Cardio-oncoimmunology: An emerging medical discipline

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The two main causes of mortality worldwide are currently cardiovascular diseases and various types of cancer. Whereas cancer constitutes the major cause of death among adults up to 74 years of age, after this age, cardiovascular disease surpasses cancer as the primary cause of mortality [1]. Recent advancements in cancer treatment and diagnosis have contributed to the presence of nearly 14.5 million American cancer survivors in 2014, that are anticipated to reach 18 million by the current year 2020 [2].

However, despite these therapeutic advancements, practicing physicians often face problems, during both chemotherapy and radiotherapy, related to cardiovascular dysfunction and cardiac function deterioration. Cardiovascular deterioration can be manifested as acute and chronic cardiac events as shown in the table 1. Chemotherapeutic drugs can affect the cardiovascular system either through direct effects to cardiac myocytes resulting in cardiomyopathy, or indirect effects, such as hypertension, subsequently increasing the risk of cardiac disease [3].

Radiation therapy can induce heart failure that may become evident months or years after radiotherapy completion. Structural abnormalities such as valvular heart disease, circulatory problems including coronary artery disease, carotid artery disease, pericarditis, pericardial effusion and myocardial infarction associated with further electrical abnormalities like rhythm and conduction disturbances may follow radiotherapy [4].

As far as the pathophysiology of chemotherapy-related cardiovascular dysfunction is concerned, there is clinical and laboratory evidence that acute coronary syndromes, myocarditis and cardiac arrhythmias are not induced

Table 1. *Potential acute and chronic cardiac events during chemotherapy.*

Acute conditions	Acute myocardial infarction
	Cardiac arrhythmias (bradycardia, tachyarrhythmias, atrio-ventricular blocks, QT prolongation, torsades de pointes)
	Coronary spasm
	Heart failure
	Hypotension
	Myocardial infarction
	Myocarditis
	Pericardial effusion
	Pericarditis
	Stroke
	Thromboembolism
Chronic conditions	Cardiomyopathy
	Congestive cardiac failure
	Coronary artery disease
	Diastolic left ventricular dysfunction
	Hypertension
	Peripheral vascular disease
	Pulmonary hypertension
	Systolic left ventricular dysfunction
	Valvular heart disease

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by cardiac toxicity, but mainly by hypersensitivity and especially by coronary hypersensitivity and Kounis syndrome [5,6].

CHEMOTHERAPY-INDUCED CARDIAC TOXICITY

Cardiac toxicity during chemotherapy, generally, refers to a dose-dependent cardiovascular adverse reaction depending on the quantity of substance to which the organism is exposed and the route of exposure, for example skin absorption, mouth ingestion, or respiratory tract inhalation, that persists despite the discontinuation of the causative treatment. The final outcome of cardiac toxicity is a fibrotic response that should be confirmed histologically, a procedure that has not been undertaken until now [7]. Cardiac toxicity can be acute involving deleterious consequences through a single or short-term exposure. Subchronic toxicity is the ability of a toxic substance to cause effects lasting for more than one year but less than the lifetime of the exposed organism, usually upon repeated or continuous exposure, sometimes lasting for the entire life of the exposed organism. Chronic toxicity is referred as the ability of a substance or mixture of substances to exert their harmful effects over an extended period. However, the definition, characterization and pathophysiology of cardiac dysfunction during chemotherapy have not been completely elucidated. There are several discrepancies among the medical societies regarding the term cardiac toxicity leading to a lack of consensus especially when this term is used to characterize the acute adverse effects of chemotherapeutic monoclonal antibodies.

The National Cancer Institute defines cardiovascular dysfunction as "toxicity that affects the heart" [8]. The American Society of Echocardiography and the European Association of Cardiovascular Imaging define cardiovascular dysfunction as a decrease of left ventricular ejection fraction of 10% that is confirmed on a repeat study within 2–3 weeks [9]. The National Comprehensive Cancer Network defines cardiovascular dysfunction as "cardiac toxicity referred to the heart damage by harmful chemicals" [10]. Finally, the most accurate definition so far has been formulated [11] by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials and includes one or more of the following:

1. Heart failure symptoms
2. Cardiac signs, including audible third heart sound associated with gallop rhythm, tachycardia, or both
3. Global or more severe septal cardiomyopathy with reduced left ventricular ejection fraction
4. Left ventricular ejection fraction reduction from baseline that is in the range of ≤5% to ≤55%, with accompanying signs or symptoms of heart failure, or a reduction in left ventricular ejection fraction in the range of ≤10% to ≤55%, without accompanying signs or symptoms. The Committee has concluded that an ideal definition is still lacking given that the above definition does not include subclinical cardiovascular damage that may occur early in response to some chemotherapeutic agents.

CHEMOTHERAPY-INDUCED CARDIAC HYPERSENSITIVITY

Chemotherapeutic agents, in several occasions, have been associated with the development of serum antibodies able to induce a variety of cardiovascular, cutaneous, gastrointestinal, muscular, neurological and respiratory hypersensitivity reactions [12]. It seems that cardiac hypersensitivity is an appropriate term that should be used along with cardiac toxicity in order to describe the adverse events elicited by several chemotherapeutic agents including monoclonal antibodies.

Cardiovascular hypersensitivity, in particular, refers to an inflammatory response that is not dose-dependent, may arise at any time during treatment, even with minimal drug concentrations and is accompanied by anti-drug antibodies. Anti-drug antibodies are the most often encountered antibodies which belong to the IgG isotype, but a proportion of hypersensitivity reactions also involve IgE antibodies [13]. Several chemotherapeutic drugs including platinum agents, taxanes, chimeric monoclonal antibodies and others have been incriminated to induce IgE-mediated hypersensitivity reactions.

Platinum agents, such as cisplatin, carboplatin, oxaliplatin inhibit DNA replication and suppress cancer cells' division and proliferation. Cisplatin's hypersensitivity prevalence ranges from 5 to 20%, carboplatin's from 9 to 27%, and oxaliplatin's from 10 to 19% [14]. Cardiac hypersensitivity reactions to platinum agents can induce acute myocardial infarction such as Kounis syndrome [5,6,15], cardiac arrest and even death [16].

Taxanes, that are commonly known as microtubule inhibitors, mitotic inhibitors, and mitotic poisons including paclitaxel, docetaxel and others inhibit cell division, chromatid separation and growth events that may lead to cell death. Hypersensitivity reactions are common in patients receiving taxanes, ranging from mild to severe or even lethal, not responding to premedication therapy, and their prevalence is estimated to reach 30%

[17]. Immunoglobulin E-mediated anaphylaxis with increased tryptase levels, direct mast cell and/or basophil activation and complement activation are some of the mechanisms potentially underlying these reactions [18].

Chimeric monoclonal antibodies, (the name originates from the Greek mythological monstrous fire-breathing hybrid chimera composed of parts of several animals e.g. a lion body with a goat head of and a tail end with a snake's head, offspring of Typhon and Echidna and sibling of Cerberus and Lernaean Hydra) are used for the treatment of systemic inflammatory, neoplastic or hematological diseases. These antibodies bind to the epidermal growth factor receptor and block receptor dependent signal transduction pathways such as anti-apoptosis, angiogenesis, and tumor metastasis. Other antibodies act against tumor necrosis factor TNF-α and are used for the treatment of chronic inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and systemic vasculitis. These chimeric monoclonal antibodies have been incriminated to underlie acute or chronic cardiac hypersensitivity reaction, including chest pain, hypotension, severe life-threatening anaphylaxis and Kounis hypersensitivity-associated acute coronary syndrome [13].

Other chemotherapeutic agents, such as capecitabine which is an orally available pro-drug converted to 5-fluorouracil within the neoplastic tissue used for the treatment of metastatic colorectal and breast cancer, may also induce hypersensitivity reactions. Cardiac manifestations such as angina, acute coronary syndrome, arrhythmias, myocarditis, and heart failure are known/common side effects induced by 5-fluorouracil use. In a report of capecitabine-induced cardiac arrest from ventricular fibrillation, immunological markers indicated a type I Kounis hypersensitivity-associated syndrome as the underlying pathophysiological mechanism [19].

The majority of chemotherapeutic drugs are able to induce hypersensitivity reactions primarily of anaphylactic type I but also of types II, III, and IV [1]. Severe and lethal reactions have also occurred [1]. In addition, there are reports indicating specific allergic tests, especially in atopic and susceptible patients, and several colleagues have already performed such tests successfully [20].

THE CARDIO-ONCOIMMUNOLOGY DISCIPLINE

All of the above suggest that an emerging medical discipline termed cardio-oncoimmunology should encompass all scientific knowledge regarding the cardiovascular effects of chemotherapeutic. In this context the interdisciplinary cooperation among cardiologists, oncologists, hematologists, cardiac imaging specialists, immunologists, pathologists, allergists together with other medical professionals involved in cancer care seems to be of paramount importance. Furthermore, the need to incorporate several tests, measures, and actions before, during and long after chemotherapy in order to monitor for cardiac adverse events should be pursued. Several disciplines should be integrated in order to identify, diagnose, prevent, and treat cardiovascular complications associated with chemotherapy. We believe that cardio-oncology, onco-cardiology, immuno-oncology, and onco-immunology should had already been merged into a single discipline, that of cardio-oncoimmunology.

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