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Left Ventricular Systolic Function Assessed by Echocardiography in Children and Adolescents with Osteosarcoma Treated with Doxorubicin Alone or in Combination with Dexrazoxane

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Objective: To evaluate left ventricular (LV) systolic function by means of echocardiography in patients with osteosarcoma treated with doxorubicin alone or in combination with dexrazoxane.

Methods: The study analyzed 55 patients with osteosarcoma, with or without metastasis, undergoing a six-cycle chemotherapy regimen of doxorubicin, who were divided into two groups according to dexrazoxane use. Group I: Thirty-seven patients who did not receive dexrazoxane (28 males, average age 15.4 years). Group II: Eighteen patients who did receive dexrazoxane (15 males, average age 15.1 years). Four echocardiographic evaluations were performed: 1) before the beginning of the chemotherapy (initial evaluation); 2) up to two weeks after the third cycle; 3) up to two weeks after the fifth cycle; and 4) up to four weeks after the sixth cycle of chemotherapy (final evaluation). The left ventricular systolic function was assessed by the fractional percentage of systolic shortening (FS%) on echocardiography. Alterations in the contractile function or cardiac toxicity were defined as FS% values equal to or lower than 29%, and/or by a drop in FS% by an absolute value equal to or greater than 10 units of the baseline value of each patient.

Results: No significant difference as to age, gender, and race was observed between the groups. The cumulative dose of doxorubicin was significantly higher in group II throughout all phases of the treatment: 174 x 203 mg/m^2; 292 x 338 mg/m^2 and 345 x 405 mg/^{2} (p < 0.0001). According to previously established criteria, the incidence of LV systolic dysfunction was not significantly different (p=0.248) between patients in group I (18.92%) and patients in group II (11.1%). The variance analysis with repeated measurements did not show significant differences in the means of fractional percentage of systolic percentage (FS%) throughout the study (p=0.967). However, a significant difference (p=0.029) was observed between the FS% means in groups I and II at evaluations 2 (35.67 x 37.21%), 3 (34.95 x 38.47%) and 4 (35.26 x 38.22%).

Conclusion: Data in this study show that in patients with osteosarcoma treated with doxorubicin alone or combined with dexrazoxane, the LV systolic function, as assessed by the fractional percentage of systolic shortening mean, showed a better performance in the group that received dexrazoxane. On the other hand, the occurrence of systolic dysfunction was similar in both groups.

Key words: Left ventricular function, echocardiography, osteosarcoma, doxorubicin, dexrazoxane.

Currently, children with neoplasms have increasingly higher chances of being cured of their diseases. The introduction of anthracyclines in chemotherapy regimens for the treatment of malignant neoplasms is one of the greatest advances in modern oncology. According to data from North-American investigators, more than 50% of children treated with this class of cytostatic agent were cured between 1974 and 1990[1]. Its broad spectrum of antitumoral activity especially encompasses the treatment of hematological neoplasms such as lymphomas and leukemia, and solid tumors including breast, ovarian, and thyroid cancer, soft tissue sarcoma, and osteosarcoma[2].

The use of new antiemetic drugs (serotonin receptor inhibitors) and granulocyte colony-stimulating factors reduced the clinical significance of adverse effects such as nausea, vomiting and neutropenia. This allowed increases in the doses of anthracyclines[3]. On the other hand, the cardiotoxicity induced by this drug has not yet been entirely overcome, and it remains a major impediment to administering higher doses that could enhance its therapeutic potential. Therefore, this is an issue that remains unsolved, despite the fact that the first reports on cardiac toxicity were published approximately three decades ago[4].

Billingham et al[5] were the first to systematically describe the histological and ultrastructural alterations in anthracycline-induced cardiac lesions. These authors described two distinct types of lesion in the myocyte: (1) myofibrillar loss, and (2)

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vacuolar degeneration. At a more advanced stage, both types of lesion progressed to mitochondrial degeneration followed by the formation of myelin figures and nuclear disintegration, culminating with myocyte death and resulting myocardial fibrosis. It has been proven that several mechanisms are involved in the pathogenesis of the myocardial injury induced by anthracyclines, which are independent of their antitumoral activity. However, most studies associate cardiotoxic effects to the formation of reactive oxygen types (free radicals) such as the superoxide anion ($O2^-$) and the hydroxyl radical (OH^-). These are responsible for the lipid peroxidation of several cellular sites including cell membranes, nuclear membranes, and the membranes of several cytoplasmatic organelles, mainly mitochondria and the cytoplasmatic reticulum, leading to a chain of autocatalytic reactions responsible for the destruction of the myocyte[6-9].

The anthracycline-induced injury to the myocardium depends on an ample individual variability and on a set of risk factors that contribute to increase the injury, such as the total cumulative dose of doxorubicin, administration form (rapid or slow infusion), combination with other cytostatic agents, previous or concomitant irradiation of the mediastinum, and patients under 15 years or over 65 years of age[10-14]. Of these, the cumulative dose of anthracycline is considered the main risk factor involved in the development of anthracycline-induced myocardic toxicity[10,12,15].

Cardiac toxicity induced by doxorubicin or similar drugs may manifest itself during any stage of the chemotherapy, or even months or years after the end of the treatment. Four different forms of cardiac toxicity are described. Acute toxicity takes place immediately or a few days after the infusion of doxorubicin and is characterized by nonspecific electrocardiographic findings, typically transient changes in T wave and ST segment, conduction disorders, and sinus tachycardia[16,17]. Subacute toxicity usually occurs a few days or weeks after the last dose of the drug, and its main manifestation is toxic pericarditis and/or myocarditis (myopericarditis syndrome), which is usually reduced upon discontinuation of anthracyclin[3,18]. Chronic toxicity may have an early onset during the first year following the end of the chemotherapy, or a late onset, when it occurs after this period. Both types of toxicity manifest themselves under the form of a diffuse myocardiopathy, with clinical symptoms similar to those of other dilated myocardiopathies[3,13,19].

Several strategies have been employed to avoid or minimize the cardiac injury caused by doxorubicin: administration of cumulative doses at levels considered more secure, slow infusion of the drug (6 to 72 hours), periodical monitoring of the cardiac function by supplementary tests (echocardiogram, radionuclide angiography, endomyocardial biopsy etc) and the use of drugs that may act as protective agents of the myocardium (dexrazoxane, probucol etc)[11,12,20,25,36].

Dexrazoxane is widely recognized as a protective agent against anthracycline-induced cardiac toxicity. It is currently the only drug authorized for this indication in the United States. Since it is a hydrosoluble nonpolar substance, dexrazoxane easily reaches the cytoplasm of the cardiac cell where it is hydrolyzed in the shape of open rings, acquiring a strong iron-chelating property by which it prevents the production of the iron-doxorubicin compound involved in the formation of the free radicals that cause cardiac injury[19]. Several studies have shown the efficacy of dexrazoxane in protecting the myocardium against the toxicity caused by doxorubicin in adults and children[20-22]. However, there are few studies on the use of dexrazoxane in children with osteosarcoma in medical literature, none in Brazil. Thus, the objective of this study was to analyze the behavior of the left ventricular systolic function by means of echocardiography in patients with osteosarcoma treated with doxorubicin alone or in combination with dexrazoxane.

Methods

Patients - Fifty-five patients were followed up at the *Instituto de Oncologia Pediátrica* (Institute of Pediatric Oncology) and at the *Setor de Cardiologia Pediátrica da Universidade Federal de São Paulo – Escola Paulista de Medicina - UNIFESP – EPM* (Department of Pediatric Oncology of the Federal University of São Paulo), from May 1996 to February 2001. This study was approved by the Institutional Research Ethics Committee of UNIFESP – EPM. An informed consent form was signed by the patients' families or, whenever possible, by the patient himself/herself, after the necessary explanations were given.

Inclusion criteria were the same as those for the Protocol IV (1996) of the *Grupo Brasileiro de Tratamento de Osteossarcoma – GBTO* (Brazilian Group of Osteosarcoma Treatment – GBTO), as follows: (1) patients recently diagnosed with highly malignant osteosarcoma not induced by irradiation, confirmed by biopsy and not previously treated; (2) patients with osteosarcoma at any primary site with or without metastases; (3) patients under the age of 21; (4) patients with no evidence of cardiovascular disease, current or previous, based on clinical history, physical examination, electrocardiogram, chest X-ray and echocardiogram; (5) patients with normal kidney and liver functions.

This is a prospective non-randomized study with two sequential groups formed according to dexrazoxane use. Group I consisted of patients who did not receive dexrazoxane as the drug was not yet available in our context, and Group II was subsequently formed by patients who received dexrazoxane when this agent became available at our institution. Group I consisted of 37 patients, 28 males and 9 females, average age 15.4 years. Group II consisted of 18 patients, 15 males and 3 females, average age 15.1 years.

Patients were treated according to Protocol IV (1996) of the *Grupo Brasileiro de Tratamento de Osteossarcoma – GBTO* (Brazilian Group of Osteosarcoma Treatment – GBTO). The chemotherapy regimen included the following drugs: cisplatin, carboplatin, doxorubicin and ifosfamide. In order to reduce kidney toxicity induced by ifosfamide, the renoprotective agent Mesna was used. Doxorubicin was intravenously administered in six cycles, three in the preoperative phase and three in the postoperative phase, in doses of 60 mg/m^2 for group I and 70 mg/m^2 for group II (in rapid infusions of 30 minutes each). Dexrazoxane was used at a rate of 20:1 relative to the dose of doxorubicin, milligram to milligram, and administered intravenously in rapid 15-minute infusions begun approximately 30 minutes before the doxorubicin infusion.

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Echocardiogram - Was performed by one single operator, blinded to dose of anthracycline given to the patients and to which patients were receiving dexrazoxane. The equipment used were Ultramak 9 (ATL – Advanced Technology Laboratories, Bothel, WA-USA) and Philips SD 800 (Irvine, CA, USA), with 2.50 and 5.0 MHz transducers, capable of obtaining uni- and bidimensional images, as well as an analysis of the flow rate by Doppler spectral techniques and color flow mapping. Four echocardiographic evaluations were performed: 1) up to two weeks before the beginning of the chemotherapy (initial evaluation); 2) up to two weeks after the third cycle of doxorubicin; 3) up to two weeks after the fifth cycle of doxorubicin; and 4) up to four weeks after the administration of the last dose of doxorubicin (final evaluation). Patients were positioned in the left lateral decumbent position. Echocardiogram images were obtained in the conventional planes and recorded on video-tape (VHS) for posterior analysis. A complete echocardiographic examination was performed. Measurements of the diastolic diameter (Dd) and systolic diameter (Sd) of the left ventricule (LV) by M or bidimensional mode were utilized for the analysis. Dd was obtained at the point of maximum diastolic posterior deflection of the posterior LV wall, and the Sd at the point of maximum anterior deflection of the same wall, according to American Society of Echocardiography recommendations[15]. The parameter used to evaluate the left ventricular systolic function was the fractional percentage of systolic shortening (FS%) that corresponds to the percentage of reduction of the left ventricular diastolic diameter after its contraction and that can be calculated as (DdLV-SdLV)/(DdLV) x 100 (%). Values equal to or higher than 30% are considered normal. Left ventricular systolic dysfunction was defined according to the report of the Committee of Cardiology of the Group of Studies of Children with Cancer in the United States as FS% equal to or less than 29%, and/or a drop in FS% by an absolute value equal to or greater than 10 units of the value recorded before the beginning of chemotherapy of each patient[22,24].

Laboratory exams - Heart rate and systolic and diastolic blood pressure for each patient were recorded during the echocardiogram, as well as the most recent blood hemoglobin and creatinine values.

Statistical analysis - The descriptive analysis of age was expressed as mean and standard deviation, whereas the cumulative dose and the shortening percentage were expressed as mean and standard error. Variance analysis with repeated measurements was used to evaluate the cumulative dose, clinical characteristics, diameters of the left ventricular cavity, and the shortening percentage. Gender, race and the incidence of ventricular dysfunction were evaluated with Fisher's exact test. Age, weight, height and body surface area were calculated with the t Student test. For all tests performed, a p<0.05 descriptive level was considered as significant.

Results

In Group I, 140 echocardiographic exams were performed and eight were not performed, five because the patients missed the exam, and three due to deaths not related to cardiac toxicity. In Group II, 59 echocardiographic exams were performed; thirteen were not performed because the patients missed the exam, and three due to deaths not related to cardiac toxicity.

No significant difference was observed between the groups as to gender (Fisher's exact test: p = 0.731), race (Fisher's exact test: p = 0.334), age (t Student test: p = 0.86), weight (t Student test: p = 0.719), height (t Student test: p = 0.563), BSA (t Student test: p = 0.563), and presence of metastases at the beginning of the treatment (Fisher's exact text: p = 1.000) as Tables 1, 2, 3 and 4 show. Likewise, there was no statistically significant difference between groups I and II throughout the study as to heart rate (p = 0.554), systolic blood pressure (p = 0.95) and diastolic blood pressure (p = 0.465) as shown on Table 5. Both groups had hemoglobin level means greater than 8.0 g/dl, and serum creatinine levels lower than 1.0 μmol/l during the echocardiographic evaluations, as shown on Table 6.

The cumulative dose mean was approximately 15% greater in Group II, as compared to Group I, in evaluations two, three and four. The statistical analysis shows that Group I presented values significantly greater of cumulative doses of doxorubicin (repeated measurement variance analysis: *p* < 0.0001) in evaluations 2, 3 and 4 as shown in Figure 1 and Table 7.

Table 8 shows the descriptive analysis of means and standard deviations of the left ventricle FS% on echocardiogram during the four evaluations. The left ventricular FS% behavior throughout the follow-up was evaluated as per the repeated measurements variance analysis. The conclusion of this statistical analysis was that there is interaction between group and evaluation (p = 0.356), which indicates that the behavior of both groups was similar throughout the study. Moreover, there is no significant difference (p = 0.967) between the means of shortening fraction percentage during the study in each group. On the other hand, there is a significant difference (p = 0.029) between the means of shortening fraction percentage in both groups in evaluations 2, 3 and 4,

| | Gender | | |
	Male	Female	Total
Group I	28	9	37
Group II	15	3	18
Total	**43**	**12**	**55**

Table 1 - Distribution of patients in groups I and II as to gender.

| | Race | | | |
	White	Black	Other	Total
Group I	25	7	5	37
Group II	14	4	0	18
Total	**39**	**11**	**5**	**55**

Table 2 – Distribution of patients in groups I and II as to race.

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		Age (years)	Weight (kg)	Height (cm)	BSA (m²)
Group I	Mean	15.4	46.96	155.76	1.38
	Standard deviation	4.18	15.92	17.57	0.31
Group II	Mean	15.1	48.64	158.48	1.47
	Standard deviation	4.57	16.4	14.85	0.29
	t Student test	p = 0.86	p = 0.719	p = 0.563	p = 0.563

Table 3 – Means and standard deviation of age, weight, height and body surface area (BSA) in groups I and II at the beginning of the study.

		Group I		Gorup II	
Metastasis		n	%	n	%
Yes		8	21.6	3	16.7
No		29	78.4	15	83.3
Total		37	100	18	100

n- number of individuals.

Table 4 – Incidence of metastasis in groups I and II at the beginning of the study.

as shown in Figure 2.

According to criteria previously defined and taking into account all evaluations, seven patients had left ventricular systolic dysfunction in group I (18.92%), and two patients in group II (11.1%). The statistical analysis showed that there was no statistically significant difference between the two groups, as shown on Table 9. In group I, out of the seven patients who had systolic dysfunction, five progressed towards normal levels before the end of the chemotherapy. In group II, the two patients who had systolic dysfunction progressed towards normal levels even before the end of the chemotherapy.

Discussion

Virtually all patients undergoing chemotherapy, or those who had been previously treated with doxorubicin, may develop cardiac toxicity induced by this chemotherapic agent. For this reason, with the development of each new protocol for the treatment of neoplasms, a few measures are taken to prevent, or at least reduce, this effect.

Concerning the prevention of doxorubicin-induced cardiac toxicity, this study had a few important aspects such as: (1) the total dose of doxorubicin was divided into six cycles, with average intervals of three weeks; (2) in each cycle, the dose of doxorubicin was divided in half and given on two consecutive days, which reduces even more the peak of the drug's serum level without compromising the area under the curve of plasma concentration; (3) cumulative dose limit of doxorubicin between 360 and 420mg/m²; (4) administration of dexrazoxane to one of the groups; and (5) the serial echocardiograhic evaluation in order to identify early cardiac changes and individualize the doxorubicin dose, if necessary.

On the other hand, the administration of doxorubicin in rapid 30-minute infusions is opposed to the trend in many oncology centers that prefer to administer doxorubicin in prolonged infusions (6 to 72 hours), claiming that this approach would produce a smaller cardiac toxicity risk[25-29]. However, despite the soundness of this argument, there are some negative aspects related to prolonged infusions of doxorubicin that keep it from being unanimously accepted. One of them is the significant increase of mucositis[30,31]. Another negative aspect is the possibility of tumor cells becoming resistant[32]. Moreover, it increases the duration of hospital stays, requires an infusion pump and central venous access catheter, making this approach uncomfortable for the patient and increasing the risk of bacteremia. In short, these factors increase the cost of the treatment, which is an important aspect to be considered in our environment.

In the United States, the recommended dosage of dexrazoxane is 10 times that of doxorubicin (10:1), i.e., for each 1 mg/m² of doxorubicin, 10mg/m² of dexrazoxane are used[19]. Also, dexrazoxane is administered from the moment the patient reaches a cumulative dose of doxorubicin equal to or greater than 300mg/m². In this study, dexrazoxane was used only for patients in group II, in an amount 20 times that of the doxorubicin (20:1) from the first dose of the chemotherapic agent, according to the recommendation made in Europe[33].

There was no significant difference between the two groups as to predisposing factors or risk factors to develop doxorubicin-induced myocardial toxicity such as age, gender, and race, indicating that both drugs are comparable in these aspects. Moreover, as none of the patients received radiotherapy of the mediastinum, this form of treatment was not considered a risk factor for cardiac toxicity. The evaluation of laboratory data over the chemotherapy period showed that the levels of hemoglobin and creatinine were not interfering factors regarding the parameters evaluated, since they remained within acceptable levels (above 7.0 g/dl) in the two groups studied.

Among the other drugs used for the treatment of the patients in this study, beside doxorubicin only ifosfamide may cause toxicity[34,35]. Although the cardiac toxicity caused by ifosfamide may be potentialized by the association with doxorubicin[13], both groups received similar doses of this medication and, therefore, it is impossible to infere that the association of these drugs resulted in an increased myocardial toxicity.

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		Evaluation 1		Evaluation 2		Evaluation 3		Evaluation 4	
		GI	GII	GI	GII	GI	GII	GI	GII
	n	37	18	35	16	35	10	33	15
Heart rate (bpm)	M	89	97.4	89.3	91.3	87.6	86.8	91.1	93.1
	SD	14.8	19.4	11.6	19.5	14.1	8.5	16.2	12.4
SBP (mmHg)	M	107.7	111.2	107.3	110.6	106.3	109	108.3	110.7
	SD	12.6	17.5	11.6	10.6	11.9	11	16.6	15.3
DBP (mmHg)	M	68.8	71.6	68.1	70.6	68.3	67	68.8	68.7
	SD	8.1	9.1	7.3	9.9	7.2	8.2	9.2	10.6

GI- group I; GII- group II; n- number of individuals; M- mean; SD- standard deviation; HR- heart rate; DBP- diastolic blood pressure; SBP- systolic blood pressure.

Table 5 – Means and standard deviation of heart rate and systolic and diastolic blood pressure in groups I and II in each phase of the study.

		Evaluation 1		Evaluation 2		Evaluation 3		Evaluation 4	
		GI	GII	GI	GII	GI	GII	GI	GII
	n	37	18	35	16	35	10	33	15
Hemoglobin (g/dl)	M	11.82	11.6	9.25	9.54	9.52	10.26	8.12	9.89
	DP	1.52	1.98	1.93	1.83	1.31	0.87	1.68	1.45
Creatinine (µmol/l)	M	0.66	0.76	0.6	0.75	0.65	0.8	0.72	0.85
	DP	0.17	0.16	0.22	0.17	0.22	0.17	0.24	0.16

GI- group I; GII- group II; n- number of individuals; M- mean; SD- standard deviation.

Table 6 – Means and deviation error of the levels of hemoglobine and creatinine in groups I and II in each phase of the study.

		Evaluation 2	Evaluation 3	Evaluation 4
Group I	Mean	174.05	292.38	345.19
	Standard error	8.52	21.71	20.3
Group II	Mean	203.79	338.7	405.17
	Standard error	10.4	12.48	15.94

Table 7 – Means and standard error of the cumulative dose of doxorubicin (mg/m2) in each phase of the study.

In this study, the occurrence of left ventricular systolic dysfunction according to criteria previously defined showed no statistically significant difference (p=0.248) in group I (18.92%) and in group II (11.1%). Moreover, none of the two groups presented significant changes in the mean values of shortening fraction throughout the study, in all evaluations. Based on this information, it is possible to deduct that dexrazoxane did not have a clear influence as to myocardial protection. Nonetheless, there is an important consideration to be made. The mean shortening fraction was greater in group II than in group I, in evaluations number two, three and four, suggesting some level of myocardial protection granted by dexrazoxane. This hypothesis is corroborated by the fact that doxorubicin-induced cardiac toxicity is dose-dependent, and in each one of these evaluations, group II received an cumulative dose mean approximately 15% greater than group I, a statistically significant difference (p < 0.001)[36,37].

These results partially differ from those found in medical literature, since several studies indicated a more evident level of myocardial protection granted by dexrazoxane, reason why many protocols indicate a greater dose of doxorubicin when dexrazoxane is being administered. In a controlled study, Wexler et al[38] evaluated the effect of dexrazoxane in children with soft tissue sarcomas over the period of chemotherapy with doxorubicin. Patients were evaluated by radionuclide angiography, and the cardiac toxicity was defined as an ejection fraction less than 45% or a drop in ejection fraction equal to or greater than 20% in relation to the pre-chemotherapy value. According to the authors, the incidence of myocardial toxicity in the group who received dexrazoxane was lower (22% x 67%), although this group had received a greater average cumulative dose of doxorubicin ($410mg/m^2$ x $310mg/m^2$). Moreover, the group that received the myocardial protective agent showed a longer survival,

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		Evaluation 1	Evaluation 2	Evaluation 3	Evaluation 4
Group I	Mean	37.03	35.67	34.95	35.26
	Standard error	3.66	3.84	3.79	3.91
Group II	Mean	36.75	37.21	38.47	38.22
	Standard error	3.52	5.64	5.14	4.52

Table 8 – Means and standard error of the shortening fraction (%) on echocardiogram in groups I and II in each phase of the study.

	Group I		Group II	
FS%	n	%	n	%
Altered	7	18.9	2	11.1
Normal	30	81.1	16	94.4
Total	37	100	18	100

n- number of individuals; FS%- fractional percentage of systolic shortening.

Table 9 – Occurrence of changes in the left ventricular systolic function.

in part secondary to the decrease in cardiac events. In a controlled study conducted in children with osteosarcoma during chemotherapy, Rubio et al[22] considered as cardiac toxicity a percentage of shortening of the left ventricle equal to or smaller than 28%, or a drop in FS% by an absolute value equal to or greater than 10 units of the value recorded before the beginning of chemotherapy. The authors found a considerable decrease of the incidence of subclinical cardiac toxicity in the group that received dexrazoxane (14% x 27%). Schiavetti et al[39] analyzed two groups of patients with several different types of solid tumors during the period of chemotherapy with doxorubicin or a similar drug, associated or not with dexrazoxane, and found a smaller incidence of cardiac toxicity, defined as a shortening percentage of the left ventricle equal to or smaller than 28% in the group that received dexrazoxane (zero% x 13.3%).

The fractional percentage of systolic shortening (FS%) is recommended as an index to be used for monitoring the systolic function of patients already treated or being currently treated with anthracyclines, by the Committee of Cardiology of the Studies of Children with Cancer in the United States[24]. Indeed, several studies based on the shortening fraction and/or the ejection fraction to evaluate the left ventricular systolic function showed the applicability of this index[36,41,42]. However, it is known that it has some limitations in evaluating the left ventricular systolic function, mainly when the patient is undergoing chemotherapy. Undoubtedly, this index is affected by some variables that may influence the pre and postload of the left ventricle, primarily during chemotherapy, such as anemia, fever, volume infusion, and renal failure[42]. Even with histological myocardial changes, when the postload is reduced (vasodilatation due to fever), the shortening fraction may remain unchanged, and when it is increased (for instance, due to hydric overload), these indices may be reduced[43]. According to McKillop et al, the shortening fraction showed 37% sensitivity and 72% specificity to predict the subsequent development of CHF in patients treated with anthracyclines. Nevertheless, the authors considered a shortening percentage smaller than 25% as abnormal, and this reduced the sensitivity and specificity of the method. Had they been used in this study, perhaps other echocardiographic parameters of left ventricular systolic function, such as the percentage of thickening and the systolic stress of the posterior wall, could detect a potential difference in the extent of injury of the left ventricle between groups I and II, as they are not influenced
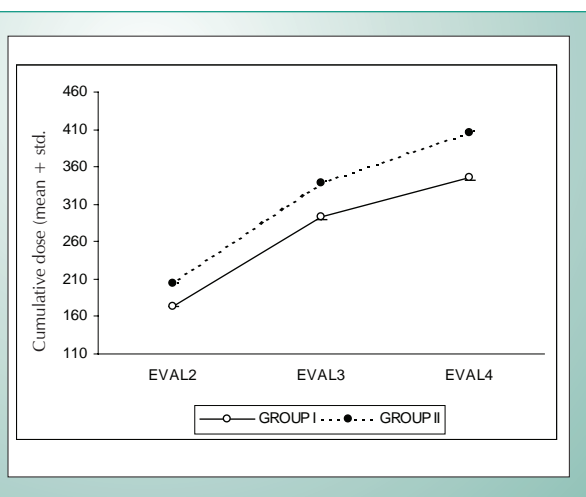

***Fig. 1** – Chart showing the mean of the cumulative dose of doxorubicin in groups I and II in each phase of the study.*
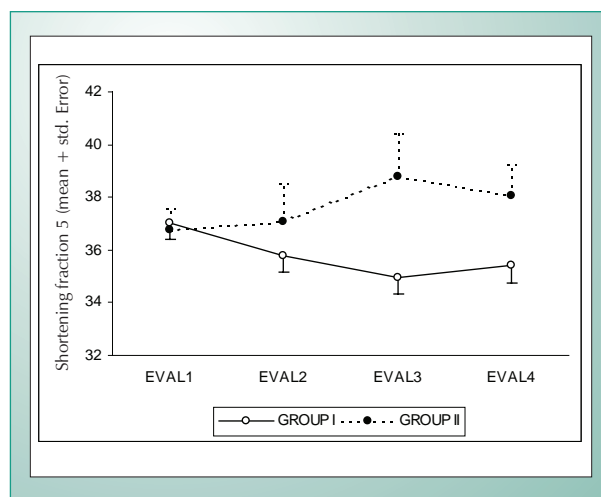

***Fig. 2** – Chart showing the mean of the shortening fraction in groups I and II in each phase of the the study.*

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by pre and postload[45]. Another limitation of this study refers to the fact that it did not include any criteria for diastolic function evaluation. Since the late 1980s, different studies began to consider that the left ventricular diastolic function in patients treated with anthracyclines is affected even before the systolic function, reason why it became an important aspect within this context[46-48]. New techniques with tissue Doppler and the dobutamine stress echocardiogram might also help in the cardiac evaluation of patients who are under the risk of developing anthracycline-induced cardiac toxicity, since they are more sensitive tools for the diagnosis of myocardial toxicity[49-50].

Other limitations in this study may have influenced the results. This was not a randomized study, and the groups were formed and treated at different periods. The clinical events with occasional signs of heart failure over the course of chemotherapy or after the study period were not included in the analysis. Another reason is the relatively small number of patients participating in both groups. Although the shortening fraction is a parameter widely used and with a high level of reproducibility and small interobserver variability, it is important to emphasize the fact that the echocardiogram is a method that relies on the operator who, despite his/her experience, may have accidentally influenced the results obtained. However, the tests were performed by one single observer who did not know in which group or treatment phase the patient was.

Due to having occurred during the chemotherapy treatment and most of them being transient, the changes in the percentage of shortening may be classifed as manifestations of acute toxicity. It is worth mentioning that data obtained in this study relate to the period of the chemotherapy with doxorubicin, and should not be extrapolated to later phases, whether mid or long-term, when the seriousness of the left ventricular dysfunction is markedly greater.

Conclusion

Data in this study show that in osteosarcoma patients treated with doxorubicin alone or associated with dexrazoxane, the left ventricular systolic function, as assessed by the shortening fraction mean, had a better performance in the group that received dexrazoxane. On the other hand, both groups of patients had similar systolic dysfunction.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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