International Journal of Cardiology 224 (2016) 366–375

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Management and research in cancer treatment-related cardiovascular toxicity: Challenges and perspectives

Jennifer Cautela [a,b,c,d], Nathalie Lalevée [e], Chloé Ammar [a,b,c,d], Stéphane Ederhy [f], Michael Peyrol [a,b,c,d], Philippe Debourdeau [c,g], Daniel Serin [c,g], Yvan Le Dolley [c,h], Nicolas Michel [c,h], Morgane Orabona [a,b,c,d], Jérémie Barraud [a,b,c,d], Marc Laine [a,d], Laurent Bonello [a,d,i], Franck Paganelli [a,d,i], Fabrice Barlési [b,c,j], Franck Thuny [a,b,c,d,*]

[a] Aix-Marseille University, Assistance Publique – Hôpitaux de Marseille (AP-HM), Mediterranean university Cardio-Oncology center (MEDI-CO center), Unit of Heart Failure and Valvular Heart Diseases, Department of Cardiology, Hôpital Nord, France
[b] Aix-Marseille University, Assistance Publique – Hôpitaux de Marseille (AP-HM), Oncosafety Network of the Early Phases Cancer Trials Center (CLIP²), France
[c] Groupe Méditerranéen de Cardio-Oncologie (gMEDICO), France
[d] Mediterranean Academic association for Research and Studies in Cardiology (MARS Cardio), France
[e] Aix-Marseille University, Technological Advances for Genomics and Clinics (TAGC), UMR/INSERM 1090, France
[f] Assistance Publique – Hôpitaux de Paris (AP-HP), Department of Cardiology, Saint-Antoine Hospital, France
[g] Sainte Catherine Institute, Department of Medical Oncology, Avignon, France
[h] Hôpital Saint Joseph, Department of Cardiology, Marseille, France
[i] Aix-Marseille University, INSERM, UMRS 1076, France
[j] Aix-Marseille University, Multidisciplinary Oncology & Therapeutic Innovations Department, Assistance Publique – Hôpitaux de Marseille (AP-HM), Hôpital Nord, France

ARTICLE INFO

Article history:
Received 19 July 2016
Received in revised form 1 September 2016
Accepted 15 September 2016
Available online 17 September 2016

Keywords:
Cardiovascular toxicity
Survivorship
Cardio-oncology
Cancer therapy
Prevention
Heart failure

ABSTRACT

Cardiovascular toxicity is a potentially serious complication that can result from the use of various cancer therapies and can impact the short- and long-term prognosis of treated patients as well as cancer survivors. In addition to their potential acute cardiovascular adverse events, new treatments can lead to late toxicity even after their completion because patients who survive longer generally have an increased exposure to the cancer therapies combined to standard cardiovascular risk factors. These complications expose the patient to the risk of cardiovascular morbi-mortality, which makes managing cardiovascular toxicity a significant challenge. Cardio-oncology programs offer the opportunity to improve cardiovascular monitoring, safety, and management through a better understanding of the pathogenesis of toxicity and interdisciplinary collaborations. In this review, we address new challenges, perspectives, and research priorities in cancer therapy-related cardiovascular toxicity to identify strategies that could improve the overall prognosis and survival of cancer patients. We also focus our discussion on the contribution of cardio-oncology in each step of the development and use of cancer therapies.

1. Introduction

Cancer and cardiovascular diseases are the two leading causes of death in the United States and Europe, where they are responsible for almost 50% of overall mortality [1]. Recent cancer therapeutic strategies have improved the survival of patients. Between 2008 and 2012, age-standardized mortality rates in women with cancer decreased by 1.5% per year and in men with cancer by 1.0% per year in Europe (National Institute of Cancer; www.e-cancer.fr). Nevertheless, the improvement in survival due to cancer therapies has a cost because these treatments can be sources of deleterious effects on the cardiovascular system. The increase in the median survival of patients treated for cancer has sometimes resulted in the development of cardiovascular events or the exacerbation of underlying cardiovascular diseases because of an increased exposure time to cancer therapies. Additionally, the median age of patients receiving cancer treatment has increased, resulting in potentially toxic drugs being prescribed to a population with a higher prevalence of cardiovascular diseases and risk factors. Therefore, the risk of developing cardiovascular events in cancer survivors can become greater than that of recurrent malignancy [2]. For example, compared with the

Abbreviations: ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CTCAE, Criteria for Adverse Events; HER/EGFR/ERBB, epidermal growth factor receptor; GLS, global longitudinal strain; LV, left ventricle; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; VEGF, vascular endothelium growth factor.

* Corresponding author at: Mediterranean Cardio-Oncology university center (MEDI-CO center), Unit of Heart Failure and Valvular Heart Diseases, Hôpital NORD, Chemin des Bourrely, 13015 Marseille, France, Assistance Publique – Hôpitaux de Marseille (AP-HM), Aix-Marseille Université.
E-mail address: franck.thuny@gmail.com (F. Thuny).

http://dx.doi.org/10.1016/j.ijcard.2016.09.046
0167-5273/

general population, survivors of childhood cancer are at a 15-fold increased risk of developing heart failure [3] and a seven-fold increased risk of premature death due to cardiac events [4]. Moreover, women who are breast cancer survivors have a significantly increased risk of death caused by cardiovascular diseases, which exceeds their risk of death from their initial cancer or recurrence. In this latter population, cardiovascular diseases are the leading cause of death [5].

Whereas the incidence of cardiovascular adverse events is relatively low in cancer clinical trials, "real-life" data have revealed a much higher incidence of adverse life-threatening effects [6]. This increased incidence results from the exclusion of patients at very high risk of cardiovascular events and the rapid development and marketing of these new effective therapies without sufficient follow-up to identify potential side effects. Furthermore, it has been shown that the majority of patients with cancer therapy-induced left ventricular dysfunction (LVD) do not receive optimal cardiologic treatment resulting in a poorer therapeutic response [7]. This fact can be explained by a long undetected asymptomatic period of cardiovascular toxicity preceding signs and symptoms, a lack of comprehensive care for patients, and the absence of a consensus regarding monitoring recommendations, limiting their applicability in practice.

Regardless of whether the "old" classes of cytotoxic chemotherapy drugs, radiotherapy, or a more recently discovered targeted therapy is prescribed, the majority of these treatments have the potential to induce cardiovascular toxicity through different mechanisms by affecting the myocytes, endothelial cells, or the cardiac conduction system. These toxicities consist mainly of direct myocardial injury with or without heart failure, systemic hypertension, QTc prolongation, arrhythmias, myocardial ischemia, pulmonary hypertension, arterial/venous thromboembolic events, accelerated atherosclerosis, pericardial diseases, and valvular heart diseases. Moreover, many anti-cancer drugs have metabolic effects that can increase the risk of cardiovascular disease. Therefore, cardiovascular toxicity management has become challenging because it could significantly influence global survival. In response, the cardio-oncology sub-specialty has recently emerged to prevent, screen, and treat cardiovascular diseases related to, or associated with, cancer treatments without compromising their effectiveness. Through a multidisciplinary approach involving cardiologists and oncologists, this discipline aims to provide optimal care for patients with cardiovascular diseases or risk factors, from the diagnosis of cancer to the remainder of their lives, even after treatment completion. Over the last few years, hospitals in the United States, Canada, and Europe have developed cardio-oncology programs [8–11], allowing for better coordination in the management of patients owing to facilitated access to comprehensive cardiovascular assessment by specialized cardiologists (cardio-oncologists) and better evaluation of the therapeutic benefit-to-risk ratio of cancer treatments by closer communication between cardiologists and oncologists. This partnership has been supported by different actions from professional scientific societies. The American College of Cardiology has approved a cardio-oncology section under its umbrella, and the Canadian Cardiovascular Society recently published guidelines for the evaluation and management of cardiovascular complications of cancer therapy, including chapters on recommendations for a multidisciplinary approach to cardio-oncology [12].

Nevertheless, substantial discrepancies exist in terms of cardiovascular toxicity definitions and cardiovascular follow-up because of a lack of strong evidence to guide therapies. In this review, we aim to discuss new challenges, perspectives, and research priorities in cancer therapy-related cardiovascular toxicity to identify strategies that could improve the overall prognosis and survivorship care of cancer patients.

2. The need for accurate and uniform definitions of cardiovascular toxicity

Cardiovascular toxicities consist mainly of direct myocardial injury with or without heart failure, systemic hypertension, QTc prolongation, arrhythmia, myocardial ischemia, pulmonary hypertension, arterial/venous thromboembolic events, accelerated atherosclerosis, and pericardial or valvular heart diseases. Although the definite implications of a cancer therapy in the occurrence of cardiovascular events are sometimes difficult, and they strongly depend on the evolution after the pre-therapeutic assessment, the definitions of cancer treatment-related LVD and systemic hypertension are especially challenging because of discrepancies between diagnostic criteria. Nevertheless, the detection of potential cardiovascular effects begins with a careful clinical assessment, paying attention to subtle signs and symptoms such as minor impairment of exercise capacity and resting tachycardia [13].

2.1. How to define cancer treatment-induced LVD and heart failure

Many cancer drugs have direct toxic effects on the myocardium, which leads to LVD and ultimately to heart failure. A classification system based on the irreversible (type I agents) or reversible (type II agents) nature of myocardial injury has been proposed [14]. Anthracyclines are considered to be a classic example of type I agents, and targeted therapies (e.g., trastuzumab) are referred to as type II agents. However, this classification is not perfect and therefore might be abandoned [15]. Indeed, cases of irreversible LVD have been reported with the use of type II agents. Additionally, anti-cancer agents from both categories are often combined, making it difficult to draw conclusions regarding the possibility of left ventricular (LV) functional recovery.

The definition of cardiac toxicity has undergone many changes in recent years. Initially, only the occurrence of clinical signs and/or symptoms of heart failure were considered. Then, following advances in cardiac imaging and the development of serum biomarkers, preclinical abnormalities were added to the definition [16–19]. Moreover, new-onset or worsening LVD can be related not only to direct myocardial toxicity but also to systemic hypertension or myocardial ischemia induced by some cancer treatments.

The Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology, used for adverse event reporting in oncology [20]. A grading scale (1 to 5) is provided for each adverse event term. Recent versions of this classification do not strictly describe each stage of cardiac toxicity (Supplement file 1), and they use definitions of LVD, depressed LVEF, and heart failure that could cause confusion because they strongly differ from those of the American College of Cardiology/American Heart Association and the ESC [21,22]. For example, LVD is defined beginning with grade 3 disease and the occurrence of symptoms due to a drop in the response of the LV ejection fraction (LVEF) to intervention. This latter definition is inadequate because it addresses only symptomatic patients and suggests no therapeutic intervention for asymptomatic patients. However, it has been strongly demonstrated that treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and beta-blockers improves outcome when introduced early in cases of reduced LVEF, even in asymptomatic patients [23,24]. Moreover, the CTCAE defines grade I heart failure as an asymptomatic condition with laboratory (e.g., B-natriuretic peptide [BNP]) or cardiac imaging abnormalities. This latter definition is also unsuitable because it does not specify the type of cardiac imaging abnormalities that should be analyzed.

The decrease in LVEF, as measured by echocardiography, a multigated acquisition scan or magnetic resonance imaging, has become the reference for defining systolic LVD. However, the threshold values used have historically been inconsistent [25]. The CTCAE defines a significant decrease in LVEF when resting LVEF = 50–40% associated with a 10–19% drop from baseline. However, a recent consensus between the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) defined cardiac dysfunction related to cancer therapies as a decrease in LVEF > 10 percentage points to a value < 53% [26]. This definition was recently slightly modified by changing the 53% cut-off value by 50% to be in accordance with the CTCAE [11]. Although this latter has the merit of consensus, it remains insufficient for identifying early myocardial injury and is