Permissive Cardiotoxicity: When the Optimal Is the Enemy of the Good

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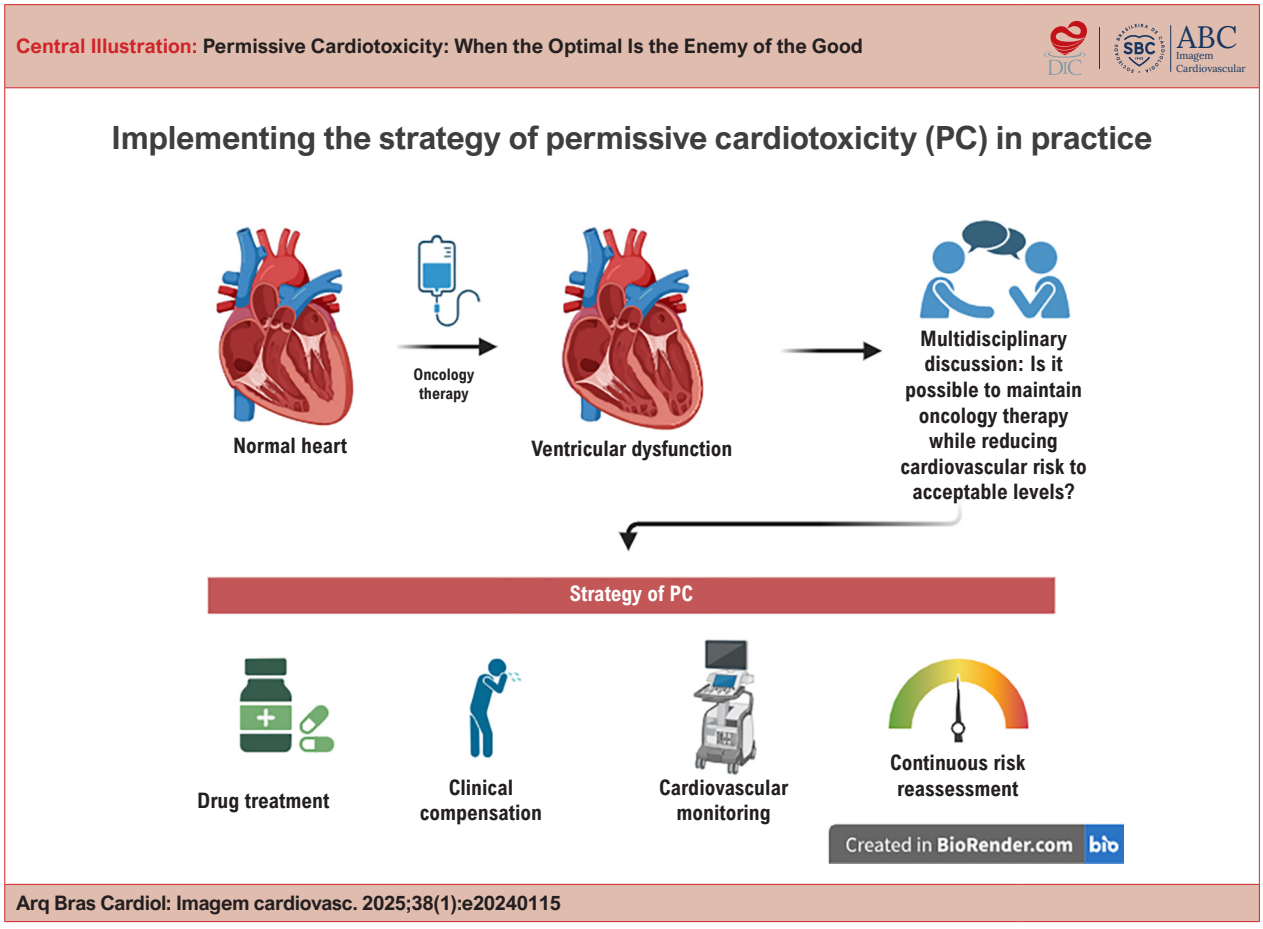
Central Illustration: Permissive Cardiotoxicity: When the Optimal Is the Enemy of the Good



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Keywords

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Abstract

Cancer and cardiovascular diseases are the leading causes of mortality worldwide. As these diseases share common metabolic pathways, patients with cancer are currently seen as having subclinical alterations with great potential for developing cardiovascular diseases (and vice versa). This tenuous interrelationship has led to the emergence of cardio-oncology (CO) as an area of study and discussion, with a major impact on the management of these cases.

In clinical practice, CO is dominated by the dilemma of how to best manage cardiovascular toxicity during cancer

treatment. The management of these cases focuses not only on restoring cardiovascular balance, but also on ensuring that the best oncological treatment will be offered, without suspensions or interruptions.

Within this context, the concept of permissive cardiotoxicity (PC) has emerged, proposing the idea of maintaining antitumor treatment in the event that ventricular dysfunction is detected, with no pauses or interruptions, provided that certain premises are respected.

This review aims to examine the concept of PC in depth, contextualizing its emergence, reviewing definitions, and analyzing the evidence from experimental clinical studies. Furthermore, management strategies are detailed, discussing the central role of cardiovascular imaging in guiding this management. Finally, limitations and gaps in the literature in the area are discussed.

Introduction

Cancer and cardiovascular diseases are currently the leading causes of mortality worldwide.[1] These diseases share not only common risk factors (for example, smoking, obesity, sedentary lifestyle, alcohol consumption, diets rich in ultra-processed foods, etc.),[2] but also equivalent metabolic pathways.[3]

Accordingly, patients receiving oncological treatment have come to be seen as having an elevated risk of cardiovascular disease.[4] This fact allows us to predict that, at some point in the oncological journey, heart disease will be part of the list of these patients' comorbidities. In this context, cardiologists have begun to face the challenge of managing cardiovascular events in patients with neoplasia, culminating in the organization of this recent area of study, CO.

Cardio-oncology: a vital field

CO emerged as a result of the intersection between cardiovascular health and cancer treatment.[5] Driven by the growing practical need to manage cardiological events associated with these treatments, CO has rapidly evolved into a field of study and research. This new area brings together specialists who share the common goal of maintaining the most effective oncological treatment available while respecting the premises of cardiovascular safety.

Although the field of CO is vast, with important windows of opportunity for action in the diverse phases of the oncological journey, the main challenge lies in the management of events throughout the active phase of antitumor treatment. The appropriate management of these cases is crucial, as it directly impacts not only cardiovascular, but especially oncological prognosis and survival.

These data, in conjunction with the development of antineoplastic treatments that have significantly increased patient survival rates, have directed the focus of attention to CO, which has become fundamental to ensuring excellence in oncological care.

Cardiotoxicity: what every cardiologist needs to know

We broadly define cardiotoxicity as any pathological alteration of the cardiovascular system induced by oncological treatment.[6] Possible cardiotoxic manifestations thus include all conditions that affect the cardiovascular system, from worsening of cardiovascular risk factors (for example, hypertension, dyslipidemia, metabolic syndrome, etc.) to major events such as acute coronary syndromes, pulmonary thromboembolism, severe ventricular arrhythmias, and others.

Although it has a broad spectrum of manifestations, the main types of cardiotoxic manifestations are presented in the form of the following two clinical syndromes: arrhythmias and chemotherapy-related cardiac dysfunction (CTRCD). Among these, systolic myocardial dysfunction has been the most impactful clinical presentation (due to its severity and risk), making CTRCD a near synonym of "cardiotoxicity." The antineoplastic medications most frequently associated with CTRCD are listed in Table 1.

The most widely accepted and internationally applied definition for CTRCD in clinical practice was standardized by the publication of the Cardio-Oncology Guideline of the European Society of Cardiology in partnership with the International Cardio-Oncology Society in 2016, which defines CTRCD as a drop in left ventricular ejection fraction (LVEF) of ≥ 10% (in relation to the pre-treatment value) in the presence of absolute values < 50%.[7] It is important to mention that CTRCD is a diagnosis of exclusion, making it mandatory to conduct differential diagnosis and rule out other etiologies related to ventricular dysfunction (especially coronary artery disease, which is the most prevalent etiology worldwide).[8]

Permissive cardiotoxicity: a new look for an old concept?

The main challenges of CO include the management of situations in which patients are exposed to a highly effective oncological treatment, but they progress with signs of cardiovascular toxicity. In this scenario, classically, a discussion takes place about whether to pause or suspend antineoplastic treatment, given that this was initially considered the most appropriate course of action. However, questions began to be raised when studies demonstrated that even brief and temporary suspension of oncological treatment resulted in a reduction in its efficacy.[9] The practical observation of the good clinical evolution of patients with discrete drops in LVEF while using trastuzumab (generally oligosymptomatic and with excellent progress after initiating use of cardiovascular medications)[10] provided the pathophysiological rationale for the concept of PC.[11]

The strategy of PC consists of maintaining the antitumor treatment underway when ventricular dysfunction is detected, without pauses or interruptions.[12] This conduct is based on the following pillars: 1 – Maintaining the antineoplastic treatment without temporary pauses or suspension; 2 – Initiating cardiovascular drug treatment that promotes the best cardiological prognosis possible.[12] The strategy of PC assumes the premise that some degree of "manageable" cardiovascular damage (i.e., that does not result in serious cardiovascular events and/or high morbidity and mortality) may be acceptable in the name of maintaining the treatment that results in the best oncological prognosis.

Table 1 – The main antineoplastic medications associated with CTRCD

Pharmacological class	Examples of agents	Indicated tumor types
Anthracyclines	Doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone	Breast, ovarian, lymphomas, and leukemias
Anti-HER therapies	Trastuzumab, T-DM1, pertuzumab, trastuzumab deruxtecan	Breast, gastric
Tyrosine kinase inhibitors	Sorafenib, sunitinib, pazopanib, afatinib, osimertinib, erlotinib	Renal carcinoma, hepatocellular carcinoma, lung cancer
Alkylating agents	Cyclophosphamide, ifosfamide	Lymphomas and leukemias, sarcomas
Immune checkpoint inhibitors	Pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab	Multiple indications, the main ones being: melanoma, bladder cancer, renal carcinoma, lung cancer, hepatocellular carcinoma
Proteasome inhibitors	Carfilzomib, ixazomib, bortezomib	Multiple myeloma
VEGF inhibitors	Bevacizumab, aflibercept	Colorectal cancer and renal carcinoma
MEK/BRAF inhibitors	Dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib	Melanoma

BRAF: serine/threonine-protein kinase; CTRCD: chemotherapy-related cardiac dysfunction; HER: human epidermal growth factor; MEK: mitogen-activated protein kinase; T-DM1: ado-trastuzumab emtansine; VEGF: vascular endothelial growth factor.

Literally speaking, the strategy of PC is indicated in cases of CTRCD during antitumor treatment. Nonetheless, it can also be applied to candidates who have elevated cardiovascular risk. In this situation, "non-ideal" conditions are tolerated in the name of obtaining a major oncological benefit. In both cases, what differentiates the approaches is the moment when the permissive strategy is instituted: during cancer treatment (in cases of established cardiovascular toxicity) or pre-treatment (in cases of high baseline cardiovascular risk).

The concept of PC assumes that, even in unfavorable cardiological scenarios, the oncological treatment of choice can be maintained as long as the cardiovascular risk is reduced to acceptable levels. It is believed that, in the absence of evidence that proves the benefit of suspending antitumor treatment, clinical optimization provides sufficient conditions to continue to offer the oncological regimen. This concept encourages care teams to change their stances, replacing reactive approaches (modifying or suspending chemotherapy regimens) with proactive approaches (aimed at reducing cardiovascular risk and enabling the continuation of the antitumor regimen). Ultimately, the aim is to achieve a residual cardiovascular risk that is outweighed by the benefits of cancer treatment.[12]

The evidence supporting the PC approach is still scarce and has been published slowly, predominating in the scenario of HER2-positive breast cancer. It is important to underscore that PC is an exceptional approach and that eligible patients are not numerous on a daily basis; therefore, as is the case with rare diseases, it is not a condition that can easily be studied by robust clinical trials with large sample sizes. Table 2 summarizes the data from the experimental studies that are available to date.

These data, although they come from small, single-center, non-randomized studies, reveal the experience of groups who opted not to deprive patients of treatments that modified the natural history of their disease, resulting in a substantial increase in disease-free survival curves.[18]

The PC approach has also been applied in other contexts in oncology. Examples include situations of re-exposure to treatment after episodes of vasospasm with 5-fluorouracil,[19] after myocarditis related to immune checkpoint inhibitors,[20] or even after ventricular dysfunction with carfilzomib.[21] Reports and case series from some centers have demonstrated that strategies of introducing cardioprotective medications before infusion, modifying the route of administration, and adjusting the combination of oncological agents can be useful to ensure continuity of the proposed treatment.[19-21] In these situations, joint work with the CO specialist is fundamental.

Role of cardiovascular imaging in the implementation of the strategy of PC

Cardiovascular imaging tools are essential when implementing the strategy of PC, because they allow for the progressive monitoring of cardiac function during cancer treatment.[22] This monitoring provides information that is essential to decision-making regarding the viability and safety of maintaining antineoplastic treatment.

Among cardiovascular imaging methods, echocardiography stands out as a non-invasive, widely available, and low-cost method, which facilitates regular, serial use in cardiotoxicity monitoring programs. This method's accessibility allows for frequent use for cardiovascular monitoring, making it possible to adjust the therapeutic strategy in real time, which maximizes the efficacy of oncological treatment without compromising patient safety. In this manner, echocardiography has proven to be a valuable resource for the dynamic management of cardiovascular risk in patients who will be exposed to potentially cardiotoxic therapeutic regimens.[23]

Myocardial strain is a quantitative measure of deformation during the cardiac cycle, and it is a sensitive tool for detecting subclinical cardiac dysfunction (before LVEF is affected).[24] The ability to detect these early changes is crucial to the management of PC, as it allows early intervention (such as dose

Table 2 – Data from experimental studies on PC

Author and year	Design	Population	Sample	Results
Nowsheen S. et al, 2018[13]	Retrospective, case-control	Patients with HER-positive breast cancer exposed to trastuzumab	- 20 cases with baseline LVEF < 53% - 408 controls with LVEF ≥ 53%	Group with LVEF < 53% at baseline did not show a higher risk of decreased LVEF
Lynce F. et al, 2019[14] (SAFE-HEaRt Trial)	Prospective, single-arm	Patients with HER-positive breast cancer candidates for T-DM1 or trastuzumab with or without pertuzumab	- 31 patients with baseline LVEF between 40% and 49% - All treated with BB and ACEI	90% of patients completed the planned anti-HER treatment
Leong D. et al, 2019[15] (SCHOLAR Trial)	Prospective, single-arm	Patients with HER-positive breast cancer candidates for trastuzumab	- 20 patients with baseline LVEF between 40% and the lower limit or ≥ 15% drop in LVEF	90% of patients received all planned cycles without interruptions
Khoury K. et al, 2021[16] (SAFE-HEaRt Trial extended)	Prospective, single-arm	Patients with HER-positive breast cancer candidates for T-DM1 or trastuzumab with or without pertuzumab	- 23 cases from the original cohort (8 of them still in continuous anti-HER therapy for metastatic disease) - Follow-up of 42 months	- Improvement in mean LVEF from 44.9% (beginning of the study) to 52.1% (end of study) - 1 case of symptomatic heart failure
Zhou S. et al, 2023[17]	Retrospective, cohort	Patients with HER-positive breast cancer exposed to trastuzumab	- 51 patients managed with PC - Follow-up of 3 years	- 92% completed the treatment - 6% suspended trastuzumab due to severe/symptomatic ventricular dysfunction

ACEI: angiotensin-converting enzyme inhibitor; BB: beta blocker; HER: human epidermal growth factor; LVEF: left ventricular ejection fraction; T-DM1: ado-trastuzumab emtansine; PC: permissive cardiotoxicity.

adjustment or inclusion of cardioprotective drugs) while the patient continues oncological treatment. In clinical practice, a 15% reduction in global longitudinal strain in relation to the baseline value is considered indicative of possible subclinical cardiotoxicity, even in the absence of a decrease in LVEF.[24]

Permissive cardiotoxicity in practice: prerequisites and management strategies

The strategy of PC has not been studied with sufficient methodological rigor to design protocols and guidelines based on scientific data. However, reports of successful experiences and studies conducted in the area[13-17] suggest that some conditions must be met for the strategy to be conducted with due precaution and safety:

1. The concept of PC is applicable in cases of mild to moderate CTRCD (LVEF > 40%), provided that there are no severe symptoms (significant pulmonary congestion with worsening of the respiratory pattern; clinical, electrical, or hemodynamic instability; poor perfusion and/or signs of low output).

2. The strategy of PC applies to manageable cases of CTRCD (patients who have a window for the introduction of cardiovascular medications), always focusing on long-term cardiological safety.

3. It is mandatory to perform strict, regular monitoring of cardiac function during PC, preferably with the same professional and on the same device.

4. It is necessary to pre-define levels of cardiac dysfunction at which it is no longer safe to continue therapy. Routinely, continuation of PC is tolerated as long as LVEF is > 40%. This value varies according to LVEF at the beginning of PC, the magnitude of the drop in LVEF in relation to baseline, and the associated clinical repercussions.

The medical management of these cases should follow the recommendations of the current guidelines for the treatment of heart failure, respecting individual limitations related to the clinical/laboratory context of each case. Below, we will briefly discuss the medical management of CTRCD according to the most recent recommendations.[4,8]

It is suggested that, initially, priority should be given to the introduction of drugs studied for heart failure that also have specific evidence of cardioprotection in patients with cancer, such as beta blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). Carvedilol and enalapril are the medications with the highest number of favorable studies in CO, and they are the most commonly used medications in practice (although other BB and ACEI/ARB indicated for heart failure also have similar effects). The combination of BB and ACEI/ARB should be initiated at low doses, with progressive escalation up to the maximum tolerated doses. In the case of hypotension that limits concomitant initiation, each medication should be introduced individually; there is no defined order based on evidence, and the choice should be based on each case's characteristics and restrictions. Depending on the presence and degree of associated pulmonary congestion, the prescription of diuretics and/or mineralocorticoid antagonists may be indicated during this first stage of drug management. During a second stage, depending on the clinical response, functional class, presence (or absence) of residual symptoms, and tolerance (also related to laboratory alterations), it is possible to assess the need to add other first-line medications for the treatment of heart failure, with SGLT2 inhibitors and sacubitril/valsartan replacing ACEI or ARB.

The key points for implementing the strategy of PC are summarized in the Central Illustration.

Limitations and gaps in the literature

The strategy of PC has numerous limitations, the main one being the lack of robust scientific evidence to support its use. A borderline context for its implementation is the presence of pre-treatment ventricular dysfunction, since further worsening of LVEF can result in significant impairment. In these cases, drug optimization should be even more immediate and aggressive, and the search for the best oncological outcome should respect the premises of cardiovascular safety. Finally, it is important to underscore that it is not considered appropriate to institute PC in cases that have therapeutic alternatives with similar efficacy or in cases where treatment is optional (a decision that should be delegated exclusively to the oncologist).

Gaps still abound in the literature regarding PC. They include the lack of studies that explore long-term cardiovascular outcomes, the lack of guidelines and standardized protocols for identifying safe levels of ventricular dysfunction to be tolerated, and the identification of specific risk predictors that could help individualize the PC approach.

Conclusions

Correct implementation of the strategy of PC depends on a combination of solid technical expertise in CO, a proactive stance regarding early interventions, and clear and effective communication (involving a medical and multidisciplinary team, patients, and family members). The main objective of this strategy is to offer oncology patients the most effective treatment available, avoiding interruptions or suspension of medications that can save lives. PC seeks to change the mindset when addressing a cardiotoxic event, encouraging professionals to seek ways to maintain cancer treatment with the greatest possible cardiovascular safety.

When facing diagnosis of CTRCD, it is up to cardiologists to weigh, equate, and manage the various factors involved, so that the choice of the PC approach will be appropriate and bring benefits, rather than risks, to the patient. In order to do so, it is essential for the diverse professionals involved in providing care for patients with cancer to share, discuss, and study this topic.

Author Contributions

Conception and design of the research: Silva CMPDC; acquisition of data: Silva CMPDC, Seabra-Garcez JD, Neves APL; writing of the manuscript: Silva CMPDC, Seabra-Garcez JD, Macedo AVS; critical revision of the manuscript for intellectual content: Silva CMPDC, Macedo AVS.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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