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Invited review article

The concomitant management of cancer therapy and cardiac therapy☆

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ABSTRACT

Antitumor drugs have long been known to introduce a measurable risk of cardiovascular events. Cardio-Oncology is the discipline that builds on collaboration between cardiologists and oncologists and aims at screening, preventing or minimizing such a risk. Overt concern about "possible" cardiovascular toxicity might expose cancer patients to the risk of tumor undertreatment and poor oncologic outcome. Careful analysis of risk:benefit balance is therefore central to the management of patients exposed to potentially cardiotoxic drugs. Concomitant or sequential management of cardiac and cancer therapies should also be tailored to the following strengths and weaknesses: i) molecular mechanisms and clinical correlates of cardiotoxicity have been characterized to some extent for anthracyclines but not for other chemotherapeutics or new generation "targeted" drugs, ii) anthracyclines and targeted drugs cause different mechanisms of cardiotoxicity (type I versus type II), and this classification should guide strategies of primary or secondary prevention, iii) with anthracyclines and nonanthracycline chemotherapeutics, cardiovascular events may occur on treatment as well as years or decades after completing chemotherapy, iv) some patients may be predisposed to a higher risk of cardiac events but there is a lack of prospective studies that characterized optimal genetic tests and pharmacologic measures to minimize excess risk, v) clinical toxicity may be preceded by asymptomatic systolic and/or diastolic dysfunction that necessitates innovative mechanism-based pharmacologic treatment, and vi) patient-tailored pharmacologic correction of comorbidities is important for both primary and secondary prevention. Active collaboration of physicians with laboratory scientists is much needed for improving management of cardiovascular sequelae of antitumor therapy. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

Abbreviations: AUC, area under the curve of plasma concentration vs time; ACEI, angiotensin converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker(s); BNP, B-type natriuretic peptide; CHF, congestive heart failure; C_{max}, peak plasma concentration; EGFR, epidermal growth factor receptor; $I_{Na,Late}$, late inward sodium current; KI, kinase inhibitor(s); LVEF, left ventricle ejection fraction; MI, myocardial infarction; NO, nitric oxide; Nt-proBNP, inactive aminoterminal fragment of B-type natriuretic peptide prohormone; PDGF(r), platelet derived growth factor (receptor); ROS, reactive oxygen species; VEGF(r), vascular endothelial growth factor (receptor).

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1. Introduction

Antitumor therapies may expose patients to cardiovascular discomfort such as transient blood pressure instability, supraventricular arrhythmias or sporadic benign ventricular arrhythmias. In the vast majority of cases such disorders occur acutely ("on-treatment"), revert spontaneously or respond to cardiovascular therapy, and do not form an indication to interrupting therapy. In other cases, however, cardiac sequelae of antitumor therapies are life-threatening. Cumulative doses of anthracyclines, mitomycin, or mitoxantrone, induce dilated cardiomyopathy and congestive heart failure (CHF) [1,2]. With the prototypic anthracycline, doxorubicin, 5% risk of CHF occurs at a cumulative dose of 400–450 mg/m^2 [3].

Our perception of the clinical manifestations of cardiotoxicity has nonetheless changed over the last years. Both retrospective and longitudinal prospective studies show that cumulative anthracycline doses lower than e.g., 400 mg of doxorubicin/m^2, cause fewer on-treatment events; nevertheless, CHF may develop five or more years after completing chemotherapy. This is seen in survivors of both childhood-adolescent and adult cancer, and suggests that there is no safe dose of anthracycline [8]. Moreover, some cancer survivors were found to develop dilated cardiomyopathy and CHF while others developed restrictive cardiomyopathy with less compromised left ventricle ejection fraction (LVEF), or developed ischemic disease and myocardial infarction (MI) [4,5]. Irradiation of cardiac area (e.g., in patients with mediastinal lymphoma) contributes to causing cardiotoxicity and in some patients, it seems to influence prevalence of ischemic disease over CHF [5]. Nonanthracycline chemotherapeutics (antimetabolites, alkylators, tubulin-active vinca alkaloids) have long been known to induce coronary endothelial dysfunction and myocardial ischemia that occurs within hours or days from treatment [2,6]; however, more recent data demonstrate that also these drugs introduce a lifetime risk of cardiovascular events [4–6]. The importance of age of first treatment has been reappraised. Children-adolescents and the elderly have traditionally been considered to be more vulnerable by anthracyclines but in defined clinical settings (breast cancer, Hodgkin lymphoma) the risk of late onset cardiac disease did not always depend on age of first treatment [5,7].

Cardiovascular events occur also with "targeted" drugs that were hoped to hit tumor cells but not the cardiovascular system and other healthy tissues. Many such drugs were in fact designed for binding to receptors or inhibiting kinases which later were identified also in healthy tissues. An antibody targeted at the epidermal growth factor receptor 2 (EGFR2), trastuzumab, precipitates CHF in breast cancer patients who receive concomitant anthracyclines, and causes moderate to severe contractile dysfunction in patients with a prior exposure to anthracyclines [1,8]. An antibody targeted at the Vascular Endothelial Growth Factor (VEGF), bevacizumab, may cause hypertension, myocardial contractile dysfunction or ischemia, peripheral vascular occlusive events [9]. Cardiovascular liability issues have been raised for sunitinib and sorafenib, small molecule inhibitors of the kinase domain of VEGF receptor (VEGFr), and for imatinib and nilotinib, small molecule inhibitors of Bcr-Abl and c-Kit of leukemic or gastrointestinal sarcoma cells [10].

The list of antitumor drugs that cause, or are suspected to cause cardiovascular events, seems to be expanding inexorably. A detailed analysis of the library of drugs possibly involved in cancer treatment-related cardiovascular events is not in the scope of this review. We would rather address some controversial issues that need to be put in context before one examined which patients would benefit most from cardiovascular prevention or treatment.

2. Mechanistic foundations for cardiovascular therapy in cancer patients: strengths and weaknesses

Mechanism-based approaches to preventing or treating cardiovascular sequelae of antitumor therapies should build on a comprehensive appraisal of how antitumor drugs cause cardiovascular toxicity. As disappointing it may sound, one such understanding is still lacking. A mechanistic insight is available for relatively few drugs.

Anthracyclines have been around for more than 40 years and many theories of anthracycline-induced cardiotoxicity have been advanced. Anthracyclines, which kill tumor cells by DNA intercalation and topoisomerase IIα inhibition, seem to induce cardiotoxicity by a constellation of mechanisms that go from oxidative stress to mitochondriopathy, changes in the expression and architectural coupling of respiratory chain components, and alterations of iron and calcium homeostasis [1,8]. Cause-and-effect relations or reciprocal interactions between one mechanism and the others are nonetheless uncertain. More recently, a unifying mechanism of cardiotoxicity was proposed: it envisioned formation of anthracyline-DNA-topoisomerase 2β complexes that caused DNA double-strands breaks and transcriptional changes associated with impaired mitochondrial biogenesis and function [11]. With that said, not all of the patients exposed to a given anthracycline dose will develop cardiomyopathy and CHF [6]. Genetic predisposition may come into a play and determine the individual risk and clinical pattern of development of cardiotoxicity. For example, two electron reduction of a carbonyl group in the side chain of anthracyclines generates secondary alcohol metabolites that are more polar than their parent drugs, exhibits a reduced elimination from cardiac tissue, and accumulates to form a long-lived cardiac reservoir of anthracycline [2,8,12–17]. It follows that regardless of the soundness of one molecular mechanism of toxicity or another, the risk of cardiotoxicity may ultimately depend on individual changes in the net levels of formation of secondary alcohol metabolites.

One should also comment on some disconnections between molecular pathways and clinical manifestations of anthracycline cardiotoxicity. The aforesaid mechanisms, primarily centered on mitochondrial dysfunction and formation of reactive oxygen species (ROS), fit quite well in a canonical phenotype of dilated cardiomyopathy and CHF. As it was said earlier, however, certain patients (childhood cancer survivors) developed subclinical dilated cardiomyopathy that eventually progressed to restrictive cardiomyopathy with preserved or less compromised LVEF [18]. Anthracycline-induced gene expression changes that caused cardiac remodeling and collagen deposition should therefore be taken in a due consideration [19]. On balance, it seems that even for 40-years old drugs, like anthracyclines, the mechanisms and clinical correlates of cardiotoxicity remain too vague or unexplored to form a solid basis for choosing one defined strategy of prevention or treatment.