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Cardiotoxicity due to targeted anticancer agents: a growing challenge

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Abstract: The emergence of various targeted anticancer agents has led us to uncharted territory secondary to their cardiotoxic potential with many burning questions, which in turn has led to the evolution of the cardio-oncology field. These targeted agents differ in their cardiovascular complication (CVC) potential even within the same class and it is very difficult to design screening tests that can predict CVCs. Moreover, there is a need for more research to answer many crucial questions, since these toxicities are unanticipated and can lead to poor overall survival of cancer patients. We still do not clearly understand the mechanism for such toxicity, risk factors, and natural history. A better understanding of the underlying risk factors and identification of biomarkers would help us develop protocols for appropriate monitoring strategies which in turn would help capture these toxicities at early stages. In this succinct review, we try to focus on CVC definition, summarize some published research, and point to areas of unmet need in this new field.

Keywords: cancer, cardiotoxicity, cardiovascular toxicity, targeted agents, therapy

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Defining the problem

Emergence of various targeted agents has shifted the paradigm of cancer treatment, and as our understanding of molecular pathogenesis expands further many more molecular agents are likely to become important in the treatment of various cancers. Apart from cancer recurrence, cancer survivors today face many challenges related to the long-term side effects of anticancer therapies, including cardiovascular complications (CVCs) that can potentially be a big obstacle in their battle against cancer.[1] In general, CVCs from cancer therapy include heart failure, coronary artery disease, arrhythmias, QT prolongation, valvular disease, arterial hypertension, thromboembolic disease, and peripheral vascular disease as per the European Society of Cardiology (ESC) guidelines.[2] According to the ESC, cardiotoxicity leading to heart failure is defined as a decrease in the left ventricular ejection fraction (LVEF) >10% points to a value below the lower limit of normality on an echocardiograph, and a relative reduction in global longitudinal strain of >15% from baseline signifies a risk for cardiotoxicity.[2] Improvement in the overall survival (OS) of patients with various cancers has led to a higher proportion of cancer patients living with concomitant cardiovascular diseases.[3] The field of cardiotoxicity induced by targeted drugs is rapidly expanding leading to the evolution of a new subspecialty of cardio-oncology to deal with the new health burden. It is imperative for an oncologist to know the toxicity profile of newer agents so that the risk of CVCs can be weighed against the benefit of these agents. The list of anticancer targeted drugs that can potentially cause CVCs is growing, and the most recent class of drugs added to the list is the immune checkpoint inhibitors which are shown to cause immune-mediated myocarditis[4–6] (Table 1). Different agents differ in their cardiotoxicity potential as well as types and this variability is seen not only among different classes but also within same class of drugs.[7–10] For instance, within the proteasome inhibitors, carfilzomib was shown to cause significantly more CVCs compared with bortezomib which is less

Table 1. Anticancer targeted drugs causing cardiovascular complications.

Agents	Type of toxicity with approximate frequency when known
Small molecule TKIs	
Imatinib	Heart failure (<1%), arrhythmias (<1%)
Dasatinib	Pulmonary hypertension (0.1–<1%), heart failure (8–9%)
Nilotinib	Heart failure, myocardial infarction/ischemia (5–9.4%), QT prolongation (1–2%), PAD, pulmonary hypertension,
Ponatinib	Arrhythmias (1–5%), heart failure (3–15%), myocardial infarction/ischemia (12%), PAD, hypertension (2–68%), thromboembolic events (3%)
Bosutinib	Pericarditis (1%), pericardial effusion, QT prolongation (<1%)
Sunitinib	Heart failure (1–27%), thromboembolic events (1–3%), hypertension (4–34%)
Sorafenib	Heart failure (1.9–11%), thromboembolic events, hypertension (9–16%)
Lapatinib	Heart failure (0.9–4.9%), QT prolongation (6.1%)
Pazopanib	Heart failure (0.6–11%), QT prolongation (<2%)
Monoclonal antibody-based	
Rituximab	Arrhythmia, heart failure, myocardial infarction/ischemia
Trastuzumab	Heart failure (2–28%), thromboembolic events (2–3%), hypertension (4%)
Bevacizumab	Heart failure (1–10.9%), myocardial infarction/ischemia (0.6–8.5%), thromboembolic events (3–21%), hypertension (5–18%)
Pertuzumab	Heart failure (0.9–16%)
Histone deacetylase inhibitors	
Vorinostat	QT prolongation (1–4%), thromboembolic events
Immunomodulators	
Thalidomide	Arrhythmia, thromboembolic events (8–22.5%)
Lenalidomide	myocardial infarction/ischemia (0–1.9%), thromboembolic events (4–9%), hypertension (7–8%), hypotension (7%)
Pomalidomide	Thromboembolic events (3%), atrial fibrillation (2%)
Proteasome inhibitors	
Bortezomib	Heart failure (2–5%), arrhythmia, myocardial infarction/ischemia
Carfilzomib	Heart failure (4–28%), hypertension (5–27%), arrhythmia, myocardial infarction/ischemia, pulmonary hypertension (1%)
Ixazomib	Heart failure (2–4%), myocardial infarction/ischemia, hypotension,

Table 1. (Continued)

Agents	Type of toxicity with approximate frequency when known
Immune checkpoint inhibitors	
Ipilimumab Pembrolizumab Nivolumab Atezolizumab Durvalumab	Myocarditis (<1%), heart failure (<1%), pericarditis (<1%)
Miscellaneous	
Temsirolimus	Hypertension (7%), thromboembolic events (2%), heart failure (<1%)
Everolimus	Hypertension (4%), heart failure (<1%), tachycardia

Abs, antibodies; PAD, peripheral artery disease; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

cardiotoxic but causes neuropathy more frequently.[11] Similarly, among different tyrosine kinase inhibitors (TKIs), imatinib showed minimal CVCs,[7] while dasatinib[12] was associated with more cardiopulmonary issues, while ponatinib was associated with more vascular than cardiac events.[13] Of note, although many of these new drugs are supposedly targeted towards one gene, apart from a few drugs, most of the time other targets or the same target in other normal organs are also affected.

Natural history and outcome

The exact mechanism for the development of CVCs secondary to various targeted agents is poorly understood. Moreover, significant uncertainty prevails in understanding the predisposing factors and the natural history of CVCs. In our retrospective study of patients,[14] who had both hematologic malignancy (multiple myeloma, leukemia, and lymphoma) and CVCs, we found that 3.5% (29 of 820) of patients experienced cardiotoxicity (study group) due to targeted agents (such as proteasome inhibitors, TKIs, anti CD20 rituximab, and immunomodulators) over the 10-year study period (2005–2014). The median time from the exposure to cardiac event was 132 days (range 1–1176 days). A total of 8 patients developed various arrhythmias, 27 patients developed reduced LVEF and were diagnosed with cardiomyopathy, while two had non-ST elevation myocardial infarction. Furthermore, we compared the study group with patients who did not develop cardiotoxicity (the reference group, $n = 70$) after exposure to similar class of targeted agents. Interestingly, we did not find any association between the development of cardiotoxicity and traditional cardiovascular risk factors such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking. Recently, another retrospective study also reported that the higher atherosclerotic cardiovascular disease score >7.5% did not significantly increase the incidence of adverse cardiovascular events.[15] This raises the possibility of genetic predisposition for the development of CVCs in some patients and not others, which needs to be further explored. Moreover, some data also suggest that there can be common genetic risk factors, such as mutations of DNMT3, TETE2 or ASXL1, which may predispose patients to various cancers as well as CVCs.[16] Clearly, and in some instances, the mechanism of CVCs related to drugs such as trastuzumab, TKIs and proteasome inhibitors, is attributed to the off-target effects of the drugs.

Unlike the anthracycline cardiotoxicity, unanticipated CVCs are not usually dose dependent and can happen any time during the course of therapy. Thus, we have to rely only on clinical judgment when weighing the risk of life-threatening CVCs against the benefit of potentially life-saving therapy. In order to understand the magnitude of these complications, it is imperative to develop a clear set of criteria that defines CVCs in the setting of targeted anticancer therapy that can help differentiate it from cardiovascular events that are not related to these drugs. Initial trials of carfilzomib mentioned dyspnea as a pulmonary

complication where it could have been secondary to pulmonary edema caused by early cardiotoxic effect and before low LVEF is detected by regular echocardiograms.[17] Clinical evidence suggests that the cardiovascular toxicity of targeted agents seems to be reversible after discontinuation of therapy.[18,19] In our study,[14] as many as 79% of patients had stable to improved LVEF on follow up. However, our study still showed that the study group had a significantly worse OS compared with the reference group, with no difference in cancer progression-free survival between the two groups. This worse OS of the patients with cardiotoxicity could be secondary to the added morbidity, interruption in anticancer therapy and more cautious use of less effective chemotherapeutic agents as a result of excluding certain drugs that can potentially add to the cardiac toxicity. Clinical trials usually exclude patients who experienced a New York Heart Association class III or IV functional heart failure or myocardial infarction in the 6 months prior to the onset of therapy,[20] which limits our understanding of the safety of using these targeted agents in such a patient population, leaving retrospective studies as the only tool for more information. Designing trials in a way so that enrolled patients reflecting the real-world patient population with cardiovascular disorders would help oncologists in creating better interventional treatment plans. Moreover, a trial design that allows long-term monitoring would be ideal to capture delayed toxicities.

Early detection of toxicity

Unfortunately, there are no known predictive risk factors for the development of CVCs, and it is usually an unanticipated complication. LVEF measurement is a relatively insensitive tool for detecting cardiotoxicity at an early stage. This is largely because considerable change in LVEF does not occur until a critical amount of myocardial damage has taken place and all the compensatory mechanisms are exhausted. One of the biggest challenges is to identify toxicity in early stages of development by proper monitoring strategies. So far studies have shown that various cardiac markers such as troponin, B-type natriuretic peptide (BNP), and echocardiography do not effectively correlate with the degree of cardiac dysfunction, although in some cases and depending on the mechanism by which CVCs occur, troponin and electrocardiogram (EKG) periodic surveillance may be useful in early detection.[20,21] In a randomized controlled trial, troponin I was used as an early detection tool which led to initiation of enalapril.[22] During the follow up, none of the enalapril-treated patients developed left ventricular dysfunction *versus* 43% in control arm.[22] In a substudy of the ENDEAVOR phase III trial, serial echocardiogram assessments were of limited utility as risk mitigation tools in patients treated with carfilzomib.[18] Recent data suggest strain echocardiography might be able to detect chemotherapy-induced cardiac damage at relatively early stages; however, it needs further validation.[23]

Protection against cardiotoxicity

Obviously, we are in dire need for further research to develop therapeutic strategies for the prevention of such CVCs and reducing their adverse effect on overall outcome in cancer patients. Since CVC occurrence is unpredictable, and the drugs causing it are effective and needed, finding ways to provide cardiac protection makes most sense. There is vast literature about the protection against anthracycline cardiotoxicity, but not much published data on the protection against targeted therapy-related CVCs with the exception of recent trials about the protection against trastuzumab-induced cardiac toxicity.[24,25] The two drug classes, beta blockers and angiotensin converting enzyme inhibitors, which are used for the treatment of cardiomyopathy and heart failure, have been reported to be protective against cardiac toxicity.[22,26] However, studies have produced inconsistent results regarding the protective effects of different agents that belong to these drug classes[27,28] and more studies and new protective agents are needed.

Future directions

The awareness of this complication is rising and the emerging of cardio-oncology is important, but we urgently need to pick up the pace to answer many of these burning questions. There are a few areas of unmet need: (1) Studies into the possible genetic predisposition to developing CVCs from targeted therapy; (2) What biomarkers can predict early cardiac damage/toxicity while cancer patients receive targeted therapies? (3) What can be done to prevent cardiac toxicity? Are there universal cardioprotective drugs that can be used concomitantly with targeted therapies? (4) What can we learn from the extensive research into the prevention of anthracycline cardiotoxicity?

Animal models and basic science laboratory research can probably answer some of these questions.[29–31] Furthermore, the establishment of the cardio-oncology discipline will hopefully help in answering some of these questions, especially with more government and industry funding and multilateral collaboration.

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Conflict of interest statement

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