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Review

Cardiotoxicity of systemic agents used in breast cancer

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ABSTRACT

Several breast cancer therapies can lead to cardiovascular toxicity: drugs such anthracyclines can cause permanent damage, anti-HER2 agents may cause transitory and reversible cardiac dysfunction and others, such as those used in endocrine therapy, primarily disturb lipid metabolism. Considering the seriousness of these complications, trials are now being conducted to address cardiotoxicity associated with new drugs; however, to fully understand their toxicity profiles, longer follow-up is needed. In this review, we compile the information available about cardiac toxicity related to well-established systemic breast cancer treatments, as well as newer drugs, including antiangiogenics, mTOR inhibitors and novel anti-HER2 agents. We also describe current and next generation cardiac biomarkers and functional tests that can optimize treatment and reduce and prevent the incidence of treatment-related cardiotoxicity

Introduction

Today systemic treatment plays an important role in modern breast cancer management and is widely used. Both endocrine therapy and chemotherapy have changed the way patients with breast cancer are treated; they have extended the life of a countless number of patients with metastatic disease and cured another significant proportion in the adjuvant setting. However, these survival gains come at the expense of increasing treatment side effects, with cardiotoxicity being one of the most significant. Potentially life threatening, this side effect can dramatically impact a patient's quality of life.

One of the challenges of modern oncology is to be able to tailor a patient's treatment by administering the drugs most adapted to the molecular characteristics of the disease while simultaneously preventing or reducing side effects. In that regard it is of fundamental importance to make the distinction between drugs that have the potential to cause irreversible cardiac damage, also known as Type I damage, from drugs that can cause reversible dysfunction, the Type II damage [1]. Another important aspect is the detection of cardiovascular conditions that predispose cardiotoxicity in daily patient care. Cardiotoxicity can be manifested through heart failure (CHF), asymptomatic left ventricular ejection fraction (LVEF) drops, hypertension, arrhythmias, QTC prolongation and myocardial ischemia.

This article reviews the literature and summarizes current knowledge about cardiotoxicity associated with systemic drugs used to treat breast cancer. These range from the "old" well-known drugs to novel targeted agents. Insight is also provided on drugs in development, and current and future cardiac biomarkers and functional imaging methods.

Cardiotoxicity related to cytotoxic chemotherapy

Anthracyclines

Anthracyclines are largely used to manage early stage and metastatic breast cancer [2]. Cardiac complications associated with their use has been reported in multiple clinical trials and several cancer types [3]. Patients treated with anthracyclines have five times more chance to have a decrease in the LVEF and chronic heart failure than those treated with non-anthracycline regimens [3]. The most important risk factors for cardiac toxicity caused by anthracyclines is the cumulative dose [4,5]. A joint analysis of three trials estimated that 26% of patients receiving a cumulative doxorubicin dose of 550 mg/m^2 would develop heart failure, with a greater risk found in older patients (≥65 years-old) [6]. The risk, however, is lower with doses inferior to 300 mg/m^2. The risk is increased when

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anthracyclines are given with high dose-volumes of cardiac radiotherapy [7] and with other cytotoxic agents [8]. Previous cardiac conditions that potentially cause reductions in the cardiac reserve, such arterial hypertension or previous ischemic conditions, are likely to contribute to anthracycline cardiotoxicity [4]. Anthracycline-mediated cardiotoxicity is classified as Type I damage, meaning that the pathophysiology is related to cell loss [1].

The clinical presentation of anthracycline-induced cardiotoxicity can be divided into categories according to the onset of symptoms. Symptomatic acute toxicity is an uncommon event (<1%), happening shortly after anthracyclines are administered. It is related to rhythm disturbances [9], ranging from asymptomatic ECG abnormalities [10] to atrial ventricular block [11] with ventricular dysfunction. It is mostly reversible and not serious [12]. Cardiomyopathy, however, is the hallmark of anthracycline-induced chronic cardiotoxicity, being also its dose-limiting side effect. Recent evidence suggests the cardiac damage induced by anthracyclines happens during the infusion or shortly after the administration of the drug. Due to compensatory mechanisms the clinical manifestations related to this damage may become apparently only many years after the drug exposure, with the exhaustion of these mechanisms and the decrease of the cardiac reserve [1,13]. The timing for the manifestation of the clinical symptoms is dependent on the extension of the damage and the capacity of the heart to compensate for it [1]. Anthracyclines are associated with increased risk of both clinical (odds ratio [OR] 5.43, 95% CI 2.34–12.62) and subclinical chronic cardiotoxicity (OR 6.25, 95% CI 2.58–15.13) [3]. Symptoms develop within the first year of treatment, normally in the first 3 months (early onset: 1.6%–2.1%) [14]. Late onset of cardiac side effects have been observed in young leukaemia patients [15] and are of major concern in the adjuvant treatment of breast cancer patients, as anthracyclines are part of several chemotherapy schedules [2]. This late onset may occur as late as 10–20 years after administration.

Chronic cardiotoxicity secondary to anthracyclines results in loss of cardiomyocytes and, despite being treatable with standard treatment for CHF, often progresses from asymptomatic heart dysfunction to irreversible CHF. The molecular mechanism is not completely understood. Some researchers have shown that the increase of free radicals and oxidative stress might contribute to the development of cardiac damage [16]; however, others postulate that it is related to the mechanism of action of anthracycline itself, namely in the topoisomerase-Iiβ expressed by cardiomyocytes [17].

Several strategies to reduce anthracycline-induced cardiotoxicity have been evaluated: First, infusional administration is preferred; bolus administration of doxorubicin is associated with a significant increase in the risk of symptomatic cardiotoxicity (OR 4.13, 95% CI 1.75–9.72) [3]. Second, epirubicin is a less toxic structural doxorubicin analogue and, despite being used in higher doses [2], is less associated with cardiotoxicity (OR 0.39, 95% CI 0.2–0.78) [3]. Pegilated formulations of doxorubicin were created to deliver a higher cumulative dose with similar efficacy and lower incidence of cardiac side effects [18,19], significantly decreasing the risk of symptomatic adverse events (OR 0.18, 95% CI 0.08–0.38) [3]. Third, the concomitant administration of heart protective compounds is another strategy to reduce the incidence of anthracycline-induced cardiac damage. Dexrazoxane is an EDTA-like chelator that is postulated to bind to iron released after secondary anthracycline-induced lipid peroxidation [20]. Although it lowers the incidence of clinical cardiac side effects (OR 0.21, 95% CI 0.13–0.33) [3], concerns have been raised about its possibly reducing the efficacy of chemotherapy [21]. Beta blockers [22] and angiotensin converting enzyme (ACE) inhibitors [23] have been evaluated as cardio-protective agents, but with only few patients assessed, their usefulness remains an open question.

Non-anthracyclines

5-Fluorouracil (5-FU)

The frequency of symptomatic cardiac side effects with 5-FU is estimated to be 1.2%–4.3% [24]. The hallmark of 5-FU cardiac toxicity is chest pain, but it can also present as rhythm disturbances, hypotension, dyspnoea, and myocardial infraction [25]. The risk of sudden death was identified to be around 0.5% [24].

Although the mechanism of toxicity is not completely understood, there is preclinical [26] and clinical [27] evidence pointing to 5-FU-induced vasoconstriction as the underlying cause. Degradation of the products used in the dissolving medium used of 5-FU has also been investigated as a possible cause [28]. Small series [29] and case report [30] data suggest that myocarditis and endothelial damage could lead to a thrombogenic state.

In a prospective study, patients were monitored with electrocardiogram (ECG) during the administration of 5-FU; 19% developed symptomatic and reversible angina with accompanying alterations in the ECG, but none presented coronary disease at arteriography exam. Three months later no difference was seen in the ejection fraction values; however, the QTC time was significantly prolonged in relation to baseline [31]. Infusional 5-FU regimens seem to have higher toxicity than bolus administration [32], and previous heart conditions increase the risk of 5-FU cardiac toxicity (4.5% versus 1.1%) [33].

Because symptoms of cardiotoxicity in connection with 5-FU are often reversible, managing them includes withdrawal of medication and anti-anginal treatment. One small series re-challenging patients with 5-FU identified that 47% of the patients reproduced cardiac symptoms and around 13% died. Thus re-challenging with 5-FU should be reserved for patients where no alternative treatment is available and performed under careful prophylaxis with nitrate and calcium-channel protection and close monitoring [25].

Capecitabine

Capecitabine is a fluoropyrimidine that metabolizes into 5-FU. There is cross-toxicity between capecitabine and 5-FU [34], with toxicity appearing to be similar to that of infusional 5-FU [35]. Its incidence is around 3%, and the most frequent clinical manifestations are angina, arrhythmias and myocardial infarction [36].

Taxanes

Paclitaxel cardiac toxicity is related to rhythm disturbances, with around 30% of patients presenting asymptomatic sinus bradycardia [37]. Other important toxicities include a range of conduction blocks, and manifestations of cardiac ischemia have been observed in 5% of patients participating in phase I and II trials [38]. Symptoms are often resolved upon termination of therapy, but paclitaxel combined with anthracyclines increases the incidence of cardiotoxicity [39,40], which occurs at lower cumulative doses than when anthracyclines are used in isolation [8]. However bradycardia is rarely a problem in clinical practice. Docetaxel appears to have a similar toxicity profile, but less evidence is available [41,42].

Alkylating agents

Cardiotoxicity mediated by cyclophosphamide is not related to cumulative dose but rather to high-dose protocols [43,44]. This is normally a concern for patients exposed to high-dose chemotherapy followed by autologous stem cell rescue. Prior irradiation of the mediastinum and the left chest wall increases the risk of cardiac complications [45]; however, this is not an issue with modern breast cancer radiotherapy that spares the heart from irradiation.