Original Article

Outcomes and survival rates of childhood osteosarcoma in Iran, A report from MAHAK Pediatric Cancer Treatment and Research Center, from 2007 to 2020

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ABSTRACT

Background: Osteosarcoma is one of the most common childhood bone malignancies. Although chemotherapy protocol including methotrexate is an effective treatment for osteosarcoma, some other regimens have excluded it because of its complications.

Methods: This retrospective study was conducted on 93 children younger than 15 years old who were diagnosed with osteosarcomafrom March 2007 to January 2020. Two chemotherapy protocols were administrated for patients, namely, DCM protocol (Doxorubicin-Cisplatin-Methotrexate) and German protocol (excluding methotrexate). All statistical analysis was conducted using SPSS-25 software.

Results: Among patients, 47.31% were male. Patients' age ranged from 3 to 15 with the mean of 10.41 ± 0.32 years. Femur was the most frequent primary tumor site (59.14%), followed by tibia (22.58%). Metastasis rate at diagnosis was 17.20% in our study. Furthermore, the 5-year overall survival (OS) of total patients was 37.3 ± 7.5%, whereas the 5-year OS of males and females was 33.6 ± 10.9% and 39.8 ± 10.6%, respectively. The 5-year OS of methotrexate regimen was 15.6 ± 9.6%, whereas that of methotrexate-free protocol was 50.2 ± 9.0%.

Conclusions: Female patients had better survival rates than males. In addition, the chemotherapy protocol excluding methotrexate significantly increased the overall and event free survival of patients.

KEY WORDS: Childhood cancer, methotrexate, osteosarcoma, pediatrics, survival rate

INTRODUCTION

Osteosarcoma is one of the most common malignancies of bone tissues in children, which usually occurs in bones with higher growth pace such as femur and humerus.[1] Osteosarcoma is responsible for nearly 2% of childhood cancer types. Annually, it is estimated that nearly 400–450 children and teenagers are diagnosed with osteosarcoma.[2]

Regarding survival rates, the 5-year overall survival (OS) for children and teens with osteosarcoma is 69%, and it may reduce to 64% if the tumor spreads to near lymph nodes, and may fall to 27% if it spreads to distant parts of the body. According to Surveillance, Epidemiology, and End Results program of National Cancer Institute, the 5-year OS of children younger than 14 years old with bone and joint tumors is 73.8% for years 2010 to 2016.[3,4]

Fortunately, the OS of childhood osteosarcoma has improved from 20% to nearly 70% in recent decade, thanks to the introduction of multi-agent chemotherapy, which includes a combination of methotrexate, doxorubicin, and cisplatin.[5] With regard to methotrexate toxicity, some studies have

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tried different treatment protocols, including carboplatin, ifosfamide, and doxorubicin.[6]

In this study, we aim to evaluate childhood osteosarcoma in patients younger than 14 years old who referred to MAHAK Pediatric Cancer Treatment and Research Center (MPCTRC) for either diagnosis, treatment, following up, or palliative care. MPCTRC is a non-governmental organization that supports children with cancer and provides multidisciplinary treatment and care for pediatric patients through Iran and even other countries. By conducting this study, we also aimed to evaluate the survival rates of patients with osteosarcoma based on different chemotherapy protocols, which are used in MRCTRC.

METHODS

Patients

This retrospective study was conducted on 123 children who were diagnosed with osteosarcoma at MPCTR among a total number of 2,760 hospitalized patients from March 2007 to January 2020. Patients younger than 15 years old were included in our study (93 patients), and older patients ($n = 7$) and those who never received any treatment in MPCTR or referred to be followed-up ($n = 23$) were excluded.

Data collection

To collect data, we referred to patients' clinical documents including different parts such as demographic information (name, gender and date of birth, and familial history of cancer), early symptoms of disease and its onset date, date of starting first therapeutic procedure, any laboratory tests, any imaging process, treatment protocol, preoperative and postoperative chemotherapy, adverse effects, outcomes (relapse and metastasis), pathology reports, etc. All information was gathered by a pediatric hematologist-oncologist and a head nurse via interviewing patients and their family as well as clinical tests.

Chemotherapy protocols

Two chemotherapy protocols were administered for pediatric patients diagnosed with osteosarcoma who referred to MPCTRC for treatment [Table 1]. The cumulative dose of agents was calculated according to the total dose that was administered through the chemotherapy cycles. Chemotherapy was started following histological diagnosis and patients randomly were categorized into two groups that used high dose methotrexate protocol or the regimen without high-dose methotrexate.

Survival and prognosis

To better understand the differences between two administrated chemotherapy protocols, we evaluated relative survivals for each regimen. OS was defined as the time between diagnosis and last evaluation of the patient. Event free survival (EFS) was defined as the time from diagnosis to first event, including relapse, metastasis, or death.

Statistical analysis

All the collected data were entered in SPSS software version 25.

RESULTS

Patients' demographic and clinical characteristics

Among 93 eligible new cases with osteosarcoma who had been referred to MPCTRC from March 2007 to January 2020, 47.31% ($n = 44$) were male and 52.69% ($n = 49$) were female. Patients age ranged from 3 to 15 years with the mean age of 10.41 ± 0.32 years, and more than 65% of them ($n = 61$) were from 10 to 15 years old. Only four patients were younger than five years old. The median height and weight of cases were 149.1 cm (ranged from 90 to 176 cm) and 36.5 kg (ranged from 11.5 to75 kg), respectively. All results related to patients' demographic and clinical characteristics are shown in Table 2.

Primary tumor sites and tumor classification

The most common primary tumor sites in considered cases were femur ($n = 55$, 59.14%) and tibia ($n = 21$, 22.58%), followed by knee humerus ($n = 9$, 9.68%), pelvis bone ($n = 4$, 4.30%), mandible ($n = 2$, 2.15%), vertebral bone ($n = 1$, 1.08%), and radius ($n = 1$, 1.08%). According to World Health Organization classification of childhood osteosarcoma, the majority of tumors were classified into high-grade osteosarcoma, namely, conventional osteoblastic (77.17%, $n = 71$), conventional chondroblastic (16.30%, $n = 15$), telangiectatic (2.17%, $n = 2$), and small cell (1.09%, $n = 1$). Additionally, 2.17% ($n = 2$) of patients were classified into intermediate-grade osteosarcoma (periosteal), and one patient was diagnosed with low-grade osteosarcoma (low-grade central). More data about primary tumor sites and classification of tumors are illustrated in Table 2.

Table 1: Different chemotherapy protocols, cumulative dosage of drugs, and administration time

Chemotherapy Protocol Name	Neoadjuvant Therapy		Adjuvant Therapy	
	Drug Name	Administration information	Drug Name	Administration information
Protocol including high dose methotrexate (DCM)	Doxorubicin[a]	75 mg/m^2 continuous infusion over 48 h	Doxorubicin[a']	75 mg/m^2 continuous infusion over 48 h
	Cisplatin[b]	60 mg/m^2/day×2 days	Cisplatin[b']	60 mg/m^2/day×2 days
	Methotrexate[c]	12 g/m^2×1 dose, maximum dose 20 g	Methotrexate[c']	12 g/m^2×1 dose, maximum dose 20 g
Protocol excluding high dose methotrexate (German)	Ifosfamide[d]	1800 mg/m^2/day×5 days	Cisplatin[f]	120 mg/m^2/day
	Doxorubicin[e]	25 mg/m^2/day×3 days	Etoposide[g]	100 or 150 mg/m^2/day×5 days
	Cisplatin[f]	120 mg/m^2/day	Ifosfamide[d']	1800 mg/m^2/day×5 days

[a]and [b]were administered through weeks 1 and 6. [c]was administered through weeks 4, 5, 9, and 10. [a']was [a]dministered through weeks 12, 17, 22, and 26. [b']was administered through weeks 12 and 17;. [c']was administered through weeks 15, 16, 20, 21, 24, 25, 28, and 29. [d]and [e]were administered through weeks 0, 6, and 12. [e]and [f]were administered through weeks 3, and 9. [f]and [g](150 mg) were administrated every 21 days alternating with [d']and [g](100 mg) for seven courses

Table 2: Patients' demographic information and clinical data at diagnosis

Variables	Female	Male	Total
Mean Age at Diagnosis (years)	10.04±0.46	10.84±0.44	10.41±0.32
Age Group at Diagnosis (*n*)			
<1 years	NA*	NA	NA
1-4 years	4 (8.16%)	NA	4 (4.30%)
5-9 years	15 (30.61%)	13 (29.55%)	28 (30.11%)
10-15 years	30 (61.22%)	31 (70.45%)	61 (65.59%)
Primary Tumor Site (*n*)			
Femur	24 (48.98%)	31 (70.45%)	55 (59.14%)
Tibia	13 (26.53%)	8 (18.18%)	21 (22.58%)
Humerus	7 (14.29%)	2 (4.55%)	9 (9.68%)
Pelvis Bone	3 (6.12%)	1 (2.27%)	4 (4.30%)
Mandible	2 (4.08%)	NA	2 (2.15%)
Radius	NA	1 (2.27%)	1 (1.08%)
Vertebral Bone	NA	1 (2.27%)	1 (1.08%)
WHO Classification (*n*)			
High-grade Osteosarcoma			
Conventional-Osteoblastic	34 (70.83%)	37 (84.09%)	71 (77.17%)
Conventional-Chondroblastic	9 (18.75%)	6 (13.64%)	15 (16.30%)
Telangiectatic	2 (4.17%)	NA	2 (2.17%)
Small Cell	1 (2.08%)	NA	1 (1.09%)
Intermediate-grade Osteosarcoma			
Periosteal	1 (2.08%)	1 (2.08%)	2 (2.17%)
Low-grade Osteosarcoma			
Low-grade central	1 (2.08%)	NA	1 (1.09%)

*NA=not applicable

Metastasis, follow-up, and survival rates

Out of 93 enrolled patients, 16 children (17.20%) experienced metastasis at diagnosis, among whom, more than 50% were diagnosed with pulmonary metastasis. Additionally, 50.53% of total patients ($n = 47$) experienced metastasis, including 18 patients with only pulmonary metastasis (38.29%), 13 patients with local metastasis (other than pulmonary, 27.65%), and 16 patients with both local and pulmonary metastasis (34.04%).

Totally, 39 children died during the study among whom, 20 patients were male and 19 patients were female. In addition, the majority of alive patients had finished their treatment procedure and were followed-up monthly ($n = 32$). The meantime of follow-up was 26.97 ± 2.59 month with the maximum of 106 months.

The 5-year OS of total patients was 37.3 ± 7.5%, whereas the 5-year OS of males and females was 33.6 ± 10.9% and 39.8 ± 10.6%, respectively. Regarding EFS, female patients had higher survival rate than males (29.6 ± 8.8% vs. 31.0 ± 8.6%, respectively)[Table 3]. Moreover, all data related to survival rates in female and male patients are categorized in Table 4 based on age groups, WHO classification of tumors and treatment protocols.

Chemotherapy protocols

More than 70% of patients ($n = 67$) were cured with the chemotherapy protocol without methotrexate (German protocol), and 26 patient underwent chemotherapy protocol including methotrexate (DCM protocol). Table 5 shows demographic and clinical characteristics of patients categorized based on their chemotherapy protocol.

Table 3: Patients' follow-up information, OS, EFS, and PFS based on gender

Variables	Female	Male	Total
Patients Status in latest Follow-up			
Off-treatment	18 (36.73%)	14 (31.82%)	32 (34.41%)
Dead	19 (38.78%)	20 (45.45%)	39 (41.94%)
During treatment	9 (18.37%)	7 (15.91%)	16 (17.20%)
Referred to their living city	3 (6.12%)	3 (6.82%)	6 (6.45%)
Mean Time of Follow-up (month)	30.97±3.68	22.52±3.56	26.97±2.59
OS			
1 year	88.6±4.8%	80.5±6.2%	84.6±3.9%
3 year	56.8±8.5%	42.0±9.9%	52.5±6.3%
5 year	39.8±10.6%	33.6±10.9%	37.3±7.5%
EFS			
1 year	31.0±8.6%	29.6±8.8%	30.4±6.1%

OS=overall survival, EFS=event free survival, PFS=progression free survival

DISCUSSION

This study was designed at MPCTR on 93 pediatric patients diagnosed with osteosarcoma. MAHAK Hospital is an NGO multidisciplinary center established for children with different types of malignancies, whether Iranian or from other nationalities. The whole therapeutic process for these children from diagnosis to treatment and regular follow-ups is conducted free of charge in this center. Furthermore, MAHAK Hospital is the only referral center of Iran for pediatric patients who develop any kind of malignancy.

It is estimated that osteosarcoma is responsible for nearly 2% of childhood cancers.[7] The incidence rate of childhood osteosarcoma in our study was around 4%. More than 65% of patients included in our study were in the 10–14-year-old age group. This fact can

Table 4: Overall survival of male, female, and total patients based on their demographic and clinical charecteristics

Variables	5-year Overall Survival		
	Female Patients	Male Patients	Total Patients
Age Group at Diagnosis			
<1 years	NA*	NA	NA
1-4 years	NA	NA	NA
5-9 years	45.6±21.4%	16.3±13.8%	31.4±13.4%
10-15 years	30.4±14.3%	45.7±12.4%	37.9±9.7%
WHO Classification			
High-grade Osteosarcoma	34.2±13.0%	26.6±13.1%	31.7±9.1%
Conventional-Osteoblastic	26.7±21.5%	55.6±24.8%	41.5±16.8%
Conventional-Chondroblastic	NA	NA	NA
Telangiectatic			
Small Cell	NA	NA	NA
Intermediate-grade Osteosarcoma			
Periosteal	NA	NA	NA
Low-grade Osteosarcoma			
Low-grade central	NA	NA	NA
Treatment Protocol			
DCM	NA	23.6±14.2%	15.6±9.6%
German	44.1±13.4%	56.7±11.2%	50.2±9.0%

*NA=not applicable

Table 5: Number of patients based on two different chemotherapy protocols and their demographic and clinical charecteristics

Variables	Number of patients	
	Patients cured with DCM protocol	Patients cured with German protocol
Age Group at Diagnosis		
<1 years	NA*	NA
1-4 years	1 (3.85%)	3 (4.48%)
5-9 years	8 (30.77%)	20 (29.85%)
10-15 years	17 (65.38%)	44 (65.67%)
WHO Classification		
High-grade Osteosarcoma		
Conventional-Osteoblastic	19 (76.00%)	52 (77.61%)
Conventional-Chondroblastic	3 (12.00%)	12 (17.91%)
Telangiectatic	1 (4.00%)	1 (1.49%)
Small Cell	1 (4.00%)	NA
Intermediate-grade Osteosarcoma		
Periosteal	1 (4.00%)	1 (1.49%)
Low-grade Osteosarcoma		
Low-grade central	NA	1 (1.49%)
Gender		
Female	15 (57.69%)	34 (50.75%)
Male	11 (42/31%)	33 (49.25%)

*NA=not applicable

be supported by American Cancer Society, which indicates that osteosarcoma is more prevalent in pediatric patients older than 10 years old. These finding may discloses that hormone changes and bone growth rate during this age (puberty) may significantly influence development of childhood osteosarcoma.[8]

Pulmonary metastasis rate was reported between 10 and 20% in some studies,[5,9] and in our study, the overall metastasis rate was 17.20%.

Since 1970s, multi-agent chemotherapy protocols without any standardized regimen have been administrated for cases diagnosed with pediatric osteosarcoma.[10] In spite of not being a consensus standard protocol, modern intensive chemotherapy regimens for non-metastatic cases can lead to 60–76% of cure rate.[11] Intensified combination of high-dose methotrexate (HD MTX) and ifosfamide especially for cases younger than 14 years old with primary pulmonary metastasis can optimize their treatment.[11]

In this regard, this study was designed to evaluate two different chemotherapy protocols based on survival rates of the active drugs (methotrexate and ifosfamide). Each protocol had significantly different results in the final status of cases and EFS time.

Different studies from 1985 to 2013 revealed that ifosfamide can be a first line chemotherapy regimen for cases with relapsed osteosarcoma.[12-14] During 1985 to 1987, the response rate of these cases to treatment with ifosfamide was 33%.[12,13] Fortunately, in 2013, Kudawara *et al*. reported that by using ifosfamide (at the dose of 15 g/m^2) therapy, response rate in cases with relapses osteosarcoma reached 66%.[14] Neoadjuvant chemotherapy for osteosarcoma studies (NECO-93J and 95J) resulted in 77.5% of 5-year OS rate for poor responder to ifosfamide regimen in patients with osteosarcoma.[15]

The efficacy of HD MTX is challengeable and some researches revealed that it may be alternated by ifosfamide regimen.[16,17] Daw *et al*.[6] in OS99 trial demonstrated that cases without tolerance to HD MTX can alternatively be treated by ifosfamide regimen. In an investigation by Epelman *et al*.,[18] the chemotherapy protocol including ifosfamide in combination with cisplatin, doxorubicin, and etoposide (without methotrexate) was evaluated. The 3-year progression free survival rate of this study was 70%. They also suggested that ifosfamide regimen without methotrexate could be more effective than using ifosfamide and methotrexate together.

The research team of Meyers *et al*.[19] in OS99 trial revealed that Ifosfamide regimen without HD MTX led to 5-year EFS of 66.7% and 5-year OS of 78.9% (in cases with localized resectable osteosarcoma). In our study, the differences between survival rates of DCM and German protocol were remarkable. Precisely, the 5-year OS of patients whose chemotherapy regimen included methotrexate was 15.6 ± 9.6%, whereas that of patients cured with the German protocol including ifosfamide was 50.2 ± 9.0%.

Female patients had better survival rates than males in our study. The 5-year OS of female and male patients was 39.8 ± 10.6% and 33.6 ± 10.9%, respectively. This fact can be supported by some other studies indicating that males have worse OS than females in childhood osteosarcoma.[20,21] It is also reported that there might be significant relationship between patients' age and gender and their prognosis and EFS indicating more favorable outcomes for younger and female patients.[5]

CONCLUSION

Overall, it seems that teenagers are more likely to be diagnosed with childhood osteosarcoma rather than other age groups. Therefore, it would be better to evaluate teenagers' bone pain to distinguish puberty from this malignancy. In addition, we strongly recommend the methotrexate-free chemotherapy regimen to reduce its complications and to increase the survival rates of pediatric children with osteosarcoma. Unfortunately, one of our limitations is the lack of information about stage of the disease, because MPCTRC is a referral center for cancer treatment and some patients' documents (especially non-Iranian ones or those whose cancer diagnosis was before the year 2012) are incomplete. A multi-center retrospective study is also recommended to have a better understanding of childhood osteosarcoma in Iran.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and it was reviewed and approved by the ethical committee of MPCTRC on July, 2020. The study number was MPCTRC-1399-4-15.

Contribution details

Azim Mehrvar: patients' visit and supervision, guarantor; Narjes Mehrvar: study design and manuscript revision; Yasaman Sadeghi: data gathering, data analysis, manuscript writing, manuscript editing, manuscript revision and guarantor; Maryam Tashvighi: patients' visit.

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Conflicts of interest

There are no conflicts of interest.

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