Review article
Korean J Pediatr 2015;58(4):123-128
http://dx.doi.org/10.3345/kjp.2015.58.4.123
pISSN 1738-1061•eISSN 2092-7258

Korean J Pediatr

Osteosarcoma in Korean children and adolescents

Jun Ah Lee, MD, PhD
Department of Pediatrics, Korea Cancer Center Hospital, Seoul, Korea

Osteosarcoma is the most frequent primary bone tumor. Advances in combination chemotherapy and surgical technique have greatly improved the survival of patients with osteosarcoma. In Korea, improvements in osteosarcoma treatment have been made over the past two decades. The 5-year event-free survival rate of Korean children and adolescents with localized disease is 64.6%, comparable to that of American or European patients. This article provides an overview of current therapies for osteosarcoma in Korea.

Key words: Osteosarcoma, Korea, Child, Adolescents

Corresponding author: Jun Ah Lee, MD, PhD
Department of Pediatrics, Korea Cancer Center Hospital, 75, Nowon-ro, Nowon-gu, Seoul 139-706, Korea
Tel: +82-2-970-1248
Fax: +82-2-970-1970
E-mail: junahlee@kcch.re.kr

Received: 2 January, 2015
Accepted: 3 March, 2015

Introduction

Osteosarcoma is the most common primary malignant tumor of the bone[1,2]. In Korea, approximately 50 children and adolescents are newly diagnosed as having osteosarcoma per year[3]. Advances in combination chemotherapy and surgical technique have greatly improved the survival of these patients[1,2]. Currently, more than 60% of patients with localized disease are cured[1,2]. In this article, the clinical characteristics and treatment outcome of Korean children and adolescents will be reviewed.

Current status of Korean children and adolescents with osteosarcoma: results of the Korean Society of Pediatric Hematology and Oncology study

In 2009, the Korean Society of Pediatric Hematology and Oncology conducted a retrospective study on the outcome of Korean children and adolescents with osteosarcoma treated between 1989 and 2009[4]. Data on a total of 320 patients were collected from 19 institutions. There were 192 male and 128 female patients with a median age of 11.8 years (range, 3.3–35.7 years) at the time of diagnosis. The distal femur (52.3%) was the most frequently affected site, followed by the proximal tibia (19.5%) and proximal humerus (11.1%). The most common histological subtype was osteoblastic, and 64 patients (19.8%) had distant metastasis at the time of diagnosis. Osteosarcoma developed as a secondary malignancy in three cases.

Treatments were heterogeneous, depending on treatment era or institutional policy. The majority of patients (252 cases, 78.0%) were treated in a standard fashion with preoperative chemotherapy followed by surgery and postoperative chemotherapy. Of the 280 patients that underwent surgery, limb salvage was performed in 253 cases (90.4%). High-dose methotrexate (HD MTX), cisplatin, doxorubicin, and ifosfamide were the core components

of combination chemotherapy. Chemotherapy regimens differed between institutions (Fig. 1). Postoperative chemotherapy was modified in 122 cases (37.8%) due to poor histological response (viable tumor cell>10%) to preoperative chemotherapy.

For survival analysis, data from the 225 cases followed-up for more than 2 years were evaluated using the Kaplan-Meier method. The probability of overall (OS) and event-free survival (EFS) at 5 years were 70.9% and 60.7%, respectively. 70.9% and 60.7%±3.6%, respectively. The 5-year OS and EFS rates were better for the 184 patients who presented without metastasis at the time of diagnosis, 80.0% and 64.6%, respectively (Fig. 2). The association between clinicopathological variables and survival was evaluated. We found that the presence of metastasis at the time of diagnosis and histological response to preoperative chemotherapy influenced survival (Table 1).

Fig. 3 shows the improvements made in osteosarcoma treatment over the past two decades. Currently, the treatment outcomes of Korean children and adolescents are comparable to those of American or European patients.

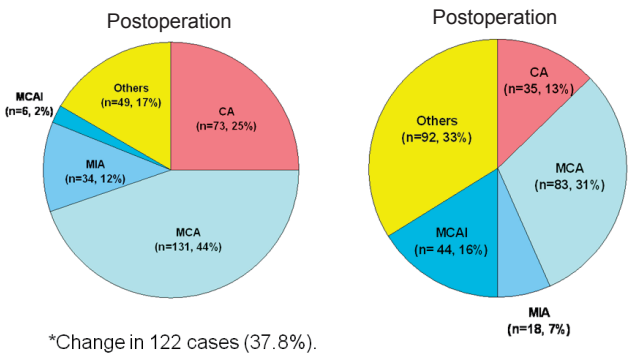

Fig. 1. The Korean Society of Pediatric Hematology and Oncology retrospective study: administered preoperative and postoperative chemotherapy regimens. CA, cisplatin+doxorubicin; MCA, high-dose methotrexate (HD MTX)+cisplatin+doxorubicin; MIA, HD MTX+ifosfamide+doxorubicin; MCAI, HD MTX+cisplatin+doxorubicin+ifosfamide.

Challenges

1. Recurrent or refractory tumors

Despite improvements with a multidisciplinary treatment approach, 30%–40% of osteosarcoma patients still relapse and eventually succumb to the disease[1,5]. Prognosis of patients with recurrent or refractory osteosarcoma is poor[1,6-8]. Lee et al.[7] reported that the 5-year survival rate of 180 patients with recurrent osteosarcoma was 13%. The survival rate was influenced by the site of recurrence (lung, 39%; local, 0%; lung and bone, 25%; others, 12%; $P<0.05$), recurrence-free interval (<12 months, 13%; ≥12 months, 44%, $P<0.05$), and treatment modality after recurrence (with surgery, 38%; without surgery, 11%; $P<0.05$). Currently, standard guidelines do not exist for the treatment of these patients[6-8]. Generally, local control surgery is performed whenever possible and additional adjuvant chemotherapy is given. Combination chemotherapy comprising ifosfamide, carboplatin, and etoposide is the most frequently used regimen[6-8]. Patients who experience treatment failure with this combination proceed to receive gemcitabine and docetaxel (GEMDOC) chemotherapy[8].

The efficacy of GEMDOC has been reported in various sarcomas, including Ewing sarcoma, malignant fibrous histiocytoma, synovial sarcoma, angiosarcoma and osteosarcoma[9-16]. Prompted by encouraging results from adult studies, GEMDOC chemotherapy is used in children and adolescents with recurrent or refractory bone sarcomas[13-16]. Due to the rarity of

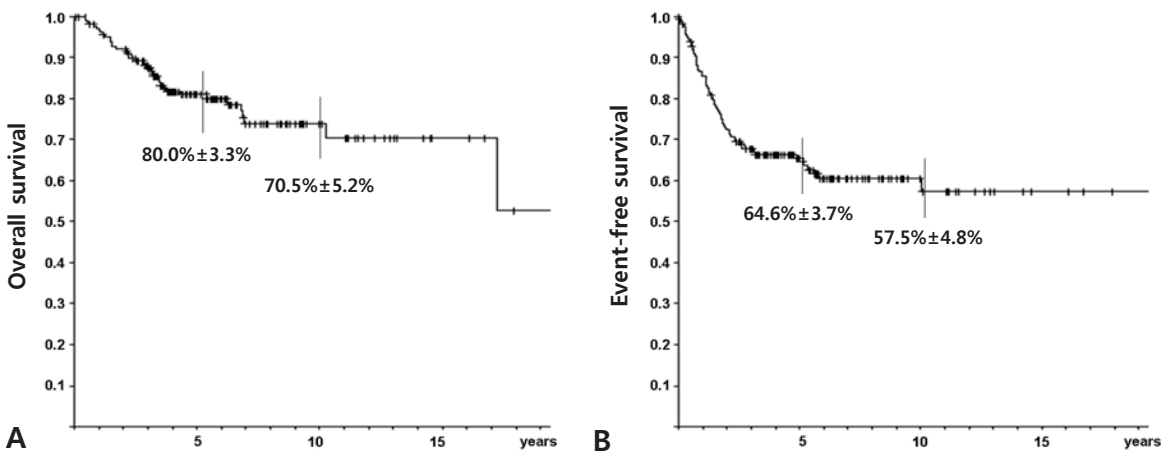

Fig. 2. The Korean Society of Pediatric Hematology and Oncology retrospective study: overall (A) and event-free survival (B) of patients with localized osteosarcoma.

 http://dx.doi.org/10.3345/kjp.2015.58.4.123

Table 1. Clinicopathological variables and 5-year event-free survival

Variable	Case number	Survival (%), mean±SD	*P* value
Age			0.13
Pubertal growth	94	55.6±5.5	
Others	120	65.6±4.9	
Sex			0.57
Male	131	58.3±4.8	
Female	62	66.0±5.7	
Maximal tumor length (cm)			0.07
≤8	81	68.3±5.7	
>8	82	56.2±5.6	
Location			0.08
Distal femur	120	61.9±4.7	
Proximal tibia	38	66.5±9.2	
Proximal humerus	19	35.3±11.6	
Proximal fibula	7	47.6±22.5	
Axial	5	37.5±28.6	
Elsewhere	25	78.5±8.6	
Histologic subtype			0.71
Osteoblastic	125	59.6±4.8	
Chondroblastic	24	60.6±10.3	
Fibroblastic	3	100	
Others	19	72.2±10.6	
Unknown	40	57.7±8.9	
Metastasis at diagnosis			0.05
No	180	65.3±3.7	
Yes	33	27.0±13.6	
Histologic response*			0.004
Good	62	75.0±5.6	
Poor	67	49.2±6.6	
Change of postoperative chemotherapy			0.1
No	97	68.1±5.0	
Yes	86	55.8±5.8	

SD, standard deviation.
*Good, viable tumor cells ≤10%; poor, viable tumor cells > 10%

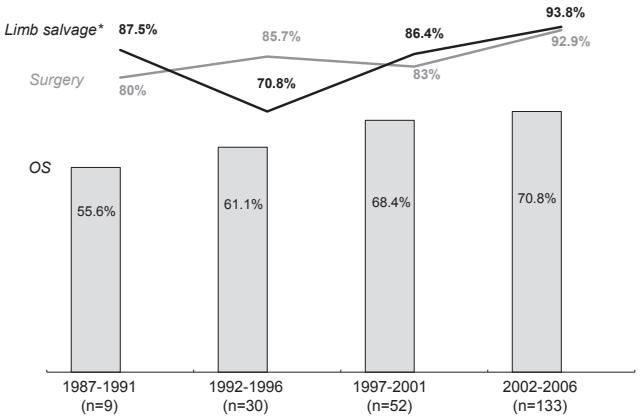

Fig. 3. The Korean Society of Pediatric Hematology and Oncology retrospective study: overall changes in the treatment and survival of children and adolescents with osteosarcoma. OS, overall survival. *Indicates the percentage of cases among those with tumors in the extremities.

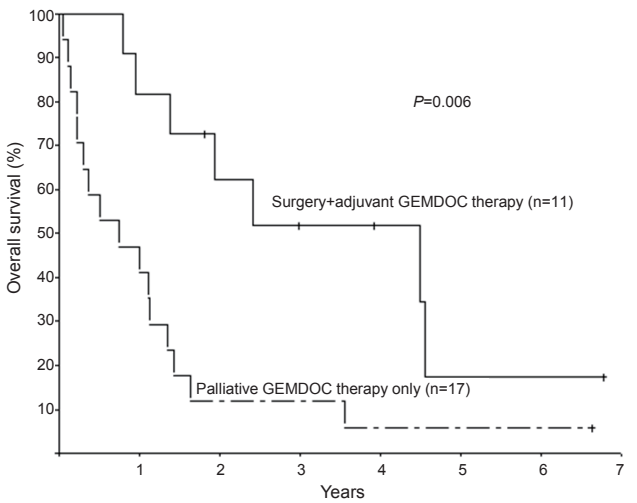

Fig. 4. The Korea Cancer Center Hospital data: comparison of the overall survival (OS) of patients receiving gemcitabine and docetaxel (GEMDOC) chemotherapy as adjuvant or palliative therapy. OS was determined from the start of GEMDOC chemotherapy to death from any cause.

bone sarcomas, case series reporting the efficacy of GEMDOC chemotherapy analyzed patients with various pathologic diagnoses[13-16]. Data from the Korea Cancer Center Hospital[8] showed that GEMDOC chemotherapy had some activity in osteosarcoma, and better than expected survival after GEMDOC chemotherapy was observed in patients both with and without surgery. The 28 patients (aged 5.0–19.7 years) received a total of 96 courses of chemotherapy (median, 3 courses; range, 1–8 courses) and were followed-up for a median of 14.9 months (range, 0.6–81.4 months). Eleven patients received GEMDOC chemotherapy after surgery as adjuvant chemotherapy. Seventeen patients received GEMDOC chemotherapy as palliative therapy and were eligible for response evaluation. Of these patients, 3 (17.6%) experienced a complete response (CR, including 2 metabolic CR); 1 (5.9%), a partial response (PR), and 3 (29.4%), stable disease (SD). The objective response rate (CR+PR) and tumor control rate (CR+PR+SD) were 23.5% and 41.2%, respectively. The median duration of response was 11.2 months (range, 2.8–14.6 months). OS at 1 year was 53.6%±9.4% and patients who received GEMDOC chemotherapy as adjuvant chemotherapy fared better than those who received GEMDOC chemotherapy as palliative therapy (Fig. 4).

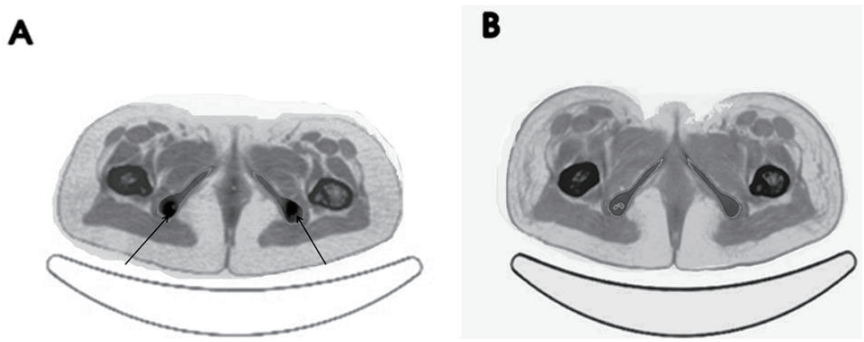

Fig. 5. Response of metastatic bone lesions to radiotherapy and gemcitabine and docetaxel (GEMDOC) chemotherapy. 18F-Flourodeoxyglucose positron emission tomography-computed tomography showed that metabolic activity of both ischia (A, standard uptake value, 3.7) disappeared after radiotherapy and GEMDOC chemotherapy (B, standard uptake value, 0) (data from the Korea Cancer Center Hospital).

2. Local therapy for recurrent, refractory, or unresectable tumors

Effective local control is a crucial element in curing osteosarcoma and complete surgery is the most effective local control measure[1,2,5]. The extremities are the most frequently affected sites of osteosarcoma[1,2], and complete surgery is feasible in the majority of cases. However, cases with unresectable lesions or cases where surgery will not yield an acceptable functional outcome require other local control measures. Radiotherapy has been a mainstay of nonsurgical local tumor control and plays a major role in the treatment of various sarcomas, such as Ewing sarcoma or rhabdomyosarcoma[17]. Osteosarcoma has a low radiosensitivity and few reports have described effective local control using radiotherapy[18-20].

New treatment approaches utilizing both radiotherapy and chemotherapy are underway for various malignancies[21]. Chemotherapeutic agents are administered concurrently or sequentially with radiotherapy and exert both systemic (anticancer) and local (radiosensitizing) effects[21,22]. The presumed mechanisms by which chemotherapeutic agents interact with radiotherapy are as follows[21,22]: (1) inhibition of radiation damage repair, (2) perturbation of cell cycling to increase the fraction of G2/M-phase cells, and (3) specific action on hypoxic cell populations. Cisplatin, 5-fluorouracil (5-FU), ifosfamide, gemcitabine, and docetaxel are frequently used in chemoradiotherapy[21]. The choice, optimal combination, and scheduling of chemotherapy with radiotherapy remain in evolution. For patients with unresectable recurrent or refractory osteosarcoma, a novel or third-line chemotherapeutic agent might be preferred. Sequential or concurrent chemoradiotherapy using gemcitabine showed efficacy in the treatment of nonsmall cell lung cancer[23]. GEMDOC combined with samarium-153 ethylene diamine tetramethylene phosphonate showed promising results in osteosarcoma patients[24,25]. Still, there are no data on the treatment outcome of GEMDOC combined with external beam radiotherapy.

We analyzed the outcomes of eight patients with unresectable recurrent or refractory osteosarcoma who were treated with radiotherapy and GEMDOC chemotherapy at the Korea Cancer Center Hospital[26]. The tumor sites were the bone in six patients and the lung in two patients. Patients received a median of 3.5 courses of GEMDOC chemotherapy (range, 2–6 courses) and the median dose of radiotherapy was 50.0 Gy (range, 46–84 Gy). The objective response rate was 50.0% (2 complete metabolic responses, 1 partial response, and 1 partial metabolic response) (Fig. 5). Responses were maintained for 4.6, 6.1, 6.2, and 13.7 months, respectively. Patients were followed for a median of 8.1 months (range, 2.7–84.6 months) and the median progression-free survival after treatment was 3.6 months (range, 1.1–13.7 months). At the time of writing, two patients were alive, one was lost to follow-up, and five are deceased.

New or other chemotherapeutic agents?

No other agent has come close to replacing the four standard chemotherapeutic agents: HD MTX, cisplatin, doxorubicin, and ifosfamide. Etoposide has shown limited activity when administered as a single agent[27] but may enhance the effect of other drugs such as cyclophosphamide[28,29]. When administered as single agents, 5-azacytidine[30], 5-FU/leucovorin[31], iproplatin[32,33], ecteinascidin-743[34], and topotecan[35] seem to be more or less inactive.

In the few reported studies, the benefits of high-dose chemotherapy and autologous peripheral blood stem cell rescue are still unproven for patients with osteosarcoma[36,37].

The American intergroup trial INT0133 evaluated the efficacy of liposomal muramyl-tripeptide-ethanolamine (MTP), an immune modulator[38,39]. A recent analysis reported a trend for better

 http://dx.doi.org/10.3345/kjp.2015.58.4.123

EFS (P=0.08) and improved OS (P=0.03) for the liposomal MTP arm[39]. Liposomal MTP is available in Korea via the Orphan Drug Center. However, routine use is hampered due to its tremendous cost and the lack of confirmatory clinical data.

Inhibitors of IGF1R and its downstream pathways have shown promise in preclinical models of osteosarcoma[40]. Tumor responses to anti-IGF1R therapy have been published for a total of 7 patients with osteosarcoma[41]. The outcomes of additional phase I and phase II studies have yet to be reported. The Italian Sarcoma Group reported that a combination of sorafenib and the mammalian target of rapamycin inhibitor everolimus showed activity as a further-line treatment for patients with advanced or unresectable osteosarcoma[42].

Conclusions

The survival of Korean patients with osteosarcoma has improved over the last 20 years and is comparable to that reported in major Euro-American studies. However, patients with metastasis at the time of diagnosis and those with relapsed tumors have poor prognosis. Currently, the search for new chemotherapeutic agents and alternative treatment strategies, such as therapies targeting biological markers, angiogenesis, and the immune system, is underway to improve the survival of these patients.

Conflict of interest

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

References

1. Jaffe N. Osteosarcoma: review of the past, impact on the future. The American experience. Cancer Treat Res 2009;152:239-62.
2. Bielack S, Kempf-Bielack B, Schwenzer D, Birkfellner T, Delling G, Ewerbeck V, et al. Neoadjuvant therapy for localized osteosarcoma of extremities. Results from the Cooperative osteosarcoma study group COSS of 925 patients. Klin Padiatr 1999;211:260-70.
3. Ministry for Health, Welfare and Family Affairs. Annual report of cancer incidence (2011), cancer prevalence (2011) and survival (1993–2011) in Korea. Seoul: Ministry for Health, Welfare and Family Affairs, 2011.
4. Lee JA, Park BK; for the Korean Society of Pediatric Hematology and Oncology. Osteosarcoma of children and adolescents: analysis from the Korean Society of Pediatric Hematology-Oncology (KSPHO). In: Proceedings of the 59th Annual Meeting of the Korean Pediatric Society; 2009 Oct 23-24; Seoul, Korea.
5. Fuchs N, Bielack SS, Epler D, Bieling P, Delling G, Korholz D, et al. Long-term results of the co-operative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. Ann Oncol 1998;9:893-9.
6. Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghi A, et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol 2003;21:710-5.
7. Lee YJ, Lee HJ, Kim DH, Lim JS, Lee JH, Park KD, et al. Outcome after relapse in childhood and adolescent osteosarcoma: single institution experience in Korea. Korean J Pediatr 2008;51:78-83.
8. Song BS, Seo J, Kim DH, Lim JS, Yoo JY, Lee JA. Gemcitabine and docetaxel for the treatment of children and adolescents with recurrent or refractory osteosarcoma: Korea Cancer Center Hospital experience. Pediatr Blood Cancer 2014;61:1376-81.
9. Leu KM, Ostruszka LJ, Shewach D, Zalupski M, Sondak V, Biermann JS, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. J Clin Oncol 2004;22:1706-12.
10. Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20:2824-31.
11. Bay JO, Ray-Coquard I, Fayette J, Leyvraz S, Cherix S, Piperno-Neumann S, et al. Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: a retrospective analysis. Int J Cancer 2006;119:706-11.
12. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007;25:2755-63.
13. Navid F, Willert JR, McCarville MB, Furman W, Watkins A, Roberts W, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer 2008;113:419-25.
14. Rapkin L, Qayed M, Brill P, Martin M, Clark D, George BA, et al. Gemcitabine and docetaxel (GEMDOX) for the treatment of relapsed and refractory pediatric sarcomas. Pediatr Blood Cancer 2012;59:854-8.
15. Qi WX, He AN, Tang LN, Shen Z, Lin F, Yao Y. Efficacy and safety of gemcitabine-docetaxel combination therapy for recurrent or refractory high-grade osteosarcoma in China: a retrospective study of 18 patients. Jpn J Clin Oncol 2012;42:427-31.
16. Mora J, Cruz CO, Parareda A, de Torres C. Treatment of relapsed/refractory pediatric sarcomas with gemcitabine and docetaxel. J Pediatr Hematol Oncol 2009;31:723-9.
17. McGovern SL, Mahajan A. Progress in radiotherapy for pediatric sarcomas. Curr Oncol Rep 2012;14:320-6.
18. Schwarz R, Bruland O, Cassoni A, Schomberg P, Bielack S. The role of radiotherapy in oseosarcoma. Cancer Treat Res 2009;152:147-64.
19. Oertel S, Blattmann C, Rieken S, Jensen A, Combs SE, Huber PE, et al. Radiotherapy in the treatment of primary osteosarcoma: a single center experience. Tumori 2010;96:582-8.
20. DeLaney TF, Park L, Goldberg SI, Hug EB, Liebsch NJ, Munzenrider JE, et al. Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 2005;61:492-8.
21. Wilson GD, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. Semin Radiat Oncol 2006;16:2-9.
22. Anderson P, Aguilera D, Pearson M, Woo S. Outpatient chemotherapy plus radiotherapy in sarcomas: improving cancer control with radiosensitizing agents. Cancer Control 2008;15:38-46.
23. Salama JK, Vokes EE. New radiotherapy and chemoradiotherapy approaches for non-small-cell lung cancer. J Clin Oncol 2013;31:

1029-38.
24. Anderson PM, Wiseman GA, Dispenzieri A, Arndt CA, Hartmann LC, Smithson WA, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002;20:189-96.
25. Anderson PM, Subbiah V, Rohren E. Bone-seeking radiopharmaceuticals as targeted agents of osteosarcoma: samarium-153-EDTMP and radium-223. Adv Exp Med Biol 2014;804:291-304.
26. Lee JA, Song BS, Choi AR, Lim SW, Ahn JH, Seo JH, et al. Radiotherapy and gemcitabine-docetaxel chemotherapy in children and adolescents with unresectable recurrent or refractory osteosarcoma. In: Proceedings of the 63th Annual Meeting of the Korean Pediatric Society; 2013 Oct 18-19; Seoul, Korea.
27. Kebudi R, Gorgun O, Ayan I. Oral etoposide for recurrent/progressive sarcomas of childhood. Pediatr Blood Cancer 2004;42:320-4.
28. Saleh RA, Graham-Pole J, Cassano W, Abbot F, Vander Griend R, Dickson N, et al. Response of osteogenic sarcoma to the combination of etoposide and cyclophosphamide as neoadjuvant chemotherapy. Cancer 1990;65:861-5.
29. Rodriguez-Galindo C, Daw NC, Kaste SC, Meyer WH, Dome JS, Pappo AS, et al. Treatment of refractory osteosarcoma with fractionated cyclophosphamide and etoposide. J Pediatr Hematol Oncol 2002;24:250-5.
30. Srinivasan U, Reaman GH, Poplack DG, Glaubiger DL, LeVine AS. Phase II study of 5-azacytidine in sarcomas of bone. Am J Clin Oncol 1982;5:411-5.
31. Pratt CB, Meyer WH, Howlett N, Douglass EC, Bowman LC, Poe D, et al. Phase II study of 5-fluorouracil/leucovorin for pediatric patients with malignant solid tumors. Cancer 1994;74:2593-8.
32. Nitschke R, Pratt C, Harris M, Krischer J, Vietti TJ, Grier H, et al. Evaluation of CHIP (iproplatin) in recurrent pediatric malignant solid tumors. A phase II study (Pediatric Oncology Group). Invest New Drugs 1992;10:93-6.
33. Pawinski A, Crowther D, Keizer HJ, Voute PA, Somers R, van Glabbeke M, et al. The EORTC Phase II study of iproplatin in advanced osteogenic sarcoma. Eur J Cancer 1999;35:163-4.
34. Laverdiere C, Kolb EA, Supko JG, Gorlick R, Meyers PA, Maki RG, et al. Phase II study of ecteinascidin 743 in heavily pretreated patients with recurrent osteosarcoma. Cancer 2003;98:832-35.
35. Blaney SM, Needle MN, Gillespie A, Sato JK, Reaman GH, Berg SL, et al. Phase II trial of topotecan administered as 72-hour continuous infusion in children with refractory solid tumors: a collaborative Pediatric Branch, National Cancer Institute, and Children's Cancer Group Study. Clin Cancer Res 1998;4:357-60.
36. Fagioli F, Aglietta M, Tienghi A, Ferrari S, Brach del Prever A, Vassallo E, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. J Clin Oncol 2002;20:2150-6.
37. Meyers PA. High-dose therapy with autologous stem cell rescue for pediatric sarcomas. Curr Opin Oncol 2004;16:120-5.
38. Chou AJ, Kleinerman ES, Krailo MD, Chen Z, Betcher DL, Healey JH, et al. Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. Cancer 2009;115:5339-48.
39. Meyers PA, Chou AJ. Muramyl tripeptide-phosphatidyl ethanolamine encapsulated in liposomes (L-MTP-PE) in the treatment of osteosarcoma. Adv Exp Med Biol 2014;804:307-21.
40. Cao Y, Roth M, Piperdi S, Montoya K, Sowers R, Rao P, et al. Insulin-like growth factor 1 receptor and response to anti-IGF1R antibody therapy in osteosarcoma. PLoS One 2014;9:e106249.
41. Bagatell R, Herzog CE, Trippett TM, Grippo JF, Cirrincione-Dall G, Fox E, et al. Pharmacokinetically guided phase 1 trial of the IGF-1 receptor antagonist RG1507 in children with recurrent or refractory solid tumors. Clin Cancer Res 2011;17:611-9.
42. Grignani G, Palmerini E, Ferraresi V, D'Ambrosio L, Bertulli R, Asaftei SD, et al. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. Lancet Oncol 2015;16:98-107.