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Cancer Therapy-Induced Cardiotoxicity: Where are We Now?

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Abstract

Cardiotoxicity effects, cardiovascular diseases (CVDs), and hypertension occurring months to several years post-chemotherapy and/or radiotherapy are well-recognized by experts. Anthracyclines were found in the late 1960s to be dose-dependently associated with induced-cardiotoxicity, often leading to cardiomyopathy and cardiac failure. Since then, epidemiologic research has led to some advances, although pivotal questions about global incidence, populations at risk, cellular mechanisms, and preventive treatments remain either incompletely understood or unaddressed. For instance, the incidence of cancer-surviving patients who die of cardiac failure after chemotherapy and/or radiotherapy is still a subject of debate - for reasons that are unclear, available statistics vary significantly from one epidemiology study to another. Moreover, no safe cardioprotective agents have yet been fully endorsed and approved by regulatory agencies for prevention or treatment of this specific medical problem. A drug called dexrazoxane was initially approved by the US Food and Drug Administration and the European Medicines Agency, but a restricted use notice was released in 2011 since several cases of secondary acute myeloid leukemia and myelodysplactic syndrome had been reported. As of today, hematologists and cardiologists remain generally reluctant to recommend dexrazoxane or other cardioprotective drugs (off-label prescription), probably because of unclear risks and lack of evidence-based medicine. Questions about unexpected adverse events or drug-drug interaction issues reducing the efficacy of specific chemotherapies also need to be addressed.

Keywords: Cardiotoxicity; Cardioprotective Drugs

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death. According to the World Health Organization (WHO), an estimated 17 million people die each year of CVDs, which corresponds to approximately 30% of all deaths worldwide [1]. Cancer is the second cause of death globally, being associated with the deaths of nearly nine million individuals each year [2]. Unfortunately, the incidence of cancer is expected to rise by about 70% over the next two decades, according to the WHO [3]. Today, 50% of those initially diagnosed with cancer survive for at least 10 years, but according to some experts, this survival rate should increase significantly in the future [4,5].

For these reasons, the number of cancer survivors expected to develop secondary conditions and life-threatening diseases associated with cancer drugs or radiotherapies will also increase. According to some researchers, this relatively new unmet medical need of chemotherapy- and radiotherapy-induced CVDs is bound to reach epidemic proportions in the near future [5, 6].

2. Cardioprotective Drugs

Anthracyclines (e.g. doxorubicin, epirubicin, daunorubicin, idarubicin) are among the first cancer drugs to be identified as medicines leading to increased risk of CVDs. They are antibiotics derived from Streptomyces and have been widely used for more than 50 years against leukemia, lymphoma, and breast, stomach, uterine, ovarian, bladder, and lung cancers [7]. Daunorubicin, one of the first anthracyclines to be used, was reported in the late 60s to induce significant adverse cardiac events, including cardiomyopathies and cardiac failures in children [8]. Dose-dependent/agent-specific cardiotoxicity is now generally considered a significant medical concern [9]. In child cancer survivors, some statistics report incidences of asymptomatic myocardial dysfunction ranging from 18 to 57%, with 5% suffering heart failure problems [10]. Comparable risks of heart failure were found with doxorubicin at a dose of 400 mg/m^2, and exponentially increasing risks at doses above 500 mg/m^2 [11]. Other studies indicate that cancer survivors have 15-fold greater risks of experiencing congestive heart failure and 10-fold higher rates of CVDs [12,13]. Furthermore, higher risks of cardiovascular morbidity and mortality may persist up to 45 years post-chemotherapy or radiotherapy [14,15]. Radiation-induced CVDs are also well-recognized. In the case of breast cancer for instance, radiotherapy has been clearly associated with myocardial fibrosis and cardiomyopathy, coronary artery disease, valvular disease, pericardial disease, and arrhythmias [43].

Anthracyclines are still today considered among the most efficient drugs currently available against most types of cancer. Of course, other drugs could be used to avoid cardiomyopathies and heart failures, but none of these alternatives have clearly been shown not to induce CVDs (see Table 1). In fact, a detailed list of all cancer drugs and their associated risks of CVDs is lacking. However, we know that alkylating agents (cyclophosphamide, ifosfamide), platinum agents, antimetabolites (5-fluorouracil, capecitabine), antibiotics (mitoxantrone, mitomycin, bleomycin), and antimicrotubule agents (taxanes) can all cause heart disease [16]. We also know that hypertension may be induced by some chemotherapeutic agents such as angiogenesis inhibitors (17%–80%), alkylating agents (36%–39%), and immunosuppressants after stem-cell transplantation (30%–80%) [17,18]. Angiogenesis inhibitors known as vascular signaling pathway inhibitors and anti-vascular endothelial growth factor antibodies (e.g.

bevacizumab and certain tyrosine kinase inhibitors such as sunitinib, sorafenib, and pazopanib) are also clearly associated with hypertension. The incidence of de novo or worsening hypertension in association with these drugs varies between 17% and 80% [19].

Families/Classes	Types	Compounds	Cardiotoxic
Alkylating drugs	nitrogen mustards	mechlorethamine	unclear
		melphalan	yes [28]
		chlorambucil	unclear
		cyclophosphamide	yes [29,30,33]
		ifeofamide	yes [30,33]
	alkyl sulphonates	busulfan	yes [31,33]
	triazines	dacarbazine	yes [32]
		temozolomide	unclear
	nitrosoureas	carmustine	yes [33]
		lomustine	unclear
		streptozocin	unclear
	metal salts	cisplatin	yes [30,33]
		carboplatin	unclear
		oxaliplatin	yes [34]
		pentostatin	yes [33]
	ethylenimine derivatives	thiotepa	unclear
Antimetabolites	antifolates	methotrexate	yes [36]
		raltitrexed	unclear
		permetrexed	unclear
	purine analogues	cladribine	yes [33]
		fludarabine	unclear
		mercaptopurine	unclear
		thioguanine	unclear
	pyrimidine analogues	azacitidine	unclear
		capecitabine	yes [30]
		cytarabine	yes [31]
		5-flourouracil	yes [30,31,33]
		gemcitabine	yes [37]
Natural products	anthracyclines	bleomycin	yes [30]
		dactinomycin	unclear

		daunorubicin	yes [38]
		doxorubicin	yes [32]
		epirubicin	yes [35]
		idarubicin	yes [38]
		mitomycin	yes [30,33]
		mitoxantrone	yes [30]
		liposomal daunorubicin	unclear
		liposomal doxorubicin	unclear
	enzymes	asparginase	yes [31,33]
	taxanes	doxcetaxel	unclear
		paclitaxel	unclear
	mitotic inhibitors	vinblastine	unclear
		vincristine	yes [39]
		vinorelbine	yes [40]
		vindesine	unclear
	topoisomerase I inhibitors	irinotecan	unclear
		topotecan	unclear
	topoisomerase II inhibitors	etoposide	yes [31,33]
		tenoposide	yes [31,33]
Other	substituted urea	hydroxyurea	unclear
	somastostatin analogues	octreotide	unclear
	adrcnoconical suppressants	mitotane	unclear
	methylhydrazine derivatives	procarbazine	unclear
	salts	arsenic trioxide	yes [41]
	phosensitizing agents	porfimer sodium	yes [42]
	substituted melamines	altretamine	unclear

Table 1: List of current standard cancer drugs with evidence or lack of evidence of CVDs

Regarding mechanisms, many questions remain. Nonetheless, there is compelling evidence suggesting that various pathophysiological mechanisms exist, and that each family of cancer drugs affects heart functions through specific actions upon these different mechanisms. Some of the proposed mechanisms include: 1) direct cellular toxicity, with a cumulative myocardial injury, resulting in both diastolic and systolic dysfunction; 2) effects on the coagulation system, resulting in ischemic events, thrombogenesis and vascular toxicity; 3) arrhythmogenic effects; 4) hypertensive effects; 5) myocardial and/or pericardial inflammation associated with myocardial dysfunction or pericardial sequels [45].

Physical activity and at least one cardioprotective agent, dexrazoxane, have been shown to prevent and mitigate cardiotoxicity (although not safely in the case of dexrazoxane, according to the restricted use notice released in 2011) [20,44], but additional studies are urgently needed to understand further the pathophysiology of chemotherapy-induced cardiotoxicity, and to explore safe and potent combination therapies capable of treating cancer while preventing CVDs.

According to the National Cancer Institute, two hundred different drugs have been approved in the US for use against cancer (www.cancer.gov). They belong to different families and a wide variety of subtypes based on chemical structure and physiological actions or targets, but the alkylating drugs, antimetabolites, and natural products constitute the main families of drugs against cancer. As of today, several of them have clearly been associated with CVDs, either based on results in dissociated cells, animal models, or patients (Table 1).

Several populations are at risk of further developing CVDs. Children are among the first groups identified to suffer specifically from chemotherapy-induced CVDs [8] and secondary acute myeloid leukemia and myelodysplactic syndrome following combination therapy with anthracyclines and dexrazoxane. CVDs also occur with greater incidence in people with a spinal cord injury or multiple sclerosis [21, 22]. Chronic spinal cord injury has also been associated with greater incidence of some cancers (e.g. bladder, esophageal, liver, and hematologic cancer) [23, 24]. People suffering from obesity and type 2 diabetes are obviously also at risk of CDVs. Actually, the first risk factors of CVDs are overweight, weight fluctuations, and related lack of physical exercise [25; see also www.world-heart-federation.org]. People at risk also include the elderly and those smoking or excessively drinking alcohol, as well as those with high levels of LDL cholesterol, triglycerides and/or hypertension [27].

In the future, several avenues should be explored by physicians and scientists. Healthcare professionals should expand and extend long-term surveillance and pharmacovigilance (i.e. greater than the five years post-treatment milestone) associated with CVDs to further document the incidence, prevalence and subpopulations most at risk. Biomedical experts and other scientists should focus on unraveling new mechanisms and cellular targets, enabling the identification of innovative solutions and alternative drug candidates. Given that chemotherapy-induced cardiotoxicity should still be considered an unmet medical need, the industry should increase efforts and investments in R&D activities for the clinical development of new candidate products. In the meantime, healthcare professionals should attempt to prevent cardiotoxicity by screening for risk factors, monitoring for signs and symptoms during chemotherapy, and continuing follow-up that may include electrocardiographic and echocardiographic studies, angiography, and measurements of biochemical markers of myocardial injury.

Conflict of Interest

None declared

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