Prevention and Treatment of Cardiomyopathy and Heart Failure in Patients Receiving Cancer Chemotherapy

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Opinion statement

Chemotherapy (CT)-induced cardiotoxicity remains an unresolved problem that strongly affects the quality of life and overall survival of cancer patients. The most typical form of cardiotoxicity, a dilated cardiomyopathy (CMP), usually becomes manifest late in the course of the disease and is classically considered to be refractory to therapy. Preventing cardiotoxicity remains the most important strategy, and several measures have been proposed, including cardiac function monitoring, limitation of CT dose, use of anthracycline analogues and cardioprotectants, and early detection of cardiotoxicity by biomarkers. The response to modern heart failure therapy of CT-induced CMP has never been evaluated in clinical trials, and no definite guidelines have been adopted. Although it is likely that medications used for other forms of CMP, particularly angiotensin-converting enzyme inhibitors and β-blockers, may be highly effective, there is still some unjustified concern regarding their use in cancer patients.

Introduction

The advent of modern cancer therapy, consisting of chemotherapy (CT), antibody-based therapy, radiation therapy, and surgery, has considerably improved the prognosis of cancer patients, reducing mortality from many forms of cancer. To achieve this result, however, a considerable price has been paid in terms of the side effects associated with intensive anticancer treatment. In particular, cardiotoxicity remains a major limitation in both standard- and high-dose CT, strongly affecting the quality of life and overall survival of many cancer patients, regardless of the oncologic prognosis. The magnitude of the problem is increasing as a result of the growing number of long-term cancer survivors, and because of the tendency to use higher doses of anthracyclines (ACs), new antitumor agents with possible, unknown, cardiotoxic effects, as well as combined treatments with synergistic harmful effects [1,2,3••,4]. As a consequence, CT-induced cardiotoxicity is a rapidly evolving area, as well as one of growing interest, involving oncologists and cardiologists.

Cardiac events associated with CT vary in incidence and may occur acutely (during or shortly after treatment), subacutely (within days or weeks after completion of CT), or chronically (weeks to months after drug administration). They also may occur as late sequelae, many years after the end of treatment. Cardiotoxicity may depend on the dose administered during each course or on the total cumulative dose, or it may be completely independent of the dose [1,4,5].

Cancer CT is moving into a new era of "targeted therapy" with the development of novel agents with more specific molecular mechanisms of action. Although cytostatic antibiotics of the AC class remain the most common cardiotoxic CT agents, many other CT agents may cause cardiotoxicity [2,4,6]. Indeed, the recognition of cardiac toxicity induced by trastuzumab, which belongs to the class of monoclonal antibodies against human epidermal receptor-2 (HER2) recently introduced to treat breast cancer, has highlighted the potential for unexpected toxic effects from novel agents.

Commonly, two forms of CT-induced cardiotoxicity may be distinguished [1,6]:

1. Acute or subacute cardiotoxicity, found more infrequently, may occur any time from the initiation of CT up to 2 weeks after termination of treatment. In this form, the most common clinical findings range from abnormalities in ventricular repolarization and QT interval prolongation to supraventricular and ventricular arrhythmias, or to acute coronary syndromes, acute heart failure (HF), and pericarditis/myocarditis-like syndromes.
2. Chronic cardiotoxicity, the most frequent cumulative dose-dependent form, may be differentiated in two subtypes based on the timing of onset of clinical symptoms: early, within 1 year of the termination of CT, and late, after 1 year. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction, which leads to severe congestive cardiomyopathy (CMP) and may, in turn, ultimately lead to death. The incidence of chronic cardiotoxicity depends on different risk factors (eg, total administered dose of antineoplastic drugs, patient age, gender, history of cardiac disorders, prior mediastinal radiation), the duration of follow-up, and the criteria used to define cardiotoxicity, and has ranged from 5% to 65% of patients in several studies [1,7••,8].

There still is no consensus definition for cardiotoxicity. Several classifications of cardiotoxicity have been proposed based on HF symptoms and left ventricular ejection fraction (LVEF) reduction and in most cases include four degrees of severity of cardiac impairment [9]. However, the LVEF decline threshold for defining first-grade cardiotoxicity is completely different among the various classifications. For example, the latest version of the National Cancer Institute classification considers an LVEF reduction below 60% to be indicative of cardiotoxicity. International oncologic guidelines define cardiotoxicity as an absolute decrease in LVEF greater than 10 percentage points, which is associated with a decline below its normal limit of 50%. Notably, in clinical trials and clinical practice, this criterion is the one most frequently used for AC therapy withdrawal [1,10].

The most common clinical presentation of cardiotoxicity is a dose-dependent CMP leading to chronic HF, frequently occurring after administration of CT including AC [1,2]. Because most studies and registries have not specifically analyzed CT-induced CMP among the several possible causes of chronic HF, its prevalence is not well known. From among the few studies evaluating the etiology of HF in detail, a prevalence of 1% of all cases of CMP has been reported [11,12]. Data from recent oncology literature, however, indicate that more than half of all patients exposed to AC will show some degree of cardiac dysfunction 10 to 20 years after CT, and 5% of them will develop overt HF. As more than 60,000 patients are treated with AC in the United States every year, the overall incidence of this complication is probably greatly underestimated [8]. The development of cardiotoxicity, even asymptomatic, not only negatively affects patients' cardiologic outcome but also seriously limits their therapeutic opportunities when adjunctive CT for cancer relapse is required. Indeed, the presence of impaired cardiac function restricts the choice of possible oncologic treatments to those considered less aggressive and, consequently, less effective [1].

Prevention

- The best treatment for CT-induced CMP is prevention of the disorder. Several preventive measures are currently being used, including closely monitoring cardiac function, limiting cumulative CT dose, altering AC administration, using AC analogues, adding cardioprotectants to the regimen, employing nutritional supplements, and detecting early signs of cardiotoxicity by biomarkers [7••].

Close monitoring of cardiac function

- For pediatric and adult patients receiving potentially cardiotoxic CT, the American College of Cardiology and the American Heart Association

recommend (class I) routine echocardiography at baseline followed by recurrent reevaluation [13]. Despite the fact that extensive and expensive monitoring programs are usually recommended to identify patients who develop cardiac dysfunction [1,2,14,15], most methods used in clinical practice (eg, echocardiography, radionuclide angiocardiography) have low sensitivity and poor predictive value [1,9,15,16].

- Some major limitations of this approach must be stressed. Not all patients treated with CT require LVEF monitoring as frequently as suggested by the guidelines; monitoring too often has a negative impact on patient management and the cost-effectiveness ratio [17]. Moreover, many doubts have been raised about the utility of monitoring cardiac function by LVEF evaluation only, because the value of this monitoring seems to be neither sensitive nor specific enough to predict the early development of cardiac dysfunction after CT. Indeed, it permits the identification of cardiac damage only after the onset of cardiac dysfunction, eliminating the ability to develop an early strategy to prevent future CMP [18].

Limiting the cumulative dose of anthracyclines

- Based on the results of previous studies indicating a rapid increase in cardiac toxicity at higher doses [3••,7••], current oncologic guidelines limit the maximal cumulative dose of AC therapy to 450 to 550 mg/m^2. This strategy, however, may compromise the clinical success of the treatment. In addition, great variability exists in the doxorubicin doses tolerated by patients; thus, some patients may show AC-induced cardiac damage at standard doses whereas others may tolerate a cumulative dose twofold higher than the conventional limiting dose [1,7••,19].

Altering anthracycline administration

- Because a clear relationship exists between the cumulative dose of AC and cardiotoxicity, administering AC via continuous infusion rather than as a bolus dose has been proposed to limit peak dose levels and reduce AC-related cardiac effects. However, replacing bolus AC administration with slow infusion remains controversial. If, on one hand, continuous infusion limits peak AC levels, on the other, it prolongs patients' exposure to the drug's toxic effects. A long exposure time has been shown to counteract functional recovery of the cardiomyocytes damaged by ACs [3••,7••].

Use of anthracycline analogues and anthracenediones

- In the attempt to create CT drugs as effective as conventional AC, but with a lower risk of inducing cardiotoxicity, novel AC analogues have been developed over the past few years [3••,7••]. Epirubicin, idarubicin, and mitoxantrone have shown lower cardiotoxicity in some preclinical and clinical studies. Despite the fact that cardiotoxicity occurs at a higher cumulative dose of epirubicin compared with doxorubicin, epirubicin must be administered at higher doses than doxorubicin to obtain the same clinical response (epirubicin 90 mg/m^2 = doxorubicin 60 mg/m^2) [7••]. Idarubicin has also shown a lower cardiotoxic profile compared with doxorubicin in preclinical and animal studies; however, clinical data from later studies have not confirmed these findings. Conflicting data also exist for mitoxantrone, an anthracenedione derivative of doxorubicin that showed cardiotoxic effects similar to those of AC in some studies; however, in different in vitro and in vivo studies, at clinically equivalent doses, these cardiotoxic effects were substantially less severe than those of doxorubicin [3••,7••].

Liposomal anthracyclines

- Available preclinical and clinical data suggest that administration of liposomal doxorubicin reduces the incidence and severity of cardiotoxicity associated with AC therapy. Because high peak plasma levels of AC may cause cardiotoxicity [3••], a possible strategy for lowering peak plasma concentrations is the use of liposomal encapsulated AC. Liposomes cannot escape the vascular space where capillaries have tight junctions, as in the heart and the gastrointestinal tract. This results in a reduced tendency for the drug to accumulate in myocardial cells, reducing cardiotoxicity. Conversely, the liposomes exit the circulatory system in areas where capillaries are disrupted by tumor growth, allowing for high concentrations of AC directly at tumor sites [3••,20]. Ongoing trials are evaluating the effect of long-term liposomal AC therapy, alone or combined with other agents (eg, taxanes or trastuzumab), on cardiac safety [21].

Adding cardioprotectants to anthracycline treatment

- Dexrazoxane, an iron-chelating agent, was shown to have a cardioprotective effect when combined with doxorubicin in three randomized trials [6]. Although in two studies time to progression of cancer disease and survival were not significantly different in dexrazoxane-treated patients, in one study there was a lower response rate to chemotherapy in the dexrazoxane arm. Another point to address is whether dexrazoxane's cardioprotective effects are maintained long term. Although the American Society of Clinical Oncology recommends dexrazoxane as a cardioprotectant in patients with metastatic breast cancer who have already received more than 300 mg/m^2 of doxorubicin, this agent's possible effects in reducing antitumor efficacy combined with its potential for myelosuppression has hindered its use in clinical practice [6,7••].
- Carvedilol functions as a β-blocker with α_1-blocking vasodilatory properties. Its potent antioxidant activity may be the mechanism underlying its cardioprotective effect (against doxorubicin) [7••]. Carvedilol's cardioprotective effect was confirmed in an in vitro study [22] and in a recent randomized study in which prophylactic carvedilol use in a small population of patients treated with AC prevented left ventricular dysfunction and reduced mortality [23•]. Further large randomized clinical trials are warranted to support this result.
- Other cardioprotective agents that have been investigated are coenzyme Q_{10}, carnitine, *N*-acetylcysteine, the antioxidant vitamins E and C, and the lipid-lowering agent probucol. Other iron-chelating agents, such as desferoxamine and EDTA (ethylenediaminetetra-acetic acid), are also of interest. Preliminary evidence shows that these agents may have cardioprotective effects, but their utility in preventing CMP requires further investigation [3••,7••].
- Although most of these strategies are promising, each has some limitations, such as the possible compromise of CT clinical success, high costs, and poor positive predictive value. However, the most critical limitation, common to all the strategies, is the indiscriminate selection of cancer CT patients for prophylactic cardioprotective therapy, which has led to a very high cost–benefit ratio. A more rational approach would target only select high-risk patients for this therapy.

Early identification of high-risk patients by biomarkers

- A primary goal for cardiologists as well as oncologists is early identification of patients at risk for cardiotoxicity, which allows for the definition of personalized antineoplastic therapeutic strategies, support of cardiac function, and monitoring of the progression of cardiac damage.
- To detect subclinical myocardial damage, time-consuming and expensive monitoring of cardiac function is still recommended, both during and after CT [1,4,14,15]. Nevertheless, most of the approaches commonly used in clinical practice (eg, LVEF assessment by echocardiography or radionuclide angiography) have been shown to have low diagnostic sensitivity and predictive power in detecting subclinical myocardial injury [1,9,15,16]. The use of other techniques, such as endomyocardial biopsy, is troublesome in clinical practice because of their invasiveness [1,4,15]. Hence, there is a growing need for newer, noninvasive, and cost-effective diagnostic tools for the early identification of patients at risk of developing CT-induced cardiotoxicity.
- Troponin I (TnI) is a protein present only in myocardial cells. The TnI plasma concentration is a well-established, specific, and sensitive marker of myocardial injury widely used for the diagnosis and risk stratification of acute coronary syndromes. More recently, TnI has been used to detect cardiac damage in other clinical settings, such as HF, acute pulmonary embolism, renal failure, sepsis and septic shock, and stroke [24,25]. Evidence of troponin's release after CT was demonstrated previously in animal models and clinical studies [26,27].
- Previous studies demonstrated that TnI is a sensitive and specific marker for myocardial injury after high-dose CT and that it can predict, in a very early phase, the development of future ventricular dysfunction as well as the severity of that dysfunction [28,29]. A more recent work considered a large population with a wide spectrum of cardiac events over a long follow-up period [30]. In this study, TnI behavior after CT allowed researchers to identify different cardiac risks according to three distinct TnI patterns. Patients without TnI elevation after CT had a good prognosis. Indeed, no significant reduction in LVEF was observed in this group, and a very low incidence of cardiac events (1%) occurred during the more than 3 years of follow-up. Hence, in consideration of the high negative predictive value of troponin (99%), low-risk patients (70% of patients in this study) who do not require close cardiac surveillance after CT may be identified accurately. In contrast, TnI-positive patients had a greater incidence of major adverse cardiac events. Among TnI-positive patients, the persistence of an elevated TnI level 1 month after CT was consistent with greater cardiac impairment and a higher incidence of cardiac events compared with patients showing only a transient increase (84% and 37%, respectively) [30].
- Identification of such a high-risk population highlights the opportunity for targeted preventive measures. Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to slow the progression of left ventricular dysfunction in several different clinical settings, including AC-induced CMP [31,32]. Furthermore, data referring to experimental models suggest that the cardiac renin-angiotensin system (RAS) plays an important role in the development of AC-induced CMP and that treatment with ACEIs may protect against CT-induced cardiotoxicity [33–38]. According to these data, a prophylactic strategy based on ACEI use could prevent cardiotoxicity in selected high-risk patients.
- In a recent study from our institute, 473 consecutive cancer patients undergoing high-dose CT were evaluated; 114 (24%) showed a TnI increase

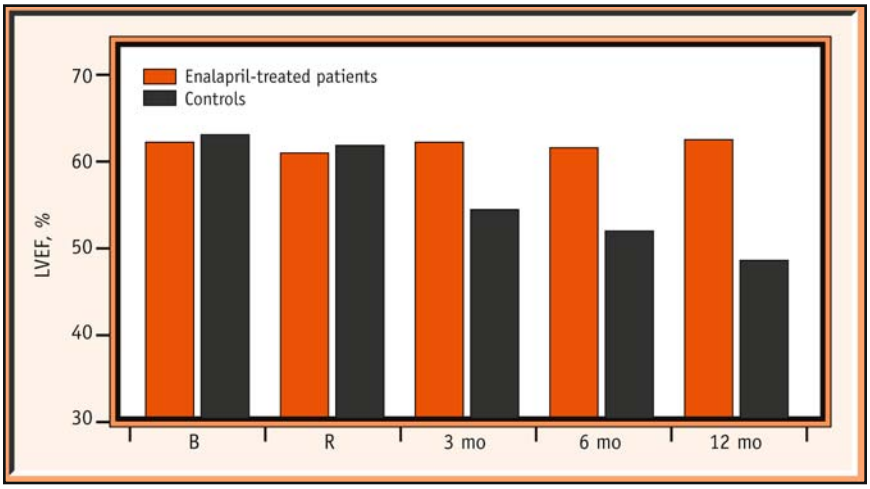

Figure 1. Left ventricular ejection fraction (LVEF) at baseline (before chemotherapy) and during 12-month follow-up in enalapril-treated patients and controls. B—baseline; R—randomization to enalapril or no therapy (1 month after chemotherapy). *P*-value for repeated-measures analysis of variance < 0.001.

Table 1. Cardiac events during 1-year follow-up in enalapril-treated and control patients

Event	Patients, *n (%)*		*P*-value
	Enalapril group (n = 56)	Control group (n = 58)	
Sudden death	0 (0)	0 (0)	1.0*
Cardiac death	0 (0)	2 (3)	0.49*
Acute pulmonary edema	0 (0)	4 (7)	0.07*
Heart failure	0 (0)	14 (24)	< 0.001
Arrhythmia requiring treatment	1 (2)	10 (17)	0.01
Cumulative events	**1 (2)**	**30 (52)**	**< 0.001**

*By Fisher's exact test.

soon after CT and were randomly assigned to receive enalapril (ACEI group, n = 56) or not to receive it (controls, n = 58) [39]. Treatment started 1 month after CT and continued for 1 year. In the ACEI group, LVEF did not change during the treatment period (Fig. 1) and a lower incidence of adverse cardiac events was observed (Table 1). LVEF was also analyzed separately in patients with only a transient TnI increase and in those with a persistent increase. In agreement with previous findings [30], untreated patients with a persistent (1 month after the end of CT) TnI increase had a greater long-term LVEF reduction than patients with only a transient TnI increase (LVEF decreased from 62% to 43% in the former group and from 63% to 57% in the latter; $P < 0.001$). In treated patients, the benefit of enalapril treatment was present in both subgroups: there was no significant change in LVEF in either group (from 61% to 62% and from 62% to 61%, respectively; *P* = not significant), confirming that patients with a persistent TnI increase are at particular risk of cardiotoxicity and may benefit from this preventive therapy.

- Although the underlying mechanisms by which ACEIs may prevent cardiotoxicity and improve outcome in high-risk CT-treated patients are not completely clear, the induction of a more favorable hemodynamic condition and counteraction of RAS activation likely play important

roles. Local inhibition of cardiac angiotensin-converting enzyme (ACE) also may be involved. Data referring to experimental models suggest that the cardiac RAS plays an important role in the development of AC-induced CMP and that the beneficial effects of ACEIs in AC-treated animals depend on inhibition of cardiac ACE [33–38]. Moreover, treatment with lisinopril, started after the end of CT, significantly inhibited cardiac ACE activity and improved mortality, cardiac remodeling, and cardiac dysfunction in an animal model [33]. Finally, increased oxidative stress has been indicated as a possible primary mechanism in the development of AC-induced cardiac toxicity, and ACEIs have been shown to exert antioxidant effects by scavenging free radicals [35].

Treatment

- There is no well-established therapy for CT-induced CMP; current management focuses mainly on treatment of only symptomatic patients. The prognosis for patients with CT-induced CMP has classically been reported to be poor, with a mortality rate of up to 50% within 2 years of diagnosis [6], and this form of CMP is considered to be refractory to conventional therapy [1]. This opinion, however, was based on findings reported in old studies in which standard therapy included only the use of digoxin and diuretics [40–42]. With the advent and use of ACEIs and β-blocking agents to treat HF, most patients have symptom relief and death from HF does not occur as frequently as in the past. However, these findings are based predominantly on clinical experience, with a few small studies supporting the evidence [18,32,44•,45,46]. The response to modern HF therapy of CT-induced CMP has never been evaluated in clinical trials. Because of the different etiology and age distribution of this type of CMP compared with the more frequent ischemic or idiopathic CMP, there is some concern as to whether the use of ACEIs and β-blocking agents, as recommended by the international cardiologic guidelines, can be transferred directly to this particular clinical setting with similar long-term benefits. Moreover, one of the more challenging features of cardiac dysfunction due to AC is the asymptomatic nature of the disease [8]. Although most studies refer only to symptomatic patients, a crucial issue is whether—and eventually how—to treat asymptomatic LVEF dysfunction detected during a routine screening examination [18,32,40–43,44•,45–48]. To date, there is no consensus on what (if anything) can be done to curtail the progression of CT-induced CMP [8]. It is likely that the typical medications used for HF are highly effective, but there may be special concern regarding their use in cancer patients and, conventionally, the tendency is not to treat these patients aggressively [49••]. On the other hand, it is very difficult to obtain evidence-based recommendations for treating CT-induced CMP from the existing literature, because an overall adult population of only 108 patients can be derived from a total of 11 previous publications (six case reports and five clinical studies; Table 2). Only two of them, however, were prospective studies, and only three had predefined end points. In these studies, only 5 patients were treated with β-blockers alone and only 25 patients received a combination of β-blocking agents and ACEIs. Therefore, although in some patients (particularly those treated with a combination of ACEIs and β-blocking agents) an improvement in systolic function and relief of symptoms were observed, the anecdotal nature of these observations does not allow us to draw clear indications from these findings in terms of defining the best therapeutic strategy for this CMP.

Table 2. Heart failure therapy for chemotherapy-induced cardiomyopathy in clinical studies performed in adult populations

Therapy	Study	Patients, *n*	Mean T-T, *mo*	Result(s)
Digitalis + diuretics	Lefrak et al. 1973 [40]	2	1	Cardiac death
	Cohen et al. 1982 [41]	1	12	Relief of symptoms
	Haq et al. 1985 [42]	43	38	Relief of symptoms, heart failure, cardiac death
Digitalis + diuretics + ACEI	Saini et al. 1987 [43]	3	4	LVEF improvement
	Jensen et al. 1996 [32]	9	24	LVEF improvement, heart failure, cardiac death
	Jensen et al. 2002 [18]	10	24	LVEF improvement, heart failure, cardiac death
ACEI	Tallaj et al. 2005 [44•]	10	19	LVEF improvement
BB	Noori et al. 2000 [45]	2	NA	LVEF improvement
	Mukai et al. 2004 [46]	3	34	LVEF improvement
ACEI + BB	Fazio et al. 1998 [47]	1	1	LVEF improvement
	Noori et al. 2000 [45]	6	NA	LVEF improvement
	Mukai et al. 2004 [46]	2	34	LVEF improvement
	Tallaj et al. 2005 [44•]	15	77	LVEF improvement, cardiac death, cardiac transplantation
	Tabet et al. 2006 [48]	1	3	Heart failure

ACEI—angiotensin-converting enzyme inhibitors; BB—β-blockers; LVEF—left ventricular ejection fraction; NA—not available; T-T—time to treatment.

- Preliminary unpublished data from our institute suggest that the period between the end of CT and the start of HF therapy (time to treatment) with ACEIs and, when tolerated, β-blocking agents is a crucial variable in the recovery of cardiac function. Indeed, the likelihood of obtaining a complete LVEF recovery is higher in patients who begin treatment within 2 months of the end of CT. After this period, however, the likelihood progressively decreases and after 6 months, complete LVEF recovery has not been observed.
- Based on these data, we can speculate that in most of the previously published studies, the poor response to therapy was possibly the result of the underuse of modern drugs such as ACEIs and β-blocking agents and to the long (> 12 months) time to treatment, that is, when cardiac damage was not reversible. This emphasizes the crucial importance of detecting cardiotoxicity early and suggests that an aggressive approach based on the association of both ACEIs and β-blocking agents should be considered, and attempted, in all cases of CT-induced CMP.

Treatment of trastuzumab-induced CMP

- Treatment of trastuzumab-related cardiotoxicity is more controversial because the clinical outcome seems more favorable and cardiac function generally improves on removal of the agent. It is generally believed that trastuzumab-associated cardiotoxicity is distinctly different from the form of CT-related cardiac dysfunction associated with the ACs [4,5]. Doxorubicin-induced cardiotoxicity is clearly dose related and caused mainly by oxidative mechanisms leading to apoptosis and necrosis [5], whereas trastuzumab-associated cardiotoxicity seems to be dose independent and often there are no ultrastructural changes detectable on myocardial biopsy [50]. Because of cell loss and the very limited capacity of cardiac cells to

regenerate, AC-related cardiotoxicity is frequently irreversible. In contrast, most patients (80%) with trastuzumab-related cardiotoxicity had significantly improved cardiac function when treated with drugs commonly used for HF [5]. Moreover, in many cases, after left ventricular dysfunction is treated with ACEIs and β-blocking agents, rechallenge with trastuzumab does not necessarily lead to redevelopment of left ventricular dysfunction or congestive heart failure, thus allowing important anticancer therapy to be continued without compromising the patient's cardiac status [4,50]. However, because patients who developed left ventricular dysfunction in the adjuvant trastuzumab trials were not treated in a systematic manner [4,9,20], the natural history of trastuzumab cardiotoxicity is currently unknown and no prospective randomized trials have investigated this point. Whether trastuzumab-related left ventricular dysfunction has a course that is modifiable with ACEIs and β-blockers is unknown; clearly, long-term data collection in a group of cancer survivors who have been treated with trastuzumab is needed. It is well known that overt AC cardiotoxicity may become manifest many years after treatment, and this may well be the case with trastuzumab [20].

Disclosures

No potential conflicts of interest relevant to this article were reported.

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