Heart Failure in Oncologic Patient: Risk Predictors

doi: https://doi.org/10.32635/2176-9745.RBC.2019v65n3.719

Insuficiência Cardíaca no Paciente Oncológico: Preditores de Risco

Insuficiencia Cardíaca en Pacientes con Cáncer: Predictores de Riesgo

Tatiana Abelin[1]; Marcos Jose Pereira Renni[2]

INTRODUCTION

The number of cancer survivors increases annually because of advances in detection and treatment of cancer and the ageing of the population and continues to grow annually[1-4]. The effects of the treatment affect the survival and the quality of life of the patients, regardless of its oncologic prognosis. Chemotherapy-related chronic heart failure is one of the undesirable effects and occurs in nearly 10% of the patients. The evolution to terminal heart failure (HF) generates a two years survival prognosis in this period[2].

The definition of cardiotoxicity (CDTX) is still controversial, but according to recent consensus, it is considered when there is a drop of the ejection fraction (EF) observed in the transthoracic echocardiogram (TTE) of more than 10% of the baseline value or when it decreases to values equal or lower than 53%[5].

The chemotherapeutic agents cause or exacerbate HF through several mechanisms: direct cardiac injury (anthracyclines, antimetabolites, alkylant agents, interleukins -2); by exacerbation of hypertension (inhibitors of the endothelial growth factors); favoring the occurrence of arrhythmias or other cardiotoxic mechanisms still not completely understood[5]. Patients with cancer or cancer survivors exposed to these agents are under major HF risk[3].

Despite these advances, studies have been made to detect early CDTX biomarkers related to several chemotherapeutics and mainly by anthracyclines. They are the main responsible for the permanent heart injury and responsible for negative outcomes in the medium and long term. Similarly, there is still no specific and universal risk score to predict more reliably the patients that are more susceptible to the development of cardiac related chemotherapy dysfunction despite the efforts of several entities involved with cardio oncology.

It is known, however, that the stratification of the patients through analysis of the risk factors is an initial step for the CDTX evaluation. The most susceptible patients are those who receive cumulative anthracycline dose higher than 250 mg/m^2, female patients, individuals older than 65 years and lower than 18 years old, with chronic kidney disorder, who underwent previous mediastinal radiotherapy (RxT) or concomitant to treatment, chemotherapy with alkylant or antimicrotubules agents, in addition to those in constant use of immunotherapies[1,5].

The risk factors for the development of CDTX for those who receive chemotherapeutics agents as cyclophosphamide, ifosfamide and taxanes (paclitaxel and docetaxel) are old age, combined therapy with others antineoplastic and mediastinal irradiation[1].

For those who receive immunotherapies as inhibitors of HER-2 (trastuzumab and pertuzumab) and inhibitors of tyrosine kinase (ITQ) as lapatinib, have greater risk of CDTX when its use is associated with antimetabolic and alkylant agents[1]. It is worth noting that even younger patients also presented increased risk of CDTX[5]. Patients with left ventricle (LV) global function close to normal were also more susceptible[1].

Based in these data and in the risk factors evaluation, there are tools which have become more frequent and important for the evaluation of the patient that is submitted to cardiotoxic chemotherapy (CT) including natriuretic peptide type B (BNP) and troponin dosages and strain echocardiography. This kind of TTE can detect myocardial fibers deformation[5].

TTE is a quite relevant method in this scenario: it is a non-expensive test, sensitive and widely available and non-invasive[6]. However, the use of EF with TTE has been shown scarcely sensitive for this evaluation as there are more innovative and sensitive techniques to predict CDTX. Therefore, during a TTE test, myocardial deformity parameter through 2D strain complement the data already often used in a routine exam.

[1] Instituto Nacional de Câncer Jose Alencar Gomes da Silva (INCA). Rio de Janeiro (RJ), Brazil. Orcid iD: https://orcid.org/0000-0001-9093-7806
[2] INCA. Rio de Janeiro (RJ), Brazil. Orcid iD: https:// orcid.org/0000-0003-3381-7394
Address for Correspondence: Tatiana Abelin. INCA. Praça Cruz Vermelha, 123 - Centro. Rio de Janeiro (RJ), Brazil. CEP 20230-130. E-mail: tabelin@ig.com.br

The principal biomarkers involved in the early detection of CDTX are dosages of troponin and BNP/ProBNP. Troponins are the golden-standard markers that diagnose the myocardial injury.

BNP and the N-terminal portion of ProBNP have been used to non-invasive evaluation of the LV systolic function during antineoplastic treatment. Its increased serum levels occur in response to the pressure and volume overload and are strongly related to cardiovascular events, HF symptoms and mortality[7].

Troponin is another important biomarker to detect myocardial injury of various causes, as, for instance, myocardial acute infarction, Takotsubo's syndrome and myocarditis[8]. Troponin measures have been used in patients receiving high AC doses. The dosage, through an ultrasensitive method of I and T troponins presents high myocardial damage sensitivity and specificity and its concentrations are associated to the severity of the injury and clinic outcome[9]. A study of Sawaya et al.[10] demonstrated that the increased troponin associated to the abnormal longitudinal strain were predictors of EF reduction.

Some services and societies propose "risk scores" or specific flowcharts to stratify the higher CDTX risk patient[4]. Its majority stratified the traditional risk factors for the development of arteriosclerosis and those intrinsic to the chemotherapy treatment. It is interesting to note that, despite the suggestion of higher and lower monitoring frequencies for each chemotherapy scheme, several services emphasize the necessity of a baseline test when it is estimated the use of cardiotoxic drugs regardless of the clinical history[1]. It is questioned, however, the economic feasibility of this suggestion as all the patients with breast cancer, for instance, would have to undergo a basal echocardiogram, which creates an additional cost to health providers services.

Similarly, the American and European societies issued a consensus in 2014[5] about the evaluation of patients during and after antineoplastic therapy. In this document, further to a detailed explanation about the imaging methods used so far to follow up these ill patients, it was created a routine to guide the medical communities about the best follow up of patients submitted to cardiotoxic therapies type I (represented by anthracyclines) and type II whose principal chemotherapy is trastuzumab. Therefore, flowcharts that identify cardiologic follow up for those patients with EF decrease below 53% or a drop of strain and increase of troponin in the case of those submitted to anthracyclines at each six months in the first year are identified. For the patients who will be submitted to trastuzumab, it is suggested a baseline evaluation of echocardiogram, strain or troponin with its serial measures at each three months.

There are some risk factors evaluation scores and follow up proposed by some services, as, for instance, the Mayo Clinic that, in 2016, suggested risk grading. This grading varies according to the risk factors and CT proposed, promoting scores pursuant to each drug and risk factor, assessing the risks for the CDTX development. Therefore, the patients will undergo more frequent evaluations per the scores reached (Table 1)[4].

There are simple stratification methods proposed by other societies as the European Society of Cardiology[5] that in 2016 published a consensus emphasizing the importance of risk factors identification related to CDTX caused by anthracyclines (doxorubicin, epirubicin), by inhibitors of the tumor growth factor VEGF-1 (antibodies represented by vacizumab and inhibitors of tyrosine-kinase exemplified by sunitinib, pazopanib, sorafenib and dasatinib),by inhibitors of HER-2 (trastuzumab) and the methods of follow up through biomarkers and imaging tests (preferentially the same) that can vary among echocardiogram, multigated acquisition scan (MUGA) and nuclear magnetic resonance (NMR). In addition, biomarkers (troponin or BNP) are attempted to be used for the detection of subclinic cardiac injuries and better management of this patient with higher CDTX risk[5].

In patients submitted to anthracycline treatment, it is unclear about the best follow up frequency with imaging tests and biomarkers, but they need to be done in the beginning and in the end of the treatment[5].

According to the European Society, it should more intensive monitoring of inhibitors of HER-2 with imaging tests at each three months during and after the end of the treatment. Many studies reveal an improvement of the early detection of the drop of EF when troponins and strain TTE were used at each three months during treatment with trastuzumab. As there is a wide variation time that dysfunction caused by this chemotherapeutic may occur, it is suggested that the measure of troponin should be done at each cycle in baseline high risk patients.

The same society additionally recommends that the patients who receive inhibitors of VEGF-1 should be monitored in the first two to four weeks from the beginning of the treatment and after its termination. However, the frequency is not well established. Frequently, it is considered a revision at each six months until the stabilization of EF when it is affected[5].

Finally, this same perspective warns that at least one baseline echocardiogram must be performed and for low risk patients (TTE of normal base and absence of risk factors), follow up for those who receive anti-HER-2 at each four cycles or after a cumulative dose of 200 mg/m^2 of doxorubicin or equivalents.

Table 1. Risk estimate and monitoring associated to ventricular dysfunction

Risk factors associated to the patient	Risk factors associated with the chemotherapeutic
1 score for each risk factor	**High risk (score 4):** anthracyclines, trastuzumab, ifosfamide, cyclophosphamide, clorafabine
Age (<15 years or >65 years)	**Intermediate risk (score 2):** docetaxel, pertuzumab, sunitinib, sorafenib
Female	**Low risk (score 1):** bevacizumab, imatinib, **lapatinib, dasatinib**
Hypertension	**Rare (score 0):** etoposide, rituximab, thalidomide
Diabetes mellitus	
Atherosclerosis (CAD, CV, OPAD)	
Previous heart disease or heart failure	
Previous use of anthracyclines	
Mediastinal or previous thoracic RxT	
RS of cardiotoxicity	
RS of cardiotoxicity **Risk factors according to the chemotherapeutic + number of risk factors related to the patient** **RS >6:** very high**; RS 5-6:** high risk**; RS 3-4:** intermediate**; RS 1-2:** low**; RS 0:** very low	
Recommendations of monitoring of Mayo Clinic	
RS>6: Strain TTE before each cycle, at the end of CT, 3, 6 and 12 months after. ECG optional and troponin with echo during CT **RS 5-6:** Strain TTE at each 3 cycles at the end of CT, 3, 6, and 12 months after. ECG optional and troponin with echo during CT **RS 3-4:** Strain TTE in the half of the cycles, 3, 6 months at the end of CT and 12 months after. ECG optional and troponin with ECHO during CT **RS 1-2:** Strain TTE optional and/or ECG at the end of the treatment **RS 0:** Exams not required	

Captions: CAD = Coronary Artery Disease; CV = Cerebrovascular disease; OPAD = Obstructive Peripheral Arterial Disease; ECG = Electrocardiogram; TTE = Transthoracic Echocardiogram; RS = Risk scores; CT = Chemotherapy; RxT = Radiotherapy; *Strain* = technique performed during the echocardiogram to evaluate the degree of myocardial deformity.

Consequently, it is observed that, even in the consensus, there is a certain difficulty of establishing the patients with greater CDTX risk and the ideal frequency of monitoring of echocardiogram and biomarkers and the best follow up marker of patients who, eventually, develop heart failure during the treatment.

CONCLUSION

It is necessary a CDTX predictive "risk score" because so far there is no specific biomarker. There is, nevertheless, a set of several of them that seemingly detect subclinic injuries. Biomarkers as troponins and BNP and echocardiogram with strain have demonstrated ability to predict patients who will develop early myocardial injuries.

CONTRIBUTIONS

The authors contributed equally and substantially in every stage of the work and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING FINANCIAL SOURCES

None.

REFERENCES

1. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the american society of echocardiography and the european association of cardiovascular imaging. J Am Soc Echocardiogr. 2014;27(9):911-39. doi: https://doi.org/10.1016/j.echo.2014.07.012
2. Miller KD, Siegel RL, Linc CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89. doi: https://doi.org/10.3322/caac.21349
3. Finet JE. Management of heart failure in cancer patients and cancer survivors. Heart Fail Clin. 2017;13(2):253-88. doi: https://doi.org/10.1016/j.hfc.2016.12.004
4. Barros-Gomes S, Herrmann J, Mulvagh SL, et al. Rationale for setting up a cardio-oncology unit: our experience at Mayo Clinic. Cardio-Oncology. 2016;2:5. doi: https://doi.org/10.1186/s40959-016-0014-2
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-2801. doi: https://doi.org/10.1093/eurheartj/ehw211

6. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc. 2008;83(6):679-86. doi: https://doi.org/10.4065/83.6.679
7. Daugaard G, Lassen U, Bie P, et al. Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. Eur J Heart Fail. 2005;7(1):87-93. doi: https://doi.org/10.1016/j.ejheart.2004.03.009
8. Jurcut R, Wildiers H, Ganane J, et al. Detection and monitoring of cardiotoxicity-what does modern cardiology offer?. Support Care Cancer. 2008;16(5):437-45. doi: https://doi.org/10.1007/s00520-007-0397-6
9. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749-54. 96. doi: https://doi.org/10.1161/01.CIR.0000130926.51766.CC
10. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5(5):596-603. doi: https://doi.org/10.1161/CIRCIMAGING.112.973321

Recebido em 12/11/2019
Aprovado em 17/01/2020