



Contents lists available at ScienceDirect

International Journal of Cardiology

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

Practices in management of cancer treatment-related cardiovascular toxicity: A cardio-oncology survey

Ludovic Jovenaux^{a,b,c,d,1}, Jennifer Cautela^{a,b,c,d,1}, Noemie Resseguier^{e,1}, Michele Pibarot^{f,1}, Myriam Taouqi^{f,1}, Morgane Orabona^{a,b,c,d,1}, Johan Pinto^{a,b,c,d,1}, Michael Peyrol^{a,b,1}, Jeremie Barraud^{a,b,1}, Marc Laine^{a,b,1}, Laurent Bonello^{a,b,1}, Franck Paganelli^{a,b,c,d,1}, Fabrice Barlesi^{c,d,g,1}, 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 Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), France

^c Groupe Méditerranéen de Cardio-Oncologie (gMEDICO), France

^d Aix-Marseille University, Assistance Publique – Hôpitaux de Marseille (AP-HM), Oncosafety Network of the Early Phases Cancer Trials Center (CLIP²), France

^e Aix-Marseille University, Department of Public Health, Research Unit EA 3279, France

^f Assistance Publique – Hôpitaux de Marseille (AP-HM), ONCO-PACA-CORSE Oncology Regional Network, France

^g Aix-Marseille University, Multidisciplinary Oncology & Therapeutic Innovations Department, Assistance Publique – Hôpitaux de Marseille (AP-HM), Hôpital Nord, France

ARTICLE INFO

Article history:

Received 23 December 2016

Accepted 13 February 2017

Available online xxxx

Keywords:

Cardiotoxicity
Cardio-oncology
Cancer therapy
Prevention
Heart failure

ABSTRACT

Background: Cardiovascular toxicity has become a challenging issue during cancer therapy. Nonetheless, there is a lack of consensual guidelines for their management. We aimed to determine the current practices of oncologists regarding cardiovascular toxicity related to anthracyclines, trastuzumab and angiogenic inhibitors and to gather their opinions on the development of cardio-oncology programs.

Methods: A cross-sectional declarative study was submitted to French oncologists in the form of an individual, structured questionnaire.

Results: A total of 303 oncologists responded to the survey. Ninety-nine percent of oncologists prescribed cardiotoxic therapies, including anthracyclines (83%), trastuzumab (51%) and other angiogenic inhibitors (64%). The method adopted for managing cardiovascular toxicity was based on guidelines from expert oncology societies for only 35% of oncologists. None was aware of recommendations from expert cardiology societies. Prescription of pre-, peri- and post-therapy cardiovascular assessment was inconsistent and significantly less frequent for all classes of angiogenic inhibitors than for anthracyclines and trastuzumab ($P < 0.0001$). Relative to pre-therapy assessment, post-therapy assessment was prescribed significantly less often for all cancer therapies ($P < 0.0001$). Attitudes regarding the onset of left ventricular dysfunction were much more inconsistent when angiogenic inhibitors were involved. Additionally, the management of hypertension and QT prolongation was also inconsistent. Finally, 88% of oncologists supported projects of cardio-oncology programs development.

Conclusions: Practices of oncologists are disparate in the field of cardiovascular toxicity. This finding underlines the complexity of managing many different situations and the need for distribution of formal guidelines from oncology and cardiology expert societies. The development of personalized cardio-oncology programs seems essential.

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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].

Cancer therapies are being rapidly developed and have improved the prognosis of many patients [2]. Nevertheless, the improvements in survival due to new cancer therapies bring a cost because these treatments can have deleterious effects on the cardiovascular system [3]. These include myocardial dysfunction, systemic hypertension, QT prolongation, arrhythmias, myocardial ischemia, pulmonary hypertension,

Abbreviations: ASCO, American Society of Clinical Oncology; ASE/EACVI, American Society of Echocardiography/European Association of Cardio-Vascular Imaging; ESMO, European Society of Medical Oncology; VSP, vascular endothelium growth factor pathway; TTE, transthoracic echocardiography.

* Corresponding author at: Mediterranean University Cardio-Oncology Center (MEDI-CO Center), Unit of Heart Failure and Valvular Heart Diseases, Hôpital NORD, Chemin des Bourrely, 13015 Marseille, France.

E-mail address: franck.thuny@gmail.com (F. Thuny).

¹ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

<http://dx.doi.org/10.1016/j.ijcard.2017.02.154>

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Please cite this article as: L. Jovenaux, et al., Practices in management of cancer treatment-related cardiovascular toxicity: A cardio-oncology survey, *Int J Cardiol* (2017), <http://dx.doi.org/10.1016/j.ijcard.2017.02.154>

thrombo-embolic events, accelerated atherosclerosis, pericardial and valvular heart diseases [4]. This toxicity can be observed very early or many years after the use of “old” classes of cytotoxic chemotherapy drugs or the most recent targeted therapies [3,5–7]. Furthermore, as a consequence of the aging population, cancer and cardiovascular diseases frequently co-exist, sometimes in an unknown manner [8,9]. Thus, cardiovascular toxicity management has become challenging because it could significantly influence global survival [10]. International guidelines on cardiovascular monitoring during and after cancer treatment lack consensus and are not based on substantial evidence, in particular for the novel targeted cancer therapies [11–16]. Additionally, the current practices regarding management of cardiovascular toxicity remain unknown.

Accordingly, we designed a national survey of French oncologists. The purpose of the study was to (1) analyze their professional practices in the field of prevention, screening, and treatment of cancer-therapy-related cardiovascular toxicity and (2) solicit their opinions on cardio-oncology programs that have recently emerged to manage cardiovascular diseases related to cancer treatments [10,17–19].

2. Methods

2.1. Study design and sample

Between August 2015 and August 2016, we conducted a cross-sectional declarative survey in the form of an individual, structured questionnaire that was submitted to the 918 French medical oncologists working in teaching and non-teaching hospitals, cancer centers and private healthcare facilities in France (data from the French National Medical Council). The oncologists were invited to participate via regional oncology networks. The oncologists were first contacted by phone or e-mail to agree on a date for an interview, either in person or by phone, during which the answers to the survey questions were collected. They also had the opportunity to complete the questionnaire via an online version that was created for this purpose. For both paper- and web-based formats, we used an established method for questionnaire distribution to maximize response rates that involved a preliminary notice, an invitation letter with a questionnaire and up to 2 reminders, and another copy of the survey for non-responders. We merged all study data into a secure central database for analysis.

2.2. Survey instrument

The questionnaire was composed of items written by four oncologists and four cardiologists specializing in cardio-oncology. The survey was arranged into three distinct sections, covering successively the following topics (Supplementary-file 1):

Section (i): The profile of the oncologist and the organization of cardiovascular monitoring and management within their healthcare facility. This profile included specialization of the practitioner, fields of competence, place of work, professional experience and prescription of drugs with potential cardiovascular toxicity. It also discussed the physical presence within the structure of a cardiologist, a cardiology department, a cardiology care unit or a cardio-oncology unit, and the access within the structure of performing transthoracic echocardiography (TTE) studies. Our survey was focused on the most commonly used drugs with potential cardiovascular toxicity including anthracyclines, trastuzumab, vascular endothelium growth factor pathway (VSP) monoclonal antibodies and other angiogenic inhibitors.

Section (ii): The practice of the oncologist in the field of cardiovascular toxicity. Questions covered awareness of the existence of guidelines from expert societies and, in particular, the recommendations of the *European Society of Medical Oncology* (ESMO) [13] and the consensus of experts from the *American Society of Echocardiography/European Association of Cardiovascular Imaging* (ASE/EACVI) [14]. It also covered awareness of cardiovascular toxicity regarding the drugs prescribed,

knowledge of screening methods and definitions of toxicity. Furthermore, it requested the cardiologist to estimate the number of patients who have presented with proven cardiovascular toxicity in association with a cancer therapy, the number of patients rejected from optimal cancer treatment because of a previous cardiovascular disease or risk factors and types of cardiovascular toxicity leading to interruption of cancer therapy. Finally, it covered modalities for pre-, peri- and post-therapy cardiovascular assessment, approaches to left ventricular dysfunction and prolongation of the QTc interval or hypertension.

Section (iii): Personal opinions regarding cardio-oncology programs; whether cardio-oncology is of any value, openness to the opinion of a specialized cardiologist, the level of cardio-oncology expertise of the cardiologists with whom he or she works and whether there are obstacles to the creation or development of cardio-oncology programs.

Information indicating that participation was voluntary and ensuring confidentiality was provided. Responding to the survey implied that the oncologists had given their consent to participate in the study.

2.3. Statistical analysis

Categorical variables are described as counts and percentages with their 95% confidence intervals. The answers to the questions were expressed using a 5- or 6-category Likert scale. To facilitate presentation, certain responses were grouped together to form three categories. χ^2 tests were used to compare the different groups. Statistical significance was defined as $P < 0.05$. All tests were 2-sided. Analyses were conducted using SPSS Statistics Software, version 20.0 (IBM Inc., New York, USA).

3. Results

3.1. Oncologists profiles and cardiovascular management organizations

Of the 918 oncologists working in France, 303 responded to the survey. All regions of France were represented (Supplementary-file 2). The profiles of oncologists and the organizations of cardiovascular management are summarized in Table 1. Three hundred and one oncologists (99%) had prescribed potentially cardiotoxic cancer therapies, including anthracyclines (83%), trastuzumab (51%), VSP antibodies (63%) and other angiogenic inhibitors (66%). Eighty-three percent of the oncologists worked with cardiologists in the same healthcare facility. To assess left ventricular function, 283 oncologists (93%) had used TTE, 156 (51%) had used isotopic ventriculography, and 75 (25%) had used cardiac MRI.

3.2. Global practices in the field of cardiovascular toxicity

The method adopted by oncologists for managing the cardiovascular toxicity of cancer therapies was based essentially (52%) on data obtained from the clinical trials conducted for each drug. Only 105 oncologists (35%) declared that they used the guidelines of expert societies of oncology. None was aware of recommendations published by expert societies of cardiology in this field.

All the oncologists were aware that anthracyclines and trastuzumab could cause left ventricular dysfunction and heart failure. However, this toxicity was known to only 55% of oncologists for the VSP antibodies and 68% for the other angiogenic inhibitors. For these two types of angiogenic inhibitors, the main types of cardiovascular toxicity cited were hypertension (cited by 90% and 74% of the oncologists, respectively) and venous thromboembolic events (83% and 51% of the oncologists, respectively).

One hundred and fifteen oncologists (38%) were unaware of the existence of early screening methods for left ventricular dysfunction. Using biomarkers such as troponin for this purpose or assessing global longitudinal strain in TTE were known methodologies to only 30% and 32% of oncologists, respectively. Seventy-five oncologists (25%) were

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