

REVIEWS

Cardiac dysfunction of antineoplastic agents in breast cancer patients

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Abstract: Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD) has become one of the main causes of morbidity and mortality in cancer survivors. If CTRCD is detected early, prompt administration of cardioprotective treatment may slow the progression of left ventricular (LV) dysfunction and improve the prognosis. Thus, the management of patients with CTRCD should focus on early detection and prompt treatment. LV ejection fraction (EF) assessment by 2D TTE has a low sensitivity in detecting CTRCD at an early stage. There is much interest in the use of myocardial deformation parameters measured by tissue Doppler imaging or speckle tracking echocardiography to identify early myocardial injury and to anticipate ventricular dysfunction in patients receiving chemotherapy. Peak systolic global longitudinal strain (GLS) could be the most consistent parameter that correlates with the subsequent development of CTRCD. Serial monitoring of GLS seems the ideal strategy for the detection of subclinical LV dysfunction. A relative percentage reduction in GLS of >15% is very likely to be abnormal, whereas a change of <8% appears not to be of clinical significance. Determining the significance of these changes will require long-term follow-up. To better understand what defines CTRCD, more research and larger studies are needed and also a dynamic partnership between oncologists and cardiologists.

Keywords: Cancer Therapeutics–Related Cardiac Dysfunction, myocardial deformation parameters, speckle tracking echocardiography, peak systolic global longitudinal strain, early detection, early myocardial injury, anthracyclines, trastuzumab

Rezumat: Disfuncția cardiacă indusă de terapia antitumorală (CTRCD) reprezintă una din cele mai frecvente cauze de morbiditate și mortalitate în rândul supraviețuitorilor unei neoplazii. Dacă CTRCD este diagnosticată precoce, administrarea promptă a medicației cardioprotectoare poate încetini progresia disfuncției cardiace cu ameliorarea prognosticului. Managementul pacienților oncologici cu risc de CTRCD ar trebui așadar bazat pe diagnosticarea și tratarea precoce a CTRCD. Frația de ejeție a ventriculului stâng (FEVS) evaluată prin ETT 2D are o sensibilitate redusă în depistarea precoce a CTRCD. Există un interes deosebit în utilizarea parametrilor de deformare miocardică, măsurați prin metodele de Doppler tisular sau speckle tracking, în identificarea precoce a injuriei miocardice induse de chimioterapie și în prezicerea instalării disfuncției cardiace. Strainul global longitudinal (SGL) pare să fie cel mai consistent parametru în acest sens și monitorizarea seriată a SGL poate reprezenta strategia ideală pentru depistarea precoce a disfuncției subclinice de VS. O reducere procentuală relativă a SGL >15% este foarte probabil să fie anormală, în timp ce o reducere <8% pare să nu aibă semnificație clinică. Semnificația acestor modificări necesită urmărire pe termen lung. Pentru a înțelege mai bine CTRCD sunt necesare ample eforturi de cercetare precum și dezvoltarea unei colaborări dinamice între cardiologi și oncologi.

Cuvinte cheie: disfuncția cardiacă indusă de terapia antitumorală, parametrii de deformare miocardică, ecocardiografie speckle tracking, strain global longitudinal, depistare precoce, injurie miocardică precoce, antraciline, trastuzumab

INTRODUCTION

Breast cancer treatment has made significant advances in recent years¹. The use of classic chemotherapy agents, such as anthracyclines, in combination with newer targeted agents, such as monoclonal antibodies,

has contributed to the increase of overall survival in breast cancer patients^{2,3}. Unfortunately, the cardiovascular side effects of the antineoplastic agents^{4,5} have made cardiac toxicity induced by chemotherapy to become one of the main causes of morbidity and morta-

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lity in breast cancer survivors⁶. In patients with symptomatic heart failure (HF) from cancer treatment, the mortality rate has been reported to be as high as 60% at two years^{7,8}. Therefore, cardiotoxicity induced by cancer therapy has become a matter of great concern and the subject of many research efforts.

Cardiac toxicity induced by chemotherapy includes a broad spectrum of manifestations that range from cardiac dysfunction and HF to arterial hypertension, myocardial ischemia, thromboembolic events, arrhythmia and QT interval prolongation. This is why the National Cancer Institute refers to cardiotoxicity caused by antineoplastic agents in a general manner, as „toxicity that affects the heart”⁹. However, the term cardiotoxicity is usually used in reference to cardiac dysfunction and symptomatic HF, which are the most severe and best studied cardiac side effects of chemotherapy. An Expert Consensus Statement, endorsed by the *American Society of Echocardiography* and the *European Association of Cardiovascular Imaging*, was recently published and a more precise term, Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD) was introduced¹⁰, cardiotoxicity remaining a broader term.

Definition of CTRCD

Since the early 60's, when cardiac dysfunction induced by anthracyclines was first reported, several definitions have been proposed, but a consensus definition lacked for many years¹¹. Back then, the diagnosis was based on the presence of signs and symptoms of HF or the evidence of ultrastructural abnormalities on endomyocardial biopsies. Later, left ventricular ejection fraction (LVEF) became the most used parameter for the diagnosis of cardiac dysfunction but with no clear cutoff values, which generated many difficulties with respect to diagnosis, monitoring and treatment-related decisions. The recently published Expert Consensus Statement finally provides a standardised definition of cardiac dysfunction induced by chemotherapy¹⁰. Cancer therapeutics-related cardiac dysfunction (CTRCD) is defined as a decrease in the left ventricular ejection fraction of >10%, to a value <53% (considered the normal reference value for two-dimensional echocardiography (2DE))¹⁰. This decrease in LVEF has to be confirmed by a reevaluation after 2-3 weeks since the first examination¹⁰. The document mentions that the reduction in LVEF can be symptomatic or asymptomatic. It also defines clear cutoff values for the concept of reversibility and classifies CTRCD accordingly¹⁰:

- Reversible: improvement in LVEF to within 5% of the baseline value¹⁰

- Partially reversible: improvement in LVEF by $\geq 10\%$ from the lowest value but remaining >5% below the baseline value¹⁰
- Irreversible: improvement in LVEF by <10% from the lowest value and remaining >5% below the baseline value¹⁰
- Indeterminate: re-evaluation of patient not possible¹⁰.

Types of CTRCD

Amongst the various antineoplastic agents with potential cardiac toxicity, anthracyclines (including doxorubicin, epirubicin and idarubicin) and trastuzumab, have been most commonly implicated and best studied in breast cancer patients. The combined therapy, using agents from both these classes, generally increases the incidence of CTRCD¹²⁻¹⁴.

Based on their potential to cause irreversible versus reversible damage to the cardiovascular system, Ewer et al. have proposed a classification of anticancer agents, with anthracyclines being classified as type I and trastuzumab as type II¹⁵. This classification has extended into distinguishing two different types of cardiotoxicity¹⁶ in the larger acceptance of the term, and, by default, two types of CTRCD¹⁰.

Type I cardiotoxicity is related to the classic chemotherapy agents (anthracyclines, mitoxantrone, alkylating agents, antimicrotubule agents, antimetabolites) and has as prototype the toxicity induced by anthracyclines¹⁶⁻¹⁸. Type I chemotherapy agents are, usually, cytotoxic, inducing cell loss (necrosis/apoptosis) which leads to progressive and largely irreversible cardiovascular damage associated with increased rates of cardiovascular mortality¹⁶⁻¹⁸. It was shown that these agents induce ultrastructural damage (vacuoles, myofibrillar disarray and dropout, necrosis) on endomyocardial biopsies and also release of myocardial injury markers (troponins), as consequence of myocyte damage and loss^{8,10,16,19}. Moreover, there is a definite relation between the cumulative dose of anthracyclines and the incidence of cardiac dysfunction, as described first by Von Hoff et al.⁸ and later, providing more accurate data, by Swain et al.²⁰.

Conversely, type II cardiotoxicity is related to the newer targeted agents (anti-HER2, angiogenesis inhibitors, BCR-ABL inhibitors) and has as prototype the toxicity induced by trastuzumab¹⁶⁻¹⁸. Type II agents are cytostatic and do not induce cell loss, but cellular dysfunction (mitochondrial/protein dysfunction) which leads to temporary and largely reversible cardiac dysfunction, not associated with increased car-

diovascular mortality¹⁶⁻¹⁸. There is no dose-dependent relation. Also, no apparent ultrastructural changes on endomyocardial biopsies have been described, though not thoroughly studied¹⁰.

This classification, however, has limitations. In patients with type I cardiotoxicity, clinical experience has shown that early detection of cardiac dysfunction and early administration of cardioprotective medications may improve LV systolic function¹⁹. In addition, trastuzumab, a type II drug, can trigger irreversible cardiac damage in patients with severe preexisting cardiac disease or it may potentiate the anthracycline type I CTRCD¹³. Moreover, as most of the newer targeted agents were introduced in oncology in the last two decades, their lack of long-term cardiac toxicity needs to be confirmed in the following years.

Anthracycline-induced type I CTRCD

Based on the time of onset and the duration of symptoms, anthracycline-induced cardiac toxicity has been categorized into acute, early-onset and late-onset chronic progressive¹³. Acute cardiotoxic events are relatively rare (<1% of patients), dose-independent and are, usually, observed from the beginning of treatment and up to 14 days after it ends^{13,17}. With few exceptions, they are transient, usually resolving within one to two weeks^{13,17}. They comprise sudden ventricular repolarization alterations, changes in QT interval, ventricular and supra-ventricular arrhythmias, acute coronary syndromes, pericarditis and myocarditis^{3,21,22}. Chronic CTRCD is dose-dependent, and more prevalent than the acute form: 1.6-5% of symptomatic HF patients during long-term follow-up 13 and up to 40% of asymptomatic patients with LV dysfunction^{3,17,21}. It may occur either in the first year after completion of chemotherapy (early-onset, 1.6% to 2.1%) or beyond the first year (late/delayed-onset, 1.6% to 5%)^{3,13,17,21,22}. Reports show that up to 10-20 years may pass until late-onset CTRCD becomes clinically evident¹³. Both forms of chronic CTRCD typically present as dilated cardiomyopathy, which can be progressive. However, this classification was made in the early 1990s and is based on retrospective, small studies in childhood cancer survivors' populations¹³. At present, there are no available prospective studies on long-term cardiac effects of anthracycline chemotherapy on adult populations¹³. Thus, the incidence and the timing of occurrence of anthracycline-induced CTRCD are not well defined¹³.

Genetic predisposition and other various risk factors (Table 1) influence the progression and degree of anthracycline-induced CTRCD. Among them, the to-

Table 1. Risk factors associated with anthracycline-induced CTRCD

Younger/ older age
Female gender
Rapid intravenous injection
Cumulative dose exceeding:
Daunorubicin 550-800 mg/m ²
Doxorubicin 400-550 mg/m ²
Epirubicin 900-1000 mg/m ²
Idarubicin 150-225 mg/m ²
Early mediastinal radiation, or concomitant doxorubicin exceeding a cumulative dose of 450 mg/m ²
Hypertension, coronary artery disease
Electrolyte disturbances: hypocalcemia, hypomagnesemia
Genetic predisposition

Adapted from 21.

tal cumulative dose of anthracyclines is the most important^{13,21,23}. The recommended maximum lifetime cumulative dose for doxorubicin is 400-550 mg/m² but it seems that there is no completely safe dose^{13,24}. Studies evaluating doxorubicin-induced CTRCD reported rates of 3-5% with 400 mg/m², 7-26% at 550 mg/m² and 18-48% at 700 mg/m²^{8,20}. Dose-limiting strategies reduce CTRCD. In breast cancer patients the currently doses of doxorubicin, used in combination with modern adjuvant therapy, are between 240 and 360 mg/m² and are associated with a incidence of HF around 2%²⁰. However, microscopic analysis shows myocardial damage even with doses of doxorubicin as low as 180 mg/m²²⁵. All risk factors are related to chronic CTRCD but not with the acute forms^{21,26,27}.

The exact pathophysiological mechanism for anthracycline-induced CTRCD is still not clearly defined. It is known that topoisomerase 2 (Top2) represents the molecular target of anthracyclines^{28,29}. Top2 is essential in modulating deoxyribonucleic acid (DNA) structure during transcription; replication and recombination^{28,30}. It has been shown that humans express two Top2 isoenzymes, namely Top2α and Top2β^{28,31}. Top2α is expressed in rapidly proliferating cells, such as the malignant cells, and it represents the primary target of the anticancer activity of the anthracyclines²⁸. On the other hand, Top2β is expressed in quiescent cells and is the only Top2 isoenzyme expressed in the heart tissue^{28,32}. Recent studies indicate that the Top2β isoenzyme is probably the target for the cardiac toxicity induced by anthracyclines²⁸. In the heart tissue, anthracyclines bind to Top2β, with the formation of ternary complexes (Top2 β -anthracycline-DNA)^{10,28}. These complexes lead to DNA double-stranded breaks and transcriptome changes which, in turn, activate the apo-

ptotic pathway and also selectively affect oxidative phosphorylation, mitochondrial biogenesis, and the p53 pathway^{10,28}. Through these main pathways: induction of cell apoptosis, reduction of adenosine triphosphate production from the mitochondria, and generation of reactive oxygen species, anthracyclines induce injury of cardiomyocytes²⁸. The injury of myocytes progresses (myofibrillar disarray, necrosis and cell loss) with the increase of the cumulative dose of anthracyclines and finally leads to the death of cardiomyocytes²⁸. The consequence is represented by a progressive decrease in the number of cardiomyocytes, leading to ventricular remodeling^{21,33}. Studies using endomyocardial biopsy and troponin I measurements showed that cardiomyocyte injury may occur during or early after anthracycline exposure^{8,16,19}. However, due to cardiac reserves and the activation of compensatory mechanisms, the clinical manifestations may become apparent after months to years from the initial exposure to anthracyclines¹⁶.

Trastuzumab - induced type II CTRCD

Trastuzumab, a recombinant humanized monoclonal antibody, is used for the treatment of HER2-positive breast cancer patients. The HER2 gene is expressed in 25-30% of breast tumors and determines an overproduction of human epidermal growth factor receptor 2 (HER2)¹³. These tumors are considered very aggressive and have a worse prognosis¹³. The introduction of trastuzumab in the treatment of HER2-positive breast cancer has determined a 50% reduction in recurrence and a 33% increase in survival^{13,14,34}.

The HER2 receptor is also expressed by the heart tissue and studies have shown that it plays an important role in the normal growth, repair and survival of cardiomyocytes^{35,36}. Trastuzumab binds to the extracellular domain of HER2 and inhibits its signal transduction, thus, directly inhibiting the antiapoptotic signaling pathways and making cardiac dysfunction possible²¹. As previously described, cardiac dysfunction induced by trastuzumab has a better prognosis than that caused by anthracyclines, as it often occurs during treatment, is reversible in most cases and it is not associated with ultrastructural lesions on endomyocardial biopsy^{18,43}. Also, trastuzumab rechallange after recovery of cardiac function is, usually, safe¹⁸.

The data from the pivotal and adjuvant trials on trastuzumab point out to the existence of an important anthracycline -trastuzumab interaction. It was observed that the most important risk factor for trastuzumab induced CTRCD is the association with high cumulative doses of anthracyclines ($>300 \text{ mg/m}^2$)²¹. It also seems

that trastuzumab potentiates anthracyclines toxicity especially when the two drugs are given concurrently, or when the time interval between the administration of the two regimens is short. In the pivotal metastatic HER-2 positive clinical trial, in which trastuzumab was administered concurrently with anthracyclines, the incidence of cardiac toxicity was very high, cardiac dysfunction being reported in 27% of cases and NYHA III/IV HF in 16% of cases^{37,38}. By contrast, in the adjuvant trastuzumab trials, in which trastuzumab and anthracyclines were given in a sequential manner, the reported incidence of cardiac dysfunction ranged from 3-18.1% and of NYHA class III-IV HF from 0-3.9%^{37,38}. Among the adjuvant trials, the HERA trial, in which the time interval between the administration of the two regimens was the longest, reported the lowest incidence of HF^{37,38}. Furthermore, when trastuzumab was given to patients who did not receive anthracyclines, the incidence of cardiac toxicity was even lower, such as in the third arm of the BCIRG 006 trial in which the incidence of cardiac dysfunction was of 8.6% and of NYHA class III-IV HF of 0.38%³⁹.

There are some relevant aspects that may explain this anthracycline-trastuzumab interaction¹⁸. Trastuzumab is, usually, administered to patients who have already been exposed to anthracyclines, and whose heart tissue is, thus, „vulnerable” in response to the injury induced by anthracyclines¹⁸. It seems that following anthracyclines administration there is a HER 2 overexpression in the „vulnerable” myocardium, by which cell repair mechanisms are activated⁴⁰⁻⁴². If trastuzumab is given during a time interval in which the myocardium is „vulnerable”, it will block the HER2 related cell repair and survival mechanisms and will potentiate and augment the injury induced by anthracyclines¹⁸. This is probably why, in some patients with a history of recent exposure to anthracyclines, trastuzumab may promote an irreversible cardiac dysfunction¹⁸.

Other risk factors for trastuzumab induced CTRCD are pre-existing LV dysfunction or systemic arterial hypertension, a body mass index >25 and advanced age^{13,21}. Chest radiotherapy associated with trastuzumab seems to be clinically safe^{21,34}. Recent evidence shows a higher incidence of trastuzumab-related cardiotoxic effects in cancer patients aged over 70, with a history of heart disease and/or diabetes^{21,44}.

Early detection of CTRCD using echocardiography

It has been shown that symptoms of CTRCD often become clinically apparent only after irreversible myocardial damage has occurred¹⁰. Also, if diagnosed late in

its course, HF due to CTRCD is often resistant to therapy¹⁰. By contrast, if CTRCD is detected early, prompt administration of HF treatments may slow the progression of LV dysfunction or prevent the development of late CTRCD³. Moreover, anticancer drug combinations could be modified as to reduce further cardiac damage³. Thus, the management of patients with CTRCD should focus on early detection and prompt treatment.

So far, early detection of CTRCD was mainly based on serial cardiac imaging to identify asymptomatic reductions in LVEF. Two-dimensional (2D) transthoracic echocardiography (TTE) is the most commonly used method in this setting. However, LVEF assessment by 2D TTE has a low sensitivity in detecting CTRCD at an early stage, due to some significant limitations: it presents technique-related variability⁴⁵; it reflects global function and it does not detect subtle regional changes^{10,22,46}; it may be affected by changes in loading conditions¹⁰; and also, the reduction in LVEF is often a late phenomenon, occurring only after a critical amount of myocardial damage has taken place^{19,45,47-50}.

Growing attention is being paid in defining markers of early myocardial changes that can predict subsequent LVEF reduction or the progression to HF. This would allow the early identification of patients at high risk for developing significant LV dysfunction and the initiation of prevention strategies by using targeted monitoring, as well as the possibility, to introduce cardio-protective medications⁴⁵.

There is much interest in the use of myocardial deformation parameters measured by tissue Doppler imaging (TDI) or speckle tracking echocardiography (STE) to identify early myocardial injury and to anticipate ventricular dysfunction in patients receiving chemotherapy^{45,51}. The advantages of these parameters include the possibility to detect regional abnormalities in LV function, their improved reproducibility and their reported ability to predict subsequent LV dysfunction^{10,45}.

It has been shown that the reduction of myocardial deformation parameters is an early sign of subclinical myocardial damage induced by chemotherapy, and occurs before any reduction in LVEF as assessed by conventional 2D TTE^{10,13,22,45,51,52}. It has also been reported that reductions of myocardial deformation parameters correlate with subsequent LVEF reduction or the development of HF, which represents the real value of these parameters¹⁰. Earlier studies focused on TDI-based strain parameters, among which inter-ventricular septal peak systolic longitudinal strain rate

was reported to be the most consistent in detecting the early myocardial changes during chemotherapy⁴⁵. Recent studies use 2D STE to measure different myocardial deformation parameters (strain, strain-rate and twist). Among them peak systolic global longitudinal strain (GLS) is significantly related to the subsequent development of CTRCD^{10,45}. Because of baseline variability in strain values between different patients, it has been shown that the within-patient change of STE-GLS is a more reliable parameter compared to a population-derived absolute cut-off value^{10,45,54}. Although the cut-off value for within-patient change in STE-GLS that predicts CTRCD is not clear, it has been reported that values between 11-15% appear to have the best specificity^{10,45,54}. In patients where a relative change in GLS is unavailable, absolute levels of GLS > -19% and -20.5%, early during chemotherapy, have been associated with CTRCD^{45,53,54}. In contrast, neither global radial strain nor global circumferential strain proved consistently predictive of CTRCD^{45,53,54}.

The recently published Expert Consensus Statement recommends the serial monitoring of GLS as the ideal strategy for the detection of subclinical LV dysfunction¹⁰. GLS assessed during chemotherapy should be compared with the one measured at baseline, and the within-patient change in STE-GLS should be noted¹⁰. The authors mention that the relative percentage reduction in GLS of >15% is very likely to be abnormal, whereas a change of <8% appears not to be of clinical significance¹⁰. Also, it is recommended to confirm the abnormal value of GLS by a repeat study that should be performed two to three weeks after the initial abnormal study¹⁰.

CONCLUSION

Advances in breast cancer treatment and the subsequent increase in disease-free survival have led to an increase of cardiac complications induced by cancer therapy. As overt HF induced by chemotherapy has such a worse prognosis, there is a stringent need to improve our ability to detect CTRCD at a subclinical level. Echocardiography has a major role in this setting, with evidence supporting the use of myocardial deformation parameters measured by 2D-STE in detecting the subclinical CTRCD. Among them, STE-GLS seems to be the most consistent parameter that correlates with the subsequent development of CTRCD. The serial monitoring of STE-GLS has been included in the assessment and monitoring of cardiac function in cancer patients as the ideal strategy for the detection of subclinical LV

dysfunction. Determining the significance of these changes will require long-term follow-up before GLS may be used in treatment related-decisions. To better understand what defines CTRCD, more research and larger studies are needed and also a dynamic partnership between oncologists and cardiologists.

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