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REVIEW

Maximizing anthracycline tolerability in hematologic malignancies: Treat to each heart's content

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ABSTRACT

Anthracyclines are the cornerstone of therapy for a wide spectrum of malignancies and have improved patient survival. Concern for anthracycline-related cardiotoxicity often leads to dose reductions or use of second-line regimens, which may adversely impact survival. Development of cardiotoxicity depends on a combination of cumulative dose modulated by individual patient characteristics, which we have termed individual cardiotoxic threshold (ICT). Patients with cancer often have characteristics such as age, gender, genetic predisposition and preexisting cardiovascular disease that can potentiate cardiotoxicity. Specialty cardiovascular assessment, more sensitive monitoring technology, and timely interventions in selected patients can decrease cardiotoxicity and improve patient outcomes. Prophylaxis with cardioprotective agents and other strategies have shown promising results in randomized trials and may improve tolerance to anthracyclines. In this review we introduce the concept of ICT and critically analyze the evidence supporting existing strategies to modulate it and increase cardiovascular tolerability of anthracyclines.

Contents

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1. Introduction

Anthracyclines remain the cornerstone of therapy for a wide spectrum of malignancies and have markedly improved survival of patients with lymphoma [1], AML [2], breast cancer [3], among other cancers. Their anti-neoplastic effect is often limited by cardiotoxicity, which has been shown to impact early and late patient survival [4,5]. Anthracyclines inhibit cardiomyocyte topoisomerase IIB, resulting in DNA breaks mediated by free oxygen radicals with accelerated mitochondrial death and apoptosis [6]. This effect is clinically evident by a progressive, dose-dependent loss of cardiomyocytes with ensuing contractile deficit and left ventricular dysfunction (LVD) with or without heart failure (HF).

Concern for anthracycline-associated cardiotoxicity often leads to dose reductions or use of second-line regimens [8]. While the maximal permitted cumulative dose of anthracyclines (i.e. daunorubicin or doxorubicin) is usually quoted to be around 450 mg/m^2, it has been increasingly recognized that lower doses may also be associated with irreversible cardiac dysfunction [7,8].

The development of anthracycline-induced cardiotoxicity during cancer treatment has several potential consequences. Most critically, it leads to premature anthracycline discontinuation, use of less efficacious second-line agents, and sometimes cessation of cancer therapy entirely. Indeed, anthracycline discontinuation results in lower cumulative doses, potentially leading to suboptimal cancer outcomes of patients who could have benefited from higher doses [9]. Similarly, interruptions in cancer therapy have been associated with decreased survival [10] and cardiotoxicity-induced LVD with or without HF. Whereas cardiac dysfunction can sometimes be reversible [4], especially if treated early [11], the lack of reversibility has been linked to reduced overall survival [4] (Fig. 1).

Whereas anthracycline cardiotoxicity is clearly related to total lifetime dose, accumulating evidence unequivocally shows that some patients develop cardiotoxicity at unexpectedly low doses while others can tolerate doses that far surpass the maximal recommended dose of around 450 mg/m^2. This paradox has compounded unpredictability to the problem of cardiotoxicity and introduced the concept that a completely safe dose of these agents probably does not exist. It appears, in fact, that the threshold to development of cardiotoxicity depends on a combination of dose and individual patient characteristics. To better express this relationship we have coined the term "individual cardiotoxic threshold" (ICT) for anthracyclines and will discuss how it is determined by both modifiable and non-modifiable factors intrinsic to each patient.

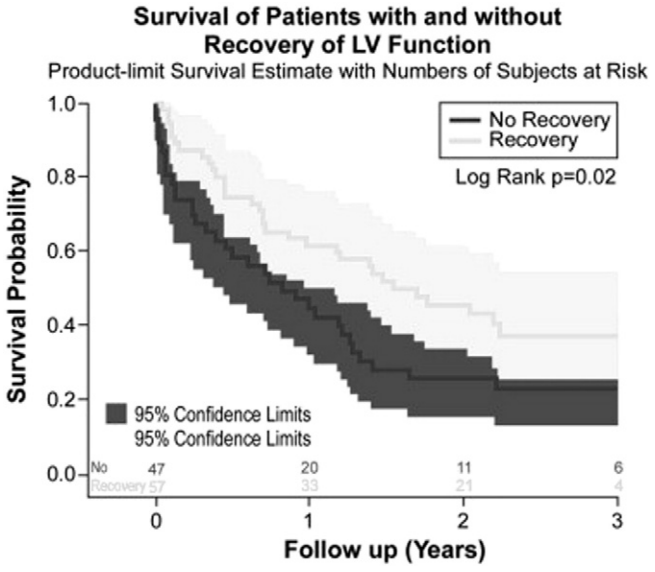

Fig. 1. Overall survival in patients with cancer who develop cardiotoxicity (stratified by reversibility). Obtained with permission from Oliveira AJC 2014 [4].

This review aims to introduce the concept of ICT, critically appraise the problem of cardiovascular tolerability of anthracyclines, and discuss strategies aimed at optimizing cardioprotection in order to maximize the benefits of anthracycline therapy. It is important to note that some of the onco-cardiology literature is derived from patients with solid tumors or from children with leukemia. Thus, throughout this review, we will extrapolate some of these studies to adults with hematologic malignancies, keeping in mind the different doses, regimens, and comorbidities in those patients.

2. Epidemiology of anthracycline cardiotoxicity

In their classic study, Von Hoff and co-workers [12] reported HF in 3%, 7%, and 18% in patients who received a cumulative dose of 400, 550, or 700 mg/m^2 of doxorubicin, respectively. In the current era, about 10%–30% of anthracycline-treated patients may develop evidence of cardiotoxicity with an absolute left ventricular ejection fraction (LVEF) decrease of >10%, or overt HF symptoms [13]. The vast majority of anthracycline cardiotoxicity occurs within the first year. In a recent series of 2625 cancer patients undergoing anthracycline therapy, 226 (9%) developed cardiotoxicity (defined as 10% or more LVEF reduction, and below LVEF < 50%), with 221 (98%) of those occurring in the first year [14].

The prevalence of cardiotoxicity seems to be higher in patients with hematologic malignancies than other cancers. For example, in a recent study of 2285 patients with different cancers receiving anthracyclines, patients with hematologic malignancies had 6-fold increase in incidence of cardiac events (symptomatic HF or cardiac death) than patients with breast cancer ($p < 0.0001$) [15]. The development of cardiotoxicity limits chemotherapy dosing and may result in worse overall outcomes. In a study of 265 patients with various malignancies (40% breast, 21% NHL, 16% uterine, 5% ovarian, 18% miscellaneous) receiving doxorubicin followed with multi-gated radionuclide angiography (MUGA), 15.4% developed cardiotoxicity (10% or greater point fall in LVEF to a final value of less than 50% during doxorubicin therapy) of which half had early discontinuation of doxorubicin [16]. In another study, 14% of 509 patients receiving doxorubicin for breast cancer discontinued treatment early due to cardiotoxicity [17]. Also, among 106 children treated with doxorubicin, 43 (40.6%) required permanent discontinuation of treatment prematurely [18].

Anthracycline cardiotoxicity and HF development appear to be in part related to baseline cardiovascular risk factors and comorbidities. In a population study of 3164 elderly patients with DLBCL who received doxorubicin-based chemotherapy, CHF risk increased with number of doxorubicin sessions, increasing age, prior heart disease, diabetes, and hypertension [19]. This was also shown in another study of 208 patients with NHL receiving anthracyclines with or without baseline hypertension. The hypertensive cohort had higher incidence of new LVSD (19.7% vs. 6.6%; $p = .004$), which translated into more delays of subsequent chemotherapy cycles (26.8% vs. 14.6%; $p = .03$), more reductions