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Pediatrics

Doxorubicin Dose Deintensification in Pediatric Osteosarcoma, Is Less Better?

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Abstract

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Introduction We implemented new clinical practice guidelines (CPG) for patients with osteosarcoma starting in January 2009. These guidelines were based on standard European and American Osteosarcoma Study regimen, which includes six cycles of doxorubicin with a cumulative dose of 450 mg/m^2. Aiming to reduce cardiac toxicity at our center, we opted to reduce the cumulative dose of doxorubicin to 375 mg/m^2.

Materials and Methods This is a retrospective cohort of osteosarcoma patients aged <18 years, treated at our center between 2009 and 2018. Patients were treated with unified CPG and were prospectively followed. Disease and treatment characteristics were depicted, and survival rates were calculated. When needed, comparison of survival of different groups were conducted using log-rank test.

Results After a median follow-up of 43.3 months (range, 2–153 months), 79 patients were diagnosed with osteosarcoma and treated with dose-reduced doxorubicin. Median age at diagnosis was 12.8 years. At diagnosis, 58 patients (73%) had localized disease. The 5-year event-free survival (EFS) for the whole group was 50 ± 5.9%, and overall survival (OS) was 64 ± 5.7%. For patients with extremity nonmetastatic tumors ($N = 56$), 5-year EFS and OS were 60 ± 6.9% and 70 ± 6.8%, respectively, and for this group of patients, response to chemotherapy was associated with better EFS ($p = 0.0048$) and OS ($p = 0.013$). Only two patients suffered transient cardiac dysfunction, which was resolved after treatment.

Conclusion Our findings suggest that deintensification of doxorubicin may provide adequate control for pediatric osteosarcoma. In the absence of large randomized clinical trials addressing this issue, developing countries with less resources to treat patients with heart failure may consider using the lower dose.

Keywords

- osteosarcoma
- doxorubicin
- developing countries
- cardiotoxicity

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Introduction

Over the past years, multiagent chemotherapy has been used for the treatment of osteosarcoma. Cisplatin, doxorubicin, and high-dose Methotrexate, Adriamycin, Cisplatin (MAP) are the most widely used regimen.[1–3]

Cooperative groups, such as Children's Oncology Group, Cooperative Osteosarcoma Study Group, the European Osteosarcoma Intergroup, and Scandinavian Sarcoma Group, used different regimens in treating patients with osteosarcoma; however, the total cumulative dose of doxorubicin in all protocols was 450 mg/m^2 or more.[1–5] This resulted in survival rates exceeding 60%.

Side effects of doxorubicin, similar to other chemotherapy agents, include nausea, vomiting, hair loss, and neutropenia. However, other more serious side effects remain the major concern in pediatrics age group. Cardiac toxicity is well described with the use of doxorubicin, and arrhythmias can be observed in early or late course of treatment.[6,7] Furthermore, at higher doses of the agent, there is a risk of developing congestive heart failure and dilated cardiomyopathy. The incidence of anthracycline-related cardiac toxicity in childhood cancer survivors ranged between 5 and 20%.[8–11]

At our center, we established clinical practice guidelines (CPG) for osteosarcoma in 2009. The CPGs were acknowledged in concordance with European and American Osteosarcoma Study (EURAMOS)-1 protocol. However, in pursuance of decrease cardiac toxicity, we decreased the cumulative dose of doxorubicin from 450 to 375 mg/m^2 by omitting one dose.

In this study, we explored cardiac-related toxicity and disease outcomes in patients with osteosarcoma, who received deintensified doxorubicin chemotherapy regimen.

Materials and Methods

Following Institutional Review Board approval, we performed a comprehensive chart review for patients aged $\leq$ 18 years with newly diagnosed osteosarcoma. Children managed at our center between January 2009 and May 2018 were included. Follow-up data were depicted through December 2021. We excluded patients presented for consultation or patients who presented for surgery only. Demographic and clinical data obtained included age, gender, primary tumor site, presence of metastases at diagnosis (M1), local treatment modality, percentage of necrosis following neoadjuvant chemotherapy, and outcomes including recurrence/progression, site(s) of recurrence, and duration of follow-up. Cardiac-related toxicity was documented.

Chemotherapy consisted of five cycles of MAP: cisplatin (120 mg/m^2/cycle, it was omitted in the fifth cycle and the total cumulative dose kept at 480 mg/m^2), doxorubicin (37.5 mg/m^2/d given over 1 hour on days 1 and 2), and methotrexate (12 g/m^2/cycle given on 2 consecutive weeks). Patients received two cycles before primary tumor local control. The accumulative dose of doxorubicin was 375 mg/m^2. Patient with M1 disease at initial diagnosis and those with poor histologic response to chemotherapy (necrosis $<$90%) had intensification of their chemotherapy by adding ifosfamide and etoposide (IE) to the postoperative chemotherapy. After the EURAMOS-1 trial published data revealed no added benefit from adding IE in patients with poor histologic response to chemotherapy, IE was not delivered to patients for poor histologic response to chemotherapy or presence of metastasis starting in March 2015.

Patients underwent local control after two cycles of MAP. Surgery was the main modality of treatment if feasible and limb salvage surgery (LSS) was the preferred procedure if attainable with negative resection margins. If surgery was not feasible, patients were offered definitive course of radiation therapy.

At initial diagnosis, a set of imaging obtained to all patients (X-ray, computed tomography of the chest, bone scan, and magnetic resonance imaging of the involved bone). According to our institutional guidelines, all cases were discussed in weekly sarcoma multidisciplinary clinic (MDC) at multiple time points: at diagnosis, time of local control, and with any major event (progression, recurrence, etc.). The MDC included at least an oncologist, orthopaedic surgeon, pathologist, radiation oncologist, and radiologist.

An expert pediatric cardiologist (K.S.) did echocardiogram to all patients at specific time points per our protocol: before starting chemotherapy, every other cycle with doxorubicin, at the end of chemotherapy, and then yearly.

Statistical Analysis

Demographic, tumor, and treatment characteristics were summarized by descriptive analysis. Overall survival (OS) was defined as the time between diagnosis and death from any cause or last follow-up for patients remaining alive. Event-free survival (EFS) was defined as the time between diagnosis and occurrence of disease recurrence or progression, second malignancy, death, or last follow-up for patients who did not experience an event. OS and EFS distributions were calculated using the Kaplan–Meier method. Log-rank test was used to compare survival curves when needed. A p-value of 0.05 or less was considered statistically significant.

Results

Patients' Characteristics

Between January 2009 and May 2018, we identified 79 patients. The median age at diagnosis was 12.8 years (range, 3.6–18). Forty-one patients (52%) were females, 58 (73%) had localized disease, 15 (19%) had lung only metastasis, and 6 (8%) had multiple sites metastasis. Patients' characteristics are summarized in ►Table 1. Of the 79 patients, 71 completed the whole MAP protocol, and the other 8 patients progressed before finishing the whole protocol.

Local Control

After neoadjuvant chemotherapy, 16 patients manifested radiologic disease progression, local progression in 10 patients, and combined local and metastatic sites in 6. After two cycles of MAP, patients underwent primary tumor local control.

Table 1 Patients' characteristics

Variable	Number (percentage)
All patients	**79**
Gender	
Male	38 (48%)
Female	41 (52%)
Age (y)	
Median	12.8
Range	3.6–18
Tumor site	
Extremity	75 (95%)
Others	4 (5%)
Metastasis	
No	58 (73%)
Yes	21 (27%)
Lung only	15
Lung and bone	4
Lung and bone and LNs	1
Lung and liver	1
Surgery	69 (87%)
Amputation	16
LSS	51
Others	2
No	10 (13%)
Necrosis	
<90	38 (55%)
≥ 90	31 (45%)

Abbreviation: LN, LSS, limb salvage surgery.

Surgery was the principal management option for local control when feasible ($n=69$): LSS in 51 (65%), amputation in 16 (20%), 1 hemipelvectomy and 1 hemimandibulectomy.

Ten patients did not undergo local control: three of them had primary unresectable pelvic tumors, all received radiation therapy. Three refused surgical amputation, and four showed refractory disease in metastatic sites despite different chemotherapeutic regimens. For the 69 patients who underwent surgery, necrosis was $\geq$ 90% in 31 (45%, good response), and margins were negative in all resections except 1.

Of the 15 patients with lung-only metastasis, 8 patients underwent thoracotomy with complete excision of all lung nodules, 5 had complete resolution of lung nodules with chemotherapy at the end of treatment, and 2 patients had disease progression after neoadjuvant chemotherapy: 1 of them refused any further therapy, and the other 1 had refractory disease.

Events

Forty patients (50%) developed at least one event during follow-up. Three patients were lost to follow-up: one was alive with disease and two had no disease at last contact. The other 37 patients developed disease recurrence or progression. Seven patients had progression or recurrences at local site only, 17 in lung only, and 13 patients had disease recurrence or progression in multiple sites. At the time of last follow-up, 30 patients were dead, 5 had no evidence of disease, and 5 were alive with disease (►**Table 2**).

Table 2 Events

Event	Number of patients	Outcome
All patients	**79**	
Lost to follow-up	3	1 AWD 2 NED
Local only progression/ recurrence	7	1 NED 1 AWD 5 DOD
Lung only progression/ recurrence	17	14 DOD 1 AWD 2 NED
Multiple sites progression/ recurrence	13	13 DOD
No events	39	39 NED

Abbreviations: AWD, alive with disease; DOD, died of disease; NED, no evidence of disease.

Outcomes

After a median follow-up time of 43.3 months (range, 2–153), the 5-year event EFS was $50 \pm 5.9\%$ and OS was $64 \pm 5.7\%$ (►**Fig. 1**). For patients with extremity nonmetastatic (M0) tumors, 5-year EFS and OS were $60 \pm 6.9\%$ and $70 \pm 6.8\%$, respectively. Patients with M0 extremity tumors who had good response to neoadjuvant chemotherapy had better 5-year EFS ($84 \pm 8.4\%$ vs. $45 \pm 9.1\%$, $p=0.0048$) and 5-year OS ($89 \pm 7.2\%$ vs. $58 \pm 10\%$, $p=0.013$).

On multivariable Cox proportional hazards analysis for the whole cohort of patients, the only factor that significantly predicted worse EFS was poor histologic response to neoadjuvant chemotherapy (hazard ratio [HR]: 2.59, 95% confidence interval [CI]: 1.12–5.97, $p=0.026$); however, it did not affect the OS (HR: 2.3, 95% CI: 0.96–5.74, $p=0.074$). The presence of metastasis predicted lower OS (HR: 4.18, 95% CI: 1.51–11.58, $p=0.006$); however, the effect on EFS did not reach clinical significance (HR: 2.47, 95% CI: 0.99–6.19, $p=0.053$) (►**Table 3**).

Cardiac Toxicity

Two patients developed transient cardiac dysfunction: the first patient was an 11-year-old girl, underwent resection of localized left distal femur tumor, and showed necrosis of 47%. She received a cumulative dose of doxorubicin of 375 mg/m^2. She developed heart failure 7 weeks after chemotherapy completion, she presented with shortness of breath and general fatigability, echocardiogram showed an ejection fraction of 25%, she required antifailure medications that

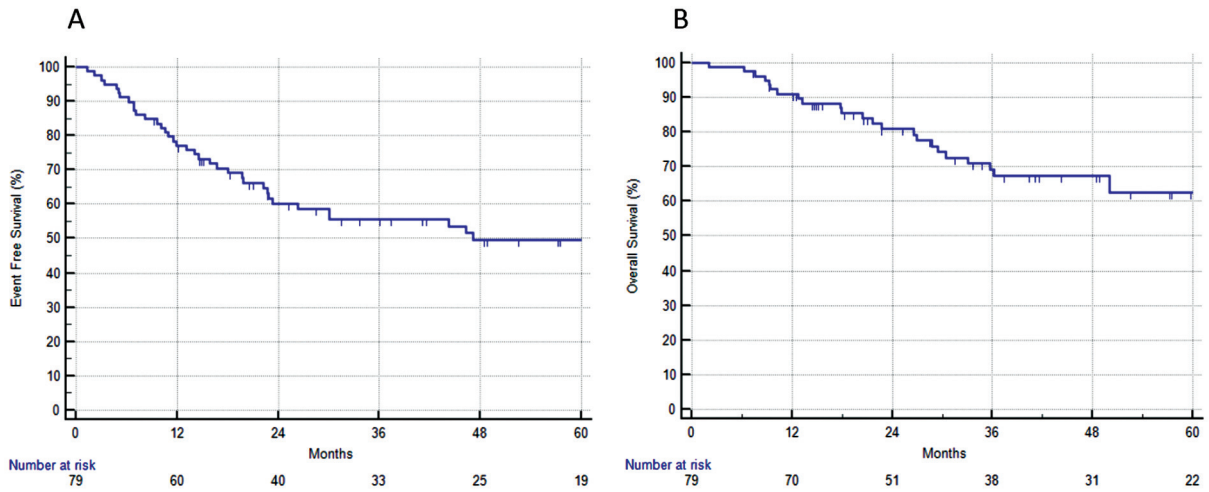

Fig. 1 Kaplan–Meier plots for event-free survival (A) and overall survival (B) for all patients.

were eventually stopped, she has been off antifailure medications for 20 months. The other patient was a 9.9-year-old girl, had a localized distal femur tumor; she underwent surgery and had a necrosis of 90%, she received a cumulative dose of doxorubicin of 375 mg/m^2. She developed heart failure 5 weeks after chemotherapy completion, she presented with orthopnea and tachypnea; echocardiogram showed an ejection fraction of 35%. She needed antifailure medications for a short period that she eventually stopped and she has been off them for 6 years. At the time of last follow-up, none of the patients was on heart failure medications or had an abnormal echocardiogram.

Discussion

Chemotherapy was first introduced in the treatment of osteosarcoma in 1960s, after which cure rate of osteosarcoma has improved from 10 to 15% to 60 to 75%.[1–4,12–14] Doxorubicin use for the treatment of osteosarcoma started since the 1970s.[15–17] Initially, it was used in patients with pulmonary metastases and this resulted in response rates of 35 to 40%, with some patients showing complete response in lung.[15–18] Later due to its high activity in osteosarcoma, doxorubicin was included in almost all protocols.[19,20] The optimal dose of doxorubicin is not well established; however, cumulative doses of 450 mg/m^2 is currently used in many protocols.

The main toxicity of doxorubicin is cardiac toxicity. Multiple risk factors are associated with increased anthracycline-induced cardiac toxicity including age, gender, and infusion time. However, the main risk factor is the cumulative doses administered. After 500 mg/m^2 cumulative dose of doxorubicin, the incidence of cardiac toxicity is significant.[9–11]

The initial cumulative doses of doxorubicin used in osteosarcoma were high, exceeding 450 mg/m^2. These doses exhibited superior efficacy, nevertheless resulted in fatal drug-related cardiotoxicity. High doses are associated with increased incidence of cardiac toxicity during chemotherapy or years after completing treatment, which can develop cardiomyopathy or even result in death. The incidence of cardiotoxicity in survivors of pediatric bone and soft tissue sarcomas varies between 1 and 20%.[11,21] In a report by Brown et al, 25% of patients developed systolic cardiac dysfunction beyond 15 years.[10]

An old study by Bacci et al suggested that lower cumulative doses of doxorubicin had a significant effect on survival rates in patients with osteosarcoma. They compared two consecutive studies, IOR/OS2 and IOR/OS3, where in IOR/OS3, the cumulative dose of doxorubicin was 390 mg/m^2 (84 patients) compared with 480 mg/m^2 in the IOR/OS2 (144 patients). Despite intensification of therapy in the lower doxorubicin dose group by adding cisplatin and decreasing the total duration of therapy, a lower survival rate was reported in the IOR/OS3 compared with the IOR/OS2 (73 and 85%, respectively, $p \leq 0.008$). As expected, the lower dose of doxorubicin resulted in decrease in cardiac toxicity, none in the IOR/OS3 compared with five including two deaths and one heart transplant in the IOR/OS2.[22]

In our study, the 5-year OS for the whole group was 64%, but when we looked for patients with complete surgical resection (CSR) and M0, the 5-year EFS was 60% which is parallel to the EURAMOS-1 results at 64%; notably, the cumulative dose of doxorubicin in this study was 450 mg/m^2.[1] Our results were comparable to those published by different studies, especially for patients with CSR and M0 disease (►Table 4).

Metastasis, poor histologic response (necrosis < 90%), and positive resection margins are the most reported adverse prognostic factors in osteosarcoma.[24–26] In patients with poor necrosis, the 5-year EFS report is 40 to 50% in comparison to 65 to 80% in patients with good necrosis.[27–29] Likewise, patients with metastasis at diagnosis continues to have a poor survival with reports of 5-year EFS between 10 and 40%.[25] Our results were comparable to the published data. On subset analysis, we found that patients with localized extremity site and had necrosis ≥90% carried the best EFS and OS (82 ± 9.7 and 86 ± 9.5%, respectively).

In the Bacci et al's study, which included only patients with M0 extremity site disease, a reduced total cumulative

Table 3 Cox model for EFS and OS for all patients

	N	EFS				OS			
		Univariable		Multivariable		Univariable		Multivariable	
		HR	*p*-Value	HR	*p*-Value	HR	*p*-Value	HR	*p*-Value
Metastasis									
No	58	3.67 (1.87–7.2)	<0.001	2.47 (0.99–6.19)	0.053	5.63 (2.75–11.53)	<0.001	4.18 (1.51–11.58)	0.006
Yes	21								
Subtype									
Chondroblastic	23	0.61 (0.28–1.31)	0.207	NA	NA	0.84 (0.37–1.9)	0.68	NA	NA
Small cell/NOS/NA	34	0.92 (0.4–2.11)	0.851			0.84 (0.32–2.21)	0.72		
Osteoblastic	19	0.46 (0.06–3.54)	0.457			0.0 (0.0–0.inf)	0.90		
Telangiectatic	3								
Necrosis									
< 90%	38	2.50 (1.1–5.68)	0.029	2.59 (1.12–5.97)	0.026	2.14 (0.87–5.22)	0.096	2.3 (0.96–5.74)	0.074
≥90%	31								
Surgery									
LSS	51	3.48 (1.81–6.68)	0.001	1.65 (0.71–3.86)	0.246	3.64 (1.79–7.42)	0.001	1.04 (0.37–2.9)	0.937
Others	18								

Abbreviations: EFS, event-free survival; HR, hazard ratio; LSS, limb salvage surgery; NA, not available; NOS, nonotherwise specified; OS, overall survival.

Table 4 Comparison with different studies, all patients, nonmetastatic either extremity site or complete surgical resected disease

Study	Number of patients	Age	Doxorubicin dose	Patients	5-year EFS	5-year OS
Halalsheh et al (2022, present study)	79	<18	375 mg/m^2	All patients	50%	64%
	54			Extremity, M0	60%	70%
	55			CSR, M0	62%	73%
Smeland et al (2019)[1]	2,186	<40	450 mg/m^2	All sites, M0, M1, CSR	54%	71%
	1,549			CSR, M0	64%	79%
Schwartz et al (2016)[23]	242	<31	450–600 mg/m^2	CSR, M0	62%	74%
Ferrari et al (2002)[24]	246	<40	420 mg/m^2	Extremity, M0	60%	74%
Bacci et al (2000)[5]	146	<40	480 mg/m^2	Extremity, M0	63%	75%

Abbreviations: CRS, complete surgical resection; EFS, event-free survival; M0, nonmetastatic; OS, overall survival.

dose of doxorubicin was used in the IOR/OS3; however, this was achieved by decreasing the single dose per cycle. In our study, the single dose per cycle was higher compared with the IOR/OS3 (75 mg/m^2 compared with 60 mg/m^2, respectively).[22] This fact may be attributable for better survival in our study compared with the Bacci et al.

For patients with M1 disease who underwent Limb Salvage Surgery (LSS) ($n = 6$), we reported high 5-year Event Free Survival (EFS) and Overall Survival (OS) (67 ± 19 and 67 ± 19%, respectively). This exceeds survival rates in other major study groups. However, this conclusion is restrained by the small number of patients.

Dexrazoxane has been used in combination of doxorubicin to prevent heart failure.[30–33] Schwartz et al used dexrazoxane as a cardioprotection to enable the use of higher cumulative dose of doxorubicin in children with osteosarcoma, cumulative dose of doxorubicin of 450 to 600 mg/m^2 was used. Out of 242 patients, only 5 developed grade 1 or 2 left ventricular dysfunction. They concluded that dexrazoxane allowed for therapeutic intensification by increasing the cumulative doxorubicin dose.[23] In adult experience, higher cumulative dose could be given with liposomal formulation of doxorubicin.[34,35] Despite the proven benefit of decreasing cardiac toxicity, cost as well as access to these medications could be a major issue in countries with limited resources.

In countries with limited resources, access to therapy of cardiac disease as well as cardiac rehabilitation could be a challenge.[36,37] In our study, with doxorubicin dose reduction, we could achieve adequate control for children with osteosarcoma and we had improved cardiac toxicity; only two of our patients had a transient heart failure, and none developed major late sequelae. Developing countries with less resources to treat patients with heart failure may consider using the lower dose.

This study suffers multiple limitations; relatively small number of patients, its retrospective nature and associated selection bias in addition to relatively short median follow-up. Our patients were treated using Clinical Practice Guidelines (CPG) and were followed up prospectively. Meticulous cardiac follow-up was done. Despite all limitations, we present a modification that may best suit patients in less developed countries, where optimal resources to treat patients with heart failure are suboptimal.

Conclusion

Our findings suggest that deintensification of doxorubicin may provide adequate control for pediatric osteosarcoma. We report improved cardiac toxicity with dose reduction, as no patient developed major late sequelae. In the absence of large randomized clinical trials addressing this issue, developing countries with less resources to treat patients with heart failure may consider using the lower dose. Our findings as well suggest that some subset of patients with osteosarcoma may have a noninferior outcome with deintensified dose of doxorubicin compared with standard regimen. Aforementioned, larger studies are warranted to confirm these outcomes and identify subgroup of patients who would benefit the most from this regimen.

Conflict of Interest

None declared.

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