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Review article

Current approach for detection of sub-clinical left ventricular dysfunction associated with chemotherapy

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ABSTRACT

The article describes the current knowledge concerning approaches for detection of sub-clinical left ventricular dysfunction associated with chemotherapy. The authors focused on the problem of defining cardiotoxicity as well as diagnostic methods, which may be useful in predicting the occurrence of such complications. Currently, cardiac biomarkers measurement (troponin, NT-proBNP), tissue Doppler-based strain imaging and peak systolic longitudinal strain rate are most useful for detection of early myocardial changes during therapy, whereas speckle tracking echocardiography (STE) and peak systolic global longitudinal strain (GLS) appear to be the best measure.

The problem of cardiotoxicity requires close cooperation between oncologists and cardiologists, particularly in light of the growing number of cancer cases.

There are different classes of drugs available, with variable mechanisms and targets of action, for systemic anticancer therapies. Conventional chemotherapy includes alkylating agents (cyclophosphamide), platinum-based drugs (cisplatin), antimetabolites (methotrexate, 5-fluorouracil, capecitabine), microtubule agents (vinca alkaloids, taxanes), antibiotics (anthracycline, actinomycin D, bleomycin). There are also alternative anticancer strategies available, such as hormone therapy (tamoxifen), immunotherapy (most commonly monoclonal antibodies) or molecularly targeted agents (mostly protein tyrosine kinase inhibitors) [1–4]. During the therapy of cancer, besides the most common complications such as nausea, vomiting, bone marrow suppression, tumor lysis syndrome, extravasation of cytostatic drugs, radiation dermatitis and mucous membranes, there is significant increase in the incidence of cardiotoxicity [5]. The literature describing anti-cancer therapy often defines cardiotoxicity as asymptomatic left ventricular dysfunction or heart failure resulting during or after chemotherapy and/or radiotherapy [6–12]. The incidence of cardiovascular adverse effects of anti-cancer therapy is not well-defined and varies among different agents [13]. According to Cardiac Review and Evaluation Committee, cardiotoxicity can be described as a reduction of the left ventricular ejection fraction (LVEF) of ≥5% to <55% with symptoms of heart failure or an asymptomatic reduction of the LVEF of ≥10% to <55% [14,15]. The experts of the American Society of Echocardiography and the European Association of Cardiovascular Imaging define cancer therapeutics–related cardiac dysfunction on the basis of a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for 2DE – two-dimensional echocardiography). The decrease should be confirmed by repeated imaging (2–3 weeks after the baseline diagnostic study) [16].

Long-term studies on the toxicity of chemotherapy shows that, apart from the aforementioned asymptomatic left ventricular systolic dysfunction or heart failure, as a cardiac complication may also occur (Table 1) [17–19];

1 hypertension or hypotension;
2 myocardial ischemia;
3 arrhythmias, especially torsade de pointes (TdP) induced by QT prolonging drugs;
4 sudden cardiac death;
5 pericarditis;
6 thromboembolism; and
7 other chemotherapy-induced ECG abnormalities.

Therefore, it appears that a new term could be introduced – cardiovascular toxicity, defined as any disorder (abnormality) of heart or circulatory system that occur during or after anti-cancer therapy with cardiotoxicity being a part of it concerning direct myocardial damage.

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Table 1
Cardiovascular adverse effects of anticancer drugs.

Adverse effect	Drug
Left ventricular dysfunction, heart failure	Anthracyclines, 5-fluorouracil, taxanes, vinca alkaloids, cyclophosphamide, trastuzumab
Ischemia	5-Fluorouracil, taxanes, cisplatin, capecitabine
Arrhythmia, atrioventricular block	Anthracyclines, taxanes, vinca alkaloids, trastuzumab, thalidomide
Hypertension	Bevacizumab, cisplatin
Hypotension	Etoposide, paclitaxel, alemtuzumab, cetuximab, rituximab, homoharringtonine, interleukin-2, denileukin, interferon-α, all-trans retinoic acid
Thromboembolism	Tamoxifen, bevacizumab, cox-2 specific inhibitors
Pericarditis	5-Fluorouracil

Cardiotoxicity can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary LVEF decline, to life-threatening events such as congestive HF (heart failure) or acute coronary syndromes [20]. Cardiac dysfunction associated with chemotherapy can be acute/subacute (developed up to two weeks after the completion of therapy) or chronic (early cardiotoxicity, which appears within one year after completion of therapy and late cardiotoxicity – appearing more than one year after chemotherapy) [19]. Such categorizing is typically used for anthracycline-induced cardiotoxicity.

Another possible classification of cancer therapeutics-related cardiac dysfunction, which can be found in various publications (including current expert consensus statement of the American Society of Echocardiography and the European Association of Cardiovascular Imaging), is based on the reversibility of cardiac abnormality and the mechanism of toxicity of the anti-cancer agents [2,6,16,21,22]:

1. Irreversible cardiotoxicity (type 1): frequently caused by anthracyclines (doxorubicin, epirubicin, idarubicin, liposomal anthracyclines, cyclophosphamide, and docetaxel), it leads to cardiac dysfunction in dose related fashion. The toxic effect is associated with microscopic ultrastructural changes, and frequently results in myocardial cell death (partially, due to oxidative stress on cardiac myocytes resulting in free radical formation and cell death). In patients with cancer who develop asymptomatic or symptomatic anthracycline-induced cardiotoxicity, LV ejection fraction (LVEF) recovery and cardiac event reduction can occur if there is early detection and treatment with modern HF therapy.
2. Reversible cardiotoxicity (type 2): evoked by trastuzumab, typically is not dose related and can be associated with reversible myocardial dysfunction rather than structural damage. Reversibility is defined as recovery of LVEF to the normal range.

In many scientific articles related to this topic the definition of cardiotoxicity is frequently based on echocardiography evaluation (e.g. EF). The authors usually use echo's criteria originally proposed by the National Cancer Institute in 1998. However, analyzed volumes of EF has changed significantly. Currently recommended criteria are based on decrease in EF below 50–60% [23]. Jurczak et al. in a multicenter study on premature cardiovascular mortality in lymphoma patients defined clinical cardiotoxicity as any manifestation of cardiovascular abnormalities, including typical symptoms of HF, electrocardiographic changes or symptoms related to IHD (ischemic heart disease) [23]. According to the authors, the diagnosis of cardiotoxicity should be based on combined clinical and echocardiographic criteria. This is due to the fact that in many cases cardiac damage may proceed initially without remarkable impairment of systolic function, and ejection fraction estimation is strongly dependent on many factors (e.g. inter-observer variability, heart rate at examination, quality of equipment). Monitoring LVEF with echo-cardiography and radionuclide-angiocardiography may not be sensitive or specific enough to detect early cardiac dysfunction after CT (chemotherapy), as it detects cardiac damage after significant myocardial dysfunction has already occurred and thus limits very early pharmacologic intervention. Moreover, lack of cardiac dysfunction does not exclude the possibility of later cardiac deterioration [24]. Therefore, development of quite new, sensitive technics for early detection of cardiac damage seems to be necessary.

According to Oreto et al., the role of echocardiography in the detection and prediction of chemotherapy-induced cardiotoxicity is still evolving. Diastolic dysfunction which can occur after chemotherapy is frequent and early symptom of cardiotoxicity. Abnormal values of isovolumic relaxation time (IVRT), early diastolic velocity (E), late diastolic velocity (A), early tissue Doppler velocity (e′), late tissue Doppler velocity (a′), deceleration time of early diastolic filing (DT) reflect diastolic dysfunction [2]. The study of DiLisi et al. assessing diastolic dysfunction in patients with breast cancer revealed greater sensitivity of tissue Doppler in measurement of myocardial early diastolic velocity to myocardial atrial velocity ratio [25]. Significant decrease in E, e′ and the E/A ratio reported by Tassan-Mangina were associated with a significant reduction in EF after 3–5 years of chemotherapy [26]. However, other studies did not confirm this observation. Ganame et al. observed impaired diastolic parameters (weeks to months) in the absence of reduced LVEF in anthracycline-treated patients [27]. The same diastolic and systolic patterns were observed during much more longer follow-up (up to several years) [28]. Considering these reasons, diastolic parameters are currently not good predictors of future systolic dysfunction and are not recommended in predicting left ventricular dysfunction [2,16].

In the recently published systematic review including 1504 patients during or after cancer chemotherapy, the utility of advanced echocardiographic techniques (such as deformation imaging) in the diagnosis and prognostication of patients receiving potentially cardiotoxic cancer therapy confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy [29].

Currently, myocardial deformation can be measured using tissue Doppler imaging (TDI) and 2- and 3-dimensional speckle tracking echocardiography (STE). The latter is favored due to lack of angle dependency. Echocardiographic measures of LV strain (S) and strain rate (SR) have become a robust method to measure myocardial deformation.

Strain is a dimensionless index reflecting the total deformation of the ventricular myocardium during a cardiac cycle as a percentage of its initial length (reported as percentage). Strain rate (SR) is the rate of deformation or stretch. Both S and SR can be measured in the longitudinal (L), radial (R), and circumferential (C) directions.

The real value of these changes lie in their ability to prognosticate clinically relevant outcomes such as subsequent