Management of Osteosarcoma

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Opinion statement

Improving cure rates for osteosarcoma continues to be a major challenge. The clinical management of individual patients is exacting and requires a skilled, experienced team including a surgeon, pathologist, oncologist, and radiologist, with support from specialist nurses and rehabilitation teams. Outcomes from treatment have improved little in 20 years and remain disappointing. Chemotherapy for osteosarcoma is among the most grueling of any given for solid tumors, and treatment of the primary tumor is associated with permanent disability of some degree in a significant proportion of patients. New systemic treatments remain beyond the horizon. In recognition of these difficulties, an international cooperation has begun with the opening of a randomized trial, European and American Osteosarcoma (EURAMOS) 1, in Europe and the United States. This study heralds a new era of clinical investigation into osteosarcoma, with the promise of valuable biologic insights and rapid evaluation of investigational strategies. Osteosarcoma should always be treated under the guidance of a specialist team, and we recommend that whenever possible, patients be offered entry into EURAMOS 1 or other well-designed clinical trials.

Introduction

Osteosarcoma is a bone-forming tumor arising from osteoblasts. Classically it affects extremity bones around the knee, hip, and shoulder girdles, but any bone may be affected. Much of the emphasis of clinical research in osteosarcoma has been on localized extremity tumors in the young, but pelvic and other tumors of the axial skeleton and craniofacial tumors present major management problems. These latter tumors also more frequently affect adults.

It became apparent in the 1970s that a proportion of osteosarcomas could be cured with surgery and chemotherapy. Attention since has concentrated on reducing the functional morbidity of excision of the primary tumor and optimizing chemotherapy. Approximately two thirds of patients with localized disease will achieve long-term survival, but this is achieved for a much smaller proportion of those with axial or metastatic disease. Relatively little knowledge is available regarding the biology of osteosarcoma that holds real promise for alternative therapeutic approaches.

Treatment

Diet and lifestyle factors

- There are no known dietary associations with osteosarcoma. Exposure to ionizing radiation, most often therapeutically, leads to an increased risk of developing bone cancers, including osteosarcoma [1•]. Radium dial painters are a well-described group with an occupational risk, and a recent study has drawn attention to an excess risk in people in wood-working

occupations [2]. The peak incidence of osteosarcoma in adolescence suggests a link to dysregulation of bone growth. There is no evidence to date demonstrating a link to trauma.

Chemotherapy

- Before 1970, osteosarcoma was a disease with a very poor outcome, with a 5-year overall survival rate of no more than 20%. Friedman and Carter [3] systematically reviewed studies between 1945 and 1972, effectively summarizing the experience of surgery and/or radiotherapy in the treatment of osteosarcoma. Approximately 80% of patients developed locally recurrent or metastatic disease at a median of 10 months after surgery, and the median time to death after development of metastases was 6 months. This suggested that at the time of diagnosis, a large proportion of patients had micrometastases that were clinically undetectable by the imaging techniques then available. In the early 1970s, there was interest in using adjuvant chemotherapy in patients with newly diagnosed nonmetastatic osteosarcoma to prevent the large number of early relapses [4,5]. The development of limb salvage techniques led to the use of chemotherapy before surgery, and the era of neoadjuvant chemotherapy as standard treatment for osteosarcoma was born [6].
- The early drive for neoadjuvant treatment came from the group at Memorial Sloan-Kettering Cancer Center (MSKCC), who published several consecutive series using increasingly complex chemotherapy regimens (T4, T5, T7, T10, T12) [7–10]. The initial published results for the T10 regimen claimed an unparalleled disease-free survival rate of 93% at a median follow-up of 20 months [9] and 76% at 7.75 years, which set the benchmark for other groups [10]. The Scandinavian Sarcoma Group and the Children's Cancer Study Group both carried out multicenter confirmatory studies (protocols SSG-II and CCSG-782, respectively) using the T10 regimen [11,12]. The overall and event-free survival rates were remarkably consistent between the two studies but were inferior to the MSKCC results. However, the latter were from a single institution and might therefore be expected to be better than those achievable in a multi-institutional setting. At the same time, in Germany the Cooperative Osteosarcoma Study (COSS) group performed a series of studies using multiagent regimens [13,14]. The best results were those from the COSS-86 study using a five-drug regimen (doxorubicin, methotrexate, cisplatin, etoposide, and ifosfamide), which produced 10-year overall and event-free survival rates of 72% and 66%, respectively. In addition, the Rizzoli Institute in Italy, using a similar five-drug regimen, achieved a 5-year event-free survival of 63% [15,16].
- The common trend from the American, German, and Italian groups was the progressive use of more drugs in prolonged schedules to try to increase cure rates. An alternative approach was that of the European Osteosarcoma Intergroup (EOI) collaboration, which sought to use shorter dose-intense regimens in a series of large prospective, randomized, controlled studies [17,18•,19••]. An initial study demonstrated no benefit to the addition of methotrexate to doxorubicin and cisplatin, the two-drug combination producing a 5-year disease-free survival of 57% [17]. A second study made the important comparison of doxorubicin and cisplatin with a multiagent combination very similar to the T10 regimen [18•]. The investigators reported no benefit from the longer multiagent protocol, although the overall 5-year event-free survival for the whole study group, at 43.7%, was inferior to the results of the previous EOI study. Nevertheless, the doxorubicin and cisplatin combination was adopted as standard treatment.

The subsequent study examined whether it was possible to improve results by increasing dose intensity by use of colony-stimulating factors [19••]. Results showed that although the proportion of good responders (ie, those achieving ≥ 90% necrosis in the resection specimen) was increased in the more dose-intense arm, this did not translate into improved overall or event-free survival rates. Moreover, the EOI overall survival results remained inferior to those achieved in Germany, Italy, and the United States.

- The most recent US randomized, controlled study in newly diagnosed nonmetastatic osteosarcoma, INT-0133, was designed to investigate whether the addition of ifosfamide and/or the immune adjuvant liposomal muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE) to the standard treatment of doxorubicin, cisplatin, and methotrexate, could improve event-free survival [20••]. L-MTP-PE activates circulating monocytes and pulmonary macrophages to destroy residual tumor cells that are not eliminated by chemotherapy. It has been shown to have activity in rodent xenograft models [21], spontaneous canine osteosarcoma [22], and humans with relapsed osteosarcoma [23–25].
- In INT-0133, all patients received identical cumulative doses of cisplatin, doxorubicin, and high-dose methotrexate and underwent definitive surgical resection of their primary tumor. They were randomly assigned to receive ifosfamide and/or L-MTP-PE in a 2 × 2 factorial design. Disappointingly, an apparent unexpected interaction between the study interventions complicated analysis. However, the overall results are informative. No advantage is shown for the addition of either ifosfamide or L-MTP-PE alone, although event-free survival was significantly increased by the addition of both agents. At present, the nature of this apparent synergy is unclear. The standard regimen of doxorubicin, cisplatin, and methotrexate was associated with a 71% and 64% probability of event-free survival at 3 and 5 years respectively, whereas the addition of ifosfamide and L-MTP-PE resulted in a 78% and 72% probability of event-free survival at 3 and 5 years, respectively.
- In response to the publication of this study, the commercial developer of L-MTP-PE, IDM Pharma (Irvine, CA), suggested that patients with unresectable disease should not have been included in the analysis and event-free survival should not have included second malignancies. Based on these comments, a reanalysis of the data demonstrated a relative reduction in the risk of recurrence of 25% and a relative reduction in the risk of death of 30% in patients who received L-MTP-PE [26]. Overall, this agent holds promise for improving outcomes from osteosarcoma, the first new agent in two decades to do so. However, further studies are necessary to confirm the clinical value of L-MTP-PE, either as a single agent or in combination with conventional chemotherapy.

Prognostic importance of histologic response to chemotherapy

- The introduction of neoadjuvant chemotherapy led to the recognition that the tumor resection specimens could be examined histologically for evidence of response to neoadjuvant chemotherapy by grading the degree of chemotherapy-induced tumor necrosis. An initial system was devised that classified responses as grade I (little or no effect), grade II (partial response, ≥ 50% necrosis), grade III (> 90% necrosis), and grade IV (no viable tumor) [8,27]. Subsequently, responses were grouped as poor (grade I/II, < 90% necrosis) or good (III/IV, ≥ 90% necrosis), and this classification has now been generally adopted. The early MSKCC studies suggested that patients achieving a poor histologic response to chemotherapy had inferior survival compared with

those achieving a good response [9,10]. Subsequent studies have consistently demonstrated 5-year event-free survival rates of 35% to 45% for poor responders and 70% to 80% for good responders.

- The importance of preoperative chemotherapy was investigated in a study by the Pediatric Oncology Group recruiting patients between 1986 and 1993 but not published until 2003 [28•]. Patients were randomly assigned to receive preoperative chemotherapy followed by surgery at week 10 or immediate surgery with postoperative chemotherapy. The overall results of the study were good, with 5-year event-free survival of 65%. No difference was evident between the two treatment arms. However, the amputation rate in the study, at nearly 50%, was unacceptably high whether preoperative chemotherapy was given or not, and despite the long accrual time, only 100 eligible patients were randomized.
- In response to the publication of this study, Bacci et al. [29] claimed that the original justifications for preoperative chemotherapy in osteosarcoma were no longer valid because of improvements in surgical technique and bioengineering that eliminated the need for a long period of preoperative chemotherapy; the failure to demonstrate, albeit in uncontrolled trials, a benefit for changing chemotherapy for poor histologic responders; and a concern about denying patients all active cytotoxic agents. Prompted by the very high amputation rate, the authors also argued for centralization of the specialty surgery required for osteosarcoma to a very few centers. Unfortunately, comparative data of outcomes from surgical centers treating different numbers of patients with osteosarcoma are lacking.

Intensification of postoperative chemotherapy for poor responders

- With the consistent observation of the prognostic significance of a poor response to neoadjuvant chemotherapy came the hypothesis that changing poor responders to a different chemotherapy regimen postoperatively might improve their long-term survival. Early reports of the T10 regimen claimed that such salvage of poor responders was indeed achievable [9], but later publication of the 10-year results did not bear this out [10]. Following the early positive claims, a number of groups adopted this approach [12,13,15,30], but few have been able to demonstrate salvage of poor responders (Table 1). One study reported 5-year event-free survival rates of 67% for good responders and 51% for poor responders, claiming success on the basis of the difference not being statistically significant [31]. The authors did, however, acknowledge that the study might have been underpowered to detect a significant difference. Thus, it appears that there is little evidence to support the concept that modification of postoperative chemotherapy can salvage patients whose tumors demonstrate a poor histologic response to preoperative chemotherapy. An explanation for this may be that response to neoadjuvant chemotherapy is a surrogate measure of biologic aggressiveness of the tumor, which may not be modifiable by currently available therapies.

Intensification of preoperative chemotherapy to increase good responders

- An alternative strategy to modifying postoperative chemotherapy in poor responders to improve survival is to intensify preoperative chemotherapy to increase the proportion of good responders. A number of recent studies have used this approach (Table 2) [14,20••,32,33•], but only one has shown it to be beneficial [20••]. INT-0133, a randomized controlled study discussed previously, randomized patients to receive ifosfamide, L-MTP-PE,

Table 1. Studies of neoadjuvant chemotherapy in nonmetastatic extremity osteosarcoma

Study	Type	Patients, *n*	Chemotherapy	Good responders	Modify postop chemotherapy by histologic response?	Outcome	Outcome better for poor responders by changing chemotherapy?
MSKCC T7 (1982, 1992) [9,10]	Single center	75	Preop and postop: BCD, MTX, V, D	65%	No	12-year DFS 72%	NA
MSKCC T10 (1982, 1992) [9,10]	Single center	153	Preop: MTX, V; postop: D, P, BCD (poor) or D, MTX, BCD (good)	34%	Yes	5-year DFS 72%	No
SSG-1 (T10) (1991) [11]	Multicenter	97	Preop: MTX, V; postop: D, P, BCD (poor) or D, MTX, BCD (good)	17%	Yes	5-year DFS 54%, 5-year OS 64%	No
CCSG-782 (T10) (1997) [12]	Multicenter	268	Preop: MTX, BCD; postop: D, P, BCD (poor) or D, MTX, BCD (good)	28%	Yes	8-year DFS 53%, 8-year OS 60%	No
COSS-80 (1984) [62]	RCT	158	Preop: MTX, D; BCD or P; postop: MTX, D; BCD or P ± IFN	Not reported	No	2.5-year DFS 68%	NA
COSS-82 (1988) [13]	RCT	125	Preop: MTX, BCD or MTX, D, P; postop: modified on response	MTX, BCD 28%; MTX, D, P 60%	Yes	4-year MFS 58%	No
COSS-86 (1998) [14]	Multicenter	171	Preop and postop: MTX, D, P; I (high-risk patients)	76%	No	10-year EFS 66%, 10-year OS 72%	NA
Rizzoli study 1 (1990) [15]	Single center	127	Preop: MTX, P; postop: MTX, D, P (good) or D, BCD (poor)	52%	Yes	5-year DFS 49%	No
Rizzoli study 2 (1993) [16]	Single center	164	Preop: MTX, D, P; postop: MTX, D, P (good) or MTX, D, P, I, E (poor)	71%	Yes	5-year DFS 63%	Yes
EOI study 1 (1992) [17]	RCT	198	Preop and postop: P, D ± MTX	30%	No	D, P: 5-year DFS 57%, 5-year OS 64%; D, P, MTX: 5-year DFS 41%, 5-year OS 50%	NA
EOI study 2 (1997) [18•]	RCT	391	Preop: D, P or MTX, D, V; postop: D, P or MTX, D, V, BCD	D, P 30%, multidrug 29%	No	5-year PFS 44%, 5-year OS 55%	NA
EOI study 3 (2003) [19••]	RCT	504	Preop and postop: D, P ± GCSF	D, P 36%; D, P, GCSF 51%	No	D,P: 5-year DFS 37%, 5-year OS 54%; D,P, GCSF: 5-year DFS 40%, 5-year OS 56%	NA
INT-0133 (2005) [20••]	RCT	507	Preop and postop: MTX, D, P ± I, ± MTP-PE	Not reported	No	3-year EFS: D, P, MTX 71%; D, P, MTX, MTP-PE 69%; D, P, MTX, I 60%; D, P, MTX, I, MTP-PE 78%	NA

BCD—bleomycin, cyclophosphamide, actinomycin D; COSS—Cooperative Osteosarcoma Study; D—doxorubicin; DFS—disease-free survival; E—etoposide; EFS—event-free survival; EOI—European Osteosarcoma Intergroup; GCSF—granulocyte colony-stimulating factor; I—ifosfamide; IFN—interferon; MFS—metastasis-free survival; MSKCC—Memorial Sloan-Kettering Cancer Center; MTP-PE—muramyl tripeptide-phosphatidylethanolamine; MTX—methotrexate; NA—not applicable; OS—overall survival; P—cisplatin; PFS—progression-free survival; postop—postoperative; preop—preoperative; RCT—randomized controlled trial; SSG—Scandinavian Sarcoma Group; V—vincristine.

Table 2. Studies of nonmetastatic extremity osteosarcoma in which preoperative chemotherapy has been intensified aiming to increase the proportion of patients with a good histologic response to preoperative chemotherapy

Study	Type	Patients, *n*	Chemotherapy	Good responses	Outcome	Intensification judged beneficial?
COSS 86 (1998) [14]	Multicenter	171	Methotrexate, doxorubicin, cisplatin, ± ifosfamide (in high-risk patients)	—	10-year EFS 66%, 10-year OS 72%	No
MSKCC T12 (1998) [32]	RCT	73	Methotrexate, BCD, ± cisplatin, doxorubicin	Standard arm 37%, intensified 44%	5-year EFS 73%, 5-year OS 78%	No
INT-0133 (2005) [20••]	RCT	507	Methotrexate, doxorubicin, cisplatin ± ifosfamide and/or MTP-PE	Not reported	3-year EFS: standard 71%, ifosfamide, MTP-PE 78%	Yes
ISG/SSG (2005) [33•]	Multicenter	181	Methotrexate, doxorubicin, cisplatin, ifosfamide	60%	3-year EFS 68%, 3-year OS 86%	No

BCD—bleomycin, cyclophosphamide, actinomycin D; COSS—Cooperative Osteosarcoma Study; EFS—event-free survival; ISG—Italian Study Group; MSKCC—Memorial Sloan-Kettering Cancer Center; MTP-PE—muramyl tripeptide-phosphatidylethanolamine; OS—overall survival; RCT—randomized controlled trial; SSG—Scandinavian Sarcoma Group.

or both in addition to the standard of doxorubicin, methotrexate, and cisplatin. Interestingly, only the addition of both agents improved event-free survival. The remaining three studies failed to demonstrate either an increase in the proportion of good responders or improved survival with intensified preoperative chemotherapy. Thus at present, it is unclear whether this is a beneficial strategy.

Current status of chemotherapy in osteosarcoma

- Currently, the management of nonmetastatic extremity osteosarcoma may be summarized as using dose-intense, multiagent neoadjuvant chemotherapy based on high-dose methotrexate, cisplatin, and doxorubicin, with or without ifosfamide. It has yet to be demonstrated that modification or intensification of postoperative chemotherapy in poor responders is beneficial, and it is unclear whether intensification of preoperative chemotherapy improves survival. A caveat is that the immune adjuvant L-MTP-PE is not currently licensed or widely available, so demonstration of its benefit may ultimately prove to be irrelevant.
- This review of adjuvant and neoadjuvant studies suggests that any further improvements in survival in osteosarcoma by modification of chemotherapy are likely to be small. Large numbers of patients will need to be enrolled in future studies, which given the rarity of the disease, highlights the need for international collaboration. To this end, the European and American Osteosarcoma (EURAMOS) 1 study has been launched in Europe and the United States and is the culmination of collaboration between the North American Children's Oncology Group (COG), the German-Austrian-Swiss COSS Group, the EOI, and the Scandinavian Sarcoma Group (SSG) [34••]. The aim of the study is to evaluate whether it is possible to improve the outcome of both poor and good responders by modification of postoperative chemotherapy. All patients receive preoperative methotrexate, doxorubicin (Adriamycin), and cisplatin (MAP) as given in the control arm of the INT-0133 study. Poor responders are randomized to receive MAP with or without ifosfamide and etoposide. Good responders continue on MAP and are randomized to maintenance pegylated interferon-α or observation. In contrast with previous studies, EURAMOS 1 includes axial as well as extremity tumors and patients with metastatic as well as nonmetastatic disease. Assessment of quality of life and parallel biologic studies are included. Such concerted international collaboration presents extraordinary obstacles but holds the promise for identifying more rapid improvements in treatment.

Other therapeutic approaches

Immune therapy

- Though some experts contend that osteosarcoma is relatively biologically inert, immune approaches to therapy continue to provoke interest. The agents that have been studied the longest are the interferons, a group of cytokines with antiangiogenic activity, direct antitumor activity, and immunostimulating properties. They have shown high activity against osteosarcoma in vitro and in xenograft models [35–37]. Most clinical information comes from two Scandinavian series in which, between 1971 and 1990, 89 patients with primary high-grade osteosarcoma were treated with interferon-α as a single adjuvant to surgery, with an apparent increase in relapse-free survival [38,39,40•].

- Experimental data suggest that multidrug-resistant osteosarcoma cell lines are sensitive to interferon-α [41]. Moreover, interferon has been shown to modulate cytotoxicity by induction of p53 [42] and to increase the chemotherapy sensitivity of several drug-resistant cell lines, including osteosarcoma cell lines [41,43]. EURAMOS 1 (see earlier text) is investigating the benefit of a pegylated formulation of interferon-α in good responders to preoperative chemotherapy as maintenance treatment for 74 weeks following completion of postoperative chemotherapy.
- Other agents have attracted attention, including L-MTP-PE, as described earlier. A phase I study used 105AD7, an anti-idiotype monoclonal antibody against CD55, a complement regulatory protein overexpressed in osteosarcoma. Toxicity was low, and 20 of 28 patients showed a significant immune response to 105AD7 when administered repeatedly starting within 6 months of chemotherapy [44]. Further evaluation of this agent has yet to be undertaken.

Radioisotopes

- Some groups have explored the use of bone-seeking radioisotopes chiefly as a method to provide palliation for patients with bone metastases [45,46]. A potential attraction of this type of approach would be to maximize benefit from irradiation in patients with unresectable primary osteosarcoma. These reports indicate feasibility, but so far only limited clinical benefit has been clearly demonstrated. Additionally, challenges remain regarding dosimetry, particularly in showing that there is dose superiority for radioisotopes versus conventional external-beam radiotherapy in known sites of disease.

Local therapy

- Complete surgical resection of all disease has been clearly demonstrated to be an absolute prerequisite if cure of osteosarcoma is to be achieved [47••], although reports of cure with chemotherapy alone [48] or with radiotherapy to the primary tumor are tantalizing [49,50]. The use of high-intensity focused ultrasound to achieve local control is being evaluated in a range of tumor types. Reports of its effectiveness in replacing surgery for osteosarcoma await confirmation [51].
- In osteosarcoma of craniofacial bones, surgery has often been relied on as the sole treatment modality, and certainly tumors arising in this region are less likely to metastasize. A recent analysis of data from nearly 500 patients, which had been submitted retrospectively from many centers to a central database, showed an overall survival rate of 60%. Five-year survival was 74% for those treated by surgery alone and 71% for surgery and chemotherapy, despite the latter group's having a disproportionate number of patients with factors defined by the study to indicate a poorer prognosis (ie, tumor size, nonmandibular location, positive margins, advanced stage, nonsurgical initial management, and age over 60 years) [52•]. These findings suggest that expert evaluation by an experienced team is essential for all patients with craniofacial osteosarcoma, many of whom should be considered for chemotherapy.

Prognosis

- Although substantial numbers of patients with osteosarcoma are cured after initial combined modality treatment, treatment at time of relapse remains an important problem. A number of groups have reported series of patients with extended follow-up [53–55,56•,57]. Such studies are particularly valuable as a background for interpretation of trials reported with short median follow-up. The greatest number of recurrences occur within the first 2 years of diagnosis, but survival curves are not stable at 5 years.

Complications of management

- Both surgery and chemotherapy are associated with varying degrees of morbidity. Both limb salvage surgery and amputation may result in surgical complications. Moreover, all chemotherapy agents used have a transient toxic effect on proliferating tissues, such as bone marrow, gastrointestinal mucosa, and hair follicles. In addition, they all have other specific toxicities.
- Doxorubicin may cause acute and late cardiac toxicity, which may manifest clinically as congestive heart failure or life-threatening arrhythmias. The risk of cardiac toxicity is related to both dose intensity and total cumulative dose. Recommendations for reducing this risk include close monitoring of cardiac function during treatment, longer infusion over 48 hours, and use of dexrazoxane when sustained reductions in left ventricular ejection fraction or fractional shortening occur.
- Cisplatin causes high-frequency hearing loss, which has been reported in as many as 11% of patients [20••]. It also results in nephrotoxicity, which may be reduced by maintaining good diuresis.
- Methotrexate is used at high doses of 12 g/m^2 administered with vigorous patient hydration, urinary alkalinization, and pharmacokinetically guided folinic acid rescue. Despite these precautions, however, methotrexate-induced toxicities such as mucositis, myelosuppression, nephrotoxicity, hepatotoxicity, and less commonly dermatitis and encephalopathy still occur. There is wide inter- and intrapatient variability regarding methotrexate tolerance, the primary determinant of which appears to be variation in the drug's pharmacokinetics. Methotrexate and its metabolites may precipitate in acid urine to cause renal dysfunction and, in some cases, acute renal failure. Because this agent is cleared primarily by renal excretion, nephrotoxicity results in delayed excretion and sustained elevated plasma methotrexate concentrations, which may lead to marked enhancement of the drug's other toxicities. A review of 3887 patients treated with high-dose methotrexate revealed that 1.8% developed nephrotoxicity (World Health Organization grade ≥ 2), and the mortality rate among those patients was 4.4% [58]. The management of such renal dysfunction includes renal replacement therapy and intravenous administration of carboxypeptidase G2. Carboxypeptidase G2 is an enzyme that cleaves the terminal glutamate from methotrexate and results in the production of the inactive metabolite 4-deoxy-4-amino-N10-methylpteroic acid. Dialysis-based methods have limited effectiveness in removing methotrexate compared with carboxypeptidase G2, which achieves rapid reductions of more than 98% in plasma methotrexate concentrations. However, carboxypeptidase G2 does not appear to increase the time to recovery of renal function compared with supportive treatment including dialysis [58].

Emerging therapies

- In recent years, no new agents have been demonstrated to be active in osteosarcoma. Notable agents tested include taxanes as single agents [59,60] and the DNA minor groove inhibitor trabectidin. With the latter agent, there were three minor responses among 23 evaluable patients, a disappointing result considering the anecdotal reports of trabectidin's activity in osteosarcoma when the drug was first introduced [61]. Ongoing and planned phase II studies of patients with relapsed disease will evaluate the combinations of gemcitabine and docetaxel and gemcitabine and oxaliplatin. Single-agent data for each of these three agents have either been negative or not systematically studied. Licensing of L-MTP-PE is pending and will allow a more extensive evaluation of this agent to address the many remaining questions about its role in osteosarcoma.
- The evolution of systemic treatments for osteosarcoma over the past two decades has been disappointing. Increasing intensity of chemotherapy, with a greater burden of both acute and late toxicity, has not been followed by step-wise improvement in survival. The continuing absence of active new agents in this disease and the lack of interest shown by pharmaceutical companies to resource clinical investigation in this area are of great concern. Recognition of common problems and goals leading to the international collaboration exemplified by the EURAMOS group provides some hope for the future.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Virtanen A, Pukkala E, Auvinen A: **Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients.** *Int J Cancer* 2006, **118:**1017–1021.

An informative report on potential etiologic factors for osteosarcoma.

2. Merletti F, Richiardi L, Bertoni F et al.: **Occupational factors and risk of adult bone sarcomas: a multicentric case-control study in Europe.** *Int J Cancer* 2006, **118:**721–727.
3. Friedman MA, Carter SK: **The therapy of osteogenic sarcoma: current status and thoughts for the future.** *J Surg Oncol* 1972, **4:**482–510.
4. Cortes EP, Holland JF, Wang JJ, et al.: **Amputation and adriamycin in primary osteosarcoma.** *N Engl J Med* 1974, **291:**998–1000.
5. Jaffe N, Frei EI, Traggis D: **Adjuvant methotrexate citrovorum factor treatment of osteogenic sarcoma.** *N Engl J Med* 1974, **291:**996–997.
6. Rosen G, Tan C, Sanmaneechai A, et al.: **The rationale for multiple drug chemotherapy in the treatment of osteogenic sarcoma.** *Cancer* 1975, **35:**936–945.
7. Rosen G, Murphy ML, Huvos AG, et al.: **Chemotherapy, en bloc resection, and prosthetic bone replacement in the treatment of osteogenic sarcoma.** *Cancer* 1976, **37:**1–11.
8. Rosen G, Marcove RC, Caparros B, et al.: **Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery.** *Cancer* 1979, **43:**2163–2177.
9. Rosen G, Caparros B, Huvos AG, et al.: **Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy.** *Cancer* 1982, **49:**1221–1230.
10. 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.
11. Saeter G, Alvegard TA, Elomaa I, et al.: **Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of preoperative chemotherapy with single-agent high-dose methotrexate: a Scandinavian Sarcoma Group study.** *J Clin Oncol* 1991, **9:**1766–1775.
12. Provisor AJ, Ettinger LJ, Nachman JB, et al.: **Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group.** *J Clin Oncol* 1997, **15:**76–84.
13. Winkler K, Beron G, Delling G, et al.: **Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response.** *J Clin Oncol* 1988, **6:**329–337.

14. Fuchs N, Bielack SS, Epler 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:**893–899.

15. Bacci G, Picci P, Ruggieri P, et al.: **Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. The Istituto Rizzoli Experience in 127 patients treated preoperatively with intravenous methotrexate (high versus moderate doses) and intraarterial cisplatin.** *Cancer* 1990, **65:**2539–2553.

16. Bacci G, Picci P, Ferrari S, et al.: **Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 164 patients preoperatively treated with high doses of methotrexate followed by cisplatin and doxorubicin.** *Cancer* 1993, **72:**3227–3238.

17. Bramwell VH, Burgers M, Sneath R, et al.: **A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup.** *J Clin Oncol* 1992, **10:**1579–1591.

18.• Souhami RL, Craft AW, Van der Eijken JW, et al.: **Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup.** *Lancet* 1997, **350:**911–917.

A large multi-international randomized study that demonstrated no survival advantage for a multiagent T10-based chemotherapy regimen over a combination of doxorubicin and cisplatin alone.

19.••Lewis IJ, Nooij M: **Chemotherapy at standard or increased dose intensity in patients with operable osteosarcoma of the extremity; a randomised controlled trial conducted by the European Osteosarcoma Intergroup (ISRCTN 86294690).** *Abstract presented at the Annual Meeting of the American Society of Clinical Oncology.* Chicago, IL; May 31–June 3, 2003.

A large randomized trial comparing a dose-intense schedule of doxorubicin and cisplatin with a standard schedule. The final results will be published in full imminently.

20.••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.

The largest randomized trial of chemotherapy in osteosarcoma. The results have caused debate as an absolute advantage for MTP-PE was not clearly demonstrated.

21. Fidler IJ, Sone S, Fogler WE, Barnes ZL: **Eradication of spontaneous metastases and activation of alveolar macrophages by intravenous injection of liposomes containing muramyl dipeptide.** *Proc Natl Acad Sci U S A* 1981, **78:**1680–1684.

22. MacEwen EG, Kurzman ID, Rosenthal RC, et al.: **Therapy for osteosarcoma in dogs with intravenous injection of liposome-encapsulated muramyl tripeptide.** *J Natl Cancer Inst* 1989, **81:**935–938.

23. Kleinerman ES, Jia SF, Griffin J, et al.: **Phase II study of liposomal muramyl tripeptide in osteosarcoma: the cytokine cascade and monocyte activation following administration.** *J Clin Oncol* 1992, **10:**1310–1316.

24. Kleinerman ES, Meyers PA, Raymond AK, et al.: **Combination therapy with ifosfamide and liposome-encapsulated muramyl tripeptide: tolerability, toxicity, and immune stimulation.** *J Immunother Emphasis Tumor Immunol* 1995, **17:**181–193.

25. Kleinerman ES: **Biologic therapy for osteosarcoma using liposome-encapsulated muramyl tripeptide.** *Hematol Clin N Amer* 1995, **9:**927–938.

26. Romet-Lemonne JL, Mills B, Fridman WH, Munsell M: **Prospectively planned analysis of data from a phase III study of liposomal muramyltripeptide phosphatidylethanolamine in the treatment of osteosarcoma.** *J Clin Oncol* 2005, **23:**6437–6438.

27. Huvos AG, Rosen G, Marcove RC: **Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy, en bloc resection, and prosthetic bone replacement.** *Arch Pathol Lab Med* 1977, **101:**14–18.

28.• Goorin AM, Schwartzentruber DJ, Devidas M, et al.: **Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651.** *J Clin Oncol* 2003, **21:**1574–1580.

A small but important study investigating the timing of surgery for osteosarcoma. No advantage for neoadjuvant treatment was seen, but the amputation rate was unacceptably high by current standards.

29. Bacci G, Ferrari S, Longhi A, et al.: **Preoperative therapy versus immediate surgery in nonmetastatic osteosarcoma.** *J Clin Oncol* 2003, **21:**4662–4663.

30. Bacci G, Picci P, Ferrari S, et al.: **Neoadjuvant chemotherapy for nonmetastatic osteosarcoma of the extremities: the recent experience at the Rizzoli Institute.** *Cancer Treat Res* 1993, **62:**299–308.

31. Bacci G, Ferrari S, Bertoni F, et al.: **Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli/Osteosarcoma-2 protocol: an updated report.** *J Clin Oncol* 2000, **18:**4016–4027.

32. Meyers PA, Gorlick R, Heller G, et al.: **Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol.** *J Clin Oncol* 1998, **16:**2452–2458.

33.• Ferrari S, Smeland S, Mercuri M, et al.: **Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups.** *J Clin Oncol* 2005, **23:**8845–8852.

Very intensive chemotherapy proved toxic and not obviously superior to standard schedules in this prospective but non-randomized study.

34.••The European and American Osteosarcoma Study Group: **The EURAMOS I trial.** Available at: http://www.euramos.org. Accessed August 9, 2006.

Updated information is available about a major international trial between four osteosarcoma study groups.

35. Einhorn S, Strander H: **Is interferon tissue specific? Effect of human leukocyte and fibroblast interferons on the growth of lymphoblastoid and osteosarcoma cell lines.** *J Gen Virol* 1977, **35:**573–577.

36. Hofmann V, Groscurth P, Morant R, et al.: **Effects of leukocyte interferon (E. coli) on human bone sarcoma growth in vitro and in the nude mouse.** *Eur J Cancer Clin Oncol* 1985, **21:**859–863.
37. Brosjo O: **Osteosarcoma and interferon. Studies of human xenografts in the nude mouse.** *Acta Orthop Scand Suppl* 1989, **229:**1–36.
38. Adamson A, Aparisi T, Brostrom LA: **Interferon treatment of osteosarcoma.** *Pontificiae Acad Scient Scripta Varia* 1979, **43:**383–406.
39. Strander H, Bauer HC, Brosjo O, et al.: **Long-term adjuvant interferon treatment of human osteosarcoma. A pilot study.** *Acta Oncol* 1995, **34:**877–880.
40.• Muller CR, Smeland S, Bauer HC, et al.: **Interferon-alpha as the only adjuvant treatment in high-grade osteosarcoma: long term results of the Karolinska Hospital series.** *Acta Oncol* 2005, **44:**475–480.

Updated results of the most extensive clinical experience of interferon in osteosarcoma.

41. Manara MC, Serra M, Benini S, et al.: **Effectiveness of type I interferons in the treatment of multidrug resistant osteosarcoma cells.** *Int J Oncol* 2004, **24:**365–372.
42. Takaoka A, Hayakawa S, Yanai H, et al.: **Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence.** *Nature* 2003, **424:**516–523.
43. Stein U, Walther W, Shoemaker RH: **Modulation of mdr1 expression by cytokines in human colon carcinoma cells: an approach for reversal of multidrug resistance.** *Br J Cancer* 1996, **74:**1384–1391.
44. Pritchard-Jones K, Spendlove I, Wilton C, et al.: **Immune responses to the 105AD7 human anti-idiotypic vaccine after intensive chemotherapy, for osteosarcoma.** *Br J Cancer* 2005, **92:**1358–1365.
45. Anderson PM, Wiseman GA, Dispenzieri A, 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:**189–196.
46. Franzius C, Schuck A, Bielack SS: **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:**1953–1954.
47.•• Bielack SS, Kempf-Bielack B, Delling G, et al.: **Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols.** *J Clin Oncol* 2002, **20:**776–790.

A very valuable analysis of prognostic factors from a large database reporting on multicenter outcomes.

48. Jaffe N, Carrasco H, Raymond K, et al.: **Can cure in patients with osteosarcoma be achieved exclusively with chemotherapy and abrogation of surgery?** *Cancer* 2002, **95:**2202–2210.
49. Machak GN, Tkachev SI, Solovyev YN, et al.: **Neoadjuvant chemotherapy and local radiotherapy for high-grade osteosarcoma of the extremities.** *Mayo Clin Proc* 2003, **78:**147–155.
50. DeLaney TF, Park L, Goldberg SI, et al.: **Radiotherapy for local control of osteosarcoma.** *Int J Radiat Oncol Biol Phys* 2005, **61:**492–498.
51. Wu F, Wang ZB, Chen WZ, et al.: **Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview.** *Ultrason Sonochem* 2004, **11:**149–154.
52.• Smith RB, Apostolakis LW, Karnell LH, et al.: **National Cancer Data Base report on osteosarcoma of the head and neck.** *Cancer* 2003, **98:**1670–1680.

A large series of craniofacial osteosarcoma that details valuable prognostic factors.

53. Strauss SJ, McTiernan A, Whelan JS: **Late relapse of osteosarcoma: implications for follow-up and screening.** *Pediatr Blood Cancer* 2004, **43:**692–697.
54. Chou AJ, Merola PR, Wexler LH, et al.: **Treatment of osteosarcoma at first recurrence after contemporary therapy: the Memorial Sloan-Kettering Cancer Center experience.** *Cancer* 2005, **104:**2214–2221.
55. Bacci G, Briccoli A, Longhi A, et al.: **Treatment and outcome of recurrent osteosarcoma: experience at Rizzoli in 235 patients initially treated with neoadjuvant chemotherapy.** *Acta Oncol* 2005, **44:**748–755.
56.• Kempf-Bielack B, Bielack SS, Jurgens H, et al.: **Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS).** *J Clin Oncol* 2005, **23:**559–568.

Important series detailing outcomes after relapse following optimal first-line therapy.

57. Hauben EI, Bielack S, Grimer R, et al.: **Clinico-histologic parameters of osteosarcoma patients with late relapse.** *Eur J Cancer* 2006, **42:**460–466.
58. Widemann BC, Balis FM, Kempf-Bielack B, et al.: **High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma.** *Cancer* 2004, **100:**2222–2232.
59. Patel SR, Papadopoulos NE, Plager C, et al.: **Phase II study of paclitaxel in patients with previously treated osteosarcoma and its variants.** *Cancer* 1996, **78:**741–744.
60. McTiernan A, Whelan J: **A phase II study of docetaxel for the treatment of recurrent osteosarcoma.** *Sarcoma* 2004, **8:**71–76.
61. Laverdiere C, Kolb EA, Supko JG, et al.: **Phase II study of ecteinascidin 743 in heavily pretreated patients with recurrent osteosarcoma.** *Cancer* 2003, **98:**832–840.
62. Winkler K, Baron G, Kotz R, et al.: **Neoadjuvant chemotherapy for osteogenic sarcoma: results of a cooperative German/Austrian study.** *J Clin Oncol* 1984, **2:**617-624.