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Use of chemotherapy for patients with bone and soft-tissue sarcomas

ABSTRACT

For patients with bone sarcomas, chemotherapy has a proven role in the primary therapy of osteogenic sarcoma and Ewing sarcoma but no role for chondrosarcoma. Chemotherapy's role is currently more limited for patients with soft-tissue sarcomas, as it is generally used to palliate metastatic disease in most subtypes of soft-tissue sarcoma and remains largely investigational in the treatment of operable disease. The chemotherapy regimens for musculoskeletal sarcomas often carry significant potential toxicities, so the efficacy of less intensive and less toxic regimens is a focus of ongoing research.

Surgical resection is the mainstay of treatment for musculoskeletal sarcomas, as detailed earlier in this supplement, but chemotherapy also has a proven role in the primary therapy of most bone sarcomas and a potential role for some patients with soft-tissue sarcomas. This article provides an overview of the roles of chemotherapy for patients with bone and soft-tissue sarcomas and addresses key considerations surrounding chemotherapy in the context of overall patient management.

BONE SARCOMAS

Because most bone sarcomas occur in pediatric patients and young adults, studies of chemotherapy in this disease have often enrolled predominantly young subjects. As a result, very limited data are available in older adults. Single-institution experiences indicate that adults with bone sarcomas have inferior outcomes compared with their pediatric and adolescent counterparts,[1] but the literature on these tumors in adults is scant. Therefore, the following discussion on chemotherapy for bone sarcomas incorporates data from trials conducted predominantly in children and young adults (ie, generally younger than 30 years and with a very large majority younger than 20 years).

Chemotherapy for osteosarcoma

At present, neoadjuvant (preoperative) chemotherapy followed by definitive resection with subsequent adjuvant (postoperative) chemotherapy is the well-established approach to treatment of localized osteosarcomas. Chemotherapy can eradicate the micrometastatic disease that is believed to be present in the majority of patients with clinically resectable cancer.[2]

Efficacy. Historically, prior to the institution of effective chemotherapy, metastatic disease developed in 80% to 90% of patients who underwent curative resection with or without radiation therapy, which resulted in a long-term survival rate of less than 20%.[3] In the 1980s, clinical trials that randomized patients with resectable osteosarcoma to surgery alone or to surgery plus chemotherapy found that the addition of perioperative chemotherapy led to significant improvements in recurrence rates and survival.[4,5] More recent randomized trials have shown that treatment of such patients with modern multiagent chemotherapy regimens results in a 5-year survival rate of approximately 70%.[6] Additionally, response to neoadjuvant (preoperative) treatment has become the most important predictor of outcome, as the median survival of osteosarcoma patients who have greater than 90% necrosis in the resected specimen following neoadjuvant chemotherapy is about 90% at 5 years.[7,8]

Toxicity. Current chemotherapy regimens are based on high doses of methotrexate and leucovorin in combination with doxorubicin, ifosfamide, and platinum. Long-term effects of such regimens include the following[3]:

- Azospermia (in 100% of patients who received a total ifosfamide dose > 75 g/m^2)
- Subclinical renal impairment (in 48% of patients treated with high doses of ifosfamide)
- Hearing impairment (in 40% of patients treated with cisplatin)
- Second malignancies (in 2.1%)
- Cardiomyopathy (in 1.7%).[3]

In light of this, the development of equally effective but less intensive regimens for patients whose disease carries a better prognosis is highly desirable. Ongoing clinical trials are investigating this strategy.

Metastatic disease. Metastatic osteosarcoma is found in approximately 20% of patients at the time of diagnosis. Sarcoma mainly spreads hematogenously, and the lungs are the most common initial site of metastases, being affected in more than 60% of patients who develop metastatic disease.[9] Patients with metachronous lung lesions are initially considered for aggressive treatment with neoadjuvant chemotherapy and subsequent resection of clinically apparent disease, which results in event-free survival rates of 20% to 30%.[3]

Patients with disease limited to the primary tumor and no more than one or two bone lesions fare best. The pres-

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ence of multiple metastases is associated with the poorest prognosis, as few patients with this profile live past 2 years.[10] In a review of 202 pediatric and adult patients with documented metastases at the time of osteosarcoma diagnosis, the presence of more than 5 metastatic lesions (which was reported in 91 patients) was associated with a 5-year overall survival rate of 19%.[9]

Chemotherapy for Ewing sarcoma

Perioperative chemotherapy in patients with localized Ewing sarcoma is believed to reduce the burden of micrometastasis that is thought to be present in most patients with early-stage disease. Five-year survival rates of 50% to 72% have been reported among patients with resectable Ewing sarcoma treated perioperatively with multiagent chemotherapy.[11,12] Notably, randomized trials that studied intense multiagent chemotherapy regimens (consisting of doxorubicin, cyclophosphamide, vincristine, and dactinomycin alternating with etoposide and ifosfamide) reported the best outcomes despite significant but acceptable toxicity. In a large randomized trial involving 398 patients with resectable disease, a 5-year survival rate of 72% was achieved with the above regimen, compared with 61% in patients treated with a less intense regimen that did not contain ifosfamide and etoposide ($P = .01$).[12]

Compressing these standard regimens to an every-14-day instead of every-21-day schedule improved event-free survival at 3 years from 65% to 76% ($P = .028$) without any significant increase in toxicity in a randomized trial involving 568 patients.[13] Data on overall survival from this trial are not yet published.

Metastatic disease. Metastatic Ewing sarcoma is found in 15% to 35% of patients with newly diagnosed disease and is treated with multiagent chemotherapy; resection of residual disease is considered in good responders.[3] This approach produces objective responses to therapy, but long-term survival is rare.

Toxicity. Myelodysplastic syndrome and acute myeloid leukemia are the most dreaded long-term complications of intensive multiagent chemotherapy for Ewing sarcoma and develop in up to 8% of patients.[14] Additionally, ifosfamide can lead to hematuria (~12% incidence), encephalopathy (mild somnolence and hallucinations to coma), chronic renal impairment (6% incidence), and hemorrhagic cystitis (though administration of mesna and generous intravenous hydration can minimize this latter complication).[15] Recent efforts are therefore focused on testing less-intensive regimens in patients who have good prognostic features.

Chondrosarcoma: No role for chemotherapy

Chondrosarcoma, which represents approximately 20% of all bone sarcomas and has a peak incidence in older adults (ie, in the sixth decade of life), is insensitive to chemotherapy. Radiotherapy is also of limited value and is reserved for patients treated in the palliative setting.[16] Definitive management of chondrosarcoma involves adequate surgical resection alone.

SOFT-TISSUE SARCOMAS

Aside from recent advances in the treatment of gastrointestinal stromal tumors with the small-molecule tyrosine kinase inhibitors imatinib and sunitinib (which are beyond the scope of this article), an overall survival advantage with chemotherapy has not been demonstrated in adults with soft-tissue sarcoma.[17]

Resectable disease

The decision to use chemotherapy needs to be weighed against the magnitude of potential clinical benefit and the acute and chronic toxicities that can develop.

Toxicity. Chemotherapy regimens with activity against soft-tissue sarcomas often contain anthracyclines, alkylating agents, and taxanes. These agents can produce serious long-term toxicities, which is especially important in patients treated with curative intent. Doxorubicin and other anthracyclines, for example, may result in cardiomyopathy, the risk of which rises with increasing cumulative dose.[18] In addition, acute myeloid leukemia may develop in 2% to 12% of patients treated with anthracyclines or alkylating agents such as ifosfamide and dacarbazine.[3,19] Renal failure and an elevated risk of bladder carcinoma are uncommonly reported in patients with a history of ifosfamide treatment.[15] Sensory neuropathy associated with the use of taxanes (eg, paclitaxel and docetaxel) is dose dependent and reversible in more than half of patients. However, some patients treated with high doses of these agents can have persistent symptoms of paresthesias, burning, and decreased reflexes, which can be debilitating.[20]

Efficacy of adjuvant chemotherapy. Because chemotherapy puts patients at risk of such serious chronic toxicities, its use can be justified only if it results in significant benefit, such as prolongation of survival. A 1997 meta-analysis of 14 clinical trials evaluating adjuvant chemotherapy in patients with resectable soft-tissue sarcomas found chemotherapy to have an absolute benefit of 10% in recurrence-free survival at 10 years (ie, from 45% survival to 55% survival), with a hazard ratio of 0.75 (95% confidence interval [CI], 0.64–0.87; $P = .0001$) for recurrence or death.[21] However, when the analysis was limited to overall survival at 10 years, the survival difference between patients who received adjuvant chemotherapy and those who did not (54% vs 50%, respectively) was not statistically significant (hazard ratio = 0.89; 95% CI, 0.76–1.03, $P = .12$).[21]

The concept of adjuvant therapy has been revisited since the antisarcoma activity of ifosfamide was established. A large European trial randomized 351 patients with resected soft-tissue sarcoma either to placebo or to doxorubicin and ifosfamide given every 21 days.[22] The preliminary results, reported in abstract form at the 2007 annual meeting of the American Society of Clinical Oncology, showed a higher 5-year survival rate in the placebo arm (69%) compared with the chemotherapy arm (64%).[22] This and other trials using ifosfamide in various drug combinations showed no difference in survival, suggesting that adjuvant chemotherapy should not be considered to be standard practice

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outside of a clinical trial.

Efficacy of neoadjuvant chemotherapy. Neoadjuvant chemotherapy also has been studied in patients with soft-tissue sarcomas. A retrospective analysis found that the greatest benefit is derived in patients with primary tumors larger than 10 cm, in whom neoadjuvant chemotherapy increased 3-year disease-specific survival from 62% to 83%.[23] However, differing results came from a prospective multicenter trial that randomized patients with large primary and recurrent tumors to either surgery alone or surgery preceded by three cycles of neoadjuvant doxorubicin and ifosfamide (all patients could also receive adjuvant radiation therapy, depending on grade and adequacy of resection).[24] The trial suffered from slow accrual, and only 150 patients were enrolled. At 5 years, survival was similar between the groups with and without neoadjuvant chemotherapy.[24] Therefore, neoadjuvant chemotherapy is not yet recommended pending results of larger randomized trials.

No clear role for recurrent disease. Local recurrence of the primary tumor after resection occurs in 10% to 50% of cases of soft-tissue sarcoma, with the specific rate depending on the primary tumor location. The highest incidence of recurrence is found in patients with retroperitoneal and head and neck sarcoma (40% and 50%, respectively), mainly because of the difficulty of obtaining clear margins. Chemotherapy has not been well studied in this setting and is of uncertain value.[3]

Metastatic disease

Metastatic soft-tissue sarcomas may respond to chemotherapy, but there is a lack of evidence that chemotherapy improves overall survival. Pulmonary lesions are the most common site of distant recurrence, and resection of such metastases is sometimes undertaken in well-selected patients. However, there is no level 1 evidence supporting chemotherapy in this clinical setting despite its common preoperative use. There is a paucity of randomized phase 3 trials that compare established palliative chemotherapy regimens to best supportive care. It is believed that some groups of patients do benefit, however, including those who are young and have good performance status, low tumor grade, absence of liver metastasis or pulmonary metastasis only, and a long interval between treatment of the primary tumor and development of metastatic disease.[3] Some histologies, such as uterine leiomyosarcomas and facial/scalp angiosarcomas, respond better to chemotherapy.[17]

Drugs found to have activity against metastatic sarcoma include doxorubicin, ifosfamide, platinum agents, gemcitabine, taxanes, and dacarbazine. Used either alone or in combinations, these drugs produce responses (ie, shrink metastatic tumors) in about 13% to 33% of patients.[3] Use of chemotherapy is frequently curtailed by the acute toxicity of these agents, which includes pancytopenia, transfusion requirements, febrile neutropenia, nausea, alopecia, and significant fatigue, as well as renal failure with ifosfamide or cisplatin and peripheral neuropathy with platinum agents or taxanes. Appropriate patient selection for chemotherapy and exclusion of those who should be managed solely with best supportive care is an important challenge that oncologists often face when managing patients with metastatic soft-tissue sarcoma.

Future directions

Trabectedin (ET-743) is a novel compound with promising activity against soft-tissue sarcomas that acts by inhibiting cell-cycle transition from the G_2 to M stages. The drug covalently binds to the minor grove of the DNA molecule, changing its three-dimensional structure and impairing transcription and possibly DNA repair.[25] Phase 2 studies showed durable responses to trabectedin in 3% to 8% of heavily pretreated patients[26–28] and in 17% of treatment-naïve patients with advanced soft-tissue sarcomas.[25] Time to progression of up to 20 months has been reported in patients who respond or develop stable disease.[3]

Toxic effects of trabectedin include myelosuppression, fever, edema, arthralgias, hepatotoxicity, and (rarely) rhabdomyolysis. To date, these toxicities have been self-limiting. Larger clinical trials and longer follow-up is needed to assess whether this agent has any significant long-term toxicities.

Trabectedin has already been approved in Europe for treatment of chemotherapy-refractory soft-tissue sarcoma when given as a 24-hour infusion every 21 days.

More broadly, an active effort is under way to better understand the molecular derangements in a variety of soft-tissue sarcoma subtypes. The hope is that this understanding will lead to improved therapies that target aberrant proliferation, angiogenesis, and other biologic processes that drive the growth and metastasis of soft-tissue and bone sarcomas.

REFERENCES

1. **Meyers PA, Heller G, Healey J, et al.** Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol 1992; 10:5–15.
2. **Bruland OS, Høifødt H, Saeter G, Smeland S, Fodstad O.** Hematogenous micrometastases in osteosarcoma patients. Clin Cancer Res 2005; 11:4666–4673.
3. **Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ, eds.** Cancer Management: A Multidisciplinary Approach. 11th ed. Manhasset, NY: CMP Medica; 2009.
4. **Link MP, Goorin AM, Miser AW, et al.** The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986; 314:1600–1606.
5. **Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J.** Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol 1987; 5:21–26.
6. **Meyers PA, Schwartz CL, Krailo M, et al.** Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol 2005; 23:2004–2011.
7. **Winkler K, Beron G, Delling G, et al.** Neoadjuvant chemotherapy of osteosarcomas: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol 1988; 6:329–337.
8. **Bramwell VH, Steward WP, Nooij M, et al.** Neoadjuvant chemotherapy with doxorubicin and cisplatin in malignant fibrous histiocytoma of bone: a European Osteosarcoma Intergroup study. J Clin Oncol 1999; 17:3260–3269.
9. **Kager L, Zoubek A, Pötschger U, et al.** Primary metastatic osteosar-

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coma: presentation and outcome of patients treated on Neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol 2003; 21:2011–2018.
10. **Longhi A, Fabbri N, Donati D, et al.** Neoadjuvant chemotherapy for patients with synchronous multifocal osteosarcoma: results in eleven cases. J Chemother 2001; 13:324–330.
11. **Nesbit ME Jr, Gehan EA, Burgert EO Jr, et al.** Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol 1990; 8:1664–1674.
12. **Grier HE, Krailo MD, Tarbell NJ, et al.** Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003; 348:694–701.
13. **Womer RB, West DC, Krailo MD, et al; for the Children's Oncology Group AEWS0031 Committee.** Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors. J Clin Oncol 2008; 26(May 20 suppl):10504. Abstract.
14. **Rodriguez-Galindo C, Poquette CA, Marina NM, et al.** Hematologic abnormalities and acute myeloid leukemia in children and adolescents administered intensified chemotherapy for the Ewing sarcoma family of tumors. J Pediatr Hematol Oncol 2000; 22:321–329.
15. **Brade WP, Herdrich, K, Kachel-Fischer U, Araujo CE.** Dosing and side-effects of ifosfamide plus mesna. J Cancer Res Clin Oncol 1991; 117(suppl 4):S164–S186.
16. **Healey JH, Lane JM.** Chondrosarcoma. Clin Orthop Relat Res 1986; 204:119–129.
17. **Clark MA, Fisher C, Judson I, Thomas JM.** Soft-tissue sarcomas in adults. N Engl J Med 2005; 353:701–711.
18. **Alexander J, Dainiak N, Berger HJ, et al.** Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979; 300:278–283.
19. **Felix CA.** Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta 1998; 1400:233–255.
20. **Postma TJ, Vermorken JB, Liefting AJ, Pinedo HM, Heimans JJ.** Paclitaxel-induced neuropathy. Ann Oncol 1995; 6:489–494.
21. **Sarcoma Meta-analysis Collaboration.** Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997; 350:1647–1654.
22. **Woll PJ, van Glabbeke M, Hohenberger P, et al.** Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): interim analysis of a randomised phase III trial. J Clin Oncol 2007; 25(June 20 suppl):10008. Abstract.
23. **Grobmyer SR, Maki RG, Demetri GD, et al.** Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol 2004; 15:1667–1672.
24. **Gortzak E, Azzarelli A, Buesa J, et al.** A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer 2001; 37:1096–1103.
25. **Garcia-Carbonero R, Supko JG, Maki RG, et al.** Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. J Clin Oncol 2005; 23:5484–5492.
26. **Yovine A, Riofrio M, Blay JY, et al.** Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004; 22:890–899.
27. **Garcia-Carbonero R, Supko JG, Manola J, et al.** Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol 2004; 22:1480–1490.
28. **Le Cesne A, Blay JY, Judson I, et al.** Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol 2005; 23:576–584.

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