presence of previous heart disease, comorbidities, and use of other ACTs.[1] In addition to secondary malignancies, childhood cancer survivors are more prone to cardiovascular death.[2]

Ventricular dysfunction is one of the most serious complications of cancer treatment, with high morbidity and mortality rates. Chronic cardiomyopathy leading to severe heart failure (HF) secondary to chemotherapy-induced cardiotoxicity is classically described. Heart transplantation (HT) remains the best treatment for refractory HF.[3]

The objective of this study was to report the experience of the first HT center in Rio de Janeiro, Brazil, with 3 cases of chemotherapy-induced cardiotoxicity progressing to advanced HF and requiring HT. The decision on whether to perform HT was made by the cardiology and oncology teams, in the absence of active malignancy and risk of recurrence.

Case 1

A White male patient was diagnosed with testicular cancer (surgically resected) and acute lymphoblastic leukemia at 9 months of age in April 1994. The patient was treated according to the St Jude R11 protocol with the following induction agents: daunorubicin, vincristine, cytarabine, prednisone, and methotrexate. Maintenance therapy included cyclophosphamide, vincristine, and methotrexate, among others. Treatment was intensified with vincristine and daunorubicin. Total dose of daunorubicin was 164 mg. Induction therapy was terminated in August 1994 and maintenance therapy in October 1996, with complete remission. At 15 years of age, in 2008, the patient suffered a cardioembolic ischemic stroke and was diagnosed with cardiomyopathy. The patient had hypothyroidism and was on levothyroxine. He presented at the National Cardiology Institute (Instituto Nacional de Cardiologia, INC) in Rio de Janeiro, Brazil, in February 2011 with complaints of tiredness and dyspnea on vigorous exertion for approximately 5 months. The patient remained in New York Heart Association (NYHA) functional class II until 2012 and underwent a HT at 21 years of age. Pre-transplant echocardiography showed Teicholz ejection fraction (EF) = 29%, end diastolic volume (EDV) = 166.6 mL, end systolic volume (ESV) = 118.2 mL, left ventricular (LV) systolic mass = 148.8 g, pulmonary artery systolic pressure (PASP) = 36 mmHg, enlargement of the four cardiac chambers, severe global LV systolic dysfunction with diffuse hypokinesia, severe right ventricular (RV) contractile dysfunction, moderate functional mitral insufficiency (MI), tricuspid insufficiency (TI), and moderate pericardial effusion. In the postoperative period, the patient had worsening of renal function and required hemodialysis, with subsequent recovery of renal function and hospital discharge 32 days after the HT. The echocardiogram showed Teicholz EF = 71.4%, PASP = 48 mmHg, mild biatrial and RV enlargement, RV systolic dysfunction, and mild MI and TI. He was readmitted for cytomegalovirus colitis and treated with ganciclovir. During readmission, he required pleural and pericardial drainage. The patient remains in outpatient treatment.

Case 2

A Black female patient was diagnosed with osteosarcoma at 14 years of age in 2012. The patient underwent surgical resection of the tumor and chemotherapy (cisplatin, doxorubicin, and methotrexate). In 2013, she was diagnosed with dilated cardiomyopathy and HF with reduced EF. She evolved to dialysis treatment due to chronic kidney disease due to treatment with multiple antimicrobial regimens for osteomyelitis as well as amputation of the left leg. An echocardiogram conducted in May 2019 showed EF = 30%, diffuse hypokinesia, thrombus in the inferoapical region of the LV, mild MI, and PASP = 23 mmHg. She remained in NYHA functional class I until 2018. The patient started

Keywords

Heart Transplantation; Cardiotoxicity; Heart Failure

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treatment at INC in June 2019 due to worsening of symptoms 3 months earlier, during pregnancy. At 23 years of age, after 2 months of hospitalization, in INTERMACS 3 and renal failure classified as stage 5 according to the Kidney Disease: Improving Global Outcomes, she underwent a combined heart and kidney transplant from a single donor. Orthotopic HT was initially performed, followed by heterotopic kidney transplantation. The patient was discharged from hospital 41 days after the transplant and remains in outpatient treatment.

Case 3

A Black female patient was diagnosed with osteosarcoma in the left femur in 2011 at 21 years of age. She underwent surgical resection of the tumor, knee prosthesis implantation, and 3 cycles of chemotherapy with neoadjuvant doxorubicin, with no metastasis. After surgery, the patient underwent 3 more cycles of chemotherapy. The treatment was terminated in 2012, when she was diagnosed with HF after complaining of intense tiredness. The patient attended follow-up visits close to home but had difficulty adhering to treatment due to the side effects of medications. She started treatment at INC in December 2018 in NYHA functional class II. She was hospitalized for community-acquired pneumonia and decompensated HF and progressed with refractory cardiogenic shock, requiring intra-aortic balloon pump therapy and biventricular circulatory support. She also required massive blood transfusion and hemodialysis due to acute renal failure and underwent a simultaneous heart and kidney transplant in May 2009. Pre-transplant echocardiography revealed enlargement of right cavities and severe biventricular systolic dysfunction with diffuse hypokinesia. During surgery, after donor heart implantation, there was difficult-to-control bleeding in the aortic arch, progressive deterioration of RV function, and death.

Discussion

As ACTs continue to evolve, the number of cancer survivors increases, and 1% to 5% of them develop chemotherapy-induced cardiomyopathy (CCM).

We described 3 cases of CCM from the series of 135 HTs performed from 2007 to 2022 at the first HT center in Rio de Janeiro, Brazil. In a series of HTs between 1987 and 2011, 453 were due to CCM and 51,312 due to other causes.[4] Patients with CCM had improved survival without greater risk of death due to the malignancy. In another study conducted between 2000 and 2008, 232 HTs were conducted due to CCM and 8,890 due to other causes.[5]

The 3 patients included in this case report were in the third decade of life at the time of transplantation and received anthracyclines during cancer treatment. Although well-established chemotherapeutic drugs, anthracyclines are associated with cardiac dysfunction, cardiomyopathy, and HF. Anthracycline cardiotoxicity is considered an ongoing phenomenon that starts at the time of exposure to ACT and persists for months or years.

In the initial evaluation of patients receiving ACT, a thorough clinical history is imperative to define the follow-up strategy. Childhood cancer survivors are especially vulnerable to having limited information about their cancer and treatment because of their early age at diagnosis. Two of the 3 reported cases involved patients diagnosed with cancer in childhood. The importance of communication between the oncologist and cardiologist in patient follow-up is demonstrated.

Cardiac dysfunction related to ACT is a serious adverse event that may lead to severe HF and death. Early identification is essential, allowing implementation of appropriate treatment. Regular cardiac surveillance using cardiac biomarkers and/or cardiac imaging is recommended during and after treatment with anthracyclines; regularity depends on the initial assessment of cardiovascular risk. Symptoms of HF should be evaluated during clinical visits and, if necessary, the patient should be referred to the cardio-oncology department and/or to a specialist in HF and HT.[6]

Patients with advanced HF and a history of cancer who are considered free of disease may be candidates for mechanical circulatory support as bridge to transplantation, with the involvement of an oncologist.[7] Of the 3 reported cases, 2 required circulatory support. The waiting period after cancer remission for HT candidacy is based on patient-specific factors and tumor type.[8]

Severe CCM, when refractory to drug therapy, may require therapies destined for advanced HF, such as mechanical circulatory support and HT. The cardiologist and oncologist should work together to make a decision. Early diagnosis and referral of patients with advanced HF to specialized centers is essential.

Author Contributions

Conception and design of the research: Issa AFC, Guimarães TCF; Acquisition of data: Issa AFC, Vidotti V, Zagni G, Miranda J; Analysis and interpretation of the data: Issa AFC, Guimarães TCF, Vidotti V, Zagni G; Writing of the manuscript: Issa AFC, Guimarães TCF, Vidotti V, Santos M; Critical revision of the manuscript for important intellectual content: Issa AFC, Guimarães TCF, Vidotti V, Zagni G, Santos M, Miranda J.

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Study association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 64611922.1.0000.5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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