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Research article

Role of echocardiogram in children with cancer

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ABSTRACT

Background. Currently, anthracyclines have been used in >50% of cancer treatment protocols in children. The clinical usefulness of these agents is limited by the onset of cardiomyopathy whose presence depends on the total dose of drug and usually is irreversible. Echocardiography is used to study detection of anthracycline cardiotoxicity. The aim of this study was to describe the evolution of cardiac function reported by echocardiography for treatment of children with cancer whose medications contain anthracyclines.
Methods. We included pediatric patients diagnosed with osteosarcoma and acute myeloid leukemia treated between January 2006 and May 2011 at the Hospital Infantil de México Federico Gómez. In the clinical files, values were documented for ejection fraction (EF) and fractional shortening (FS) reported before each cycle, using descriptive statistics for reporting results.
Results. The EF experiences virtually no changes until the 6th cycle of treatment to a cumulative dose of 332.5 mg/m^2/sc, demonstrating afterwards an accelerated decline. According to the FS, the most significant change occurs after the seventh cycle at a cumulative dose of 450 mg/m^2/sc.
Conclusions. Recognizing the damage that occurs during the early stages is a critical step in preventing complications. The challenge is to implement new tools that will allow us to achieve the objective of preventing or diagnosing subclinical disease.

Key words: anthracyclines, cardiac function test, cardiotoxicity, echocardiogram.

INTRODUCTION

Advances in pharmaceutical treatments for cancer have recently led to a significant improvement in the prognosis of cancer patients. However, a high cost in terms of secondary cardiac effects has been paid, associated with treatment.[1]

Anthracyclines, considered today as the most important antitumor drugs, have this precise limitation. Their clinical utility is restricted due to the appearance of cardiomyopathies.[2,3]

These compounds intercalate with DNA, inhibiting the synthesis of both DNA and RNA. Breakages occur in the filaments. Thus, anthracyclines are mutagenic and carcinogenic. It is believed that the breakdown of DNA is mediated by the binding of the pharmaceutical to DNA and to topoisomerase II, an action that prevents the resealing of the DNA breaks created by the enzyme. Under its quinone groups, the anthracyclines also generate free radicals in solution and in the tissues, both normal as well as malignant. Anthracyclines react with cytochrome P450 reductase in the presence of adenine dinucleotide phosphate and reduced nicotinamide (NADPH) to form radical intermediate products of semiquinone which, in turn, react with oxygen and produce superoxide anion radicals. These generate hydrogen peroxide and hydroxyl radicals (-OH), which attack DNA and oxidize its bases.[3-5]

The cytotoxic effect on cardiomyocytes is irreversible and dependent on a cumulative dose; therefore, the heart is one of the most vulnerable organs to suffer damage from its low level of antioxidant enzymes.[2,3]

Anthracycline cardiotoxicity corresponds to all those structural changes that occur in cardiomyocytes secondary to the use of these pharmaceuticals. A clinical definition exists that evaluates myocardial function following use of anthracyclines. It is defined as a decrease in the left ventricular ejection fraction (LVEF) of >20% in patients

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with normal LVEF or as a decrease in LVEF of >10%, in baseline values <50% or clinical manifestations with signs and symptoms of congestive heart failure.[6,7]

Approximately one-fourth of the patients have myocardial failure when the dose of anthracyclines is >500 mg/m^2; 50% have cardiac events with cumulative doses >600 mg/m^2 and virtually all patients with doses >800 mg/m^2 demonstrate cardiotoxicity.[8] The frequency of subclinical myocardial alterations reported after treatment with anthracyclines reaches 57% and for symptomatic cardiac alterations up to 16%.[9]

Currently, the recommended approach for detecting anthracycline-induced cardiac damage is mainly based on a systematic assessment of cardiac function at the beginning of the study and during chemotherapy treatment by measuring the LVEF using two-dimensional (2D) transthoracic echocardiography (TTE) and radionuclide angiography.[10-12] The main limitation of this approach is its low sensitivity for detection of cardiotoxicity at an early stage.[1]

SUBJECTS AND METHODS

The study was conducted at the Department of Oncology of the Hospital Infantil de México Federico Gómez (HIMFG). The objective of the study was to describe the evolution of cardiac function indices reported by sonography in children with cancer undergoing treatment with anthracyclines.

The study included patients <18 years of age undergoing treatment for osteosarcoma (OS) or acute myeloid leukemia (AML). We excluded patients with acquired or preexisting congenital heart disease and those who received radiation therapy.

We obtained the records of patients from the clinical archives of the HIMFG. Files were searched of those patients who were diagnosed with OS or AML and who were discharged from the Oncology Department of HIMFG from January 2006 to May 2011. A stratified simple random sampling was conducted to form two groups of 25 subjects with the two diagnoses included in the study. We collected information according to sampling for later analysis. Descriptive statistics were used for the demographic variables.

For description of the cumulative dose of anthracycline, treatment was divided according to cycles of administration and obtaining the average of the administered dose in each cycle. Likewise, we calculated the average of the LVEF.

RESULTS

We included 30 patients who received treatment with anthracyclines: 16 with a diagnosis of OS and 14 diagnosed with AML. Of these, 90% were undergoing treatment and 3% died (one due to cardiotoxicity secondary to anthracycline). The average age was 143 months (range: 15-353 months) (Table 1).

Description of the population studied

From the OS group, 12 patients presented with metastases at the time of the study and in four patients this could not be evidenced. Of the AML group, the predominant diagnosis was type M2 (50% of the participants) of which 57% were found in remission induction.

The cumulative anthracycline dose found in the participating patients was a mean of 192 mg/m^2 SC (range: 60-450 mg/m^2 SC) (Table 2). Patients were grouped according to number of cycles of chemotherapy received, secondary to the similarities found in the treatment schedules. For each cycle we calculated an average cumulative dose of anthracyclines in patients who were in that stage of treatment, and we separately obtained the mean ejection fraction (EF) and fractional shortening (FS) (Table 3).

Figure 1 shows the association between the progression of the cumulative dose of anthracyclines with the EF and FS an average determined for each cycle. It was observed that the variation of these two cardiac function indices did not change significantly with chemotherapy cycles subsequent from the first through the sixth. However, after the sixth cycle, with a mean cumulative dose of

Table 1. Distribution according to age of patients undergoing treatment with anthracyclines

Age interval (months)	*Frequency*	*Percentage (%)*
0-60	3	10.0
61-120	7	23.3
121-180	14	46.7
181-240	5	16.7
241-300	0	0.0
>300	1	3.3
Total	30	100.0

332.5 mg/m^2 SC, both parameters decreased significantly and rapidly.

DISCUSSION

The results of this study offer an overview of the changes in the EF and FS values with increasing doses of anthracyclines using echocardiogram. It has been described that the highest frequency of cardiotoxicity is found with a cumulative dose >450 mg/m^2 sc. However, it is shown that even at lower doses, myocardial damage already exists.

It was observed that 10% of the study population died by the time of the study. In one of these patients (3.3%) the documented diagnosis was heart failure secondary to the use of anthracyclines. Although it has been reported that with the use of anthracyclines mortality due to cardiomyopathy was 7.5% with a cardiovascular event rate of up to 50%, these indices were obtained in patients with higher cumulative doses of 550 mg/m^2 sc. The highest value observed in this study was 450 mg/m^2 sc.

The cumulative dose in this group was 192.5 mg/m^2 sc (range: 60-450 mg/m^2 sc, already considered a safe limit for the presence of cardiotoxicity). In the population studied, the EF virtually did not change until the sixth treatment cycle, equivalent to an average cumulative dose of 332.5 mg/m^2 sc. However, it began to decline at an accelerated pace for the next cycle, with a decrease of 8% from one cycle to the next. With respect FS, the most significant change occurred after the seventh treatment cycle where we observed a decrease of 9% to a cumulative dose of 450 mg/m^2 sc.

According to the clinical definition of cardiotoxicity, which is defined as a decrease of LVEF by >20% in patients with normal LVEF or a decrease of LVEF by >10% in baseline values of <50%, only one patient was found who fulfilled this description. However, the clinical manifestations were not evaluated because they were not part of the objectives planned in this research project.

Heart failure secondary to cardiotoxicity caused by the use of anthracyclines has been extensively documented in the literature. It is related to the dose and the remaining risk throughout life, despite no longer undergoing treatment with anthracyclines. It has been observed that mortality from this disease exceeds 50% once the disease has been established.

Results of myocardial biopsies show strong evidence that the damage begins at the time of the initial exposure, although the cardiac reserve prevents clinical recognition until sufficient damage has occurred for cardiac compensation.

At the HIMFG we observed that echocardiograms conducted in the at-risk population remain virtually unchanged for an average cumulative dose of 300 mg/m^2 sc. However, progressive and irreversible decrease of their values begins later until reaching actual heart failure.

Although in this institution the dose of anthracyclines used is lower than reported in the literature as being at

Table 2. Distribution of patients according to cumulative dose of anthracyclines

Cumulative dose (mg/m^2 sc)	*Frequency*	*Percentage (%)*
0-50	0	0.0
51-100	7	23.3
101-150	10	33.3
151-200	0	0.0
201-250	6	20.0
251-300	3	10.0
>300	4	13.3
Total	30	100.0

Table 3. Average cumulative dose of anthracyclines, ejection fraction (EF) and fractional shortening (FS) according to treatment cycle

Cycle #	*Cumulative dose of anthracyclines (mg/m^2 sc)*	*EF*	*FS*
1	0.0	70.03	37.5
2	72.4	70.90	39.3
3	137.3	67.90	36.3
4	192.6	65.40	35.8
5	251.0	69.00	37.3
6	332.5	68.50	36.0
7	382.5	60.50	33.0
8	450.0	48.00	24.0

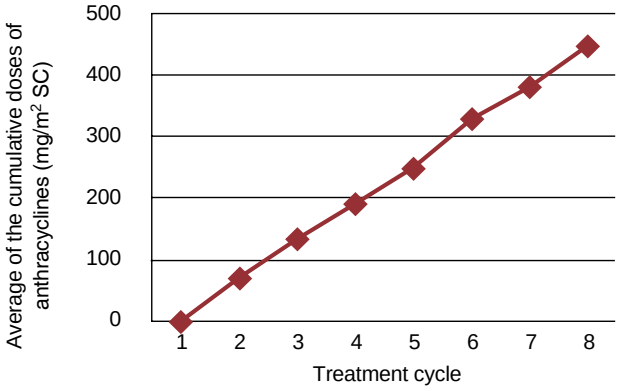

Figure 1. Average cumulative dose of anthracyclines according to treatment cycle.

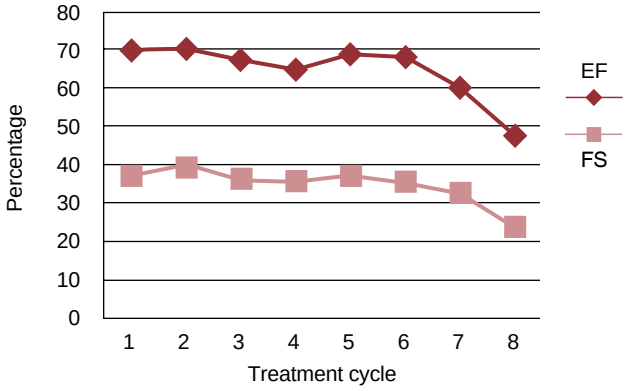

Figure 2. Average of ejection fraction (EF) and fractional shortening (FS) according to treatment cycle.

higher risk, microscopic changes have been demonstrated; hence, myocardial function is established well before actual clinical deterioration. The challenge is to recognize the damage that occurs early because it is a critical step in preventing the onset of heart failure.

The prognosis of children with cancer has improved substantially over time. However, the increase in survival rates has revealed an increase in the rates of adverse secondary events. The challenge is to identify new tools to aid in the prevention of additional conditions due to cancer and secondary to treatments such as cardiotoxicity caused by the use of anthracyclines and to improve the prognosis and quality of life of these children.

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