Cardiotoxicity of Cancer Chemotherapy Agents

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Keywords: cardiotoxicity

1. Introduction

Over the last few decades, due to the immense progress in the field of cancer treatment, there has been an important prolongation in life expectancy of patients diagnosed with malignancies. However, now that traditional cytotoxic chemotherapy along with molecular-targeted therapies and immunotherapy have improved the survival rates, it is very crucial that the off-target adverse effects are also given the proper attention [1]. In particular, complications of the cardiovascular (CV) system are considered significant, and they usually lead to higher morbidity and mortality rates of patients.

Cardiotoxicity is defined as every CV event related to the use of cancer medication. The diagnostic criteria are the same as those used for the common population apart from the cardiac dysfunction associated with antitumor therapy, which is defined as a decrease in a left ventricular ejection fraction (LVEF) > 10% from baseline to a final LVEF below the lower limit of 53% [2]. Additionally, cardiotoxicity is divided into two different types in respect to reversibility, with reversibility referring to the recovery of cellular or organ function. Thus, type I cardiotoxicity is considered irreversible due to the cumulative administrated dose that causes myocardial cell loss, with anthracyclines being the most representative agents in this category [3]. In contrast, type II cardiotoxicity is not considered dose dependent and organ dysfunction can be reversed upon cessation of the treatment segment, with trastuzumab being the best representative agent [4].

It is very important for patients with cancer to be stratified according to their risk of developing CV toxicity, so that physicians can take precautionary measures and manage the delivery of the most appropriate cancer treatment. Although many stratification scores have been proposed for these patients, none of them are established yet. Patients considered as high risk for developing CV toxicity are shown in **Table 1** [5]. Aside from the cytotoxic chemotherapy such as anthracyclines, alkylating agents and antimetabolites, the most representative target therapies that are also correlated with cardiotoxicity are human epidermal growth factor receptor 2 (HER2) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, Bcr-Abl tyrosine-kinase inhibitors (TKI), proteasome inhibitors, and immune checkpoint inhibitors.

Table 1. Patients with higher risk for cardiotoxicity.

- High-dose anthracycline (e.g., doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (e.g., doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) or HERis or VEGFis or proteasomeis or Bcr-Ablis and presence of any of the following factors:
  - Age ≥60 y
  - Previous heart disease
  - Lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field
  - ≥2 risk factors including: smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity
- Elevated cardiac biomarkers before initiation of anticancer therapy

2. HER-2 Targeted Therapies

About 15% of all breast cancers are human epidermal growth factor receptor 2 positive, which indicates a poorer prognosis [6][7]. Anti-HER 2 treatment is associated with cardiac dysfunction through impaired proliferating signals [7]. Even though the exact mechanisms are still unclear, experiments indicate that myocardial cell death is erbB2-dependent, since treatment that blocks this pathway can lead to mitochondrial dysfunction and the formation of reactive oxygen species [8].

Three percent to seven percent of patients treated only with trastuzumab, a recombinant human monoclonal antibody against HER2, may manifest some sort of cardiac toxicity [6]. A review of seven clinical trials reported cardiotoxicity events including congestive heart failure and reduced LVEF after trastuzumab administration [9]. Anthracycline monotherapy resulted in a lower incidence of cardiac dysfunction compared to combined therapy with trastuzumab [6][9]. The occurrence of cardiotoxicity events was irrelevant of whether trastuzumab was used as a first line treatment or for metastatic breast cancer [6]. Based on five trials of women with breast cancer, 5.9% of trastuzumab-treated women experienced a reduction in their LVEF compared to 2% of women in the control group [9]. Although the trastuzumab label suggests cardiac evaluation before, during and after administration, The management of drug-induced cardiac dysfunction that may occur should be prepared [6]. As suggested in a previous study, early administration of b-blockers or angiotensin-converting enzyme (ACE) inhibitors may prevent cardiotoxicity in the setting of treatment with trastuzumab [10]. The American Heart Association proposes cardiovascular evaluation during treatment with HER-2 inhibitors, with the assessment of blood pressure, blood tests, echocardiography, and further evaluation, if needed based on these exams, every 3 months [5]. Cardiovascular abnormalities are thought to repair after discontinuation of anti-cancer treatment and heart failure (HF) therapy [11]. The United States Food and Drug Administration (FDA) suggests a 4 week discontinuation of trastuzumab if the LVEF drop is over 16% of the initial values or an absolute 10% fall occurs [12].

3. Cardioprotection

Strong interest has emerged to further examine the role of cardioprotective strategies and minimize treatment-related cardiotoxicity. In this context, various cardioprotective strategies have been evaluated to prevent the development of chemotherapy-related cardiotoxicity, with mixed findings [13][14][15]. A large, randomized trial compared lisinopril vs. carvedilol in patients with breast cancer receiving trastuzumab. Both treatments resulted in fewer cardiotoxicity events compared to placebo in patients receiving anthracyclines. Patients on placebo needed to interrupt their trastuzumab therapy more often than patients on preventive treatment with ACE inhibitors, ARBs or b-blockers [14]. The OVERCOME trial assigned patients with hematological malignancies to receive enalapril, carvedilol or placebo. Patients on enalapril or carvedilol presented less often with heart failure, LVEF < 45% or sudden cardiac death compared to the placebo group [15]. A previous meta-analysis of cancer patients with recent chemotherapy across 17 studies, showed significant benefits from the use of neurohormonal therapy with higher LVEF and better LV strain on follow up and no changes in other LV parameters in patients receiving chemotherapy. The absolute benefit in attenuating declines in LVEF was less than 5% and could be explained by inter-test variability [16]. These modest treatment effects on LVEF were consistently observed in trials examining strategies with renin-angiotensin-aldosterone-system inhibitors and beta-blockers and in the large subgroup of trials that exclusively examined breast cancer patients and those on anthracycline-based chemotherapy. Furthermore, there were numerically, but with statistical significance, fewer major clinical adverse events in the neurohormonal therapy arm. A more recent meta-analysis of nine randomized controlled trials [17] (n = 1362, all females) demonstrated that beta-blockers and ACEI/ARBs attenuated the decline in LVEF during trastuzumab and anthracycline treatments (with a mean difference of 2.4 and 1.5, respectively). Compared with placebo, LVEF was significantly higher in patients assigned to beta-blockers or ACEI/ARB on trastuzumab but not on anthracyclines. Recently, in a large double-blind, multicenter, placebo-controlled trial of 468 women, cardiotoxicity and treatment interruptions in patients with HER2-positive breast cancer treated with trastuzumab for 12 months were evaluated over a two-year period. Patients were stratified by anthracycline use and then randomized to receive lisinopril, carvedilol, or placebo. In those patients with HER2-positive breast cancer treated with trastuzumab, both lisinopril and carvedilol prevented cardiotoxicity specifically among patients receiving anthracyclines [16]. Finally, the recent SAFE trial was a four-arm, randomized, phase 3, double-blind, placebo-controlled, national multicentric study conducted at eight oncology departments in Italy. Bisoprolol, ramipril, or both drugs compared with placebo were administered for one year from the initiation of chemotherapy or until the end of trastuzumab therapy in case of ERBB2-positive patients. At 12 months, 3D-LVEF worsening was significantly lower in the bisoprolol and ramipril combination patients and a significantly lower percentage showed a 10% or greater worsening of GLS in the cardioprotection arms [18].

In contrast to anthracycline and HER-2 targeted agents, limited data are available on cardioprotection from potential cardiac adverse events related to other molecularly targeted agents. These agents are generally newer drugs with lower rates of toxicity, often reversible adverse events and less experience of toxicities compared with anthracyclines and HER-

2 targeted agents. Furthermore, patients at the highest risk for developing such cardiac toxicity are often excluded from clinical trials that evaluate efficacy and safety of newer anti-neoplastic agents. Nevertheless, general principles apply for minimizing the development of cardiotoxicity across all classes of anticancer agents, including the molecularly-targeted agents. Patients treated with these agents should be stratified according to the risk for cardiac events based on their comorbidities. Primary prevention measures should be emphasized and the data available for HER-2 targeted therapies' cardioprotection should be extrapolated to these agents. Evaluation and monitoring of LVEF or other biomarkers should be considered on a case-by-case basis and the toxicity profile, patient, and disease characteristics should be considered when making decisions about the monitoring of adverse events. Typically, the LVEF monitoring parameters recommended in the prescribing information for individual agents should be followed and patients with underlying cardiovascular disease or those developing early signs of cardiotoxicity based on echocardiographic parameters and biomarkers may need more frequent follow-up testing.

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