Sub-acute Versus Late-onset Presentation of Oncotherapy Related Cardiotoxicity: Predictors of Cardiac Function Recovery and Long-Term Outcome

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ABSTRACT: Background: Cardiac damage caused by oncological therapy may manifest early or many years after the exposure. Objectives: To determine the differences between sub-acute and late-onset cardiotoxicity in left ventricular ejection fraction (LVEF) recovery as well as long-term prognosis. Methods: We studied 91 patients diagnosed with impaired systolic function and previous exposure to oncological therapy. The study population was divided according to sub-acute (from 2 weeks to ≤ 1 year) and late-onset (> 1 year) presentation cardiotoxicity. Recovery of LVEF of at least 50% was defined as the primary end point and total mortality was the secondary end point. Results: Fifty-three (58%) patients were classified as sub-acute, while 38 (42%) were defined as late-onset cardiotoxicity. Baseline clinical characteristics were similar in the two groups. The mean LVEF at presentation was significantly lower among patients in the late-onset vs. sub-acute group (28% vs. 37%, respectively, P < 0.001). Independent predictors of LVEF recovery were trastuzumab therapy and a higher baseline LVEF. Although long-term mortality rates were similar in the groups with sub-acute and late-onset cardiotoxicity, improvement of LVEF was independently associated with reduced mortality. Conclusions: Our findings suggest that early detection and treatment of oncological cardiotoxicity play an important role in LVEF recovery and long-term prognosis.

KEY WORDS: cardiotoxicity, left ventricular ejection fraction (LVEF), trastuzumab

T he past four decades have witnessed a tremendous development in chemotherapeutic and other oncological therapies targeting a diverse group of malignancies. These agents have significantly improved survival rates in cancer patients, but at a cost of considerable adverse effects, including cardiotoxicity [1-3]. The incidence of cardiotoxicity varies considerably by the chemotherapeutic agents used [4,5].

The incidence of anthracycline cardiotoxicity varies greatly by the dose and the definition used, with estimated rates varying from 5% to 50%. This toxicity has been recognized to be cumulative and dose dependent [6,7]. Monoclonal antibodies such as trastuzumab have a considerable incidence of cardiotoxicity, although with less dose dependency [8,9]. Distinct types of presentation have been recognized according to the time of onset. Acute toxicity occurs after a single dose, or after a course of anthracyclines, with the onset of manifestations within 2 weeks after treatment. Sub-acute presentation is defined by diagnosis from 2 weeks to 1 year after the end of treatment. The late-onset/chronic form presents years or even decades later. The sub-acute and late-onset forms are the most commonly encountered and clinically relevant forms of cardiotoxicity in the outpatient situation.

Limited data exist regarding the outcomes of patients who develop chemotherapy-induced left ventricular dysfunction. Moreover, the differences in the clinical presentation and the outcome of patients with sub-acute vs. late-onset cardiotoxicity are poorly defined. Accordingly, the aim of the present study was to characterize a cohort of consecutive cardio-oncological patients with impaired systolic function and to define the predictors of LVEF recovery and long-term prognosis based on the mode of onset of cardiotoxicity.

PATIENTS AND METHODS

STUDY POPULATION
We conducted an observational study in the Heart Failure Institute at the Leviev Heart Center, Sheba Medical Center. The study was approved by the institutional review board. Sheba Medical Center is a tertiary care hospital, which includes Israel’s leading cancer and hematology centers and treats approximately 4500 new cancer patients each year. Consecutive patients, older than 18 years of age who were referred to our clinic during years 1998–2016 with left ventricular systolic dysfunction (LVEF ≤ 45%) and a history of ongoing or past oncology therapy, were included in this study. Documentation of normal cardiac function by any imaging modality prior to initiation of cancer therapy was required. We did not include patients with acute anthracycline cardiotoxicity (n=3) since these patients were treated as an emergency situation. Patients with an alternative explanation for reduced LVEF (such