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Therapy for Children's Cardiac Dysfunction Associated with Cancer Treatment

Ariel Pablo Lopez*

Department of Genetics, Molecular Biology Laboratory, Universidad de Buenos Aires, Argentina

Correspondence to: Ariel Pablo Lopez, Department of Genetics, Molecular Biology Laboratory, Universidad de Buenos Aires, Argentina; E-mail: aplopez@prensamedica.com.ar

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Introduction

A major health burden for pediatric cancer patients is cardiovascular disease. The study of cardiovascular diseases that emerge because of cancer therapy, including their diagnosis, tracking, and management, is the emphasis of the emerging discipline of cardio-oncology [1]. Limited smoking, early cancer detection, and novel therapies, particularly molecularly targeted therapy and immunotherapy are just a few of the variables that improve cancer survival [2]. Cardiotoxicity is also increased by additional risk factors like concurrent radiotherapy or chemotherapy, lower age at onset, feminine gender, comorbidities, lifestyle factors, and hereditary factors like hemochromatosis gene mutations. Childhood cancer mortality rates have greatly increased in recent years, with 5-year overall survival rates now surpassing 80%. Anthracyclines prevent cancer cells from proliferating by blocking topoisomerases, DNA crosslinking, Ribosome replication, and DNA replication [3]. When given anthracyclines (doxorubicin and daunorubicin) at dosages greater than 300 mg/m^2, about 10% of infants experience side effects. Anthracycline exposure during childhood increases the risk of developing heart failure by 15 times and the risk of dying from cardiovascular illness by 8 times. Different pediatric cancer victims with cancer-related cardiovascular events appear clinically in different ways. congenital heart disease has become the most prevalent congenital malformation, ranges from mild heart failure to over heart failure, and its prevalence has stayed high in recent years [4], CTRCD (cancer treatment-related cardiac dysfunction) is a range of cardiac dysfunction spanning from overt indications and clinical symptoms of heart failure to asymptomatic heart injury identified only by elevated biomarkers like troponin or brain natriuretic peptide (BNP). An interdisciplinary strategy among doctors is necessary for secondary prevention after the end of cancer therapy, such as improved monitoring, suitable screening methods, and prophylactic treatment of cardiovascular complications. Prevention, risk management, and early diagnosis are crucial because cardiotoxicity progression is permanent. Several pediatric tumors are treated with anthracyclines, an anticancer medication. Damage to the heart is a significant anthracycline adverse effect that can cause either asymptomatic (non-complaint) or symptomatic (complaint) cardiac issues during and after cancer therapy. The Children's Oncology Group's Guidance for Long-Term Obey in Children, Adolescents, and Adolescents [5] offer comprehensive information for organizations interested in developing and enhancing long-term follow-up initiatives for children with cancer. It is significant to observe that there are variations in CV monitoring between centers, resulting in significant practice variance.

Methods

Cardiovascular Toxic Effects Pathophysiology in Cancer Patients

A higher risk of cardiotoxicity was seen in the Childhood Cancer Survival Study (CCSS) at smaller total doses of 250 mg/m^2 as opposed to 400 mg/m^2. According to the CCSS, there may not be a secure number of anthracyclines for toddlers to take. In one trial, unlike that in grownups, there was no distinction between bolus and anthracyclines in children's cardiotoxicity results [6]. Patients with pediatric cancer or those who have endured anthracycline-related heart issues should be able to make educated choices about their care based on high-quality proof of the advantages and disadvantages of treatment alternatives. We located two randomized studies comparing the effects of two various medications on two various patient populations. Enalapril, an ACE inhibitor, is one of these medications that improves heart function in pediatric cancer patients with asymptomatic anthracycline-induced cardiac issues in comparison to placebo in the short term. We located two randomized studies comparing the effects of two various medications on two various patient populations. Enalapril, an ACE inhibitor, is one of these medications that improves heart function in pediatric cancer patients with asymptomatic anthracycline-induced cardiac issues in comparison to placebo in the short term. Doxorubicin is the anthracycline that is most frequently used to treat childhood cancer. It inhibits cellular proliferation and function, alters deoxyribonucleic acid regulation in cardiac tissue, and acts as an anticancer agent by interacting to topoisomerase II. By chemically reacting with Fe^{+2}, doxorubicin causes lipid peroxidation in cells and mitochondrial membranes. It also causes mortality, mitochondria damage to DNA damage, and ecological collapse by releasing reactive oxygen species (ROS) [7]. There is no treatment for cancer that is completely safe, and all chemotherapy drugs can result in long-term cardiotoxicity [8].

Cardiotoxicity can be brought on by alkylating substances like cisplatin and carboplatin that enhance the generation of ROS and interfere with the antioxidant system [9]. Long-term cardiology follow-up is crucial because cisplatin and carboplatin can also cause late-onset CTRCD [10]. Cardiomyocyte apoptosis, inflammation, endothelial dysfunction, calcium dysregulation, and mitochondrial damage have all been linked to cyclophosphamide and have been shown to cause high blood pressure, cardiomyopathy, myocardial infarction, arrhythmias, and eventually heart failure. Several pediatric cancer patients are being treated with targeted cancer therapy. The processes driving cancer development have improved immune checkpoint inhibitors, also known as ICIs, such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab, as well as tyrosine kinase inhibitors, or TKIs, are used as treatment (imatinib, dasatinib, bevacizumab, bosutinib, sunitinib, pro sornanitinib, pro sornanitinib). Hypoxia-inducible factor 1-alpha (HIF-1) is a protein that is targeted by vascular endothelial growth factor inhibitors, which results in myocardial hypoxia and cardiac failure. Refractory blood malignancies and acute lymphoblastic leukemia are being treated with cell treatments such chimeric antigen receptor T (CAR-T) cells. The carcinogenesis caused by CAR-T cells results from the direct cell-mediated lysis of cancer cells as well as a rise in serum potassium and uric acid. Syndrome of lysis six months after receiving CAR-T cell treatment, Burstein et al. found that 25% of children had hypotension and 10% had diminished cardiac function [11].

Heart Failure and Myocarditis in Oncology

Systolic or diastolic heart dysfunction is a common pathological defect in all CTRCDs. Cyclophosphamide, 5-FU, cisplatin, and RT are examples of secondary modifications that can cause inflammatory myocarditis or microvascular damage and fibrosis that causes cardiac dysfunction (immune checkpoint inhibitors and RT). Left ventricular (LV) dysfunction and heart failure are categorized into five categories by the National Cancer Institute as standard terminological criteria for cancer-related adverse outcomes in adults. Grade 1 biomarker increase, or imaging abnormality has no symptoms. Mild and moderate exertion-related symptoms were categorized into Grade 2 and Grade 3, respectively. Grade 4 symptoms are severe and life-threatening and require hemodynamic care, whereas Grade 5 symptoms are fatal. 62% of childhood cancer survivors have a major or life-threatening condition such a stroke, heart failure, or renal failure, and 27% of them have at least one chronic illness [12]. Anthracyclines' ability to produce cardiotoxicity in children has been thoroughly researched. Nevertheless, at dosages as high as 60 mg/m^2, cardiovascular illness in children has been shown [13]. Chemotherapy causes a number of ongoing changes, including a rise in cardiac biomarkers, regional myocardial deformation (abnormal tension), and asymptomatic LV systolic or diastolic dysfunction, which ultimately result in heart failure [14]. Based on the emergence of clinical signs of persistent cardiotoxicity, childhood cancer survivors can be categorized into two categories. The second subtype develops later, more than a year after chemotherapy, and is often progressive. The first subtype manifests early, within a year following treatment. With a mean follow-up of 11.8 years, children receiving doxorubicin have lower LV wall thickness in proportion to somatic development when compared to untreated children [15]. Since injured myocytes fail to recover and are replaced by interstitial fibrosis following doxorubicin therapy, cardiac dysfunction persists and worsens [16]. Although LV mass and cavity size steadily decline in relation to body size, progressive restrictive cardiomyopathy is often permanent and is a long-term risk factor for heart failure with maintained EF in pediatric cancer survivors [17].

Diagnostic and Risk Analysis

Careful assessment of cardiovascular risk factors previously, all through, and then after cancer treatment with basic history, diagnostic and laboratory tests for cardiac biomarkers, and screening tests is required for the detection of high-risk patients and diagnosis of cardiotoxicity in children before symptoms of heart failure appear (Figure 1). Cardiotoxicity risk is influenced by the patient's cancer diagnosis, the type of therapy they got, and risky health habits including smoking, drinking, using drugs (such as cocaine, diet pills, and ephedra), eating poorly, being sedentary, and having comorbid conditions. existing cardiomyopathy, congenital cardiac disease, high blood pressure, hyperlipidemia, diabetes, and obesity [18]. Notably the Childhood Cancer Survivor Study have revealed characteristics that raise the risk of cardiotoxicity, such as younger patient age (5 years), smoking, and obesity. Trisomy 21, total anthracycline dosage, female gender, African American race, concomitant radiation, heart illness, premodern radiation procedures (before 1975), and length of time since therapy [19]. Also, there is proof that cancer patients already have subclinical cardiac impairment prior to receiving cancer therapy, which highlights the need of evaluating patients' heart health prior to receiving cancer treatment [20]. In patients undergoing anticancer therapy who do not have CAD, elevated levels of cardiac troponin T, BNP, or NT-pro-BNP suggest subclinical cardiac injury and are linked to decreased LV function [21, 22]. Lower LV mass, wall thickness, and echocardiographic remodel five years after anthracycline treatment is related with cardiac damage (measured by blood cardiac troponin T 99th percentile) [23]. Serial biomarker screening is crucial for CTRCD adopt and prevent complications in childhood cancer survivors. A biomarker identified as galectin-3 has been linked to cardiac fibrosis and inflammation, whereas ST2, also known as soluble interleukin-1 receptor-like elevated myeloperoxidase was demonstrated to predict cardiotoxicity [24]. Exosomes have recently been discovered to be useful indicators of doxycycline-induced cardiotoxicity [25]. Exosomes are a subpopulation of extracellular vesicles that influence a number of pathophysiological processes.

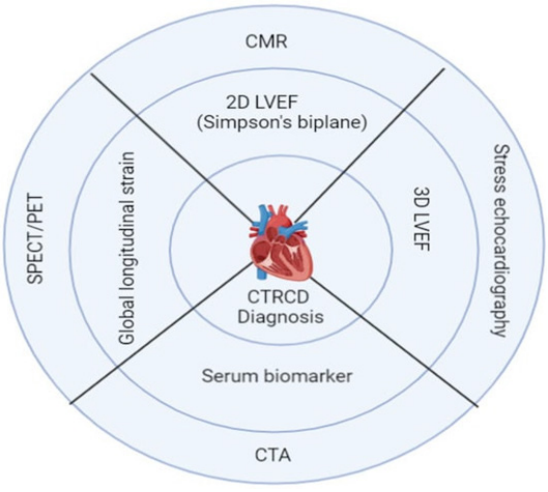

Figure 1: Serum cardiac biomarker and imaging to detect cardiotoxicity. First-line tests are represented in the inner circle, and second-line tests (represented in the outer circle), including advanced imaging techniques, are reserved for a certain group of patients where first-line tests are inadequate or specific information about coronary artery disease is needed [26].

Note: 2D: two-dimensional; LVEF: left ventricular ejection fraction; 3-D: three-dimensional; CTRCD: cancer treatment-related cardiac dysfunction; CMR: cardiac magnetic resonance imaging; CTA: computerized tomographic angiography; SPECT: single-photon electron computed tomography; PET: positron emission tomography.

Conclusion

Decreased exercise capacity is the greatest indicator of a modest deterioration in cardiac health for long-term cancer victims receiving cardiotoxic medication. Surgical intervention improves the quality of life and health in children with coronary artery disease, in addition to treating congenital abnormalities. To enhance the quality of life connected to health, children with coronary heart disease should be identified and treated as soon as feasible. Cardiotoxicity related to cancer treatment has the potential to be systemic, chronic, and progressive, and it may go unnoticed by doctors. One significant hypothesis is that chronic cardiotoxicity may be linked to persistent mitochondrial damage. As the number of cancer survivors rises, so does the health burden brought on by cardiovascular disease. Continuous follow-up is vital as the community of survivors of childhood cancer matures, and being able to provide quality care will help us do better. The healthcare system in the US is evolving, somewhat unsteady, and politically driven. It is a system that is experiencing a crisis, and just a little bit of funding has been set aside to avoid it. Lifelong follow-up is necessary for childhood cancer survivors, especially for those who are at high risk for developing CTRCD.

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