Progress in Pediatric Cardiology 36 (2014) 51–55

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Lessons from the hearts of survivors of childhood cancer

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ARTICLE INFO

Available online 2 October 2014

Keywords:
Anthracycline
Childhood cancer survivor
Dexrazoxane
Cardiotoxicity
Late effects

ABSTRACT

With growing numbers of childhood cancer survivors, it becomes increasingly important to understand the long-term toxicities associated with cure from malignancy. Many survivors were exposed to cardiotoxic chemotherapeutic agents at young ages. Indeed, cardiotoxicity is a leading cause of treatment-related morbidity and mortality in survivors of childhood cancer, and anthracycline exposure is a leading cause of these late cardiac effects. Nonetheless, anthracyclines remain critical agents in treating many pediatric cancers. Strategies to prevent anthracycline-associated cardiotoxicity include limiting lifetime cumulative anthracycline doses and adding cardioprotectant agents, such as dexrazoxane, to anthracycline-based regimens. However, attempts to reduce the cardiotoxicity of anthracyclines must also consider their effect on anti-cancer efficacy as well as new potential toxicities. In survivors of childhood acute lymphoblastic leukemia, the data suggest that including dexrazoxane in anthracycline-based regimens can prevent heart damage, does not reduce anti-leukemic efficacy, and can be safely administered. The controversies associated with dexrazoxane exemplify the challenges of changing therapy in cancers with a relatively good chance of event-free survival in efforts to prevent long-term sequelae. Studies of very-long-term survivor cohorts will continue to inform current practices. Continued efforts are needed to minimize cardiotoxic exposures during cancer treatment, to deliver safe and effective cardioprotectant measures when cardiotoxic agents cannot be avoided, to identify patients at greatest risk of serious cardiac toxicity, and to educate providers in the optimal care of survivors.

1. Introduction

As the number of survivors of childhood cancer has increased, so has the recognition of the life-long implications of cancer therapy. The range and scale of late cardiac effects experienced by childhood cancer survivors have been reviewed in detail [1]. Anthracycline chemotherapy is most strongly associated with cardiac morbidity and mortality. However, anthracycline agents remain critical in treating many pediatric cancers. Any attempt to reduce the cardiotoxicity of anthracyclines must also consider the potential impact on anti-cancer efficacy, as well as on new toxicities. Here, we discuss the cardiac implications from the long-term follow-up of childhood cancer survivors with a focus on survivors of childhood acute lymphoblastic leukemia (ALL). We discuss the strategies for preventing anthracycline-associated cardiotoxicity, the challenges in implementing preventative interventions, and the need for continued measures to prevent cardiac toxicity in newly diagnosed patients.

2. The Risk of Cancer Treatment-Related Cardiotoxicity

In the United States, the number of adult survivors of childhood cancers is estimated to be more than 300,000, and this population is steadily increasing because of overall survival rates that now approach 80% [2,3]. The most common cancer diagnoses in children up to 15 years of age include ALL and brain tumors; the most common diagnosis in adolescents 15 through 19 years of age is Hodgkin lymphoma [4]. These diagnoses contrast with those most common in adults, including prostate, lung, breast, and gastrointestinal cancers [5]. Members of the oldest cohorts of childhood cancer survivors are only now approaching their sixth decade of life, whereas more than 50% of survivors of adult cancers are more than 70 years old [6,7]. Even as cancer-directed therapies improve, studies of these very-long-term survivors offer important lessons in caring for childhood cancer survivors and children newly diagnosed with cancer.

Cardiotoxicity is a leading cause of treatment-related morbidity and mortality in childhood cancer survivors. For example, in the Childhood Cancer Survivor Study, survivors were seven times more likely to die from cardiac-related events than was the general population [8].

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http://dx.doi.org/10.1016/j.ppedcard.2014.09.008
1058-9813/

Numerous studies have reported significantly increased risks of heart failure, coronary artery disease, and cerebrovascular events in childhood cancer survivors [1,9,10].

Anthracycline treatment is the chemotherapy most strongly associated with cardiac toxicity. In a recent study of validated, symptomatic cardiac events, a higher cumulative anthracycline dose or a higher cumulative radiation dose was associated with a higher risk-ratio for cardiac events in survivors of childhood cancer [10]. Those who received both anthracyclines and cardiac irradiation were at the highest risk for a cardiac event.

Current practice in cancer treatment is to reduce or eliminate the use of radiation whenever feasible. For example, an adult survivor of pediatric Hodgkin lymphoma treated in the 1960s was likely to have received high-dose, extended-field radiation therapy, which increased the risk of marked cardiac toxicity (as well as for developing breast cancer and other second cancers in the radiation field) [11–13]. In current regimens for treating children and young adults with Hodgkin lymphoma, radiation therapy is limited to involved disease sites or to locations of persistent disease identified by functional imaging assessment or is not used at all [14]. Limiting or avoiding toxic exposures has the potential to prevent marked cardiac toxicity in long-term survivors. The ongoing risk of reducing the intensity of any de novo therapy to prevent late-occurring toxicities might result in less effective disease control by potentially compromising the efficacy of therapy [15]. Consideration of the optimal balance of risk and benefit is relevant to the use of anthracyclines as well as the use of radiation.

The most commonly used anthracyclines, doxorubicin and daunorubicin, have been important agents in treating childhood cancers, and many survivors of pediatric hematologic malignancies and solid tumors received anthracyclines at a young age. Risk factors for late-onset anthracycline cardiomyopathy include higher cumulative anthracycline dose, concomitant cardiac radiation, female sex, younger age at exposure, and a history of acute cardiac toxicity [1]. Survivors exposed to equivalent cumulative doses of doxorubicin greater than 250 to 300 mg/m^2 appear to be at greater risk for cardiomyopathy [16–18]. Nonetheless, anthracyclines remain necessary in treating many childhood cancers, leading to the critical question, can anthracycline-related cardiotoxicity be prevented?

3. Limiting Anthracycline Exposure

The cumulative dose of anthracycline in treating childhood malignancy has been reduced as clinical trials have become more refined; however, establishing the optimal efficacy-toxicity ratio is difficult in the context of clinical trials. The evolution of therapy for newly diagnosed childhood ALL in serial trials by the Dana-Farber Cancer Institute (DFCI) ALL Consortium is an example of the effort to limit anthracycline exposure. Since the 1970s, event-free survival (EFS) for patients with newly diagnosed ALL has improved substantially and now exceeds 80% (Fig. 1) [19]. Also in the 1970s, the maximum planned cumulative dose of anthracycline reached 450 to 550 mg/m^2 for all patients, whereas in the 1980s and 90s, maximum doses were reduced to 300 to 360 mg/m^2 [20–24]. In the effort to limit cardiotoxicity, the maximum cumulative anthracycline dose was further decreased on the basis of the risk of leukemia relapse. Currently, children with “standard risk” ALL receive a total anthracycline dose of 60 mg/m^2, whereas those with “high-risk” ALL receive 300 mg/m^2 and always accompanied by dexrazoxane as a cardioprotectant (see below) [19]. However, even these anthracycline doses remain problematic. Patients in whom leukemia recurs often receive additional doses of anthracycline, thus incurring further cumulative lifetime exposure. In addition, even low-dose exposure to anthracyclines may be associated with cardiotoxicity in some patients [25]. Consideration of further reductions in the cumulative dose of anthracyclines must be balanced with concern for impacting leukemia-treatment efficacy.

Lowering the cumulative anthracycline dose has been important in the attempt to minimize long-term cardiotoxicity in ALL and other childhood cancers, but other approaches to reducing anthracycline-related cardiotoxicity have been attempted. One approach was to use lower individual doses of anthracyclines. Generally, doses for

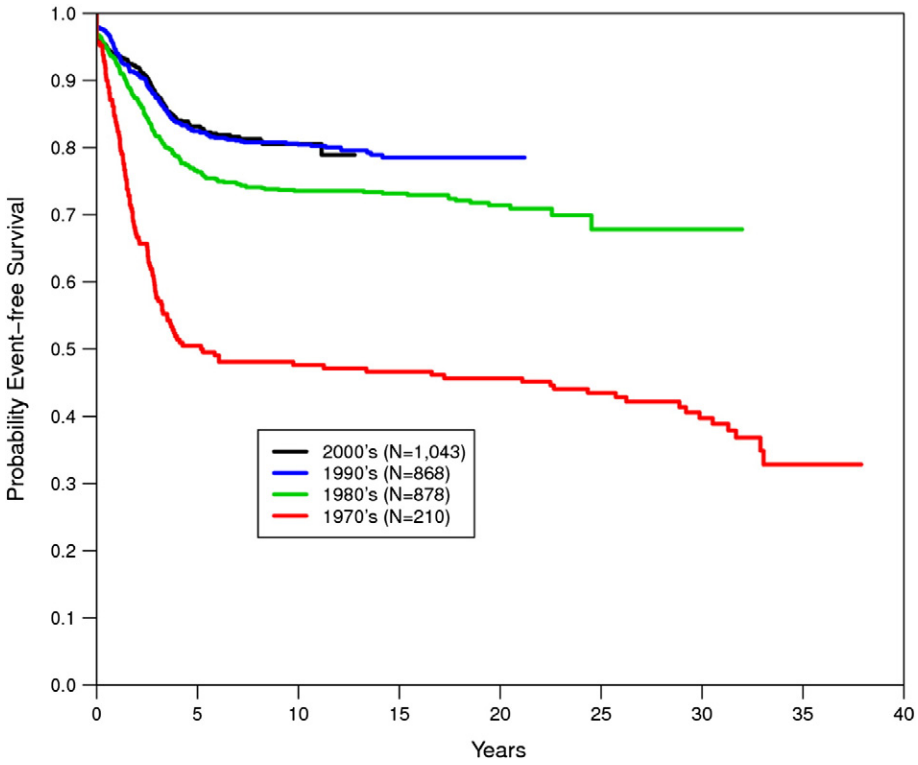

Fig. 1. Event-free survival in children and adolescents with acute lymphoblastic leukemia treated on consecutive Dana-Farber Cancer Institute ALL Consortium protocols, by decade. N = number of patients in each trial era.