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REVIEW ARTICLE

Cardiotoxicity in anthracycline therapy: Prevention strategies☆

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Abstract The increasing use of anthracyclines, together with the longer survival of cancer patients, means the toxic effects of these drugs need to be monitored. In order to detect, prevent or mitigate anthracycline-induced cardiomyopathy, it is essential that all patients undergo a rigorous initial cardiovascular assessment, followed by close monitoring. Several clinical trials have shown the cardioprotective effect of non-pharmacological measures such as exercise, healthy lifestyles, control of risk factors and treatment of comorbidities; a cardioprotective effect has also been observed with pharmacological measures such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, statins, dexrazoxane and liposomal formulations. However, there are currently no guidelines for managing prevention in these patients. In this review the authors discuss the state of the art of the assessment, monitoring, and, above all, the prevention of anthracycline-induced cardiotoxicity.

PALAVRAS-CHAVE
Antraciclinas;
Cardiotoxicidade;
Prevenção;
Quimioterapia

Cardiotoxicidade na terapêutica com antraciclinas: estratégias de prevenção

Resumo O crescente uso de antraciclinas, aliado ao aumento da sobrevida dos doentes oncológicos, motiva a necessidade de monitorizar os efeitos tóxicos destes fármacos. Para que a sua cardiotoxicidade possa ser detetada, prevenida ou atenuada, torna-se essencial que todos os doentes sejam, do ponto de vista cardiovascular, submetidos a uma rigorosa avaliação inicial e a um estreito acompanhamento. Diversos ensaios clínicos comprovaram o efeito cardioprotetor produzido por medidas não farmacológicas como o exercício físico, a adoção de um estilo de vida saudável, o controlo de fatores de risco e o tratamento de comorbilidades;

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foi também verificado um efeito cardioprotetor com estratégias farmacológicas como o uso de bloqueadores-beta, inibidores da enzima de conversão da angiotensina, antagonistas do recetor da angiotensina, estatinas, dexrazoxane ou derivados lisossomais. No entanto, atualmente não existe qualquer diretriz científica que oriente as estratégias de prevenção nestes doentes. Com esta revisão propomo-nos abordar o estado da arte relativo à avaliação, monitorização e, principalmente, à prevenção da cardiotoxicidade provocada pelas antraciclinas.

Introduction

According to the World Health Organization, cancer is the second leading cause of death worldwide.[1] The considerable and ongoing advances in treatment have increased survival of cancer patients, but the adverse effects of chemotherapy, particularly on the heart, are a significant cause of mortality and morbidity. Mortality among cancer patients who develop anthracycline-induced cardiomyopathy is high (over 60% at two years),[2] but prognosis can be improved by early detection and prevention.

Anthracyclines such as doxorubicin, daunorubicin, epirubicin, mitoxantrone and idarubicin are the most commonly used chemotherapy drugs in cancer. They are a known cause of cardiotoxicity (Table 1), with acute or/and subacute effects that can manifest as electrocardiographic changes, ventricular and supraventricular arrhythmias, cardiac conduction disturbances (atrioventricular or branch block), ventricular dysfunction, rises in brain-type natriuretic peptide (BNP, a marker of increased preload and heart failure [HF]), myocarditis and pericarditis, and that may occur at any time between beginning of treatment and two weeks after the end of treatment. These effects are relatively uncommon and most revert a week after treatment cessation. Chronic cardiomyopathy is defined as early if it begins within a year of ending chemotherapy and late after that period. In either case, systolic or diastolic dysfunction are observed (Table 2) that can progress to severe cardiomyopathy and may even lead to death.[3] Although some studies have suggested that the risk of developing ventricular dysfunction and its severity can be predicted on the basis of acute myocardial injury,[4] the relationship between acute and chronic toxicity is not fully understood. Diagnosis of cardiac dysfunction induced by cancer therapy has been the subject of various studies,[3,5] one of which[5] is considered the reference publication on the subject, and is based on HF symptoms, physical examination and parameters of left ventricular function.

One proposed classification divides chemotherapy-induced cardiomyopathy into two types: type I, caused by anthracyclines, which induce irreversible dose-dependent cardiac injury; and type II, caused by trastuzumab, which is not related to the cumulative dose and is often reversible after treatment discontinuation.[6] The second type will not be discussed in this review article.

In this review the authors discuss strategies in patients being treated with anthracyclines in order to prevent or mitigate their main adverse effects on the heart.

Initial assessment

In view of the cardiotoxicity of anthracyclines, all patients referred for chemotherapy should undergo a cardiac assessment to establish their baseline cardiovascular characteristics, which can then be used during the treatment regimen for purposes of comparison. This assessment should include clinical history and physical examination, electrocardiography to determine cardiac rhythm and detect signs of ischemia, and cardiac imaging, usually transthoracic echocardiography with complete Doppler study (Tables 3 and 4). When the echocardiogram is provides insufficient information, cardiac magnetic resonance imaging (CMRI) is recommended. Baseline troponin levels should also be measured for future comparisons.[5]

Monitoring during therapy

It is important to monitor for signs and symptoms of cardiotoxicity during chemotherapy (Table 5). The 12-lead electrocardiogram can be used routinely to screen for arrhythmias due to anthracycline-related cardiotoxicity, while 24-hour Holter monitoring or an event recorder can be useful to investigate the etiology of syncope presumed to result from arrhythmia or advanced atrioventricular block.[7] Cardiac function should be monitored by echocardiography in patients under anthracycline therapy. Global longitudinal strain (GLS) as assessed by two-dimensional speckle tracking is a more sensitive predictor of HF than left ventricular ejection fraction (LVEF),[8] since during anthracycline therapy changes in GLS precede reduction in LVEF.[5] However, in clinical practice, fractional shortening and LVEF have been the most widely used parameters,[9] although fractional shortening is proving to be less reliable in this context. These parameters, being dependent on pre- and afterload, are less sensitive for early detection of preclinical cardiac disease. Various studies have suggested that assessment of diastolic function by Doppler echocardiography may enable early detection of anthracycline-induced cardiomyopathy.[10,11] If LVEF is <53%, GLS below the limit of normal (Table 6), and/or