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Research Article

Cardiac Toxicity Secondary to Anthracycline Treatment in Diffuse Large B-Cell Lymphoma

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Abstract

Cardiac toxicity associated with oncology drugs, is a known risk, although multiple studies has been performed to detect this problem in an early stage, no definitive results has been achieved. We conducted a clinical study in a large number of patients with a longer follow-up, to evaluate if surveillance tests, such as 2D echocardiogram (ECHO) and radionuclide ventriculography (RNV) can detected early cardiac damage in patients who received anthracycline-based chemotherapy. We conducted a cohort clinical study in 3073 patients with pathological confirmed of diffuse large B-cell lymphoma who had a complete response with a longer follow-up: 18. (range 6.8 to 32.3) years: the mentioned test was performed periodically: every 6 months the first 5 years, an annually from 5 years until relapse, death from any cause or last of follow-up, or the presence of congestive heart failure.

Asymptomatic abnormalities in surveillance studies, without clinical and radiological evidence of cardiac damage were observed in 58 cases (1.21%); none of these patients developed clinical evidence of cardiac damage; and eight patients developed clinical and radiology evident changes of heart failure, neither of they showed previous abnormalities in surveillance studies. Multivariate analysis did no show any statistically difference, even in patients whose received > 450 mg/m2.

The use of surveillance studies did not predict early cardiac damage and will not be used as surveillance tests. Now resources will be developed, because the risk of cardiac damage secondary to anthracyclines remains constant.

Keywords: Diffuse large B-cell lymphoma; Anthracyclines; Doxorubicin; Cardiac toxicity; Congestive heart failure

Introduction

Anthracyclines remain and important a potent cytotoxic chemotherapy of choice in the management of hematological malignancies and breast cancer> Although the benefits of anthracyclines are very compelling, the rare but most important adverse event that is cardiotoxicity, tends to be a major limitation of their regular use.

Multiple studies have been performed to define the best approach to detect early and possibly reversible effects of cardiac damage [1-8]. The most common surveillance tests to detect abnormalities in left ejection ventricular fraction (LVVF) are two-dimensional Echocardiogram (ECHO) and radionuclide ventriculography (RNV); other tests as magnetic resonance imagen and positron-emission tomography have been proposed, but these are very expensive. Recently, the role of these has been questioned and it is proposed that this test be eliminated as methods to detect cardiac damage secondary to anthracyclines. However, until now not definitive conclusions about the utility of these surveillance test have been achieved. In the other hand, most of the studies are retrospective analysis that compared patients and the moment of the presence of cardiac event, with a population normal, or that no was treated with anthracyclines [2]. Prospective studies, planned to detect early cardiac damage has not been performed. Thus, we performed open label prospective study;

The primary objectives were to evaluate the occurrence and evolution of subclinical lesions at myocardial levels, as measured using ECHO and RNV, and to evaluate the variables that can influence the possibility of cardiac damage; such age, anthracyclines doses, smoking, obesity and the use of radiation therapy.

Patients and Methods

Between January 1986 to December 2016, 4916 patients were identified; they had a pathological confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL) and were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP (CHOP + rituximab, in standard doses (CHOP or R CHOP 21) or with intense doses: CHOP or RCHOP 14. Some patients with primary mediastinal lymphoma or primary breast lymphoma, received radiotherapy to the thorax. They were monitored to cardiac damage using ECHO and RNV. Both tests were performed before the patient began chemotherapy, and at every 6 months from the first 5 years, subsequently were annually until relapse, death, evidence of cardiac damage.

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Criteria to define cardia damage:

Asymptomatic: The patient did not have evidence of Congestive Hearts Failure (CHF): fatigue, dyspnea, edema, tachycardia, and ECHO and RNV showed a decrease value < 50%, or well and decrease to 15% over normal values (> 50%).

Symptomatic: the patient shows dates of CHF with abnormalities in surveillance tests.

Ethical considerations: The work was performed according to the Ethical recommendations, include in 1946 Declaration of Helsinki, and was approved by the Ethical and Scientific Committee of our Institution (HO: 1988-03)

Results

The baseline of patient's characteristics from the 4916 patients who were enrolled in this analysis; 41.6 % were > 60 years older; 80 % had advance stage; 58 % were smokers and 71 patients received > 450 mg/m2, patients included received anthracyclines in salvage regimen at relapse or progression as well.

Asymptomatic cardiac event was observed in 58 cases (1.26 %), between 4.8 and 13.3 (median 6.9) years. None of these patients developed clinical CHF during period, ending in December 2019. Eight patients (0.16 %) developed symptomatic cardiac dysfunction will full clinical and radiological evidence of CGF, but none of these patients had an abnormal surveillance test before the emergence of CHF. One patient died secondary to CHF, but, the cardiac event presented
when the patient was 89 years old, and 17 years after the administration of anthracyclines.

The association between cumulative doses of anthracyclines and the present of cardiac event. No statistical differences were observed. Also, the use of radiation therapy to the thorax did not influence the possibility of a cardiac event. Smoking and obesity did not influence the appearance of cardiac event.

Discussion

Cardiac toxicity has been a central consideration in clinical trials that evaluate the use of anthracyclines as the principal drug. Although multiple studies have carefully documented the incidence of cardiac damage with cumulative doses of, in long-term assessment, until now, no definitive rules have been proposed to evaluate the risk of cardiac damage [1,2].

Some studies have been employed pegylated anthracycline, that could avoid the cardia risk, however, it is not definitive results [9]. Recently, has been proposed guidelines, to assessment in cancer patients, candidates to received anthracyclines, to define he clinical risks, the type of surveillance studies, but, its propositions have not adopted has not been accepted and adopted in cancer centers not has [10].

ECHO and RNV studies were the first tests that were employed to detect early cardiac toxicity; however, the efficacy of these tests was considered that have a minimal role in the detection of cardiac damage.

Others studies has been performed, including coronary angiography, coronary artery calcium score, magnetic resonance imaging, but no definitive study was found. ET al, performed a deep revision of these studies and did not find any specific tests; probably because these studies were performed in a heterogenous population, different drugs, schedules and doses, and primary end points no defined.

Oliva et al, in a review analyzed the factors associated to developed cardiac event [1]. We show the results of study with a homogenous population, the same schedules and doses, with a very longer follow-up, and surveillance studies were done periodically, to search if these studies could detect early cardiac damage.

Our results showed a very low number of cardiac events, even in patients that received higher doses of doxorubicin, and even in patients that received radiation therapy. We did not have any specific cause to explain these results. Bias could be considered, it is a retrospective analysis, performed in a single cancer center, but our hospital is tertiary center, with a homogenous population, treated with the same schedule of doxorubicin. Thus, we no can compare our results with other studies, and the unique difference were that our population is a Mestizo race, and more studies were performed in white and Asiatic populations [7].

Conclusion: the surveillance studies analyzed in this study; did not o detect cardiac damage secondary to anthracyclines are not adequate and we considered that can be eliminated. But it is evident that anthracyclines produce cardiac damage, and it is necessary to developed another resource.

In the other hand been introduced the use of checkpoints inhibitors in the treatment of hematological malignancies, and these drugs has been associating with cardiac toxic events [11] Recently, biomarkers has been suggested that can be useful, however, it is necessary more time to observed if any benefit, in the hand, these studies could be not available in some cancer centers, and are expensed [12].

Authorship: Both authors working in the concept and design data acquisition, analysis and interpretation of data, drafting the article, revised critically the intellectual content, and approved the final revision of the article.

Conflict of Interest: Both authors disclose any conflict of interest.

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