

## CHEMOTHERAPY-INDUCED CARDIOTOXICITY IN ONCOLOGY DRUGS INVOLVED AND CLINICAL ASSESSMENT

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### Abstract

Cancer represents an important public health challenge worldwide due to the continuous increase of its incidence. The general prognosis is more and more favourable with new treatments which allow long survival. Chemotherapeutical treatments affect the patients, one of the most important issues being represented by cardiotoxicity, which is low responsive to conventional treatments and finally will determine the survival rate. In this paper we discuss the chemotherapeutical category of agents incriminated to produce cardiac toxicity and the workup indicated for an early diagnostic.

### Rezumat

Cancerul reprezintă o problemă de sănătate publică, din cauza incidenței în continuă creștere. Prognosticul general este din ce în ce mai favorabil, datorită noilor tratamente, care permit prelungirea duratei de viață. Chimioterapia afectează acești pacienți, una din cele mai importante aspecte fiind cardiotoxicitatea, care este puțin responsivă la tratamentele convenționale și care va determina în final rata de supraviețuire. În acest articol se vor prezenta categoriile de agenți chimioterapeutici care provoacă cardiotoxicitate și protocoalele necesare pentru un diagnostic precoce.

**Keywords:** anti-cancer drugs, cardiotoxicity, pathogenesis, prognosis

### Introduction

Cancer represents an extremely important public health issue. According to World Health Organisation (WHO), the incidence of this pathology was, in 2012, of 14.1 million cases every year. This figure is expected to increase to 19.3 million annual cases by 2025, thus exceeding the incidence of cardiovascular diseases [11]. The cancer treatments are more and more effective and could cure, or at least transform cancer into a chronic disease with long-term survival. It is estimated that, in 2012, there were at least 13.5 million cancer survivors treated with chemotherapy in the United States [35].

### Childhood Cancer Incidence. Survival Data

If the rate of cancer-free adult patients does not generally exceed 40% worldwide, in paediatric oncology, over 80% of the patients suffering from this disease are cured [32]. Nevertheless, the long-term toxicity induced by the treatment received during childhood is responsible for cardiovascular morbidity and other health issues during adulthood. Several studies have already pointed out higher incidence rates for cardiovascular diseases, new malignancies, endocrinopathies, muscular or kidney

diseases in patients previously treated with chemotherapy. The incidence of these pathologies increases with age and shows no tendency to plateau [22].

The negative prognosis in the case of anthracycline-induced cardiomyopathies is explained by the lack of effective treatments, the 2-year mortality rate being of over 60% [19]. Over 50% of the patients under chemotherapy suffer from subclinical heart dysfunction, 5% to 16% of them developing a cardiomyopathy that deteriorates into heart failure. The 5-year survival rate is below 50% [19].

Cardiovascular complications represent the main cause of morbidity and mortality in childhood cancer survivors. The Childhood Cancer Survivor Study shows that the mortality risk associated with cardiovascular diseases is eight times higher in cancer-free patients who were treated with anthracycline than in the rest of the population [19, 22, 35]. Modern cancer treatment encompasses a great variety of active agents used in regimens that combine several classes of chemotherapeutic agents. The newest class of targeted molecular agents is just an example. We will further detail the most important classes of chemotherapeutic agents that cause cardiotoxicity. As far as polichemotherapy regimens are concerned, it is very difficult

to assess the degree by which each class of cytostatic drugs could affect the cardiac function.

### Standard therapies

#### *Anthracyclines*

Anthracyclines are key components of chemotherapy regimens in oncology. As in the case of adult chemotherapy, over 60% of the regimens prescribed in paediatric oncology include one anthracycline [34].

Anthracycline-induced toxicity may be acute (during treatment or shortly after the completion of the chemotherapy cycles) or late – occurring years after the oncologic treatment is completed. The incidence of the anthracycline-induced cardiotoxicity varies significantly contingent on the study that is taken into account – from 5.5% 20 years after the end of chemotherapy to 10% for a cumulative dose of 300 mg/m<sup>2</sup> [17, 20, 34]. Depending on the associated risk factors, the incidence rate may reach 57% 6.4 years from the completion of the treatment [34].

The heart damage induced by anthracycline is irreversible. Even years after the administration of the treatment, it prevents the resumption of anthracycline-based chemotherapy in the event of a relapse, given the high risk of cardiomyopathy. Anthracycline-induced cardiotoxicity already represents an increasingly important issue since oncologic therapies are becoming increasingly successful in ensuring long-term survival. Even minor symptoms could affect the patients' quality of life: they last, on average, at least three months from the completion of chemotherapy [15]. The mortality rate associated with heart damage is 8 to 10 times higher in these patients than in the rest of the population [21, 32].

The cumulative dose approved for adults is of 550 mg/m<sup>2</sup> for doxorubicin (800 - 1000 mg/m<sup>2</sup> for epirubicin). It is reduced to 450 mg/m<sup>2</sup> if the left hemi-thorax was irradiated > 20 Gy (Gray = unit of absorbed radiation) (radiation accelerates atherosclerosis) [7]. Past the before mentioned dose, the incidence of anthracycline-induced cardiomyopathy increases exponentially – to 26% for doses exceeding 550 mg/m<sup>2</sup> and to 48% for doses of over 700 mg/m<sup>2</sup> [37]. No international consensus has been reached concerning the dose approved for children. Doses exceeding 410 mg/m<sup>2</sup> cause cardiomyopathy in over 10% of the children treated with anthracyclines [15, 21].

#### *The pathogenesis of anthracycline-induced cardiotoxicity*

It seems that anthracyclines cause myocardial toxicity through their interference with mitochondria, the energy depletion resulting from the mitochondrial destruction being responsible for the decrease in

myocardial contractility. The oxygen-free radicals generated by anthracyclines may determine additional cell destruction or accelerate apoptosis [5, 33].

#### *Alkylating Agents*

Cyclophosphamide and ifosfamide are the most frequently used alkylating agents in oncology treatment. High doses (> 1000 mg/m<sup>2</sup>) may affect the endocardium or the myocardium and entail modifications in vascularization. These changes are transitory and tend to regress upon treatment completion, the highest cardiotoxicity being recorded during the first ten days of treatment [13].

#### *The pathogenesis of the cardiotoxicity induced by alkylating agents*

Studies on animals revealed that alkylating agents seem to interfere with the metabolism of free long-chain fatty acids (FLCFA) at mitochondrial level, thus decreasing their mitochondrial input. The high pool level of FLCFA damages muscle cells [29]. Other hypotheses are linked to the fact that cyclophosphamide increases the production of oxygen-free radicals, the ineffectiveness of the inactivation mechanism being responsible for the myocardial lesions induced [30].

#### *5 FU/prodrug of 5 FU (5-fluorouracil)*

5-fluorouracil (5 FU) may determine cardiotoxicity through induced coronary artery spasm which may lead, in extreme cases, to myocardial infarction [26]. Toxicity seems to depend on the regimen schedule of administration: 5 FU administered by continuous perfusions in conjunction with folinic acid seems to be more cardiotoxic than 5 FU by continuous perfusions without folinic acid, which is sequentially more toxic than 5 FU administered by short perfusion [8]. Toxicity does not seem to depend on the dose and the presence of other cardiovascular risk factors is not predictive for 5 FU cardiotoxicity [26].

Another possible mechanism is represented by the alteration of the electrical potential of the mitochondria, which will eventually lead to the activation of caspase-3 and to myocardial necrosis, which seems to be a common feature of both 5 FU and capecitabine (prodrug of 5 FU) [8].

Even prodrugs of 5 FU (capecitabine) maintain the coronary artery risk reported for 5 FU; the estimated risk is of up to 6% [40].

#### *Taxanes*

Taxanes are used as standard therapy in various lines of treatment for breast cancer, lung cancer, prostate cancer, head and neck cancers, stomach cancer. In the chemotherapy regimens commonly used in the clinic, these compounds are either associated with anthracyclines or follow a first-line anthracycline-based chemotherapy regimen [39].

The data published on the cardiotoxic effect of taxanes are contradictory: some support their cardiotoxicity whereas others underline their protective effect [31].

The studies conducted *in vitro* and on animals revealed that taxanes (paclitaxel and docetaxel) increase the metabolic rate of doxorubicin with the formation of an alcohol metabolite – doxorubicinol – at mitochondrial level, which damages muscle cells [27]. The concentration of this metabolite depends on the taxane dose – low doses stimulate its formation while high doses inhibit it [27]. In light of the existing data, it is still debated whether or not the weekly administration of taxanes involves a higher toxicity risk.

There are also data which shows that taxanes have a protective role, mainly by inhibiting free radical formation and lipid peroxidation [38]. The protective effect seems to be more complex and is related to the proteins involved in glycolysis, in the tricarboxylic acid cycle and at mitochondrial level [23]. In the laboratory animals, the levels of these proteins were assessed, extremely significant differences being noted, contingent on the treatment administered: doxorubicin alone, taxane followed by 12 hours of doxorubicin or simultaneous administration of taxane and doxorubicin [23].

Data on blood, neurological, liver and kidney toxicity do not favour this association. Still, pharmacokinetic data would probably impose the administration of taxanes as first-line therapy and the putting back by at least 12 hours of the administration of doxorubicin. The data for over 18,000 patients treated with chemotherapy using this association of cytostatics, which were published in a meta-analysis, support the feasibility of this association from the point of view of cardiotoxicity, the risk being statistically significantly lower than for anthracyclines administered independently [10].

#### *Vinca alkaloids*

*Vinca* alkaloids are known to cause neuropathies mainly at the level of the autonomic nervous system, which regulates the heart rate, innervates the coronary vascular system etc. Since *Vinca* alkaloids (alkaloids from *Vinca minor*) are part of many chemotherapy regimens for malignant hemopathies or solid tumours, the possibility of cumulative cardiotoxicity was assessed. Contrary to prior beliefs, the studies conducted proved that *Vinca* alkaloids seem to protect against anthracycline-induced cardiotoxicity [2] through the stimulation of an alternative pathway to inhibit apoptosis (the mitogen activated protein kinases (MAPK) pathway) and by inhibiting the synthesis of a gene which generates a protein that decreases intracellular NAD levels and causes cell-death [2].

#### **Targeted therapies**

The main adverse feature of conventional chemotherapy is the fact that it is non-selective – it kills both cancer cells and healthy cells. For this

reason, conventional chemotherapy regimens have multiple adverse effects. The progress made during the last few years allowed a better understanding of the genesis and progression of malignant tumours, which outlined multiple potential therapeutic targets specific solely to cancer cells. Thus, in recent years, new molecules characterized as „targeted” therapies were discovered. It must be underlined that these new drugs have adverse effects as well, which differ nevertheless from the toxicities specific to conventional chemotherapy. The cardiotoxicity-related data for these new drugs will be presented hereinafter.

#### *Anti EGFR (epidermal growth factor receptor) antibodies: trastuzumab, lapatinib*

The emergence of a new chemotherapeutic class in oncology – the “targeted therapy” – and its associated toxicities must be approached separately. In patients with Her2/neu-positive breast cancer, the administration of trastuzumab as an adjuvant or in metastases already represents standard therapy. As this new medication is becoming increasingly accessible, cases of initially unreported toxicity appear, as in the case of herceptin, which causes cardiotoxicity mainly in patients who received anthracyclines in previous chemotherapy regimens.

The incidence of the trastuzumab-induced cardiotoxicity appears to be between 0.6 and 4% [3]. The level of toxicity seems to be lower in the case of a monotherapy with trastuzumab than in the case of its association with other agents, more precisely of 3-7% by comparison with 27% respectively [12].

The pathogenesis of cardiotoxicity is different from that of anthracyclines and is not fully understood from the point of view of electron microscopy. It is not additive or dose-dependent, it is reversible for most cases and the patients’ heart tolerates well the resumption of the therapy [9].

#### *Anti VEGF (vascular endothelial growth factor) antibodies (angiogenesis inhibitor)*

Coupled with anthracyclines, bevacizumab increases the risk of cardiotoxicity in patients with stomach cancer, fact which is clinically reflected either by the asymptomatic decrease in the ejection fraction by more than 15%, the absolute value being below 50% (double in patients treated with bevacizumab – 21.2% compared to 11.1%) or by the clinically significant decrease in the ejection fraction by more than 10% compared to the normal lower threshold (15.3% compared to 8.9% in patients not treated with bevacizumab) [24]. Some microRNAs: miR1254 and miR579 may represent biomarkers announcing the cardiotoxicity of bevacizumab in patients with colorectal cancer under chemotherapy [41].

#### *Tyrosine kinase inhibitors*

This class includes more and more therapeutic agents which, by interfering with the intracellular signalling pathways, block several carcinogenesis

pathways. Examples include imatinib, sunitinib and sorafenib, which are used to treat hepatocellular carcinoma, renal cell carcinoma and gastrointestinal stromal tumours. This new class of drugs may induce cardiotoxicity through its intrinsic pharmacological target: tyrosine kinase. The more it inhibits (to block as many carcinogenesis pathways as possible), the higher the chances that muscle cells are damaged [14].

The pathogenesis of the Sunitinib-induced cardiotoxicity is unknown but it could be linked to the coronary and cardiac dysfunction. A study conducted on 175 patients suffering from kidney cancer treated with sunitinib revealed a frequency of heart dysfunctions of 6.9%. Imatinib rarely damages the myocardium, the pericardium being affected more often [1, 6, 16].

### Assessment of Cardiotoxicity

Nowadays, a very important issue that cardiologists and oncologists come up against is the proper assessment and the early detection of heart diseases caused by chemotherapy in oncology patients. So far, no consensus has been reached with regard to a tracking and decision algorithm for patients under cardiotoxic chemotherapy.

The most common method to assess these patients is echocardiography with ventricular ejection fraction measurement [25]. Apart from this imaging method, which is becoming increasingly complex and time-consuming due to the in-depth assessment using the strain method – which tries to evaluate myocardial function as well – the literature describes a series of biomarkers that may prove useful in the early assessment of the cardiotoxicity risk. These biomarkers include: troponin, atrial natriuretic peptide and certain cytokines such as ST2 (a member of the interleukin family) [28]. Their early increase may be an alarm signal regarding the subsequent development of cytostatic-induced cardiomyopathy [18].

The Doppler myocardial imaging, which assesses myocardial function, seems to be more sensitive than the conventional one, which only measures the ejection fraction (LVEF), because these modifications seem to occur earlier, before the decrease in LVEF; the differences are statistically significant [5].

The frequency at which echocardiograms must be performed is yet to be clarified; generally, it is recommended to repeat them every 6 to 8 weeks during chemotherapy (every two chemotherapy cycles) [36].

### Conclusions

In conclusion, the early and reliable detection of the cardiotoxicity of conventional or modern “targeted” chemotherapy must be a priority given the long-

term survival obtained in oncology; besides of that, heart damage has a vital prognosis and sometimes has an irreversible or little reversible character, as well as limited possibilities of specific therapy.

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