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Editorial

Cardio-oncology, Immuno-oncology, Onco-cardiology and Onco-immunology

Nicholas G. Kounis *, Ioanna Koniari, George Hahalis

Department of Cardiology University of Patras Medical School, Rion, Patras, Achaia, Greece

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Cardiovascular disease and cancer are the two main causes of mortality worldwide. Cancer constitutes the major cause of death among adults up to 74 years of age while following this age the cardiovascular disease surpasses cancer as the primary cause of mortality [1]. Recent advancements in cancer diagnosis and treatment have contributed to the presence of nearly 14.5 million American cancer survivors in 2014 [2], that are anticipated to reach 18 million by 2020 [3]. The lifetime probability of developing cancer in any site is 1 in 2 among men, and 1 in 3 among women [4]. Cancer incidence increases with age, and as life expectancy increases, there are rising numbers of elderly patients with cancer. In such an aging population with traditional cardiovascular risk factors, the chemotherapeutic drug administration has been correlated with further cardiovascular deterioration due to cardiac side-effects induced by these agents. Indeed, a childhood cancer survivorship study has reported that when hypertension and other cardiac risk factors operate on a cardiovascular system exposed to cancer therapy, survivors demonstrate a high risk of cardiac disease [5].

Cardiovascular dysfunction or cardiac function deterioration during chemotherapy might be attributed to either chemotherapeutic drugs or to radiation therapy. Cardiovascular deterioration can be manifested as acute cardiac events including coronary spasm, acute myocardial infarction, hypotension, cardiac arrhythmias (bradycardia, tachyarrhythmias, atrio-ventricular blocks, QT prolongation, torsades de pointes), pericarditis, myocarditis, pericardial effusion, thromboembolism, or as chronic conditions, such as hypertension, systolic and diastolic left ventricular dysfunction presenting clinically as heart failure or cardiomyopathy. Drugs can affect the cardiovascular system either through direct effects to cardiac myocytes resulting in cardiomyopathy, or have indirect impact, such as hypertension, subsequently increasing the risk of cardiac disease [6].

Radiation therapy can induce heart failure that will become evident after months or years after radiotherapy completion. Structural abnormalities as valvular heart disease, circulatory problems such as 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 [7].

The definition, characterization and pathophysiology of the cardiac dysfunction during chemotherapy have not been completely elucidated. The term cardiotoxicity lacks consensus across the medical societies, especially when this term is used to characterize the acute adverse effects of chemotherapeutic monoclonal antibodies. Cardiac toxicity, generally, refers to a dose-dependent cardiovascular adverse reaction involving 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. Acute toxicity involves deleterious consequences in an organism through a single or short-term exposure. Subchronic toxicity is the ability of a toxic substance to cause effects for more than one year but less than the lifetime 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.

The National Comprehensive Cancer Network defines cardiovascular dysfunction as “cardiac toxicity referred to the heart damage by harmful chemicals” [8], the National Cancer Institute as “toxicity that affects the heart.” [9]. The American Society of Echocardiography and 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 [10]. Finally, the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials has

* Corresponding author at: Queen Olgas Square, 7 Aratou Street, Patras 26221, Greece.
E-mail address: ngkounis@otenet.gr (N.G. Kounis).

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offered a most accurate definition [11] that includes one or more of the followings:

1) Global or more severe septal cardiomyopathy with reduced left ventricular ejection fraction
2) Heart failure symptoms
3) Cardiac signs, including audible third heart sound associated with gallop rhythm, tachycardia, or both
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 because the above definition does not include subclinical cardiovascular damage that may occur early in response to some chemotherapeutic agents.

As far as the pathophysiology of cardiovascular dysfunction associated with cancer drug therapy is concerned, there is clinical and laboratory evidence that acute coronary syndromes, myocarditis and cardiac arrhythmias are induced by cardiac hypersensitivity rather than by cardiac toxicity. Cardiac hypersensitivity 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 most often of the IgG isotype, but a proportion of hypersensitivity reactions involve IgE antibodies. Indeed, IgE mediated hypersensitivity reactions have been documented with specific chemotherapeutic drugs. 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 (Table 1).

Chimeric monoclonal antibodies (stemmed from the Greek mythological monstrous fire-breathing hybrid chimera composed of parts of more than one animal e.g. a lion, with the head of a goat, a tail end with a snake's head, that was one of the offspring of Typhon and Echidna and a sibling of monsters as Cerberus and the Lernaean Hydra) are used as second line drugs 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 chimeric antibodies are acting against tumor necrosis factor (TNF-α) and are used for treatment of chronic inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and systemic vasculitis. Both non anti TNF-α and anti TNF-α chimeric monoclonal antibodies have been incriminated to develop acute or chronic cardiac hypersensitivity reactions [11,12] including chest pain, hypotension, severe life threatening anaphylaxis and Kounis hypersensitivity associated acute coronary syndrome (Fig. 1).

Table 1
Hypersensitivity reactions induced by chimeric monoclonal antibodies.

Infliximab
Acute myocardial infarction (type I variant of Kounis syndrome)
Allergic contact dermatitis
Allergic pulmonary aspergillosis
Alopecia areata
Atopic dermatitis
Cutaneous vasculitis,
Eruption
Erythema nodosum
Eczematoid eruption
Eczematoid dermatitis
Eczematic-like purpura of Doukas-Kapetanakis
Granuloma annulare
Lichen planus
Necrotizing fasciitis
Niacin-like reaction
Nummular eczema
Psoriasiform eruption
Pustular eruption
Red man syndrome (striking, “glowing” red discoloration of the skin)
Serum sickness
Urticarial rash
Urticarial vasculitis
Rituximab
Acute myocardial infarction
Acute respiratory distress syndrome
Anaphylactoid events
Angioedema
Bronchospasm
Cardiogenic shock
Hypotension
Hypoxia
Pulmonary infiltrates
Ventricular fibrillation
Urticaria

Cetuximab is a chimeric IgG1 monoclonal antibody that contains polypeptides from different species including humans in order to reduce antibody's immunogenicity. Cetuximab binds to the epidermal growth factor receptor and blocks receptor-dependent signal transduction pathways such as anti-apoptosis, angiogenesis, and metastasis. In a retrospective study including 153 patients treated with cetuximab, 12.4% of the patients developed severe hypersensitivity reactions, on the first cycle, despite premedication with diphenhydramine, steroid, antihistamine or bronchodilator [13]. Even higher rates of severe hypersensitivity reactions have been reported [14] in Tennessee (18.9%) and North Carolina (25.7%). A cut-off level of IgE antibodies against cetuximab has been established in association with the hypersensitivity reactions [15]. Furthermore, skin tests [16], desensitization methods [17] and IgE-cetuximab binding on basophils assays [18] constitute current methods used for diagnosing, preventing, predicting and treating hypersensitivity reactions.

Platinum agents such as cisplatin, carboplatin, oxaliplatin are used for chemotherapy as they inhibit DNA replication thus leading to suppression of division and proliferation of cancer cells. All these agents have been incriminated to induce hypersensitivity reactions [19] usually of type I (Immediate type), but rarely also type II (Cytotoxic type), type III (immune complex type) and type IV (delayed type). Cisplatin hypersensitivity [20] ranges from 5 to 20%, carboplatin from 9 to 27%, and oxaliplatin from 10 to 19%. Cardiac hypersensitivity reactions to platinum agents expressed with the typical symptoms of IgE/mast cell-mediated hypersensitivity reactions can be severe consisting in acute myocardial infarction such as Kounis syndrome [21], cardiac arrest and even death [22].

Taxanes such as paclitaxel, docetaxel and others are among the most promising antitumor agents currently available**.** Their mechanism of action involves the inhibition of cell division, chromatid separation and growth ultimately leading to cell death. They are commonly known as microtubule inhibitors, mitotic inhibitors, and mitotic poisons. Hypersensitivity reactions are common ranging from mild, severe, and lethal [23] not responsive to premedication therapy. Approximately 30% of patients receiving taxanes have induced hypersensitivity reactions. Proposed mechanisms include IgE-mediated anaphylaxis with increased tryptase levels, direct mast cell and/or basophil activation and complement activation [24].

Other chemotherapeutic agents can also induce hypersensitivity reactions making the immunology discipline to be involved in the chemotherapeutic cascade. Capecitabine, an orally available pro-drug converted to 5-fluorouracil within tumor tissue used for t metastatic colorectal and breast cancer treatment is an additional example. Cardiac manifestations as angina, acute coronary syndrome, arrhythmias, myocarditis, and heart failure consist several recognized side effects induced by 5-fluorouracil use. Whether these side effects are attributed to accumulation of toxic metabolites or to hypersensitivity reactions remains widely debated. In a report of capecitabine-induced ventricular