Long-term follow-up of patients with doxorubicin-induced cardiac toxicity after chemotherapy for osteosarcoma

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The overall survival of patients with osteosarcoma of the extremity with localized disease has greatly improved in recent decades and today about half of them are long-term survivors (i.e. more than 10 years). Owing to the increased number of long-term survivors, late side effects of combined chemotherapy are more evident and have been better studied. Doxorubicin-induced cardiac toxicity is still an important and ominous side effect even if the percentage of affected patients is low. In this study, we report the incidence of clinically symptomatic cardiac toxicity induced by doxorubicin, in our series of 755 patients with localized osteosarcoma of the extremity, who had been treated from 1983 to 2000 with different protocols at our institution. Thirteen (1.7%) patients developed a clinically symptomatic cardiac toxicity (New York Heart Association class II–IV). Six of them died. Of the seven still alive, three needed a heart transplant. The case report of these 13 patients is described in detail. A higher incidence of cardiac toxicity was noted in women patients (eight women = 2.5% and five men = 1.1%). Cumulative dose and dose intensity (cumulative dose/week of treatment) are the most important risk factors in developing doxorubicin-related cardiomyopathy.
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Introduction

At present, about three-quarters of paediatric cancer patients can be cured [1]. An increasing number of these children become long-term survivors and face the probability of suffering one of the late side effects of the treatment they had received (chemotherapy, radiotherapy, surgery). Long-term side effects owing to chemotherapy treatment are as follows: second malignancies, sterility, neurotoxicity, nephrotoxicity and cardiomyopathy induced by anthracycline.

About 60% of paediatric cancer protocols include an anthracycline (doxorubicin, epirubicin, daunomycin) [2]. The incidence and risk factors of anthracycline-induced cardiomyopathy have been well evaluated: In a recent review, Kremer *et al.* [3] reported an incidence of clinical heart failure that ranged from 0 to 16% in 30 paediatric cancer patients receiving an anthracycline. In another paper Kremer *et al.* [4] analyzed subclinical cardiac impairment in paediatric cancer protocols and it ranged from 0 to 57%.

Risk factors for cardiac toxicity induced by anthracyclines are cumulative dose, dose intensity, female sex, younger and older age, and a combination of other chemotherapeutic agents [5]. A total dose of 250 mg/m^2 [6] or even lower [7] is sufficient to induce subclinical or clinical cardiac abnormalities. Maximum recommended doses are 550 mg/m^2 for doxorubicin and daunomycin, and 900 mg/m^2 for epirubicin [8].

Doxorubicin-induced cardiomyopathy can occur early or late after chemotherapy. Acute or subacute cardiomyopathy occurs within 1 year of anthracycline administration. A late cardiomyopathy can even occur several years later [9], sometimes after a stress on heart performance such as pregnancy or septicaemia. It has been reported that 10% of child cancer survivors develop symptomatic cardiomyopathy, 15 years after the end of chemotherapy [10].

Clinical presentation of anthracycline-induced cardiomyopathy can be as follows: clinically evident heart failure with shortness of breath, lung effusions, peripheral oedema and arrhythmia, or clinically asymptomatic subclinical cardiomyopathy, which can be seen by abnormalities on the electrocardiogram (EKG) (T-wave changes, prolonged QT, flattening of R-wave, arrhythmia) and on the echocardiogram [reduced left ventricular ejection fraction, increased after load, reduced left ventricular (LV) wall thickness] [11,12]. Mortality by anthracycline-induced congestive heart failure (CHF) can reach 40% [13,14].

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The pathogenesis of anthracycline cardiotoxicity is the formation of the intracellular doxorubicin–iron complex that catalyzes the generation of free radicals, which react with mitochondria inside myocardial cells [15]. Mitochondrial function and transfer of energy are adversely affected, and this leads to contractile failure of the heart. The heart's limited antioxidant defences, the highly oxidative metabolism and the affinity of doxorubicin to phospholipids (cardiolipin) make the heart vulnerable to free radical damage [10]. Apoptotic changes, resulting in cell necrosis induced by anthracycline, are another pathogenetic mechanism of myocardial damage [16]. An anatomic feature of doxorubicin-induced cardiomyopathy is a dilated heart with decreased wall thickness. Myocardial damage owing to anthracycline is of more concern in children than in adults because of the need for subsequent cardiac growth to match somatic growth.

Doxorubicin-induced cardiac toxicity in osteosarcoma survivors has been well reported. In fact, doxorubicin is one of the most effective drugs to be employed in chemotherapy protocols since the 1970s [17,18].

Geidel *et al.* [17] reported 17 cases of symptomatic cardiomyopathy (CHF) in 785 paediatric osteosarcoma patients (2.2%) treated with different protocols of chemotherapy containing doxorubicin (mean cumulative dose 342 ± 113 mg/m^2) for a follow-up of 81 ± 41 months. Paulides *et al.* [18] reported an incidence of 1.5% of clinically evident cardiomyopathies (CHF) in 265 paediatric sarcoma patients, of whom 128 had osteosarcomas. The mean cumulative dose of doxorubicin was 290 mg ± 91 mg/m^2. The mean follow-up was: 34 ± 12 months.

Despite many studies dealing with on the incidence of cardiac toxicity after chemotherapy with anthracycline, few studies have evaluated the outcome, overall survival (OS) and quality of life for these patients. The aim of this study is to evaluate the long-term outcomes for patients, treated at our institution, who developed a symptomatic cardiomyopathy, after receiving chemotherapy for osteosarcoma.

Materials and methods

In March 2006, we reviewed the database of our chemotherapy unit that included 755 patients, with localized osteosarcoma of the extremities who were treated at our institution from 1983 to 2000, with neoadjuvant chemotherapy according to seven different protocols that were successively activated (Table 1) [19–25]. At the end of chemotherapy all patients were followed up with orthopaedic and oncologic exams every 3 months for the first 3 years after diagnosis with lung computed tomography (CT) scans and radiographs of the primary tumour site, then every 4 months until the fifth year and then every 6 months until 10 years. After the 10th year, they could request a visit if needed and they were contacted by phone once a year to update the follow-up. An echocardiogram at the end of chemotherapy was recommended for all patients every year for 3 years, which was performed outside our institute in different cardiologic centres near the patients' homes.

Table 1 Osteosarcoma protocols at Rizzoli Orthopaedic Institute (1983–2000)

IOR 1 (1983–1986)	PTS 127	Cardiopathy 0
Doxo: (GR) 360 mg/m^2 total dose		
Doxo: (PR): 450 mg/m^2 total dose		
CDP (GR): 300 mg/m^2 total dose		
CDP (PR):750 mg/m2 total dose		
MTX 3750 mg/m^2 total dose vs. 37.500		
IOR 2 (1986–1989)	PTS 164	Cardiopathy 6
MTX: 40.000 mg/m^2 total dose		
Doxo: 480 mg/m^2 total dose		
CDP: 600 mg/m^2 total dose (240 ia)		
IFO: 30 000 mg/m^2 total dose (in PR)		
ETO: 1080 mg/m^2 total dose (in PR)		
IOR 3 (1990–1991)	PTS 95	Cardiopathy 0
MTX: 50 000 mg/m^2 total dose		
CDP: 600 mg/m^2 total dose		
Doxo: 390 mg/m^2 total dose		
IFO: 30 000 mg/m^2 total dose (in PR)		
IOR 3b (1991–1993)	PTS 43	Cardiopathy 1
MTX: 60 000 mg/m^2 total dose		
CDP: 600 mg/m^2 total dose		
Doxo: 300 mg/m^2 total dose		
IFO: 30 000 mg/m^2 total dose		
IOR 4 (1993–1995)	PTS 132	Cardiopathy 4
MTX (GR): 60 000 mg/m^2 total dose		
MTX (PR): 72 000 mg/m^2 total dose		
CDP: (GR + PR) 600 mg/m^2 total dose		
Doxo: (GR) 390 mg/m^2 total dose		
Doxo: (PR) 480 mg/m^2 total dose		
IFO: (GR) 32 000 mg/m^2 total dose		
IFO: (PR) 42 000 mg/m^2 total dose		
Pilot ISG (1996–1997)	PTS 68	Cardiopathy 1
MTX (GR): 60 000 mg/m^2 total dose		
MTX (PR):72 000 mg/m^2 total dose		
CDP(GR + PR): 480 mg/m^2 total dose		
Doxo (GR): 330 mg/m^2 total dose		
Doxo(PR): 420 mg/m^2 total dose		
IFO: (GR) 60 000 mg/m^2 total dose		
IFO: (PR) 75 000 mg/m^2 total dose		
Protocol ISG/SSG (1997–2000)	ISG 125	Cardiopathy 1
MTX 60 000 (PR)		
MTX 48 000 (GR)		
Doxo 420 (PR)		
Doxo 330(GR)		
IFO 75 000 (PR)		
IFO 60 000 (GR)		
Total	755	13

CDP, cisplatin; CPT; cardiomyopathy; Doxo, doxorubicin; ETO; etoposide; GR, good responders; IFO, ifosfamide; MTX, methotrexate; PR, poor responders; PTS, patients; ISG/SSG, Italian Sarcoma Group/Scandinavian Sarcoma Group.

For those who were reported to have experienced cardiac toxicity after chemotherapy, we reviewed the cardiologic report in the chart.

We considered CHF as 'congestive heart failure not attributable to known causes other than doxorubicin'. Symptoms of CHF were dyspnea on exertion, decreased tolerance to physical exercise, and pulmonary and peripheral oedema.

Table 2 Patients with symptomatic cardiomyopathy

Case no.	Sex	Age	Protocol	Necrosis	Doxorubicin (mg/m^2)	Dose/week (mg/m^2/week)	Interval CT–CPT (months)	Overall survival total (months)	Status
1	F	18	IOR-OS2	PR	520	10.2	1	24	Dead with MTS
2	M	13	IOR-OS2	GR	433	12.7	2	118	Dead
3	F	15	IOR-OS2	GR	499	14.2	0	9	Dead
4	M	10	IOR-OS2	PR	480	11.1	129	200	Alive with HT
5	F	15	IOR-OS2	GR	478	12.9	110	166	Dead
6	F	14	IOR-OS2	GR	484	14.2	1	14	Dead
7	M	11	IOR-OS3	GR	297	11.8	3	48	Dead with MTS
8	M	10	IOR-OS4	PR	456	15.2	2	136	Alive
9	F	18	IOR-OS4	PR	450	12.8	1	135	Alive
10	F	6	IOR-OS4	PR	480	11.1	2	136	Alive with HT
11	M	15	IOR-OS4	PR	473	10.5	3	142	Alive
12	F	5	Pilot ISG	PR	407	9.2	5	126	Alive with HT
13	F	18	ISG/SSG	PR	324	9.2	0	75	Alive
Median		14			473	11.8	2	126	

CPT, cardiomyopathy; GR; good responders; HT, heart transplant; F, female; M, male; MTS, metastases; PR, poor responders; MTS; metastases; ISG/SSG, Italian Sarcoma Group/Scandinavian Sarcoma Group.

All the patients who reported a cardiomyopathy were also evaluated for their actual performance status, quality of life and New York Heart Association (NYHA) class on diagnosis of cardiomyopathy. All data were updated to March 2006.

We calculated the cumulative dose per square meter of each patient: the sum of drugs received during each cycle divided by body surface. We calculated the dose intensity as cumulative dose per square meter divided by weeks of treatment. This treatment time was calculated from the first day of doxorubicin administered to 3 weeks after the last cycle of doxorubicin administered according to Hryniuk's method [26].

Results

Seven hundred and fifty-five patients (435 male, 320 female) were enrolled in the seven protocols reported in Table 1. All protocols employed doxorubicin at different doses, from 300 to 480 mg/m^2. Median age at diagnosis was 15 years (3–40), median follow-up was 8.5 years (5–22), 10-year cumulative survival was 65.8% (standard error 1.8%). Fifteen patients in the first protocol did not receive doxorubicin as per the original protocol design for good responders, but, owing to subsequent protocol amendments, all the other patients received doxorubicin at the doses reported in Table 1. No difference in doxorubicin doses according to sex was foreseen. Therefore, the total number of patients who were supposed to receive doxorubicin was 740, but two additional patients did not receive doxorubicin because one died of pulmonary emboli after the first cycle of methotrexate and another died of septicaemia before receiving doxorubicin. Of the remaining 738 patients, we lack the data for 55 patients who received all or part of the chemotherapy in other centres; we do not, therefore, have the exact cumulative dose of doxorubicin they received. The mean cumulative dose of doxorubicin in the other 683 patients was 379 ± 75 mg/m^2.

Thirteen patients out of 738 (1.7%) experienced a doxorubicin-related cardiac toxicity (Table 2). Eight patients were female (2.5%) and five were male (1.1%). Median age at diagnosis was 14 years (range 5–18 years). The median cumulative dose of doxorubicin received was 473 mg/m^2 (range 297–520 mg/m^2). The real median cumulative dose received was 95% of the planned dose the time of doxorubicin infusion was 8-h infusion in protocol 1–4 and 24-h continuous infusion in the Pilot ISG and Italian Sarcoma Group/Scandinavian Sarcoma Group (ISG/SSG) protocol. The median time lapse between the end of chemotherapy and the diagnosis of CHF was 2 months (0–129 months); OS, after diagnosis of cardiomyopathy, was 91 months (0–132 ms); median OS after diagnosis was 126 months (9–200 ms).

The data of these 13 patients are summarized in Table 2. All 13 had symptomatic heart failures of varying degrees (NYHA II–IV). Eleven out of 13 patients experienced an acute CHF immediately after the end of chemotherapy (median, 3 months; range, 0–5 months). Two patients out of 13 developed a delayed symptomatic cardiomyopathy, 110 and 129 months, respectively, after the end of chemotherapy; six patients had already died: four died of cardiomyopathy and two of metastatic disease, which occurred after the diagnosis of cardiomyopathy. Of these six patients who died, two were male, four were female; seven patients are alive: three male and four female. Three of these living patients received a heart transplant 4, 5 and 5 years after the diagnosis of cardiomyopathy, and they are alive, without any evidence of disease. The other four living patients now have a compensated heart function with medical therapy. All seven living patients are, at present, free from disease. The case history of each of these 13 patients is described below.

Patient no. 1

Eighteen-year-old woman with osteosarcoma of the tibia, who received chemotherapy according to the protocol IOR-OS2 from March 1988 to December 1989. The total

dose of doxorubicin was 338 mg/m^2. A routine chest radiograph showed two metastatic nodules on her right lung so, in January 1989, she underwent a lung metastasectomy. In February 1989, she resumed chemotherapy with three more cycles of chemotherapy with a total cumulative dose of 520 mg/m^2 of doxorubicin. One month after the last cycle of chemotherapy, an echocardiogram showed an ejection fraction (EF) of 41%. She complained of fatigue and mild shortness of breath during exercise. She received medical therapy [angiotensin converting enzyme (ACE) inhibitor and diuretics] and the symptoms of heart failure improved. The lung CT was normal. Three months later, another lung CT showed the appearance of two lung nodules suggestive of metastases. Owing to the cardiac failure, a metastasectomy was not performed. In October 1989, the lung nodules increased in size and number. The patient died in February 1990 of metastatic disease.

Patient no. 2

A 13-year-old boy with osteosarcoma of the distal femur who received 433 mg/m^2 (90% of planned dose) of doxorubicin according to the protocol IOR-OS2 from November 1987 to June 1988. Two months after the end of chemotherapy, the patient was admitted for an episode of CHF (EF 37%) with ascites and pleural effusion. He received medical therapy (digoxin and diuretics) resulting in remission of symptoms. In the years that followed, he had more episodes of CHF. In 1991, he was put on the list for a heart transplant, which never occurred. In January 1996, an atrial fibrillation increased the creatinine level, which, in February 1997, resulted in renal failure (creatinine 3.4). The patient died of heart failure in August 1997.

Patient no. 3

A 15-year-old girl with an osteosarcoma of the distal femur received 499 mg/m^2 (104%) of doxorubicin from November 1989 to November 1990 according to the protocol IOR-OS2. Nine days after the end of the last cycle (doxorubicin), the patient was admitted to another hospital for acute CHF, NYHA class IV. Despite admission to the intensive cardiac unit, the patient died 3 days later. The autopsy confirmed severe heart dilatation and pulmonary oedema.

Patient no. 4

A 10-year-old boy with localized osteosarcoma of the femur received chemotherapy from July 1989 to July 1990 according to the IOR-OS2 protocol and received 480 mg/m^2 of doxorubicin. He was in good health until August 1998 when he suddenly developed symptoms of CHF. On admission to hospital, an echocardiogram showed a dilated cardiomyopathy with 40% EF, clinically in NYHA class IV. The patient received medical treatment, but owing to persistent cardiac failure in May 2002 (4 years after diagnosis of cardiomyopathy and 13 years after diagnosis of cancer) he received a heart transplant. Now the patient is alive and free of disease; his quality of life is excellent.

Patient no. 5

A 15-year-old girl with osteosarcoma of the tibia received 478 mg/m^2 (99%) according to the protocol IOR-OS2, from October 1987 to June 1988. The echocardiogram at the end of the therapy was normal. Nine years later (September 1997), during her last trimester of pregnancy, the patient developed shortness of breath and an echocardiogram revealed a dilated cardiomyopathy with 34% EF, and mild mitral and tricuspid insufficiency. The patient delivered a healthy baby by caesarean section. After pregnancy the EF rose to 39%. She received medical therapy for 2 years. Then she became pregnant again. At that time EF decreased to 25%. The patient was advised to interrupt her pregnancy and an abortion was performed. Two years later the patient's EF worsened to 20%. She was on the list for heart transplant, but developed a malignant arrhythmia episode (sustained ventricular tachycardia) and died of it in August 2001.

Patient no. 6

A 14-year-old girl with osteosarcoma of the distal femur received 484 mg/m^2 (101%) of doxorubicin according to the protocol IOR-OS2, from December 1987 to August 1988. One month after the end of chemotherapy, the patient developed a dilated cardiomyopathy with symptoms of CHF, NYHA IV. She received digoxin and diuretics, which improved the symptoms. In December 1988, after a febrile episode owing to pneumonia, the patient had another episode of acute heart failure. On admission to the hospital, an echocardiogram showed a global LV dysfunction and dilatation of all four chambers. She died of heart failure a few days later.

Patient no. 7

An 11-year-old boy with osteosarcoma of the proximal tibia he received chemotherapy according to protocol IOR-OS3 with 297 mg/m^2 (99%) of doxorubicin, from December 1992 to May 1993. Three months later, after a febrile episode owing to an upper airways viral infection, a chest radiograph showed increased heart diameters; an echocardiogram showed a severe dilated cardiomyopathy with a shortening fraction of 10%. The patient was affected by fatigue, shortness of breath, and epatomegaly. He received medical treatment with diuretics and ACE inhibitors, which improved the cardiac function. One month later shortening fraction was 19%. The patient developed bones metastases in the tibia and D2 vertebra. The tibia metastasis was resected and he received radiotherapy on the D2 vertebra. He also received two more cycles of chemotherapy with ifosfamide. In June 1996, he developed a new bone metastasis and lung metastasis. Owing to the cardiopathy, lung metastasectomy was not taken into consideration. He died of metastatic disease in November 1996.

Patient no. 8

A 10-year-old boy with osteosarcoma of the distal femur. From October 1994 to July 1995 he received chemotherapy according to the protocol IOR-OS4. He received a total doxorubicin dose of 456 mg/m^2 (93%). In September 1995, he was admitted to hospital for CHF, NYHA class IV, and an echocardiogram showed 29% EF. After treatment with ACE inhibitors and diuretics, he had a partial remission of the heart failure. Over the next 4 years, his EF was around 35–40%. In 1999, after a febrile episode, he experienced a new CHF episode and was admitted again to hospital. The patient was NYHA class III; an echocardiogram showed an EF of 32%, and mild mitral and tricuspid insufficiency; he had increased end diastolic pressure, reduced left ventricle compliance, a 'restrictive pattern' and pulmonary arterial hypertension. Holter's EKG monitoring showed sporadic ventricular and supraventricular premature beats, grade I A–V block and rare episodes of grade II (Mobitz 1) A–V block. He is currently under medical treatment and reports a satisfactory quality of life.

Patient no. 9

An 18-year-old woman with osteosarcoma of the proximal tibia received chemotherapy from December 1994 to November 1995, According to the IOR-OS4 protocol, she received 450 mg/m^2 of doxorubicin (93%). One month after the last cycle of chemotherapy, the patient was admitted to hospital for an episode of CHF, with NYHA class IV and 31% EF, and a dilated cardiomyopathy was diagnosed. At present, the patient is NYHA class I and the heart failure is being controlled by medical therapy (diuretics, ACE inhibitors, β-blockers). Her last echocardiogram showed a dilated cardiomyopathy with mild mitral and tricuspid insufficiency, and EF 36%. Holter's EKG monitoring showed sporadic ventricular and supraventricular premature beats.

Patient no. 10

A 6-year-old girl with osteosarcoma of the distal ulna who received chemotherapy according to the protocol IOR-OS4 from September 1994 to August 1995. The total doxorubicin dose was 480 mg/m^2. Two months after the last cycle of chemotherapy, the patient developed a dilated cardiomyopathy and was admitted to hospital for CHF; EF was 32%. The patient was treated only by medical therapy until May 2000 when, because of progressive heart failure, the patient received a heart transplant (5.5 years after cancer diagnosis). In October 2001, she suffered a transplant rejection, but it was controlled with immunosuppressant therapy. Her last echocardiogram in November 2003 was normal. We phoned the patient who is alive and in good health.

Patient no. 11

A 15-year-old boy with osteosarcoma of the proximal tibia who received 473 mg/m^2 (98%) of doxorubicin from May 1994 to March 1995 according to the protocol IOR-OS4. After 3 months, he complained of shortness of breath after moderate exercise, fatigue and palpitations. The echocardiogram showed a dilated cardiomyopathy with an EF of 41% and NYHA class II. He started medical therapy with ACE inhibitors and diuretics. For 5 years, he had normal cardiac function and was asymptomatic until, in September 1999, after a period of intense physical exercise (fitness, swimming, cycling), he had another episode of heart failure and was admitted to hospital, where he received medical therapy. The last echocardiogram showed an EF of 50%. Now he is asymptomatic and he is off therapy, but he is allowed only moderate physical exercise.

Patient no. 12

A 5-year-old girl with osteosarcoma of the humerus, who received 407 mg/m^2 (97%) of doxorubicin, according to the Pilot ISG protocol, from October 1995 to August 1996. Five months after the end of chemotherapy, she was admitted to hospital for an acute episode of CHF. She was NYHA class IV with EF of 20%. The patient had a severe dilated cardiomyopathy and, owing to progressive heart failure, she was on the list for a heart transplant in January 1997. In May 1997 a lung CT scan showed bilateral lung nodules suggestive of metastases; owing to the severe cardiac dysfunction, neither the biopsy nor the chemotherapy was taken into consideration. The patient received complementary alternative medication (Di Bella's therapy [27], with vitamins A, C and E, somatostatine, melatonine, and 50 mg/day orally cyclophosphamide). After 2 months a CT scan showed a partial response. The patient continued this treatment for 2 years and the lung nodules disappeared almost completely. In May 1999 (4.5 years after the cancer diagnosis), she received a heart transplant and stopped the complementary alternative medication. Now she is receiving posttransplant immunosuppressant therapy. She is, at present, in good health, with no evidence of neoplastic disease. Her last lung CT scan showed only one small residual nodule that had remained unchanged since 1999. Her last echocardiogram showed an EF of 75%. Her quality of life is excellent.

Patient no. 13

An 18-year-old woman with osteosarcoma of the humerus, who received 324 mg/m^2 (98%) of doxorubicin from January 1999 to September 1999 according to the ISG/SSG I protocol. Soon after the last cycle of chemotherapy, an echocardiogram revealed a moderate LV dysfunction with mild dilatation and an EF of 36%. She was NYHA class II. The cardiologist started treatment with ACE inhibitors and β-blockers. In March 2000, there was a worsening of the LV function (EF 22%) and of the NYHA class (III). Digitalis treatment was added to ACE inhibitors and the β-blockers were decreased, with improvement of ventricular function. EF was 36% in

February 2002, 49% in December 2004 and at the most recent follow-up in January 2006 it was 54%. Her quality of life is good and the NYHA class is I. She is receiving ACE inhibitors and β-blockers, and potassium supplements. In fact, besides cardiac dysfunction, the patient had mild renal insufficiency with hypopotassaemia (Fanconi's syndrome) as an additional, permanent, late side effect of chemotherapy.

Discussion

The outcome of cardiac toxicity related to doxorubicin that has been reported in this study – 13/738 patients treated with doxorubicin (1.7%) – is similar to that of other large studies of osteosarcoma patients [17,18]. Mortality in these 13 patients who experienced dilated cardiomyopathy was 46.1% (six out of 13). We did not observe cardiomyopathy in the IOR-OS1 protocol, although poor responders (PR) received 450 mg/m^2 of doxorubicin. This might have been due to the longer follow-up from which some had been excluded (or had died of metastatic disease before cardiomyopathy could occur).

We calculated the dose intensity of doxorubicin received by good responders (GR) and PR in each protocol (Table 3). The dose intensities ranged from 12 to 16.9 mg/m^2/week, with a median of 13.2 mg/m^2/week. It is interesting that in the IOR 2 protocol, GR and PR received the same cumulative dose of doxorubicin 480 mg/m^2, but with a difference of over 9 weeks (31 weeks in GR compared with 40 weeks in PR). In our series, six patients from the IOR 2 protocol suffered a doxorubicin-induced CHF; four out of six were GR and had, therefore, received a more intense administration of doxorubicin. All except patient no. 1 received a cumulative dose and dose intensity (doxorubicin/week) within the range planned by the protocols.

It is interesting that, in protocol 3b, we had the highest dose intensity (16.9 mg/week), but only one case of cardiomyopathy occurred; the total cumulative dose planned by the 3b protocol was 300 mg/m^2. The cumulative dose might be more relevant than the dose intensity; further studies are needed with a larger number of cardiomyopathies.

Table 3 Dose intensity for each protocol

Protocol	Cumulative dose	No. of weeks	Dose (mg/m^2/week)
IOR 1 GR	360	24	15
IOR 1 PR	450	31	14.5
IOR 2 GR	480	31	15.4
IOR 2 PR	480	40	12
IOR 3a GR	390	23	16.9
IOR 3a PR	390	29	13.4
IOR 3bPR=GR	300	25	12
IOR 4 TN	390	31	12.5
IOR 4 PR	480	40	12
Pilot GR	330	24	13.7
Pilot PR	420	33	12.7
SSG GR	330	25	13.2
SSG PR	330	25	13.2
			Median 13.2

GR, good responders; PR, poor responders; SSG, Scandinavian Sarcoma Group.

Of the patients still living, three received a heart transplant. They are in very good health, Their quality of life, measured as NYHA class and physical exercise, is the best in the group of survivors. Despite immunosuppressant therapy, they did not experience relapse of tumor. Ward *et al.* [28] reported the outcome of children treated for cancer, who had undergone a heart transplant after anthracycline cardiac dysfunction. One out of 17 had cancer recurrence, suggesting that cancer recurrence is rare after transplantation. In our series three patients received heart transplants 9, 5.5 and 4.5 years after the diagnosis of osteosarcoma. They are alive and free of disease 4.5 and 6 years after the transplant.

Two other important results are as follows: (1) the prevalence of female patients in the incidence of cardiac toxicity: eight females vs. five males, and (2) the lower incidence of cardiomyopathy in the later protocols, which employed 24 h doxorubicin infusion.

Lipshultz and Lipsitz [29] claimed that the female sex was an independent risk factor for cardiac toxicity. They observed significantly increased doxorubicin-related cardiac toxicities in female patients. Their study of 120 patients (children and adults), of whom 33 had nonmetastatic osteosarcoma and 87 had acute lymphoblastic leukaemia, was treated with bolus doses of doxorubicin in different protocols, with total doses of doxorubicin ranging from 244 to 550 mg/m^2. They reported that, for both diseases, female patients had a significantly greater reduction in contractility than males, and that the higher the cumulative dose was, the greater became the difference in contractility between female and men patients. To explain this finding, which has also been reported in other studies, different hypotheses were made. One was that female patients have more body fat than males and that, as anthracyclines are poorly absorbed in fat tissue, their cellular concentrations would be increased in nonadipose tissue (e.g. heart), in patients who received doses calculated according to body surface area or weight. Another explanation is the known sex-related difference in anthracycline pharmacokinetics, with female patients having a lower clearance and a lower ratio of area under the curve than male patients [30]. The lower incidence of cardiomyopathy in the last protocol might be because of the prolonged infusion of 24 h, instead of 8 h as in the previous protocol. Other studies have shown that prolonged doxorubicin infusions decreased cardiac toxicity. Yet Other studies have shown no difference. Casper *et al.* [31] reported a significant decrease in the incidence of CHF, when comparing

weekly doxorubicin schedule to a 3-week schedule. Legha *et al.* [32] reported that endomyocardial biopsy changes were significantly less severe in patients who had received doxorubicin by continuous infusions compared with patients who had received bolus infusions.

Another important factor is the patient's age. A few studies have reported that a lower age is a risk factor. Myocardiocyte damage by anthracycline is of more concern in children than in adults because of the need for subsequent cardiac growth to match the somatic growth. Some studies showed an increased rate of cardiac toxicity in younger children. Pratt *et al.* [33] showed that children younger than 4 years were more vulnerable to cardiac toxicity. Lipshultz *et al.* [34] also found that age below 4 years was an independent predictive factor for cardiac dysfunction, in a group of 115 children compared with the all-patient group. The median age of our group of patients who suffered cardiac toxicity was lower, compared with the median age of the all-patient group (14 vs. 15), but it was not statistically significant.

In this study, the incidence of cardiac toxicity was lower in the last two protocols, Pilot ISG and ISG/SSG, compared with the previous protocols: two events in 193 patients (1.0%) vs. 11 in 545 patients (2%). In the last two protocols 24-h prolonged infusion was employed and the cumulative dose was inferior; in fact, the maximum cumulative dose planned in the pilot study was 420–360 and in the ISG/SSG protocol it was 330 mg/m^2.

Cardiac toxicity is due mainly to anthracycline. Other drugs (alkylants, vinca alkaloids, taxanes, trastuzumab, etc.), however, have also been associated with cardiac toxicity to a lesser extent, either by direct effect or by increased toxicity in combination with anthracycline [11]. The cardiac effects of these other drugs range from EKG abnormalities, arrhythmias, myocarditis, pericarditis and acute myocardial infarction to CHF.

In these protocols, another potentially cardiotoxic drug is ifosfamide, which has been reported to increase cardiac toxicity, heart failure or arrhythmias, in doses equal to or above 15 g/m^2/cycle [35]. Nonetheless, in this study, the two protocols that employed higher doses of ifosfamide (Pilot-ISG 15 g and ISG/SSG ifosfamide at 15 g/m^2/cycle) had a lower incidence of cardiac toxicity.

Conclusion

Doxorubicin is still one of the most effective drugs in combined chemotherapy for osteosarcoma and will remain one of the most important drugs in many future chemotherapy protocols also. Review studies, as this, have shown a sustainable incidence of cardiac toxicity (2%), but with a high incidence of mortality (almost 50%).

Several attempts have been made to avoid cardiac toxicity: prolonged infusion, doxorubicin dose reduction and the use of cardioprotectants [dextrazoxane, ACE inhibitors, β-blockers], and liposomal anthracycline (still under evaluation in paediatric oncology).

Recent reports of dextrazoxane in acute lymphoblastic leukaemia in children have shown good results in terms of cardioprotection and tolerability, with no difference in effectiveness in studies on adults. Careful monitoring is recommended during chemotherapy, after a total dose of 250 mg/m^2, to detect precocious signs of cardiac toxicity by echocardiogram (like a mild LV dilatation or EF reduction). If possible, monitoring biochemical markers such as troponin I and brain natriuretic peptide should be done to prevent further chemotherapy damage. By tailoring the future doses of doxorubicin, and by starting treatment with ACE inhibitors and β-blockers, it is possible to protect myocardial cells from further damage.

Moreover, when planning future protocols for child cancer patients, we should consider all the risk factors that we already know, such as cumulative dose, younger age and female sex, and duration of infusion. It is also advisable to consider all the options that can reduce cardiac toxicity: prolonged infusion, cardioprotectants and liposomal doxorubicin compounds.

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