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Cardiotoxicity of Targeted Cancer Drugs: Concerns, "The Cart Before the Horse," and Lessons from Trastuzumab

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Abstract

Purpose of Review Modern oncology is witnessing a renaissance of its pharmacologic armamentarium. Old generation drugs, such as anthracyclines and other cytotoxic or cytostatic drugs, were plagued with a lack of specificity and with the possible occurrence of untoward effects in the cardiovascular system and other healthy tissues. The old drugs are now combined with, or replaced by, new agents that are more specific in attacking some unique moieties and vital functions of cancer cells, causing less noxious effects in healthy tissues. Regrettably, however, the new "targeted" drugs still cause varying levels of cardiac or vascular toxicity. Here, we describe the case of trastuzumab, a monoclonal antibody that dramatically improved the life expectancy of women with Erbb2-overexpressing breast tumor, while also raising concerns about a possible incidence of cardiac dysfunction.

Recent Findings The scientific community counts experts that label trastuzumab as a "cardiotoxic agent" and other experts that maintain a more benign assessment. We describe the biologic foundations and clinical evidence for such controversy. We show that trastuzumab cardiotoxicity is probably overrated, leading some experts to raise unjustified overconcerns about the cardiotoxicity of trastuzumab as a single agent or in combination with anthracyclines or other old and new drugs. We analyze the biases that caused trastuzumab cardiotoxicity to be overrated.

Summary Trastuzumab is a life-saving agent showing a moderate and clinically manageable cardiac dysfunction, and yet, it is portrayed as cardiotoxic. We take the trastuzumab lesson to reaffirm that cardio-oncologists should provide cancer patients with the best therapeutic opportunity, as is the case for trastuzumab, while also devising the necessary strategies of risk assessment and mitigation.

Keywords Targeted drugs · Cardiotoxicity · Trastuzumab

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Introduction

Antitumor drugs have long been known to cause cardiovascular toxicity. Almost all of the "old generation" drugs, primarily anthracyclines but also alkylators or tubulin-active agents or antimetabolites, were recognized or suspected to introduce a measurable risk of cardiovascular events, which increased significantly if patients presented at cancer diagnosis with traditional risk factors like hypertension, diabetes, overweight, coronary artery disease, or familial history of myocardial ischemia. Cardiac events also increased if cancer therapy required both chemotherapy and left thorax or mediastinal irradiation [1].

Cardiovascular events, and primarily anthracycline-related heart failure, were initially observed to occur during or shortly after cancer therapy; however, as oncologic protocols were improved over years, and the cumulative anthracycline dose was significantly reduced, the number of early cases of heart

failure significantly declined yet the increase in long-term survivors of childhood or adult cancer corresponded to an increase in late cardiac or vascular [2–5].

The early or delayed cardiovascular sequelae of traditional cytostatics or cytotoxics were reconducted to on-target or off-target molecular effects of these drugs in the cardiovascular system [6, 7]. It is therefore not surprising that the last two decades witnessed remarkable efforts to design new drugs that hit cancer cells but spared the cardiovascular system. Conceptual designing and molecular modeling of the new drugs were inspired by advances in our understanding of cancer cell biology and by the assumption that many cancers, whether solid or hematologic, were driven by signals that one could find primarily, if not exclusively, in cancer cells. This posed the foundation for the so-called targeted therapy.

Regrettably, however, "not all that glitters is gold." The new targeted drugs improved the life expectancy of many cancer patients but did not abate the risk of cardiovascular events. For at least some of the new drugs, untoward events build on the cardiovascular system expressing the same druggable target one considered to be mainly or solely expressed in tumor cells. Off-target effects are more plausible for other drugs but unequivocal evidence for the occurrence of one mechanism of toxicity or another is lacking. Perhaps more importantly, the actual risk of cardiovascular events from a given drug was variably reported as high or moderate or low, such that the actual risk-to-benefit ratio of using that drug became a matter of controversy.

Many targeted drugs gained approval and market access, and many more are being developed and probed in clinical trials. We will not go through a detailed analysis of all available and forthcoming drugs. The reader may want to address other authoritative reviews that explored this scenario in a comprehensive manner [8, 9, 10•]. Here, we will briefly review the cardiac safety of trastuzumab (Herceptin®), which may be taken as the prototypic targeted drug. Lessons from trastuzumab are in fact multifaceted, from the beginning of its clinical development down to recent updates of its efficacy and cardiac safety. We will briefly review the ups and downs that characterized the landing of trastuzumab in modern oncology and the "unexpected" cardiotoxicity oncologists and cardiologists had to deal with. Next, we will describe how the problem was solved and why controversies still exist about the cardiac safety of trastuzumab. Also, trastuzumab is the only targeted drug for which solid cardiac safety data exist for long-term survivors, making comparisons with the old cancer drugs plausible.

Growth Factor Receptors and Receptor-Associated Tyrosine Kinases as Pharmacologic Targets of Cancer Therapy

Growth factor receptors and receptor-associated tyrosine kinases regulate cell proliferation and govern many processes of cellular defense and repair. Dysregulation of tyrosine kinase–driven signals plays an obvious role in the pathogenesis and progression of cancer, thus illuminating tyrosine kinases as pharmacologic targets for silencing unnecessary growth signals [10•, 11, 12]. To meet this goal, both monoclonal anti-receptor antibodies and small tyrosine kinase inhibitors (TKI) have been developed.

Trastuzumab

HER2, Breast Cancer, and the "Unexpected" Cardiotoxicity of Trastuzumab

Erbb2, also referred to as HER2, is a tyrosine kinase receptor belonging to the superfamily of epidermal growth factor receptors. It is a ligandless receptor that heterodimerizes with other members of the receptor family able to bind the epidermal growth factor or neuregulin [13]. HER2 overexpression occurs in approximately 25% of human breast tumors and associates with molecular, histopathologic, and clinical characteristics of aggressiveness and poor prognosis [10•, 14, 15]. Trastuzumab, a humanized anti-HER2 monoclonal antibody, was developed for treating women with breast cancer that overexpresses HER2. Trastuzumab may kill cancer cells through inhibition of proliferation, antibody-dependent cell cytotoxicity (ADCC), and inhibition of DNA repair. ADCC probably prevails when trastuzumab is used as a single agent in chemotherapy naïve patient, while inhibition of DNA repair or cell proliferation probably prevails when trastuzumab is used, respectively, in combination with or after chemotherapy [16].

To summarize, trastuzumab changed the scenario of HER2 positive breast cancer and improved prognosis and survival when used in neoadjuvant (preoperative), adjuvant (postoperative), and metastatic settings [17]. Remarkably, however, trastuzumab caused or seemed to cause an "unexpected" cardiotoxicity. In the pivotal randomized phase III trial of women with metastatic breast cancer, treated by trastuzumab-anthracycline (doxorubicin or epirubicin) or trastuzumab in combination with the tubulin-active taxane, paclitaxel, followed by trastuzumab until disease progression, the incidence of symptomatic or asymptomatic cardiac events was significantly higher in trastuzumab arms compared with anthracycline or paclitaxel only arms [18]. Trastuzumab cardiotoxicity was remarkably higher for patients concomitantly treated by anthracyclines, drugs that unfortunately remain central in breast cancer treatment.

Was Trastuzumab Cardiotoxicity Really Unexpected?

The concept of "unexpected" cardiotoxicity needs to be scrutinized. Studies conducted before and during trastuzumab

clinical development had shown that HER2-HER4 heterodimers governed embryonic cardiac morphogenesis and function and helped the heart to withstand postnatal hemodynamic and chemical stressors such as volume overload or anthracyclines [19–22]. Thus, everything was conceptually set to anticipate HER2 expression in the heart, its role in fortifying cardiac defense against anthracyclines, and the potentially catastrophic consequences of blocking HER2 while a patient was receiving anthracyclines.

How precisely HER2 conveys cardiac survival signals remains to be established. Among the possible multitude of mechanisms one may envision, an appealing scenario is offered by cross talks between HER2 and glycoprotein 130 (gp130), a cytokine receptor that lies upstream of a survival oriented signal transduction pathway [23]. Following activation by its natural ligand, the epidermal growth factor, gp130, transactivates HER2 and involves it in inhibiting apoptosis [24]. In accordance with this possible scenario, gp130 is constitutively associated with HER2 and HER3 [25]. On a different note, HER2-HER4 heterodimerization and phosphorylation was shown to activate glucose uptake and sarcomeric protein turnover, which play an intuitive role in making cardiac cells resistant to chemical, mechanical, and hemodynamic distress [26]. The natural ligand of HER4 in HER2-HER4 heterodimers, neuregulin, is also important for the heart to find a good balance between adrenergic and vagal stimuli [27]. All such survival- and homeostasis-oriented mechanisms are probably redundant in physiologic conditions but may become important in diseased conditions [28]. For women candidates to anthracyclines, trastuzumab blockade of HER2 would therefore cause cardiotoxicity that is anything but unexpected.

Having outlined that HER2 is important for the heart, one may ask an obvious question: how could trastuzumab cardiotoxicity escape preclinical screens and early clinical studies? As for preclinical investigations, trastuzumab-chemotherapy regimens had been assessed in xenografted mice [29] but the binding affinity of trastuzumab for the ectodomain of murine HER2 is marginal as compared with humans and other primates [25]. Cardiotoxicity did not occur under such defined conditions, or it was too mild to be detected by conventional morphologic or functional criteria. Few experiments were conducted with, e.g., monkeys, but none of them included anthracyclines as concomitant drugs [25]. And finally, none of the phase I-II studies that preceded the pivotal phase III trial had explored the efficacy of trastuzumab in combination with anthracyclines [29–35].

Was the Unexpected Cardiotoxicity of Trastuzumab Overestimated?

In the pivotal trial that documented the "unexpected" cardiotoxicity of concurrent use of antracyclines and trastuzumab, increasing age was the only baseline characteristic that could be identified as a risk factor for developing cardiotoxicity [18]. The cumulative dose of anthracycline was not identified as a risk factor. The study protocol dictated 360 mg of doxorubicin/m^2 or 450 mg of epirubicin/m^2 (corresponding to approximately 300 mg of doxorubicin myelotoxic equivalents). For either anthracycline, these doses were lower than those associated with 5% risk of congestive heart failure (CHF) induced by doxorubicin (550 mg/m^2, subsequently refined to 380–400 mg/m^2) or epirubicin (800–900 mg/m^2, corresponding to approximately 530–590 mg of doxorubicin equivalents) [36–38]; interestingly, however, some patients received higher anthracycline doses at the physician's discretion. Moreover, and importantly, patients who experienced disease progression were given the opportunity to participate in a non-randomized open-label extension trial in which trastuzumab with or without anthracyclines or other cancer therapies was offered. As many as 66% percent of patients of the pivotal trial accepted to participate in the extension trial.

In post hoc analyses, the cardiac safety of trastuzumab in the pivotal trial was scrutinized by a Cardiac Review and Evaluation Committee (CREC) [39]. Some details need to be kept in mind when CREC analysis is put in a context. The analysis was performed for a selected group of patients recruited in the pivotal trial. Patients treated by doxorubicin or doxorubicin-trastuzumab were for the most part (99%) anthracycline-naïve at the time of recruitment. In contrast, as many as 91% or 97% of patients treated by paclitaxel-trastuzumab or paclitaxel without trastuzumab, respectively, had received an adjuvant anthracycline. Patients treated by epirubicin were excluded from analysis.

CREC analysis confirmed that trastuzumab remarkably increased the incidence of NYHA class III-IV heart failure in patients treated by trastuzumab-anthracycline, but this occurred to a lower extent for patients treated by trastuzumab-paclitaxel. The same difference occurred when reporting trastuzumab effects on cardiac dysfunction (CD) (Table 1), defined as any of the following signs or symptoms (i) cardiomyopathy (characterized by a decrease in cardiac left ventricular ejection fraction, LVEF, that was either global or more severe in the septum); (ii) symptoms of CHF; (iii) associated signs of CHF; (iv) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms; (v) any NYHA class heart failure [39].

Product-limit estimates were also calculated and used by CREC to build risk versus dose curves. For patients treated by trastuzumab-doxorubicin, the risk versus dose curve was similar in shape to that obtained for patients exposed to doxorubicin only; however, it was shifted to the left. For doxorubicin-trastuzumab patients, the risk of cardiac dysfunction increased

Table 1 CREC adjudication of cardiac events in the pivotal trial of anthracycline-based chemotherapy or paclitaxel, with or without trastuzumab, in women with metastatic breast cancer

CREC adjudication	Trastuzumab-doxorubicin (%)	Doxorubicin (%)	Trastuzumab-paclitaxel (%)	Paclitaxel (%)
Cardiac dysfunction	27	11	12	1
NYHA class III/IV heart failure	16	4	2	1

Cardiac dysfunction was defined as described in the text

CREC Cardiac Review and Evaluation Committee

(Adapted from Seidman et al. [39])

dramatically between 360 and 390 mg of doxorubicin/m^2 while, for patients treated by doxorubicin without trastuzumab, this occurred between 460 and 490 mg/m^2 (Fig. 1). Over these defined dose ranges, the two curves had the same slope ($P = 0.564$ at a ROC analysis performed by the authors of this commentary). Risk versus dose curves therefore showed three facts: (i) trastuzumab caused cardiotoxicity to occur after lower cumulative doses of doxorubicin; (ii) trastuzumab caused an effect size of approximately 100 mg of doxorubicin/m^2; (iii) once a critical dose was exceeded, there was no significant difference in CD rates from doxorubicin-trastuzumab or doxorubicin without trastuzumab.

Data reported in Table 1 and Fig. 1 strongly suggested that trastuzumab cardiotoxicity was caused by an aggravation of anthracycline-related cardiotoxicity. This was largely consistent with the role of HER2 in protecting the heart from stressor agents. We nonetheless suspect that cardiotoxicity was overrated. The rather broad definition of CD adopted by CREC, including such marginal events as LVEF decrements ≥ 5% to below 55%, may have led CREC to over-adjudication of cardiotoxicity. To explore this possibility, we compared the product-limit estimates calculated by CREC with the probability of CHF development in three prospective trials of patients treated by doxorubicin without trastuzumab [37]. The risk versus dose curve calculated for these patients was significantly shifted to the right as compared with patients who received doxorubicin without trastuzumab in the pivotal trial (Fig. 1). This supports that CREC analysis may have overestimated cardiotoxicity of doxorubicin, and hence of doxorubicin in combination with trastuzumab. On a different note, the reporting of high rates of CD in the pivotal trial probably caused an impetus to reporting cardiac events also in the open-label extension trial. Given that cause-and-effect relations between early CD, as defined by CREC, and late CHF remain uncertain at this point in time, one cannot exclude that trastuzumab-related cardiotoxicity was in fact overrated [40].

It is important to note that as many as 79% of patients with CREC-defined signs and symptoms of CD improved following a standard therapy with diuretics, angiotensin-converting enzyme inhibitors, or inotropic agents. This showed that trastuzumab cardiotoxicity was clinically manageable [39]. Compared with paclitaxel alone, adding trastuzumab to paclitaxel improved disease time to progression (TTP), time to development of NYHA class III-IV heart failure, and time to development of class III-IV heart failure that did not improve to class < III upon medication. In the very critical setting of anthracycline-based chemotherapy, characterized by the higher burden of cardiotoxicity, adding trastuzumab to anthracycline did not significantly improve CD-free TTP as compared with anthracycline alone; however, trastuzumab significantly improved TTP that was free of drug-responsive or drug-unresponsive class III-IV heart failure (Table 2) [41]. The latter finding denoted how the definition of cardiotoxicity influences the event rate. Trastuzumab was apparently ineffective when cardiotoxicity was defined by "soft" endpoints such as the broadly defined CD, showing that efficacy and safety analyses were biased by the adjudication of possibly irrelevant cardiac events; in contrast, trastuzumab introduced a measurable advantage over anthracycline alone when "hard" endpoints were adopted (symptomatic heart failure, either responsive or unresponsive to conventional therapies). On a different note, but still relevant to cardiotoxicity, reasons for discontinuing trastuzumab after adjudication of CD were mainly due to disease progression (52%) rather than any cardiac adverse event (27%) or heart failure in isolation (9%) [41].

Methods for Reducing Trastuzumab Cardiotoxicity

Regardless of methodological biases that probably caused trastuzumab cardiotoxicity to be overestimated, the pivotal trial of women with metastatic breast cancer highlighted two major messages: (i) trastuzumab showed the potential for aggravating cardiotoxicity induced by concomitant anthracyclines, (ii) trastuzumab-paclitaxel was well tolerated by patients who had received anthracyclines in the adjuvant setting. These facts led to exploring if patients requiring anthracyclines and trastuzumab could benefit from a new

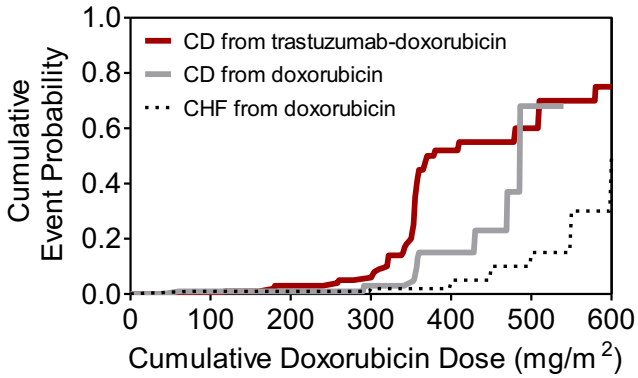

Fig. 1 Product estimate-limit curves for cardiac dysfunction induced by doxorubicin or doxorubicin-trastuzumab in the pivotal trial, and for congestive heart failure induced by doxorubicin-based chemotherapy in three independent prospective trials. CD, cardiac dysfunction as defined in the text. CHF, congestive heart failure (adapted from Seidman et al. [39] and Swain et al. [37])

schedule in which the two agents were administered sequentially rather than concomitantly.

In the Herceptin Adjuvant (HERA) trial, probing the efficacy and safety of 1 or 2 years of trastuzumab after (neo)adjuvant cancer chemotherapy with or without radiotherapy, all cardiac endpoints recorded after 1 year of trastuzumab were higher compared with patients given chemotherapy only; however, the net incidences of severe CHF (0.06%), symptomatic CHF (2.2%), or confirmed significant LVEF drops (3%) were remarkably lower compared with the incidence of CD or NYHA class III-IV heart failure in the pivotal trial [42]. Switching from concomitant to sequential administration therefore offered the expected improvements in cardiac safety. Equally interesting was the risk profile of patients who experienced cardiac events in the face of a sequential treatment. Patients with trastuzumab-associated cardiac events were in fact characterized by the typical risk factors for anthracycline cardiotoxicity (higher cumulative doses of anthracyclines, lower LVEF, and higher body mass index at screening) [42]. This confirmed that the molecular foundations of cardiotoxicity were laid during anthracycline administration, while the clinical manifestations of cardiotoxicity occurred when trastuzumab impeded cardiomyocytes from repairing the anthracycline-related damage; however, and again, most patients with cardiac events recovered upon appropriate medication or trastuzumab momentary discontinuation.

The incidence of NYHA class III-IV heart failure remained 0.8%, also at 8 years follow-up and regardless of whether trastuzumab had been administered for 1 or 2 years [43••]. Given that trastuzumab, administered after anthracycline, still offered a clear benefit in terms of disease-free survival [44], switching from anthracycline-trastuzumab to antracycline followed by trastuzumab has become routine in clinical practice.

From Trastuzumab to Other Anti-HER2 Agents

The great therapeutic success of trastuzumab paved the road to developing other HER2 blocking agents. Pertuzumab was developed to inhibit HER2 homo- or hetero-dimerization [14, 45] and was approved for use in metastatic breast cancer in association with trastuzumab and docetaxel, a chemotherapy agent of the taxane group, or for use in combination with trastuzumab for the neoadjuvant treatment of high-risk HER2^{+} breast cancer in patients naïve to anti-HER2 agents or chemotherapy. The available evidence shows that double HER2 blockade offers therapeutic advantages over trastuzumab alone and does not introduce an added risk of cardiotoxicity [17, 46–48], not even when it is used after a dose-dense (this is a standard oncologic term to define anthracycline every 2 rather than 3 weeks) doxorubicin-cyclophosphamide and then followed by adjuvant trastuzumab [49].

Table 2 Effects of trastuzumab added to paclitaxel or anthracycline on CD or heart failure-free time to disease progression

Treatment	Trastuzumab	TTP or any CD (months)	TTP or NYHA class III-IV heart failure (months)	TTP or unresponsive NYHA class III-IV heart failure* (months)
Paclitaxel	–	2.8	2.8	2.8
	+	6.6	6.9	6.9
		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Anthracycline[a)]	–	6	6.0	6.0
	+	6.6	7.2	7.6
		$P = 0.24$	$P < 0.025$	$P < 0.01$

*Defined as class III-IV heart failure that did not improve to class < III

[a)] Includes doxorubicin and epirubicin

CD cardiac dysfunction, *TTP* time to progression

Based on intent-to-treat analyses by Tripathy et al. [41]

Ado-trastuzumab (TDM1) is a drug-antibody conjugate coupling trastuzumab with the tubulin-active agent, emtansine. It was developed to exploit trastuzumab internalization and degradation for targeted delivery of a chemotherapeutic in HER2$^+$ mammary cancer cells. Ado-trastuzumab does not show significant cardiotoxicity when used in its approved indication for patients who failed trastuzumab and a taxane for treatment of metastatic breast cancer [50]. Likewise, ado-trastuzumab does not cause significant cardiotoxicity when used for approximately 1 year after adjuvant anthracycline-based chemotherapy in a clinical trial [51].

Lapatinib is an oral dual TKI that inhibits HER1 and HER2 tyrosine kinases by binding to the intracellular domain of either receptor. It is approved for use in combination with the fluoropyrimidine, capecitabine, in patients with advanced HER2$^+$ breast cancer that progressed after anthracyclines, taxanes, and trastuzumab. It is also approved for combination with trastuzumab in patients with metastatic HER2$^+$/hormone receptor-negative breast cancer that failed prior trastuzumab and chemotherapy, and for combination with the aromatase inhibitor, letrozole, in women with postmenopausal advanced HER2$^+$/hormone receptor-positive breast cancer [52]. Data from 44 clinical studies showed that lapatinib caused low levels of cardiotoxicity, cardiac events were usually asymptomatic or reversible, and events occurred independent of prior patient's exposure to anthracyclines or trastuzumab [53].

In sum, trastuzumab inspired the development of an avalanche of anti-HER2 agents and oncologic regimens that proved effective and relatively free of cardiac toxicity or associated with mild clinically manageable cardiac events. This leitmotiv led to a new classification of cancer drugs. According to the proposed classification, type 1 drugs cause a dose-dependent and potentially irreversible damage that is characterized by morphologic lesions of cardiomyocytes and precludes treatment continuation once a clinically relevant event has occurred. In contrast, type 2 drugs cause a dose-independent and reversible cardiac dysfunction that is not associated with morphologic lesions, does not preclude continuing treatment once a cardiac event has occurred, or does not preclude resuming treatment once a cardiac event resolved spontaneously or upon medication. Anthracyclines would be prototypic type 1 agents that cause direct cardiotoxicity, while trastuzumab and other anti-HER2 agents would be prototypic type 2 drugs that lack a direct cardiotoxicity but may render the heart more vulnerable by anthracyclines or pathophysiologic insults [54].

Questioning the Cardiac Safety of Trastuzumab and Type 1 Versus Type 2 Agent Classification

The aforesaid low incidence of heart failure at 8 years of follow-up originates from survivors in the HERA trial. Much higher rates of heart failure were defined in retrospective population-based studies; here, trastuzumab alone or anthracyclines followed by trastuzumab caused, respectively, a cumulative incidence of 10% or 20% at 5-years from cancer diagnosis and treatment [55]. Did therefore the HERA trial or other similar clinical trials underestimate trastuzumab cardiotoxicity? Those who describe trastuzumab as a (highly) cardiotoxic agent for the general population might in fact argue that the inclusion criteria of HERA trial selected a patient population that was less vulnerable by anthracyclines and trastuzumab as compared with patients of the population-based study. In other words, patients of the HERA trial were younger, showed fewer or no comorbidities, and presented at screening with a higher LVEF or a lower body mass index. In contrast, those who describe trastuzumab as a (reasonably) non-cardiotoxic agent might argue that the population-based analysis was plagued with the lack of echocardiographic records, and hence with uncertainties about how cardiac events were adjudicated, e.g., insurance purposes [55]. The two positions would have opposite clinical implications. Should trastuzumab and other anti-HER2 agents be confirmed as highly cardiotoxic agents, then all candidate patients should be given an intensive and costly cardiac surveillance. Should the contrary be true, cost-saving less intensive surveillance would be recommended [56, 57].

As usual, the truth lies somewhere in between. When patients recruited in clinical trials of adjuvant trastuzumab for early operable breast cancer were re-called for cardiac evaluation some 5–10 years later, the incidence of cardiac abnormalities at medical inspection or imaging was significantly higher if patients had received an anthracycline-based chemotherapy rather than non-anthracycline regimens [58]. This was the same finding as that observed for 5–10 year survivors of breast cancer patients who received chemotherapy without trastuzumab: patients treated by anthracyclines showed a higher risk of developing heart failure as compared with patients treated by non-anthracycline drugs [59].

These observations form the basis for the first conclusion: trastuzumab *can* cause cardiotoxicity but much of the cardiotoxic burden that is attributed to trastuzumab actually depends on anthracyclines, and hence, the hiatus one interposes between the two agents may not always abate the risk of cardiac dysfunction. A single-center study provided an indirect evidence to support this notion. It showed that, in patients treated by anthracyclines, the first administration of adjuvant trastuzumab caused a significant number of patients to develop increased circulating levels of troponin, marker of cardiomyocyte necrosis; however, this did not occur or occurred in much fewer patients when subsequent trastuzumab cycles were administered [60]. Keeping in mind that trastuzumab per se would not cause cardiomyocyte necrosis [61], one cannot escape the conclusion that trastuzumab was started at a time when some cardiomyocytes were still recovering from the damage inflicted by anthracyclines, and that trastuzumab caused these cardiomyocytes to die.

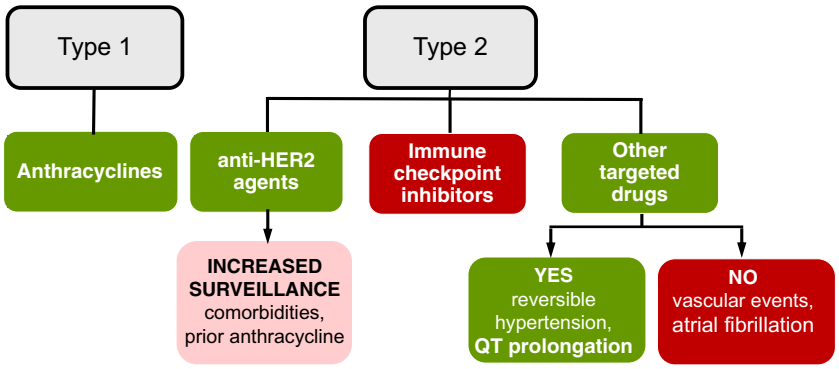

Fig. 2 Revised type 1 versus type 2 classification of cancer drugs. *Green boxes* identify cancer drugs that are congruent with the type 1–type 2 classification. *Red boxes* identify drugs or events that are not congruent with the classification. *Pale red box* denotes recommendations for using type 2 agents in high-risk patients

On a different note, when metanalyses scrutinized the frequency with which cardiac imaging was used outside of clinical trials, it turned out that baseline echocardiography was offered on the basis of the chemotherapy regimen patients were scheduled to receive, while patient-specific risk of heart failure was not a decisional factor [62••]. This paves the road to a second conclusion: in retrospective population-based studies, high-risk patients were very likely to have received suboptimal cardiac evaluation and medication. This would be a gross mistake, especially if one appreciates that trastuzumab blockade of HER2 diminishes cardiac defense against other cardiovascular insults, e.g., hypertension [27]. Absent an adequate strategy of protection, cardiotoxicity of trastuzumab in high-risk patients is an anticipated event that reflects risk underestimation and pharmacologic ignorance of vicious cycles between HER2 blockade and comorbidities.

In summary, trastuzumab is neither cardiotoxic nor innocuous to the heart. The available evidence favors the cardiac tolerability of trastuzumab in many settings but some unproductive arguments were built on population-based studies to undermine this concept, or even worse, to question trastuzumab indication for some patients [63]. We believe the gratifying results of long-term follow-up of HERA trial patients should be considered. Likewise, while it is advisable to not use trastuzumab, or other HER2 blockers, concomitantly with anthracyclines, this should not be held as a dogma. Some neoadjuvant schedules for high-risk breast cancer may in fact benefit from a concomitant administration of trastuzumab and anthracyclines, which may prove cardiac tolerable if the cumulative dose of anthracycline does not exceed 200 mg/m^2 in doxorubicin equivalents [64]. There is indeed a body of evidence supporting that trastuzumab cardiotoxicity is of mild to moderate severity and clinically manageable with standard therapies.

In a similar manner, we believe the type 1–type 2 classification is valid but needs to be protected from unnecessary generalizations, particularly for the so-called type 2 agents. This classification was born to anthracyclines and anti-HER2 agents, but it cannot be applied to any new targeted drug. Angiogenesis inhibitors may qualify as type 2 agents for arterial hypertension, which is reversible [65], but not for arterial thrombosis, venous thromboembolism, or vascular perforation which quite evidently do not meet the characteristics of type 2 [66]. Many TKI cause QT prolongation that is clinically manageable or reversible upon drug discontinuation [67], as one would expect for type 2 agents, but they may also cause vascular occlusive events or atrial fibrillation that are more difficult to qualify as type 2 events in terms of reversibility and opportunity for treatment continuation or safe rechallenge [66]. Immune checkpoint inhibitors may cause acute myocarditis and other autoimmune disorders that still need to be scrutinized for manageability and reversibility, but clearly do not qualify as type 2 [68].

The type 1–type 2 classification should be properly considered as reported in Fig. 2. Whereas anthracyclines remain type 1 agents by definition, anti-HER2 agents per se would qualify as type 2 agents but an increased surveillance is recommended if these drugs are considered for patients with comorbidities or prior anthracycline. Immune checkpoint inhibitors are prototypic examples of new "targeted" drug that cannot be grouped with type 2 agents. On the other hand, many other targeted drugs cause clinical events that may or may not be type 2-like. The level of congruence of cancer drugs with the type 1–type 2 classification therefore needs to be scrutinized by agent and events.

Conclusions

Trastuzumab use can cause cardiotoxicity. In most of the cases, however, the clinical benefit associated with trastuzumab outweighs a risk of moderate, reversible, and manageable cardiac toxicity. In large part, the toxicity of trastuzumab is related to the toxicity of anthracycline, which is potentially enhanced when transtuzumab is given concomitantly or shortly after anthracyclines. In general terms, trastuzumab cardiotoxicity was and is overestimated. Preventing the use of trastuzumab for the fear of cardiotoxicity is not justified, it would be like "putting the cart before the horse."

Compliance with Ethical Standards

Conflict of Interest Pierantonio Menna, Giorgio Minotti, and Emanuela Salvatorelli declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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