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Review

Cardiac Outcomes in Survivors of Pediatric and Adult Cancers

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ABSTRACT

More than 80% of children and 60% of adults with cancer will become long-term survivors, emphasizing the importance of late effects of cancer therapy. Cardiotoxicity due to chemotherapy and radiation is a frequent cause of serious morbidity and premature mortality in survivors. Anthracyclines, a core component of many treatment regimens, have been implicated as a principal cause of irreversible cardiomyopathy. Approximately 60% of anthracycline-treated children will develop echocardiographic evidence of cardiac dysfunction, and 10% of those treated with high-dose anthracyclines will develop congestive heart failure within the 20 years after therapy. Adults treated with trastuzumab are at risk of a cardiomyopathy that is usually reversible. As many as 12% of adults treated with trastuzumab and 20% of those who have also received an anthracycline will develop cardiotoxicity within 5 years. Risk factors for cardiomyopathy include patient (eg, age, sex, genetic predisposition) and treatment characteristics (eg,

RÉSUMÉ

Plus de 80 % des enfants et 60 % des adultes atteints de cancer y survivront à long terme, ce qui met en évidence l'importance des effets retards du traitement anticancéreux. La cardiotoxicité causée par la chimiothérapie et la radiothérapie est une cause fréquente de morbidité grave et de mortalité précoce chez les survivants. Les anthracyclines, une composante importante de nombreux schémas thérapeutiques, ont été pointées du doigt comme principale cause de la cardiomyopathie irréversible. Environ 60 % des enfants traités par des anthracyclines présenteront des signes de dysfonction cardiaque à l'échographie et 10 % des patients ayant reçu de fortes doses d'anthracyclines seront atteints d'une insuffisance cardiaque dans les 20 années suivant le traitement. Les adultes traités par le trastuzumab sont exposés à un risque de cardiomyopathie habituellement réversible. Jusqu'à 12 % des adultes traités par le trastuzumab et 20 % de ceux ayant également reçu une anthracycline présenteront une

The Growing Population of Cancer Survivors

With contemporary therapies, more than 80% of children diagnosed with cancer will become long-term survivors.[1] There are almost 400,000 childhood cancer survivors (CCS) alive in the United States,[2] with the survivor population in Canada approximating 40,000. CCS are at significant risk of serious morbidity and premature mortality as a result of their cancer therapy[3,4]; 80% of survivors will develop one or more severe or life-threatening chronic health conditions by the age of 45 years.[5] Of those children who survive 5 years from their initial cancer diagnosis, almost 10% will die in the next 10 years.[6] Although cancer recurrence is the primary cause of mortality early in the survivor period, second malignant neoplasms and cardiac and pulmonary disease account for greater proportions of premature deaths over time.[7] In fact, cardiac disease is the third leading cause of premature death in CCS (after cancer recurrence and second malignant neoplasms), with a 7-fold increased risk of premature cardiac death compared with the general population. The relative risk of cardiac death remains elevated even in CCS who have survived for more than 25 years after their primary cancer.[7]

There are similar concerns within the population of adult cancer survivors. In 2009, there were an estimated 810,045 Canadians who had been diagnosed with a malignancy in the preceding 10 years. This equates to approximately 1 in 40 adult Canadians being a cancer survivor.[8] As a result, assessment of the risk-benefit of specific cancer therapies is now expected to factor in their long-term impact on survivors'

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cumulative anthracycline dose). Radiotherapy to a field involving the heart increases the risk of cardiomyopathy, coronary artery disease, valvular dysfunction, arrhythmias, and pericardial disease. Surveillance guidelines are available to guide long-term cardiac follow-up of childhood cancer survivors, but not for survivors of adult cancers; however, periodic follow-up to detect cardiac dysfunction may be reasonable. Modifiable cardiac risk factors such as hypertension, smoking, and dyslipidemia interact with cancer therapies to increase the risk of cardiac disease, emphasizing the importance of risk-factor control. Coordination of care between oncologists and cardiologists would optimize care for those individuals at high risk of cardiotoxicity who would benefit from appropriate surveillance and treatment strategies.

cardiotoxicité dans les 5 ans. Les facteurs de risque de cardiomyopathie comprennent les caractéristiques du patient (par ex., âge, sexe, prédispositions génétiques) et du traitement (p. ex., dose cumulative d'anthracycline). La radiothérapie ciblant une région où se trouve le cœur augmente le risque de cardiomyopathie, de coronaropathie, de dysfonction valvulaire, d'arythmies et de maladie péricardique. Il existe des lignes directrices en matière de surveillance qui permettent d'orienter le suivi cardiaque à long terme chez les personnes ayant survécu à un cancer dans l'enfance, mais non chez celles ayant survécu à un cancer à l'âge adulte; ainsi, un suivi à intervalles réguliers pour dépister toute dysfonction cardiaque pourrait être une pratique raisonnable. Les facteurs de risque modifiables de maladie cardiaque, tels que l'hypertension, l'usage du tabac et la dyslipidémie, interagissent avec les traitements anticancéreux et augmentent, de ce fait, le risque de maladie cardiaque. La prise en charge de ces facteurs de risque revêt donc une importance accrue. La coordination des soins entre l'oncologue et le cardiologue optimiserait les soins chez les personnes exposées à un risque élevé de cardiotoxicité qui pourraient bénéficier d'une surveillance et de stratégies thérapeutiques appropriées.

health.[9] In malignancies with a large survivor population such as breast cancer, the most common cause of death among older patients is cardiovascular disease.[10]

Cardiac Outcomes in Survivors of Childhood Cancer

Cardiac toxicity in CCS is caused mainly by anthracycline chemotherapy agents (most commonly doxorubicin and daunomycin) that are administered to more than 50% of children with cancer.[11] Although observed frequencies vary between studies, up to 60% of children treated with an anthracycline will develop at least some subclinical cardiac dysfunction.[12] These abnormalities are progressive in a significant proportion of patients.[13-15] The risk of congestive heart failure (CHF) in children exposed to a cumulative anthracycline dose greater than 300 mg/m^2 approaches 10% by 20 years after their cancer therapy,[16] but even children exposed to lower doses are at significantly increased risk of CHF.[12,17] Compared with their siblings, CCS have a 15-fold increased risk of developing CHF.[18]

Cardiac disease in cancer survivors extends beyond damage to the myocardium. Cancer treatments that include radiation therapy to a field that includes the heart can impact any of the cardiac structures. Thus, survivors treated with radiation are at increased risk of coronary artery disease (CAD), valvular abnormalities, arrhythmias, and pericardial disease.[17] Among adult survivors of childhood cancer (median age at assessment, 32 years) assessed as part of the St Jude Lifetime Cohort Study,[5] 57% of those treated with radiation to a field that involved the heart were found to have a valvular abnormality, most frequently mild-to-moderate tricuspid regurgitation or mitral valve regurgitation. Fourteen percent of survivors treated with an anthracycline, anthraquinone, or radiation had developed a conduction disorder. By the age of 45 years, 5.3% of survivors in the Childhood Cancer Survivor Study, only 39% of whom had received an anthracycline and 26% chest-directed radiotherapy, had developed severe or life-threatening CAD or had died of a myocardial infarction.[19]

Cardiac Outcomes in Survivors of Adult Cancers

A paradigm for cancer therapeutics-related cardiac dysfunction (CTRCD) has been proposed in adults, with classification into an irreversible type I form, and a type II form that is believed to be reversible with timely intervention (Fig. 1).[21] However, this simple dichotomization is most useful as a framework to conceptualize the spectrum of CTRCD rather than an absolute distinction between 2 nonoverlapping entities. Anthracyclines are the chemotherapy agents most commonly associated with type I CTRCD. In a seminal study, CHF was observed in 88 (2.2%) of 3941 doxorubicin-treated patients (median dose 183 mg/m^2).[22] In contrast to children in whom CHF is usually a late occurrence, CHF was recognized at a median of 23 days (mean 30 days) after the last administered dose of chemotherapy in this adult cohort. The most potent predictor of heart failure was the cumulative doxorubicin dose; the median dose was 390 mg/m^2 in patients who developed heart failure and 180 mg/m^2 in those who did not. The incidence of CHF was 3% in patients who received $<$ 400 mg/m^2, 7% in patients who received 400-550 mg/m^2, and 18% at higher doses. However, the risk may have been underestimated because of limited follow-up and lack of image-based assessment of subclinical left ventricular (LV) dysfunction. More recent

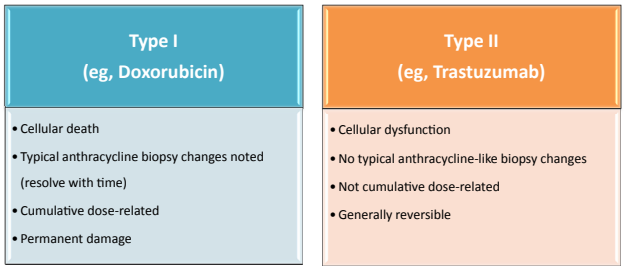

Figure 1. Type I and II cancer therapeutics-related cardiac dysfunction. Reproduced from Ewer and Ewer[20] with permission of Springer.