Current management of pediatric osteosarcoma

Dr. Sergey Postovsky, Clinical Assistant Professor, Rambam Medical Center

Epidemiology

Osteogenic sarcoma (OS) is the most common malignant bone tumor in childhood. It accounts approximately 2 per cent among all childhood cancers. The incidence rates and 95% confidence intervals of osteosarcoma for all races and both sexes are 4.0 (3.5-4.6) for the range 0-14 years and 5.0 (4.6-5.6) for the range 0-19 years per year per million persons (1). OS is tumor of predominantly seen in adolescent population and its peak is coincident with growth spurt typically seen in this age population. Since growth spurt begins in females earlier than in males, peak of OS incidence in females occurs typically 2-4 years earlier. The most frequently affected anatomical parts of long bones in OS are metaphyses. The most prominent growth of human bones takes place in metaphyses; hence most OS originate from these locations. Notwithstanding with this, sometimes other parts of long bones may be source of primary tumor. Practically, all bones, including any flat bones may be place of origin of OS. The most common sites are the femur (42%, with 75% of tumors in the distal femur), the tibia (19%, with 80% of tumors in the proximal tibia), and the humerus (10%, with 90% of tumors in the proximal humerus) (1). (Fig.1).

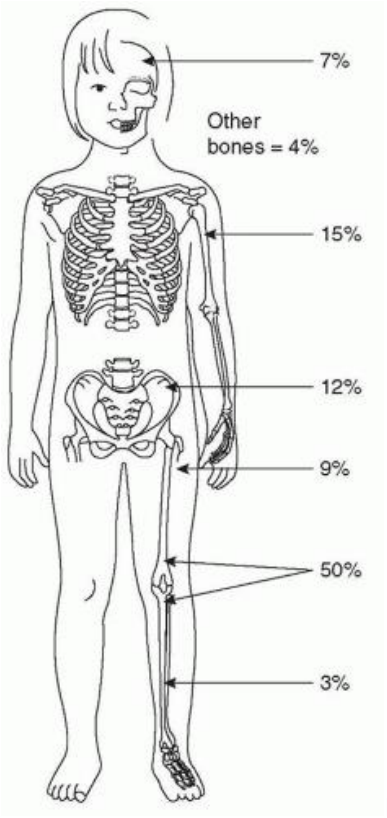


Fig 1: Site of primary tumor in patients with osteosarcoma.[1]

[1] From Gorlick R, Persioglou M, Whelan J, Bone Tumours in Estlin E, Gilbertson R, Wynn R (eds.): Pediatric Hematology and Oncology, Hoboken, NJ, Wiley-Blackwell, 2010.

Most of OS cases are sporadic, but significant albeit relatively small group of OSs are associated with various genetic conditions. OS is a cardinal feature of Li-Fraumeni syndrome that is characterized by increased incidence of various malignant tumors within one family. Germ-line mutations in tumor suppressor gene p53, most frequently occurring within axons 5-8, are responsible of genesis of malignant brain tumors, breast cancer in premenopausal women, acute myelogenous leukemia, and several other types of cancer in addition to OS within affected families (2).

Increased incidence of OS in patients with Retinoblastoma is well established fact. Children with Rb gene (located on long arm of chromosome 13) mutation are prone to develop OS in irradiated bones after radiotherapy was delivered as a part of their retinoblastoma treatment. But even without radiotherapy such children have increased incidence of OS that may occurs practically in any bone (3). Rb gene plays a pivotal role in normal cell division and has been the first gene described as a tumor-suppressor gene in human body.

OS also occurs with increased frequency in patients with Thompson-Rothmund syndrome (4), FEO (familial expansile osteolysis syndrome) (5), Paget disease (very rare in children) and some other genetic syndromes (6).

One other group of OSs is associated with previous radiation therapy. These radiation-induced secondary OSs are frequently characterized by rapid progressive growth, preponderance for early metastasizing, and relative résistance to commonly used chemotherapy. Latent period between previous radiotherapy and development of OS is usually measured by years. There is no clear correlation between radiation dose and probability of development of OS (7).

Clinical Picture and diagnosis

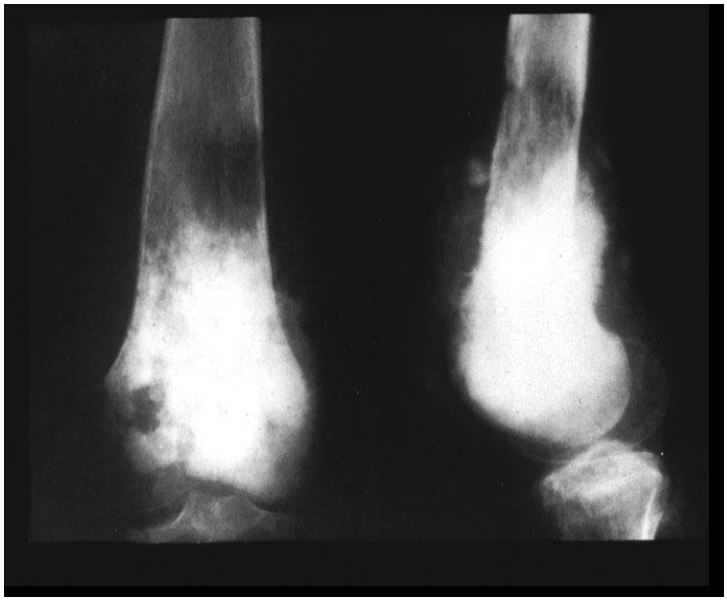
The first complaint that makes a child seek medical help is pain. Frequently this pain is associated with minor traumas which so frequently occur in adolescents. Pain may reach significant intensity thus interfering with normal child's everyday activity. Usually effective simple analgesics such as dipyrone, acetaminophen, or ibuprofen gradually become non-sufficient for reducing pain intensity. Other symptom is limping that lead to significant limitation of physical activity. Typically, the time from appearance of first symptoms till first visit to doctor varies from several days to several weeks and sometimes even months. Interestingly, that despite this lag in time, prognosis usually is not worse for "late-comers" (8).

Children with OS usually first evaluated by family doctors, pediatricians, or orthopedic surgeons. Trauma, infection, rheumatic diseases are among the most common entities included in differential diagnosis. Lack of systemic symptoms such as fever, general weakness, weight loss along with lack of local signs of trauma or inflammation allows competent physician to suspect tumor already at an early stage of diagnostic process. Such local signs as local warmth and redness are typically absent in patients with OS. On the other hand, local pain, swelling, and disturbed function of extremity are present.

Various blood tests are usually of limited help since elevated Alkaline phosphatase (Alk Ph) level is measured only in minority of patients (9). But for those who present with elevated Alk Ph levels in their plasma it may become useful marker of efficacy of treatment and early

indicator of relapse. Another non-specific indicator of tumor burden is LDH which is sometimes is elevated too.

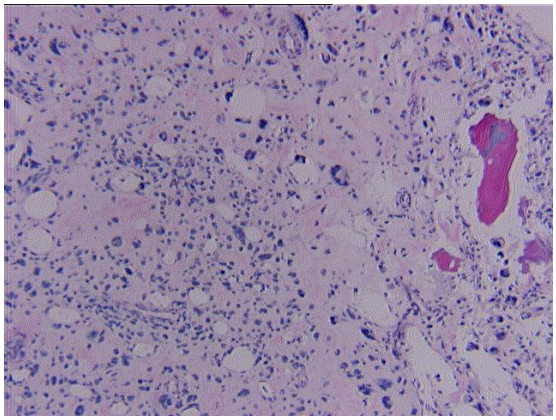
OS is usually well recognized on plain x-rays of affected part of extremity (Pic. 1). CT and especially MRI further establish local extent of tumor and its relation to surrounding soft tissues, blood vessels and nerves.



Pic 1: X-ray of distal femur affected by OS.

The final diagnosis is established by biopsy: Core needle biopsy usually taken under ultrasound guidance or open biopsy performed in surgical suit.

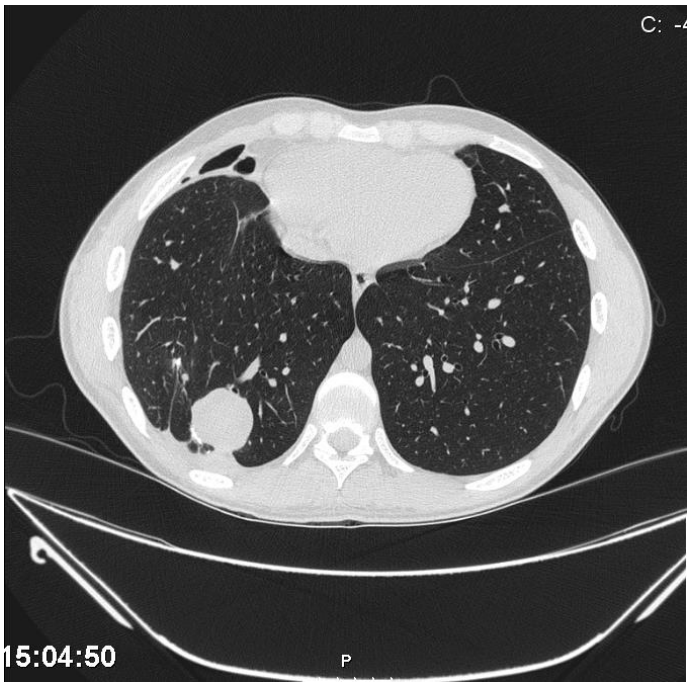
Typical histological picture is characterized by malignant cells producing osteoid or bone with calcification. There is often areas with chondroblastic or fibroblastic differentiation. (Pic. 2) . Among other primary malignant bone tumors, one should first of all exclude Ewing sarcoma that in most cases has its own specific roentgenologic and histologic characteristics.



Pic 2: Microscopic picture of typical (classic) high grade OS.

Metastatic check-up performed usually immediately after establishing histological diagnosis or sometimes even before biopsy when roentgenological picture is straightforward.

Metastatic work-up includes CT of chest and Bone scan with Tc99m. Pulmonary metastases occur in approximately 20% of newly diagnosed patients. They usually subpleural in location and sometimes have calcificates within (Pic.3). Bone metastatic spread is encountered significantly rare on diagnosis and usually accompanies by pulmonary involvement as well. Despite several publications describing use of PET-CT-FDG in staging of OS patients, this method of imaging has not become widely used yet. Despite high sensitivity of PET-CT, its main drawback is relatively low specificity leading in increased incidence of false positive findings frequently necessitating performance of additional diagnostic tests, biopsies, and obsolete anesthesia. Since most metastases are found exclusively in lungs, high resolution CT of chest makes PET-CT unnecessary. In addition, most pulmonary metastases are not sufficiently avid for FDG and this observation coupled with the fact that resolution of pulmonary images obtained on many PET-CTs are frequently inferior to that obtained on modern CTs explains why PET-CT adds little if any useful diagnostic information for OS patients.



Pic 3: Large metastasis within right lung with signs of pleural involvement.

Treatment

As absolute majority of other solid tumors, OS patients cannot be cured without proper local ablation of primary tumor. Before chemotherapy was introduced in the treatment of patients with OS the only therapeutic modality for these patients was surgery, frequently amputation. Despite this seemingly radical method of treatment, most of patients (approximately 85%) ultimately succumbed to their disease, mainly as a result of metastatic spread to lungs. Along with these gruesome results has come understanding that typical OS is a systemic disease in majority of patients even if there is no roentgenological evidence for metastatic spread. The first chemotherapeutic agents were introduced in early 70s of last

century. Among these drugs were HD-MTX, Cisplatin, Vincristine, Doxorubicin, and lately Ifosfamide and Etoposide. Despite that there have been no published studies randomly evaluating chemotherapy influence on survival giving in neoadjuvant setting (before surgery) versus adjuvant, it has gradually become uniformly practice to treat patients first with chemotherapy and perform radical surgery after several courses of chemotherapy (10).

The frequently cited objectives of neoadjuvant chemotherapy are following:

1. Addressing micrometastatic disease without further delay after diagnosis of OS is established.
2. Reducing the overall volume of tumor by decreasing size of soft tissue component of tumor and, thus "making life of orthopedic surgeon easier" during surgery.
3. Allowing pathologist evaluating resected tumor to establish percentage of chemotherapy-induced necrosis that leads to more correct prediction of prognosis.

Currently, the cut-off for discerning "poor" responders from "good" responders is 90 per cent of necrosis. In clinical practice, however, 90 per cent is frequently not sufficient. Most pediatric oncologists are satisfied only with 95 per cent and more. Obviously and unfortunately, even 100 per cent necrosis of tumor tissue after neoadjuvant chemotherapy in pathology lab is not equivalent with 100 per cent survival in clinical practice.

In Israel absolute majority if not all of OS patients are treated according to the EUROAMOS protocol with MAP chemotherapy. Original EUROAMOS protocol used randomization of patients according to whether they were poor or good responders. Those who had their tumor with more 90 per cent necrosis continued to receive MAP and were further randomized to receive or not interferon. The idea to use interferon originated from early publications from Scandinavian researchers (11). Subsequent results of this randomization showed that addition of interferon to chemotherapy does not convey any survival benefit and currently, this drug is not longer used in the treatment of OS patients (12). "Poor" responders were randomized to receive or not two more drugs (in addition to MAP): Ifosfamide and Etoposide. Results of this randomization reported in 2014 on CTOS annual meeting in Berlin showed that addition of these two drugs does not improve survival, at least when giving in the setting of EUROAMOS protocol. The publication of these results in scientific literature is still pending.

Along with chemotherapy, surgical management of OS patients has evolved significantly during last decades as well. Amputations have become rarity. Absolute majority of patients undergo tumor resection with insertion of some kind of endoprosthesis. Incidence of local recurrence is not above 4-7 per cent in Israel while world-wide incidence of local recurrences is reported as high as 8 – 12 per cent (13).

Using contemporary methods of treatment, it is possible to reach 5-year overall survival approximately 65 – 70 per cent and disease-free survival 60 -65 per cent. Most relapses are metastatic, mainly in lungs and occurs during first three years after completion of treatment in majority of cases.

In attempt to further improve survival of non-metastatic patients principally new, non-chemotherapy-based approaches were evaluated. Thus, immune therapy directed at activation of macrophage-mediated phagocytosis of microscopic pulmonary metastatic disease with i.v. infusion of mifamurtide (Mepact) has been shown as potentially efficacious.

In group of macroscopically non-metastatic OS patients therapy with this drug resulted in 8 per cent improvement in survival in comparison with group of patients who received standard chemotherapy alone (14). This drug was approved for clinical use in Europe by EMA in 2009. FDA has not approved Mifamurtide in USA. Unfortunately, certain methodology faults in conducting clinical study with Mifamurtide and lack of credible published data confirming efficacy of this drug in large homogenous groups of patients put the real efficacy of Mifamurtide under question. Further studies may further clarify this complex issue. The accepted policy in Israel regarding Mifamurtide is to administer it to all non-metastatic patients with OS after resection of tumor (in adjuvant manner) and therefore all pediatric oncologists in Israel do routinely administer Mepact in these circumstances.

Recurrence

Approximately 30 per cent of initially non-metastatic at diagnosis patients with OS will eventually recur. Most of recurrences occurs within first three years of diagnosis. Late recurrences that diagnosed after first five years are relatively rare. Most of patients who ultimately recur are "poor" responders to neoadjuvant chemotherapy, albeit even those who had 100 necrosis may develop recurrence as well. In majority of patients with recurrent disease there is evidence for metastatic spread, mainly in lungs. Isolated recurrences are very rare in Israel and almost uniformly forbear systemic spread. The only known curative treatment for recurrent disease, be it isolated local or disseminated, is complete surgical removal of all visible foci of OS. Role of chemotherapy is debatable in this setting. Chemotherapy is given after surgery (if surgical intervention seems feasible) with aim at preventing following recurrences or, in cases when surgery not an option, with aim to modify natural history of disease, hopefully with prolongation of life as main objective. Prognosis for survival after recurrence depends on several factors such as following:

1. Period of time lapsed from initial diagnosis till recurrence (Late or early), usually with cut-off of 12 - 18 months
2. Feasibility of resection of all visible metastatic foci
3. Degree of metastatic spread (lungs only or combined with other organs such as bone, brain, and other locations)
4. Location of pulmonary metastases (unilateral or bilateral)
5. Number of pulmonary metastases
   For those who recurs only in lung after period of at least 18 months since initial diagnosis, has single completely removable metastasis prognosis is relatively good with reported survival that may reach 40 - 50 per cent (15, 16). If metastatic spread in lungs is bilateral but all metastases are seemed feasible for removal, surgery usually performed as a two-step procedure.

Chemotherapy as a second-line treatment was proposed for many patients with recurrent OS. Many options exist. For those who previously had not been treated with Etoposide and Ifosfamide, these drugs may be used in this situation (17).

Other options are Ifosfamide only (18), combination of Gemcitabine and Docetaxel (19, 20), Gemcitabine alone (21). All this chemotherapy is no without side-effects, sometimes serious. On other hand, its efficacy in this setting (recurrent disease) is not firmly established.

Available published data are based on studies which included very limited number of non-homogeneous patients with chemotherapy given in non-randomized manner. In situation when quality of life is becoming the priority as in patients with recurrent metastatic non-operable OS, treating pediatric oncologist should think at least twice before recommending above-mentioned chemotherapy to these patients.

In later years with advent of various sophisticated methods of molecular biology, it has become relatively common practice to evaluate RNA and DNA of tumor tissue for identification of various genetic aberrations with treatment purposes. Unfortunately, in OS percentage of failure of such approach is relatively high and therapeutic yield is low (22). Treatment with multi-kinase inhibitor, Pazopanib is a reasonable option in patients with incurable OS (23, 24). Another approach with "smart" molecules was recently reported by Italian group and included Sorafenib and Everolimus (25). Despite relatively wide arsenal of second-line options, it should be stressed that the only curative method of treatment of patients with recurrent metastatic OS is definitive surgery. Therefore, if surgery is not an option, elements of palliative medicine should be introduced early in this group of patients.

The main mechanism of death in metastatic OS patients is respiratory failure due to progressive growth of pulmonary metastases with resultant breathlessness, air hunger, and hypoxia. Progressive respiratory failure in patients with sarcoma at the end of life is the primary indication for initiation of palliative sedation in children with cancer (26).

Follow-up after completion of treatment

Follow-up after treatment is completed can be divided into two subgroups:

1. Oncological follow-up, and
2. General (pediatric) follow-up

The incidence of developing of recurrent disease in non-metastatic patients is approximately 25 – 30 per cent. Regular oncological follow-up consists from detailed questioning of a child and his parents about newly appeared pain, limping, and other symptoms that may indicate return of disease. Physical examination may reveal limps, local pain. Auscultation of lungs is often non-informative since metastatic pulmonary involvement should be quite extensive in order to manifest on physical examination. Laboratory is usually not helpful as well besides repeated progressive increase in Alk Ph level in those patients whose Alk Ph level was elevated at the time of initial diagnosis, and therefore served as a marker of tumor activity.

Follow-up after primary site usually performed with guidance of operating orthopedic surgeon and consists in most instances of plain x-rays and sometimes, MRI. Systemic oncological follow-up consists of repeated chest CT (usually without injection of contrast media) and bone scan. Since metastatic spread to bones occurs exclusively rare without concomitant pulmonary metastatic disease, many clinicians nowadays perform bone scan with Tc 99m only when diagnosis of pulmonary metastatic disease is established or when specific complaints or findings on physical examination suggest such spread. Spread to other organs also may occur but usually in the context of widely disseminated disease and as a rule at the last stages of disease. Spread to brain may be seen in approximately 8 per cent of terminal OS patients (27).

Imaging during follow-up is performed at regular intervals, usually every three months during the first year after completion of therapy with subsequent lengthening of intervals in the course of time. Rational for such schedule is not entirely clear, seems voluntary and strict following after these recommendations may not lead to earlier diagnosis and to better survival (28).

Pediatric follow-up is executed by pediatric oncologist during first several years after diagnosis (usually 5 years) and thereafter by pediatrician with special knowledge in long-term survivors' pathology. Problems in long-term survivors may be many both medical, psychological, and social. Special attention is paid to cardiac function since all patients in Israel receive Doxorubicin as part of their chemotherapy with cumulative dose reaching 450 mg/m2. EUROAMOS protocol does not prescribes obligatory use of Cardioxane (Dexrazoxane) for prevention of cardiac toxicity, the only drug that may diminish risk of congestive heart failure in such patients in the future. Despite this, accumulating data suggest use Cardioxane in all children who received Doxorubicin for OS treatment (29).

References

1. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. Cancer Treat Res. 2009; 152: 3-13
2. Correa H. Li-Fraumeni Syndrome. J Pediatr Genet. 2016; 5: 84-8.
3. Temming, Arendt M, Viehmann A, Eisele L, Le Guin CH, Schündeln MM, et al. Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center. Pediatr Blood Cancer. 2017; 64: 71-80.
4. Zils K, Klingebiel T, Behnisch W, Mueller HL, Schlegel PG, Fruehwald M, Suttorp M, Simon T, Werner M, Bielack S. Osteosarcoma in patients with Rothmund-Thomson syndrome. Pediatr Hematol Oncol. 2015; 32: 32-40.
5. Bacri D, Arush MW, Vlodavsky E, Kollander Y, Militianu D, **Postovsky S**. Osteogenic sarcoma in a child with familial expansile osteolysis syndrome: an accidental association? J Pediatr Hematol Oncol. 2010; 32: e50-3.
6. Gnoli M, Ponti F, Sangiorgi L. Tumor Syndromes That Include Bone Tumors: An Update. Surg Pathol Clin. 2017; 10: 749-764.
7. Koshy M1, Paulino AC, Mai WY, Teh BS. Radiation-induced osteosarcomas in the pediatric population. Int J Radiat Oncol Biol Phys. 2005 15; 63: 1169-74.
8. Goedhart LM, Gerbers JG, Ploegmakers JJ, Jutte PC. Delay in Diagnosis and Its Effect on Clinical Outcome in High-grade Sarcoma of Bone: A Referral Oncological Centre Study. Orthop Surg. 2016; 8: 122-8.
9. Khoury JF, Ben-Arush MW, Weintraub M, Waldman E, Futerman B, Vlodavsky E, Postovsky S. Alkaline phosphatase level change in patients with osteosarcoma: its role as a predictive factor of tumor necrosis and clinical outcome. Isr Med Assoc J. 2014; 16: 26-32.
10. Harrison DJ, Schwartz CL. Osteogenic Sarcoma: Systemic Chemotherapy Options for Localized Disease. Curr Treat Options Oncol. 2017; 18: 24.
11. Müller CR, Smeland S, Bauer HC, Saeter G, Strander H. Interferon-alpha as the only adjuvant treatment in high-grade osteosarcoma: long term results of the Karolinska Hospital series. Acta Oncol. 2005; 44: 475-80.
12. Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, et al. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. J Clin Oncol. 2015; 33: 2279-87.
13. Amos H.P. Loh, Fariba Navid, Chong Wang, Armita Bahrami, Jianrong Wu, Michael D., et al. Management of Local Recurrence of Pediatric Osteosarcoma Following Limb-Sparing Surgery. Ann Surg Oncol. 2014; 21: 1948–1955.
14. Meyers PA1, Schwartz CL, Krailo MD, Healey JH, Bernstein ML, Betcher D, et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group. J Clin Oncol. 2008; 26: 633-8.
15. Daw NC, Chou AJ, Jaffe N, Rao BN, Billups CA, Rodriguez-Galindo C, et al. Recurrent osteosarcoma with a single pulmonary metastasis: a multi-institutional review. Br J Cancer. 2015; 112: 278-82.

16. Leary SE, Wozniak AW, Billups CA, Wu J, McPherson V, Neel MD, et al. Survival of pediatric patients after relapsed osteosarcoma: the St. Jude Children's Research Hospital experience. Cancer. 2013; 119: 2645-53.
17. Gentet JC1, Brunat-Mentigny M, Demaille MC, Pein F, Avet-Loiseau H, Berger C, et.al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. Eur J Cancer. 1997; 33: 232-7.
18. Chou AJ1, Merola PR, Wexler LH, Gorlick RG, Vyas YM, Healey JH, et al. Treatment of osteosarcoma at first recurrence after contemporary therapy: the Memorial Sloan-Kettering Cancer Center experience. Cancer. 2005;104: 2214-21.
19. Palmerini E, Jones RL, Marchesi E, Paioli A, Cesari M, Longhi A, et al. Gemcitabine and docetaxel in relapsed and unresectable high-grade osteosarcoma and spindle cell sarcoma of bone. BMC Cancer; 2016; 16: 280.
20. 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.
21. Gosiengfiao Y, Reichek J, Woodman J, Ben-Ami T, Walterhouse D. Gemcitabine with or without docetaxel and resection for recurrent osteosarcoma: the experience at Children's Memorial Hospital. J Pediatr Hematol Oncol. 2012; 34: e63-5.
22. O'Day K, Gorlick R. Novel therapeutic agents for osteosarcoma. Expert Rev Anticancer Ther. 2009; 9: 511-23.
23. Umeda K, Kato I, Saida S, Okamoto T, Adachi S. Pazopanib for second recurrence of osteosarcoma in pediatric patients. Pediatr Int. 2017; 59: 937-938.
24. Safwat A, Boysen A, Lücke A, Rossen P. Pazopanib in metastatic osteosarcoma: significant clinical response in three consecutive patients. Acta Oncol. 2014; 53: 1451-4.
25. Grignani G, Palmerini E, Ferraresi V, D'Ambrosio L, Bertulli R, Asaftei SD, Tamburini A, 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.
26. Postovsky S, Moaed B, Krivoy E, Ofir R, Ben Arush MW. Practice of palliative sedation in children with brain tumors and sarcomas at the end of life. Pediatr Hematol Oncol. 2007; 24: 409-15.
27. Postovsky S, Ash S, Ramu IN, Yaniv Y, Zaizov R, Futerman B, Elhasid R, Ben Barak A, Halil A, Ben Arush MW. Central nervous system involvement in children with sarcoma. Oncology. 2003; 65: 118-24.
28. Postovsky S, Barzilai M, Meller I, Kollander Y, Futerman B, Ben Arush MW. Does regular follow-up influence the survival of patients with sarcoma after recurrence? The Miri Shitrit pediatric oncology department experience. J Pediatr Hematol Oncol. 2008; 30: 189-95.
29. Schwartz CL, Wexler LH, Krailo MD, Teot LA, Devidas M, Steinherz LJ, et al. Intensified Chemotherapy With Dexrazoxane Cardioprotection in Newly Diagnosed Nonmetastatic Osteosarcoma: A Report From the Children's Oncology Group. Pediatr Blood Cancer. 2016; 63: 54-61.