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Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity

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ABSTRACT

Objectives: To review the evidence for the use of various biomarkers in the detection of chemotherapy associated cardiac damage.

Design and methods: Pubmed.gov was queried using the search words chemotherapy and cardiac biomarkers with the filters of past 10 years, humans, and English language. An emphasis was placed on obtaining primary research articles looking at the utility of biomarkers for the detection of chemotherapy-mediated cardiac injury.

Results: Biomarkers may help identify patients undergoing treatment who are at high risk for cardiotoxicity and may assist in identification of a low risk cohort that does not necessitate continued intensive screening. cTn assays are the best studied biomarkers in this context and may represent a promising and potentially valuable modality for detecting cardiac toxicity in patients undergoing chemotherapy. Monitoring cTnI levels may provide information regarding the development of cardiac toxicity before left ventricular dysfunction becomes apparent on echocardiography or via clinical symptoms. A host of other biomarkers have been evaluated for their utility in the field of chemotherapy related cardiac toxicity with intermittent success; further trials are necessary to determine what role they may end up playing for prediction and prognostication in this setting.

Conclusions: Biomarkers represent an exciting potential complement or replacement for echocardiographic monitoring of chemotherapy related cardiac toxicity which may allow for earlier realization of the degree of cardiac damage occurring during treatment, creating the opportunity for more timely modulation of therapy.

Introduction

Improved survival in many solid and hematologic malignancies is exposing more patients to the long-term effects of chemotherapy including cardiac toxicity [1]. With improved outcomes, increased emphasis has been placed on the side effects associated with treatment and several chemotherapeutic agents have gained notoriety for their untoward cardiovascular side effects such as arrhythmias, myocardial ischemia, hypertension, acute heart failure and late onset ventricular dysfunction [1–4]. In particular, late-onset heart failure with either reduced or preserved ejection frequently occurs years after chemotherapy has been completed and is associated with substantial morbidity and mortality [1].

Anthracyclines as well as several novel agents have the potential to cause severe cardiac toxicity which may hamper their optimal use in treatment of malignancy. Additionally, with an expanding pool of patients receiving chemotherapy, there are currently no good tools for differentiating progression of underlying cardiac disease from direct cardiotoxic effects of chemotherapeutic agents. Echocardiography is currently used to assess cardiac function prior to the initiation of chemotherapy and to monitor for the development of cardiac toxicity during therapy [5]. Unfortunately, echocardiography is an imperfect fit in this role as it is relatively insensitive for detecting early cardiac toxicity during treatment. This is because normal hearts have excellent reserve capacity, so even modest loss of left ventricular function is indicative of significant cardiovascular damage [6]. These issues in conjunction with the high cost of repeated imaging make the discovery and utilization of a biomarker guided approach a highly attractive option.

A number of chemotherapeutic agents associated with cardiac toxicity will be reviewed before discussing the utility of various biomarkers in the detection and monitoring of myocardial damage, and potential interventions that could be implemented either prophylactically or once cardiac injury is detected.

Methods

Pubmed.gov was queried using the search words chemotherapy and cardiac biomarkers with the filters of past 10 years, humans, and English language. These criteria yielded a total of 3186 articles which were then selected on the basis of their relevance to this article's topic and goals. Appropriate articles were then hand searched to identify

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additional relevant literature. An emphasis was placed on obtaining primary research articles looking at the utility of biomarkers for the detection of chemotherapy-mediated cardiac injury. Refer to Table 1 for a compilation of these studies.

Discussion

Chemotherapy induced cardiac toxicity is generally divided into two classes on the basis of its severity and reversibility. Type 1 is myocardial injury induced through damage to the microstructure of cardiac myocytes and results in cell death via necrosis or apoptosis [7]. This damage is generally considered irreversible [7]. In contrast, type 2 cardiotoxicity results in cardiac myocyte dysfunction with the notable absence of microstructural disruption [7]. This impairment resolves with the completion of therapy and sometimes even during its continuation [7].

Chemotherapeutic agents

Anthracyclines

Anthracyclines are highly effective chemotherapeutic agents commonly used in breast cancer as well as hematologic tumors [2]. These drugs act through the intercalation of nucleic acids to interfere with cell replication, leading to potent antitumor effects [8]. In addition, anthracyclines generate free radicals through an iron-dependent, enzyme-mediated reductive process [8]. It is thought that this mechanism may also lead to cardiac tissue damage through the production of superoxide anion radicals [9,10].

In response to the extensive attention on chemotherapy induced cardiac damage, a recent meta-analysis showed that 6% of patients treated with anthracycline experience clinically overt cardiotoxicity, while 18% develop subclinical cardiotoxicity [11]. This is consistent with a 5-fold increased risk in congestive heart failure in patients treated with these agents [12].

Anthracycline-related cardiomyopathy appears to be dose dependent with increasing risk and severity of cardiomyopathy correlating with the cumulative dose [13–15]. However, it should be noted that myocardial damage can occur unpredictably; doses as low as 200 mg/m^2 can be associated with injury and the frequency increases as doses exceed 550 mg/m^2 [13]. This dose response curve becomes increasingly steep as doses increase and there appears to be a synergistic deleterious effect with radiation and/or trastuzumab co-administration [16].

Cyclophosphamide

Cyclophosphamide is a nitrogen mustard alkylating agent commonly used for the treatment of both neoplastic and autoimmune conditions. Although cyclosphosphamide has most often been associated with cardiomyopathy in settings where it is used in conjunction with anthracyclines, there is evidence to suggest that cyclophosphamide itself may rarely cause direct cardiac toxicity via hemorrhagic myocarditis [17,18]. Studies specifically investigating co-administration of cyclophosphamide and anthracycline have shown that the addition of cyclophosphamide leads to an earlier peak troponin level than anthracyclines alone; however inclusion of cyclophosphamide in therapy does not appear to alter absolute peak troponin levels or overall outcome [19]. Further supporting this claim, ejection fraction decreases noted following stem cell transplantation appear to be primarily associated with cumulative anthracycline toxicity as opposed to cyclophosphamide use [20]. N-terminal pro B-type natriuretic peptide (NT-proBNP) levels show transient elevations in the setting of cyclophosphamide use prior to stem cell transplantation for non-Hodgkin lymphoma and multiple myeloma which may be indicative of some temporary cardiac stunning or alternatively the concomitant use of large amounts of fluid during administration [21,22]. It has been noted that any symptoms that develop with cyclophosphamide use occur during drug administration, and usually resolve upon discontinuation [23].

Taxanes

Taxanes are a popular chemotherapeutic class that derive their antitumor effects through interference with the formation of microtubules necessary for cellular division [23]. Cardiac toxicity typically manifests with conduction disease, principally bradycardia, which is usually asymptomatic and does not require intervention [24]. This injury is thought to be secondary to damage to subcellular organelles [25].

5-Fluorouracil

5-Fluorouracil (5-FU) is an antimetabolite agent used in the treatment of a variety of neoplastic processes. The incidence of cardiotoxicity with this drug ranges widely from 1% to 68%, with manifestations including arrhythmias, pulmonary edema, acute myocardial infarction, and cardiogenic shock [23,26–29]. The exact mechanism of these sequelae is not entirely clear but is thought to relate to coronary vasospasm based on ultrasound and angiographic studies [29]. This wide variation likely relates to differing study populations and definitions regarding cardiac toxicity [26,27,30].

Biologic agents

The term targeted therapy is often perceived to indicate highly selective killing of tumor cells through their purported pathway specific mechanisms; unfortunately it is increasingly realized that this specificity for both pathway and cellular selectivity does not always achieve perfect fidelity. Several of these new biologic agents have been linked to potential cardiovascular consequences, most notably trastuzumab and sunitinib [1].

Trastuzumab

Trastuzumab is a HER2 inhibitor which is used principally in breast and gastric cancer cases that overexpress this receptor [31]. When used in the absence of concomitant anthracycline therapy, trastuzumab is associated with minimal reversible (type 2) cardiac toxicity which tends to resolve with appropriate congestive heart failure based management [32,33]. However if administered concomitantly or in rapid succession with anthracyclines, more devastating cardiovascular consequences can occur, with multiplication of not only their antitumor effects but also the risk of cardiomyopathy. The incidence of cardiac toxicity in this setting has been reported to be around 28%, although this risk has been less substantial in a large chart review by Russell et al. [34–36] One approach that shows promise is separating anthracycline dosing and the initiation of trastuzumab by at least 90 days which may help ameliorate some of these safety concerns [37,38]. This principle is evidenced by a lower incidence of cardiac toxicity (4.3%) in the HERA cohort and has led to the recommendation that anthracyclines and trastuzumab not be used concomitantly in clinical practice to minimize their synergistic cardiac toxicity [37–39].

Animal studies have linked trastuzumab related toxicity to interference with HER2 mediated cardiac repair which leads to dilated cardiomyopathy and additional susceptibility to anthracycline based cardiac toxicity [34,40]. Through this mechanism, trastuzumab may prevent necessary myocyte repair following damage from anthracycline therapy, playing a synergistic role in its formation of cardiac damage [38]. This creates a treatment dilemma for physicians given the improved clinical outcomes for HER2 positive tumors when trastuzumab is included in the regimen [32]. This is especially poignant given the current recommendation of 1 year of therapy, associated with low recurrence rates but increased concern for cardiovascular events [41]. This issue is particularly important in older patients with co-morbidities who have an 18% risk of trastuzumab discontinuation despite its substantial benefits [42].

Multi-kinase inhibitors: sunitinib and sorafenib

Sunitinib is a tyrosine kinase inhibitor with a broad spectrum of activity shown to be effective in the management of renal cell carcinoma. This drug is unfortunately also associated with increased rates of adverse

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