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Cardiotoxicity: A Current View at the Problem

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Abstract

In majority of the developed countries populations are gradually aging, and with increasing age the number of cardiovascular diseases as well as cancer diseases is rising. As a result of the trend the cardiotoxicity after cancer treatment is quite a common problem, however it may happen in younger patients, as well. In the article the types of cardiotoxicity were discussed and the risk factors for the occurrence of it including cumulative dose of anthracyclines and age. The up-to-date European Society of Cardiology guidelines on cardiovascular toxicity were commented and additionally some problematic issues and perspectives in the field of cardiotoxicity and cardio-oncology.

Mini-Review

The incidence of cancer diseases has not decreased in last decades and still we face a lot of challenges. Our modern societies are rather aging than getting younger and this process cause the perpetual high level of neoplasms typical for older age like colon cancer, stomach cancer, lung, prostate and bladder, pancreas as well as uterine and breast cancer [1]. Additionally, depending on the country patients above 65 years old may constitute about 50% -60% cases of all cancers, and it is said that about 70% of the deaths caused by cancers occur in the elderly [2]. Moreover, it is one of the crucial points to understand that probability of cardiotoxicity will increase with age as in this group all cardiovascular diseases are commonly co-existing. On the other hand, in younger population occasionally smaller but worth-mentioning group of patients will develop cardiovascular side effects of the treatment.

According to ESC (European Society of Cardiology) cardiovascular complications of cancer therapy include: myocardial dysfunction and Heart Failure (HF), Coronary Artery Disease (CAD), valvular disease, arrhythmias, especially the ones induced by QT-prolonging drugs, also arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension and pericardial complications [3]. In the official guidelines there is clearly underlined that the anti-cancer treatment improved survival, simultaneously increasing morbidity and mortality due to side-effects [4,5]. For any physician taking care of the cancer patients it is essential to know basic information on potential cardiotoxicity and, in the same time, asking a couple of questions regarding medical history of a single patient. As a first step, in every patient the evaluation of cardiovascular risk factors (CVD) should be done as the cumulation of them significantly increases the probability of cardiotoxicity.

Cardiotoxicity may be immediate, early or observed after a year after completion the treatment, defined as late-onset one. The best known for a long time has been an anthracyclines cardiotoxicity. This group od drugs is still used in a variety of neoplasms including solid tumors and hematological malignancies and in childhood neoplasms, too [6-8]. In the early cardiotoxicity of anthracyclines, the clinical or subclinical heart failure is seen where in long-term survivors in different studies cardiac abnormalities including dysfunction of the left ventricle have been found in 20-60% of patients [9-12].

The problem hasn't changed for last 2-3 decades and as abovementioned anthracyclines are still widely used starting from ALL therapy in children and going through the range of solid tumors finishing in the field of hematology where the typical representative is still a gold standard CHOP regimen or its modifications in Non-Hodgkin's Lymphoma (NHL), such as R-CHOP [13,14].

Analyzing types of cardiotoxicity based on serving as a classical example the anthracyclines activity, as mentioned before we define acute, early and late types. The first one, acute, seen rarely in about 1% of patients immediately after drug infusion is characterized by the left ventricular dysfunction, supraventricular arrhythmias and ECG changes, which are usually reversible [3]. However, sometimes acute cardiac dysfunction may result in progressive process giving rise to late cardiotoxicity. Second type: early cardiotoxicity occurring within the year of treatment, and the late one showing effects after a year or more, usually several years [15,16].

Generally, according to Irving Perez there are also two other types of cardiotoxicity: type 1 characterized by irreversible myocardial damage due to the cumulative administered dose (anthracyclines type of cardiotoxicity) probably increasing potential for long-term cardiac dysfunction and type 2 which is dose-independent reversible myocardial damage (best representation is trastuzumab acting by binding to the human epidermal growth factor receptor 2 (HER2) and inhibiting downstream-associated signaling cascades [17,18] Irving Perez i Kuelnager).

The special attention should be paid to factors increasing the risk of cardiovascular complications after cancer therapy. There are various risk factors for cardiotoxicity development and in recent studies age and preexisting left ventricular dysfunction have been identified as most consistently to potentially cause the development of clinical heart failure or a worsening of left ventricular function [19]. However, in up-to-date literature lots of them have been discussed and summarizing among risk factors for anthracyclines and other therapies cardiotoxicity the following ones were listed: cumulative dose, female sex, age >65 years old (in some studies >50 years old), or pediatric population (<18 years), renal failure, concomitant or previous radiation therapy

involving the heart, concomitant chemotherapy with alkylating or antimicrotubular agents, immuno- and targeted therapies, pre-existing conditions including cardiac diseases associating increased wall stress, arterial hypertension and genetic factors [3,20]. There is growing evidence that Blacks are at a higher risk of developing cardiotoxicity

than Whites [21]. In European guidelines as well as in the different papers some medical conditions are selected as so-called baseline risk factors for cardiotoxicity: current myocardial disease with heart failure, asymptomatic left ventricular dysfunction, hypertension, valvular diseases, cardiomyopathies, cardiac sarcoidosis, significant arrhythmias, diabetes, and hypercholesterolemia. As abovementioned, the previous anthracycline use and radiotherapy to chest or mediastinum have been shown to be significant in many cases, and additionally some lifestyle factors like smoking, high alcohol intake, obesity and sedentary lifestyle [3,22,23].

Additionally, commenting the cardiotoxic effect of cumulative dose of anthracyclines such a dose for doxorubicin was >200 mg/m2, or >300. Among other also previous chemotherapy and suggested by some investigators the simultaneous use of cyclophosphamide may increase cardiotoxicity [24-26]. The concomitant therapy with alkylating agents like cyclophosphamide was indicated as a risk factor for cardiotoxicity following treatment with anthracyclines [3,27,28]. Cyclophosphamide cardiotoxicity depends on its dose and complications of the cardiovascular system occur after administration of 120 to 200 mg/kg of cyclophosphamide and it has been documented that that cardiotoxicity of cyclophosphamide may be present in 3% of patients who received a dose of less than 1.55 g/m2/daily and in 25% who received cyclophosphamide at a daily dose greater than 1.55 g/m2/daily [29]. The cardiovascular complications of the use of cyclophosphamide or ifosfamide, include electrocardiography changes like lower voltage QRS, supraventricular or ventricular arrhythmia, atrial flutter or fibrillation, ST changes, heart failure, myocarditis, pericarditis, cardiac tamponade in extreme cases [30-32]. Symptoms are usually detected within 1 to 3 weeks, and sometimes the mortality rate can reach 43% [33]. Cyclophosphamide-induced cardiotoxicity involves direct endocardial injury, followed by extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema [28,31,33].

Fluoropyrimidines are a class of anti-cancer drugs, antimetabolites, and the most commonly used drugs are 5-fluorouracil (5-FU) and its oral form capecitabine (CAPE) which are used to treat patients with gastrointestinal and some other solid malignancies [34,35]. 5-FU is said to be the second most common chemotherapeutic drug associated with cardiotoxicity after anthracyclines, but the use of this group of therapeutics is frequently limited by cardiotoxicity [36]. It has been found that fluoropyrimidine cardiotoxicity tends to occur most commonly during the first cycle of administration and the median time to initiation of symptoms is 12 hours after infusion initiation, although cardiotoxicity is occurring at any time during infusion up to 1–2 days after it [34,37]. Numerous clinical presentations of fluoropyrimidine toxicity have been reported including chest pain, myocardial infarction, acute cardiomyopathy, different types of arrhythmias, cardiogenic shock, and sudden cardiac death [38,39]. In European "Position Paper on cancer treatments and cardiovascular toxicity" the 5-FU and capecitabine are cited as agents causing bradycardia, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or ventricular fibrillation and 5-Fu is connected with conduction disturbances including atrioventricular block, additionally causing sudden cardiac death probably related to ischemia and coronary spasm [3]. Various authors proposed lots of mechanisms of those side effects, mainly it is ischemia due to coronary vasospasm, then coronary endothelial dysfunction, myocardial toxicity, myocarditis, and Takotsubo cardiomyopathy, arrhythmias, conduction problems in ECG [38,40] and the incidence of cardiovascular adverse effects have been estimated between 0.5 and 19% [36]. The widely discussed is the most leading theory of coronary vasospasm for 5-FU-related myocardial ischemia and in those patient's ECG findings suggestive of coronary occlusion, including ST-segment elevation may be seen together with biochemical evidence of myocardial injury with troponin elevation. Usually, there is no evidence of macrovascular disease on angiography or computed tomography imaging of the coronary vessels [41]. Generally, it is known that there are different mechanism and risk factors for cardiotoxicity of fluoropyrimidines, however there are many conflicting results. It was suggested that in case of fluoropyrimidines therapy more advanced age may be increasing the risk of cardiac complications or the pre-existing renal failure [42]. Discontinuation of chemotherapy, and then empirical treatment with calcium channel blockers or nitrates aids in up to 69% of the patients [37].

It has been documented in ESC guidelines that left ventricular dysfunction associated with chemotherapy drugs is the most common in specific conditions like: cumulative dose of Doxorubicin ≥ 700 mg/m^2 ranging from 18 to 48% or ≥ 550 mg/m^2 (7-26%), also exceeding Idarubicin cumulative dose ≥ 90 mg/m^2 (incidence of 5-18%), after cyclophosphamide use without the specific dose limit given (incidence of 7-28%), then after docetaxel treatment -ranging 13%, trastuzumab combined with anthracyclines and cyclophosphamide (up till 20%) and Carfilzomib with the incidence between 11 and 25% [3,43,44]. Other drugs used in chemotherapy may cause the dysfunction in a lesser extent, however the gate for new agents' cardiotoxicity is all the time open as we will enter them into clinical use.

The toxic effect may be different depending on the specific agent, and for the anthracycline that process is mainly characterize by the progressive decline in left ventricular ejection fraction and according to some authors the affected patients may initially be asymptomatic, then may manifest heart pathologies years later [3]. Furthermore, it is important to remember that the incidence of anthracycline-related cardiotoxicity is more likely to happen not only in conditions of high lifetime cumulative dose, or the advanced age, but specially in the setting of pre-existing cardiac disease including hypertension and coronary artery disease or valvular disease, which, could not have been fully diagnosed initially. This is why numerous oncology centers as a standard adopt echocardiography and at least 12-lead standard ECG before the potentially cardiotoxic treatment, and later repeat it when there is the need or as a routine control follow-up. Still, not everywhere, 24-hour ECG Holter monitoring is used, and it should be recommended in any case where there is a suspicion of arrhythmia or when it is a high probability of it. Out of the group of arrhythmias one of the most common is atrial fibrillation secondary to cardiotoxic treatment, however all range of other ECG changes are possible with ventricular arrhythmia, atrioventricular blocks and other conduction disturbances, then bradycardia and tachycardia [45-47]. A special group of patients are hypertensive individuals, in which frequent blood pressure measurements should be done.

Considering more clinical issues in oncologic patients with pre-existing cardiological diseases undergoing treatment the suitable electrolyte balance is essential as especially severe arrhythmias unpleasant for patients may be induced by hypokalemia or hypomagnesemia or other electrolyte abnormalities. Similarly, in case of anemia in coronary artery disease patients quite often we are obliged to do the red blood cells transfusion as soon as possible as the lowering hemoglobin may not only aggravate angina, but even accelerate myocardial infarct incidence and induce serious arrhythmias.

Tools: Pros and Cons

There are questions as to what kind of tools would serve us to evaluate cardiotoxicity.

Echocardiography - the non-invasive, widely used and easy to assess in medical centers, in the same time not too expensive, and cost-effective. Ejection fraction of left ventricle with the recommended in the aspect of cardiotoxicity the detection of at least 10% decline is taken as significant to a value below the lower limit of normality [3]. However, the parameter is not perfect, depending on every examiner's subjective opinion. In the end, it is criticized by some experts as the technique showing only serious pathologies, probably omitting and even neglecting mild changes that could influence doctor's vigilance. MUGA – nuclear cardiac imaging is a very specialized technique, with limited access in specialized centers and with additional expose to radiation. Less commonly used cardiac magnetic resonance with its limited availability and minor problems like claustrophobia for patients, additionally more expensive test.

Biochemical Markers

troponin, BNP, NT-pro-BNP are suggested by several authors as useful and correlating with the prognosis for the late onset cardiotoxicity, however still we lack evidence to establish the significance of subtle rises.

As mentioned before in each patient standard ECG should be recommended with echocardiography before the potentially cardiotoxic treatment. Then repeated follow-ups, planned as it was in numerous studies after completion the treatment, then after 1 month, 3 and 6 months and then after 1 year, and later probably after every next one year ranging to at least 10 years. The scheme should be specially applied in patients with pre-existing cardiovascular diseases or when earlier during the treatment the cardiac problem happened.

In addition, recently not only the effect of the chemotherapy itself has been investigated, but also the influence of bone marrow transplantation or widely adopted nowadays hematopoietic cells auto- or allotransplantation

performed in hematological or non-hematological neoplasms. In short-term observation transplant procedures may produce cardiac side effect not only in patients with pre-existing cardiovascular disease, but also give minor changes in subjects potentially without previously diagnosed diseases. Those include moderate changes in function of the left ventricle, BNP concentration increase, the increase in some arrhythmias and repolarization changes in ECG that may represent mild and early stage abnormalities that could prognose future susceptibility [48-50].

Long-term surveillance programs in the aspect of cardiovascular future complications for cancer survivors are recommended in European guidelines, however it is still not an obligatory policy all over the world.

It is known that both pediatric and adult survivors of anthracycline-based chemotherapy have a higher risk for the development of left ventricle dysfunction and heart failure and the time to the evident pathology may be long [51-54]. In case of the breast cancer survivors aged > 50 years, deaths due to cardiovascular disease account for 35% of non-cancer related deaths [55]. Even if a patient is still asymptomatic it is recommended to evaluate periodically cardiac imaging, out of which echocardiography is the most available method and simultaneously to perform biomarkers tests, that is BNP is mentioned in official document as it is a sensitive marker of heart failure.

In ESC guidelines experts commented among others points on the hypertensive effect of the therapy including a novel treatment method like VEGF inhibitors as lots of studies reported this trend in even more than 40% of patients and stage 3-4 hypertension exceeding 13% of the patients, which is a high number. This data may encourage us to take blood pressure measurements more frequently during and after the treatment and in some cases in fact to use ABPM (Ambulatory Blood Pressure Monitoring for 24 hours) [3,56].

There are still unanswered questions in cardio-oncology related to cardiotoxicity and one of them is the occurrence of early symptoms that do not meet the present definition. In this field somehow fresh point of view has been presented by Parr at al. who indicated that the use of arterial stiffness evaluation occurring after anticancer therapy in cancer survivors may be helpful in the identification of early cardiovascular injury and for the detection of long-term cardiovascular injury [57].

Doubtlessly, the definition should evaluate and incorporate a variety of abnormalities and changes caused by cancer treatment and this trend has been emerging. In future perspectives and new ideas will come, and one of them may be evaluating of inherited genetic make-up and diagnosing of acquired genomic variants accounting for a significant portion of observable variability in therapy efficacy and toxicity including cardiotoxicity, and that lies in the area of pharmacogenomics [58].

In modern cardio-oncology there are numerous other topics related to it and novel concepts worth discussion beyond the problem of cardiotoxicity. Among them there are: higher incidence of thromboembolic events in this group of patients, treatment with antiplatelet drugs or the use of novel versus traditional oral anticoagulants especially in patients with co-existing atrial fibrillation or such simple clinical challenges like treatment of arterial hypertension, arrhythmias or angina during or after anti-cancer treatment.

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