



Palliative Treatment for Advanced or Metastatic Osteosarcoma

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The three most common bone sarcomas in adulthood are osteosarcoma, chondrosarcoma, and malignant fibrous histiocytoma. Osteosarcoma occurs predominantly in children, adolescents and young adults. It is the most common primary malignant bone tumor (excluding myeloma), comprising 20% of all primary skeletal malignancies. Peak incidence (60% of cases) is during the second decade of life. It accounts for approximately 5% of the cancers in childhood. Chondrosarcoma is approximately half as common as osteosarcoma and accounts for 10–20% of the primary malignant bone tumors. Patients' ages range from 7 to 73 years, but most tumors are diagnosed in patients between 30 and 60 years of age. Malignant fibrous histiocytoma of bone represents 2–6% of primary malignant bone tumors and occurs at age 30–70 years [1].

Approximately 50–60% of osteosarcomas are located in the distal femur or proximal tibia, while the third most common site is the proximal humerus. In 75% of patients the disease occurs in the metaphysis of long bones. In children and adolescents, 80% of these tumors arise from the bones around the knee, whereas in patients above age 25 years 40% of lesions are located in flat bones. Chondrosarcoma most commonly involves the femur and the pelvis, with a notable preference for the secondary ossification centers. Primary fibrosarcomas and malignant fibrous histiocytomas arise most commonly in long bones, usually the shafts of the femur or tibia [1]. Other primary malignant bone tumors also exist (myeloma), but this review will concentrate only on osteosarcomas as a model.

Prior to the advent of adjuvant therapy, the natural history of localized resectable osteosarcoma was characterized by high local and metastatic rates of recurrence: most patients developed metastases within 6 months of diagnosis, and more than 80% developed local or distant recurrence within 2 years of diagnosis [2–4].

In patients with localized disease the long-term prognosis is influenced by multiple factors, such as:

- *Site:* The risk of progression and death are greater in tumors of the axial skeleton than in limb tumors. Patients with osteosarcoma of craniofacial and other flat bones have a good survival

following complete removal of the involved bone and the outcome may even be improved with chemotherapy [5–7].

- *Resectability:* This is closely related to the issue of site.
- *Prior malignancy:* Patients with osteosarcoma as a second malignant neoplasm (not radiation-induced osteosarcoma) share the same prognosis as that of newly diagnosed patients if they are treated aggressively with surgery and combination chemotherapy [8].
- *Histologic response to preoperative chemotherapy:* This is the best predictor of long-term disease-free survival among patients with resectable tumors. Patients with greater than 95% necrosis in the tumor mass after induction chemotherapy have a better prognosis than those with lesser amounts of necrosis [9–11].

Metastatic or unresectable osteosarcoma at diagnosis, although advanced and forecasting a grim prognosis, is not necessarily incurable. In the past, the progression-free survival rate for patients with metastatic or unresectable osteosarcoma was less than 20%. However, among patients with pulmonary metastatic disease, a 5 year survival of more than 40% is achievable in some situations [1,12]. Aggressive treatment, including surgical removal of primary and/or metastatic disease at the time of diagnosis or after intensive polychemotherapy, is necessary [12]. In contrast, patients with bony metastases have a poor prognosis.

Definition of advanced bone sarcoma

Advanced bone sarcoma has two distinct clinical forms: it may be either locally advanced or metastatic in various organs. Locally advanced bone sarcoma usually involves all the compartments of the limb, or a major adjacent structure such as the neurovascular bundle or organs like the chest wall or vertebra. The disease is not amenable to limited locoregional intervention such as simple limb-sparing surgery or isolated limb perfusion with chemotherapy, but necessitates a life-threatening or highly mutilating surgical procedure. Local recurrence of bone sarcoma represents failure of primary surgery with or without chemotherapy. Such tumors tend to be very symptomatic and impair the patient's quality of life, especially when their location involves a proximal limb, a major

joint or the spine. The symptoms might include severe pain, sepsis, tumor fungation, hemorrhage, thrombosis, pathologic fractures, radiation-induced necrosis and severe functional impairment. The tumor tends to be chemoresistant and requires salvage amputation for a potential cure and, even after radical amputation, metastases are common.

Diffusely metastatic bone sarcoma is usually regarded as an incurable condition that requires palliation. Metastatic disease may be the first presentation of osteosarcoma but is usually a late evolutionary phase of a formerly localized tumor that failed to respond to induction chemotherapy, limb-sparing surgery and adjuvant chemotherapy. The target organs for metastatic spread include the lung, bone, liver and brain. In such cases with diffuse spread, further chemotherapy or surgery is not effective. Exceptions are solitary metastatic lesions in certain organs that can be completely resected. In patients with solitary pulmonary metastasis, and rarely with multiple lung metastases, resection can render them disease-free.

Treatment options for advanced or recurrent osteosarcoma

Palliative chemotherapy

Advanced bone sarcoma, defined by the criteria listed above, is usually fatal and treatment options are limited. Median survival from the time metastases are detected is relatively short, although 20–25% of patients with metastatic sarcoma are alive 2 years after diagnosis [1]. By the time advanced disease is diagnosed many patients with metastatic sarcoma are asymptomatic and the alleviation of physical symptoms may not be an immediate concern [1].

Numerous drug combinations have been assessed in treated and untreated metastatic disease. The most effective of these contained cisplatin, doxorubicin, and high dose methotrexate plus leukovorin either as a two- or three-drug regimen. Numerous small phase II studies have reported response rates in the order of 25–35%. The most important studies on palliative chemotherapy in metastatic osteosarcoma include cyclophosphamide + doxorubicin + dacarbazine (29 patients, response rate 24%), cisplatin + vincristine + high dose methotrexate (29 patients, response rate 28%), dacarbazine + doxorubicin (20 patients, response rate 35%), dacarbazine + doxorubicin (19 patients, response rate 26%), and cyclophosphamide + doxorubicin + actinomycin D (20 patients, response rate 25%) [13].

When these approaches fail to provide ongoing control, decision-making becomes more difficult. Many of these patients, especially the younger ones, may still have considerable life expectancy and good performance status and they are eager to be treated, but there are few realistic treatment options.

Second-line palliative approaches

- *Radiation therapy*: Radiation therapy has a limited role in the management of osteosarcoma because of the natural history of the disease, the relative radioresistance, and the need for large doses of radiation (>70 Gy) to achieve clinical response.
- *Second-line chemotherapy*: Meaningful options for second-line chemotherapy are limited. If there has been a long disease-free

interval, it is common practice to prescribe the same agents that were used for induction and postoperative therapy – namely, doxorubicin, cisplatin and ifosfamide – provided that the left ventricular ejection fraction and renal function are preserved. The recent introduction of dexrazoxane (cardioxane) as a cardioprotector agent enables the administration of doxorubicin in total doses higher than 400–450 mg/m² as long as the cardiac function is normal.

High dose methotrexate (8–10 g/m²) and folinic acid rescue is commonly used for metastatic osteosarcoma, provided that the renal and the bone marrow reserves are adequate and there is no cardiac contraindication for massive hydration. This approach is associated with substantial morbidity: methotrexate is not well tolerated by adults due to renal toxicity, delayed clearance of the drug from the body, neurologic toxicity, and the need for relatively prolonged hospitalization (5–7 days for each methotrexate course).

Ifosfamide may be given as a single agent or in combination with etoposide, together with mesna uroprotection. While given as a monotherapy, the dose of ifosfamide ranges from 2 to 12 g/m² administered by continuous intravenous infusion at a rate of 1.8–3 g/m²/day. In combination with etoposide (100 mg/m²/day for 3–5 days) the dose of ifosfamide is 1.8 g/m²/day given for 5 days. The response rate is low and of short duration. It should be noted that high dose ifosfamide therapy may be nephrotoxic. In an important study on patients with advanced osteosarcoma who were given ifosfamide, Harris et al. [14] found that the likelihood of response was 30% among previously untreated patients but only 10% among those who had recurrent or refractory disease after prior chemotherapy.

Gemcitabine was shown to be promising. We observed that in a small series of seven patients who failed to respond to doxorubicin (adriamycin) and ifosfamide-based chemotherapy, gemcitabine achieved prolonged disease stabilization in five of the seven patients [15]. The protocol consisted of an induction treatment of 1,000 mg/m²/week for 7 weeks followed by a dose of 1,000 mg/m²/week, for 3 weeks out of 4, until disease progression was detected. Disease stabilization was observed in five of the seven patients with a time to progression of 13–96 weeks. In all cases stabilization was accompanied by a positive response (improvement in performance status, alleviation of respiratory symptoms and pain, and reduction in narcotics consumption), which occurred only in those who also achieved a progression-free state.

- *Experimental protocols*: It is accepted as ethical to enroll patients with metastatic osteosarcoma into trials using experimental agents or drug combinations. One example is the application of modulators of multidrug resistance proteins or genes. Brach Del Prever and colleagues [16] reported an important observation in a young boy with metastatic osteosarcoma who was treated by cyclosporine and verapamil in addition to adriamycin and etoposide in order to overcome multidrug resistance. Five treatment courses were provided. Electrocardiograph monitoring during verapamil infusion did not show any cause for concern; myelotoxicity was mild and there was no need for

transfusions. A lung computerized tomography scan at the end of therapy demonstrated a significant decrease in the subpleural metastasis as well as the disappearance of lung nodules. Surgical intervention was performed followed by two chemotherapy treatments. After 26 months there was no sign of disease. In a critical situation in which chemotherapy alone did not seem to offer any real possibility of cure, the combination of verapamil and cyclosporine with chemotherapy allowed a good clinical response with very low toxicity.

Special issues in the management of advanced bone sarcomas

Palliative major amputation of an involved limb

Major amputation was traditionally considered the procedure of choice in patients with bone and soft tissue sarcomas of the limbs [17], however limb-sparing surgery [18] – preceded and followed by effective chemotherapy with or without radiation therapy – has replaced amputation surgery [17] in most cases. Consequently, hemipelvectomy, forequarter amputation, and hip, knee or shoulder disarticulation have become relatively rare procedures in the primary treatment of extremity sarcomas.

For some patients however, local recurrence or persistent chemo- and radio-refractory disease constitutes a major problem, both in the absence or presence of systemic metastases. Local symptoms such as intense pain that is only partially alleviated by opioids, disease- or treatment-related fractures, persistent ulceration and localized antibiotic-refractory infection, bleeding, tumor fungation, inability to walk and to conduct daily activities, further aggravate the problem and impair the patient's quality of life. In this setting, palliative amputation of the limb should be considered [19].

Major amputation carried out on severely ill, debilitated and invalid patients, accompanied by possible morbidity and mortality and without any obvious improvement in life expectancy, raises a major clinical and ethical dilemma. Should we urge the patient to undergo major surgery, with its inherent risks, for the sole purpose of controlling pain and other local problems, without any chance of providing overall control of the disease? Is there a place for "heroic" palliative procedures in cancer patients who have a relatively short life expectancy? Do we have the right to perform a mutilating major amputation that will probably change the self-body image of the patient who already has clinical, social, psychological and emotional problems due to his or her uncontrolled malignancy? Or should we take the conservative approach and continue to try to control the pain and other symptoms by intravenous administration of opioids, even at the cost of impairment of mental functions, loss of consciousness, coma and possible death?

Amputation as a palliative procedure for patients with metastatic carcinoma, melanoma or sarcoma has been well described in the literature [17,20,21]. According to Malawer and co-workers [22], the indications for palliative major amputations include: involvement of a proximal limb or a major joint, accompanied by intractable pain, sepsis, tumor fungation, hemorrhage, vascular thrombosis, pathologic fractures, radiation-induced necrosis; or a limb with severe functional impairment. I contend that pain alone

cannot be considered an indication for major palliative amputation unless it involves a local complication such as fracture, hemorrhage, and/or tumor fungation. This opinion is disputed. According to other authors, poorly controlled pain may constitute an indication for palliative major amputation, especially if it is accompanied by pain-related limb dysfunction or low performance status due to the patient's inability to use the limb because of intractable or refractory pain.

In the absence of life-threatening vital organ involvement, the presence of metastases is not in itself a contraindication. Similarly, since pain or other complications from an extensively involved limb may undermine performance status, poor performance status *per se* may not be a contraindication for such a procedure since it is influenced by the presence of a painful and actually useless limb.

Major amputation surgery is associated with an operative mortality rate of 1–7% [17,20,21]. The perioperative morbidity is not negligible and includes blood loss, hematoma, flap necrosis and wound infection. Although postoperative phantom pain is a common concern, it was not observed among 21 patients who underwent palliative amputation in our center. These procedures included hip disarticulation, knee disarticulation or below-knee amputation, forequarter amputation, and hemipelvectomy (simple or extended). Hemipelvectomy included complete removal of the lower limb, the innominate bone from the symphysis pubis to the sacro-iliac joint and the corresponding buttock [22]. Extended hemipelvectomy also includes, in addition to simple hemipelvectomy, parts of the sacrum, the contralateral pelvic ring and adjacent organs that are infiltrated by the tumor [17,22,23]. Major amputations for palliation of agonizing pain, limb disability and fungating tumor were performed in 12 patients with low performance status. The length of hospitalization was 5–7 days in cases of upper limb amputation, 10–14 days in cases of lower limb amputation or simple hemipelvectomy, and 3–6 weeks in cases of extended hemipelvectomy.

The success of palliative major amputation can be assessed by the improvement in performance status and local control of the symptoms, the reduction in signs of the disease, the extent of rehabilitation of the patient, i.e., the use of a wheelchair versus limb prosthesis, and the lack of complications. In our experience the quality of life was greatly affected by local uncontrolled disease. Among highly selected patients considered suitable for palliative amputation, there was a trend to improved quality of life after the amputation. By these criteria, the surgical procedure was considered "successful" in 20 of the 21 patients. Among this group a median survival of 9 months was observed [19].

Pulmonary metastasectomy

Recurrence of osteosarcoma is most common in the lung. Patients with recurrent osteosarcoma confined to the lungs should be assessed for surgical resectability since cure is sometimes possible with aggressive surgical resection with or without chemotherapy [24–26]. The ability to achieve a complete resection of recurrent disease is the most important prognostic factor at the first relapse, with a 3–5 year survival rate of 20–40% following complete resection of metastatic pulmonary tumors [27]. The 5 year survival rate

following pulmonary metastatic resection is 23–31%. Factors that suggest a better outcome include four or fewer pulmonary nodules, unilateral pulmonary metastases, or longer intervals between primary tumor resection and metastases [28].

Isolated limb perfusion

The novel technique of isolated limb perfusion with tumor necrosis factor-alpha plus melphalan is often considered as a limb salvage procedure for patients with advanced primary or recurrent soft tissue sarcomas [29]. It was recently reported [30] that isolated limb perfusion with recombinant TNF α and melphalan induced major tumor responses in bone sarcomas. Based on a very limited experience, the authors concluded that isolated limb perfusion with recombinant TNF α and melphalan could allow limb salvage in patients with locally advanced bone sarcomas who had failed standard treatment options. Its potential role in the treatment of unresectable bone sarcomas of the extremities merits further evaluation. This approach is appealing as an alternative to amputation surgery, especially for recurrent symptomatic bone sarcoma without systemic spread.

Brain metastases of osteosarcoma

Cerebral metastases of osteosarcomas are rare, but this may change as a result of prolonged patient survival in the modern chemotherapy era. Pulmonary metastases usually precede the development of brain metastases. In one series brain metastases were observed in 13% of patients with prior lung metastases [31]. Such brain metastases of osteosarcoma can arise long after resection of the primary tumor [32]. In one series surgical resection was feasible in 40% of cases and resulted in a dramatic, though transient, clinical improvement [30]. In most of these cases the metastases were solitary. Resections performed in the setting of more widespread intracranial disease have been reported [33], but there is little clinical benefit.

Conclusions

There are many ways to handle an incurable advanced or metastatic bone sarcoma, such as amputation surgery, limb-sparing procedures, conventional or experimental chemotherapy, resection of metastases in specific sites, as well as good supportive care. However, we must always remember that as long as we have something to offer, patients hope for an improvement in their condition. It is this hope that keeps them alive.

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TNF α = tumor necrosis factor-alpha

Reviews

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