Chemotherapeutic Management of Soft Tissue Sarcoma

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Soft tissue sarcomas (STSs) are a heterogeneous group of connective tissue tumors, with more than 50 different subtypes. They account for approximately 1% of adult malignancies. Traditionally, the best attempt at cure for localized disease has been management with wide-excisional surgery, with or without radiation therapy. Because of their overall rarity and diversity, it has been difficult to perform chemotherapy trials in which any definitive recommendations can be made with respect to adjuvant or neoadjuvant chemotherapy. Given that more than half of patients who have sarcoma die of their disease by 5 years, the need for better systemic therapeutics and molecularly targeted therapies is imperative. This review discusses the data on chemotherapy for treatment of metastatic sarcomas and the utility of chemotherapy in the adjuvant and neoadjuvant settings. In addition, the utility of newer biologic agents in the treatment for sarcomas is considered.

Doxorubicin and ifosfamide

The two agents that reproducibly demonstrate a greater than 20% response rate in metastatic sarcoma are doxorubicin and ifosfamide. Doxorubicin (Adriamycin) is the single most effective agent against STS, with response rates reported from 15% to 35% [1–5]. Sarcoma response to doxorubicin may depend on the dose intensity. Unfortunately, increasing the dose of doxorubicin is limited by severe myelosuppression, mucositis, and cardiotoxicity. Ifosfamide (Ifex) also has activity as a single agent in the treatment of STSs [6–8] and is active in patients who have failed doxorubicin-based therapy. With the advent of the uroprotective agent mesna (Mesnex), it became possible to deliver high enough systemic doses without causing the...
damaging hemorrhagic cystitis that occurs when ifosfamide is given without uroprotection [7]. Dacarbazine (DTIC) is another agent frequently used in combination regimens for the treatment of STSs; it can be used in combination with doxorubicin and ifosfamide [9] or alone as a single agent.

To improve on the response rates seen with single-agent therapies, there have been several important randomized trials of combination chemotherapy conducted by the large cooperative groups. The Eastern Cooperative Oncology Group (ECOG) conducted a series of randomized trials comparing single-agent doxorubicin with combination regimens [10,11]. Higher response rates were observed for regimens combining doxorubicin with ifosfamide and doxorubicin with DTIC. The overall response rate was 20% for doxorubicin alone, and 34% for ifosfamide and doxorubicin, with the difference between the regimens being significant ($P = .04$). The median lengths of survival were 8.8 months and 11.5 months, respectively, for the two regimens. The combination therapies offered no overall survival advantage, however, and were associated with significantly higher toxicity. The European Organization for Research and Treatment of Cancer (EORTC) performed a phase III randomized trial comparing doxorubicin (50 mg/m$^2$) and ifosfamide (5 g/m$^2$) with a higher dose of doxorubicin (75 mg/m$^2$) and ifosfamide (5 g/m$^2$) with granulocyte-macrophage colony-stimulating factor (GM-CSF) (250 μg/m$^2$) support. There was no apparent difference in response rate or survival [12]. In 1989, Elias and colleagues [9] performed a phase II trial evaluating doxorubicin, ifosfamide, and DTIC. The overall response rate was 47%, with a notable 10% complete response (CR) rate. It is debatable whether the addition of DTIC to the doxorubicin and ifosfamide regimens adds enough significant benefit to outweigh the added toxicity; therefore, many institutions leave this drug out of the multidrug combinations.

**Beyond doxorubicin and ifosfamide**

Docetaxel (Taxotere) has been evaluated and is marginally active as a single agent [13,14] in sarcomas other than angiosarcoma [15], in which it has been used with good response. Gemcitabine (Gemzar) is minimally effective as a single agent based on phase II data, with 3 (7%) of 46 patients demonstrating a partial response and 8 patients (20%) with stable disease [16]. Maki and colleagues [17,18] published results from a phase II randomized trial using gemcitabine and docetaxel as a combination therapy compared with gemcitabine alone. The combination therapy had a response evaluation criteria in solid tumors (RECIST) rate of 16%, compared with 8% in the single-agent arm. There seemed to be a slightly more favorable response in leiomyosarcomas, and particularly in uterine leiomyosarcomas. A retrospective study published by Bay and colleagues [19] examining the same regimen did not find a statistically significant difference between leiomyosarcomas and other soft tissue tumor histologic subtypes.
Facial and scalp angiosarcomas have responded favorably to paclitaxel [20], and the taxanes have generally been shown to be efficacious in case report studies in angiosarcomas at other sites, alone or in combination with other cytotoxic chemotherapies [21–23]. Furthermore, there have been published case report responses to pegylated liposomal doxorubicin (Doxil) [24] in angiosarcomas and in two phase II studies that revealed some promise in various other sarcoma subtypes [25,26]. Whether there is any utility to using these therapies in the adjuvant setting remains to be seen; unfortunately, the overall small subpatient populations make it difficult to perform appropriately powered studies.

Adjuvant chemotherapy

The role of adjuvant chemotherapy for the treatment of STS is controversial. After adequate local treatment for STS, 50% of patients invariably relapse with local or distant disease and 45% die of sarcoma within 5 years [27]. Adjuvant systemic therapy has proved benefit in several malignancies, notably breast cancer [28], and has also been used extensively in pediatric sarcomas, such as osteosarcoma and Ewing’s sarcoma [29,30]. The goal of treating micrometastatic disease after addressing local disease becomes an important one, and starting in the early 1980s, investigators began to analyze whether adjuvant therapy aided in controlling sarcoma recurrences and, more importantly, overall survival. The Swedish Sarcoma Group (SSG) began an adjuvant study from 1981 to 1986 that accrued 240 patients who had high-grade STSs, randomized to four different groups based on margin status. Patients with adequate surgery received doxorubicin versus control, whereas patients with marginal surgery received adjuvant radiation and doxorubicin or radiation without doxorubicin. At a median follow-up of 40 months, the study was deemed negative because there was no significant difference between the four treatment groups in overall survival, disease-free survival, or local tumor control [31].

An interim analysis of a randomized phase III trial presented at the American Society of Clinical Oncology (ASCO) meeting in 2007 by the EORTC has thus far failed to show a survival advantage for adjuvant chemotherapy in STS [32]. This is contrasted with the 1997 meta-analysis published in The Lancet by the Sarcoma Meta-Analysis Collaboration, which provided evidence of statistically significant improvement in the overall recurrence-free survival and time to local and distant recurrence [33]. This study was a quantitative meta-analysis of 14 studies and examined the individual patient data of 1568 patients comparing adjuvant doxorubicin-based therapy versus no therapy in localized STS. Results of the meta-analysis provided evidence that adjuvant doxorubicin therapy significantly improved time to local recurrence and distant metastases in addition to recurrence-free survival. There was a trend toward overall survival, with an overall survival advantage of 4% ($P = .12$), and in a subset analysis of
extremity sarcomas (n = 886), there was a 7% benefit in survival (P = .029) [33]. In a recent update of the meta-analysis presented in oral abstract form at the 2007 Connective Tissue Oncology Society, this trend was shown to be statistically significant. Four new eligible and adequately randomized trials were identified from their previously used search criteria. These trials involved a total of 385 patients, allowing for the total population to reach 1953 patients. The hazard ratio with adjuvant chemotherapy for local recurrence was 0.73 (95% confidence interval [CI], 0.56–0.95). This corresponded to a 4% absolute risk reduction (ARR). For distant recurrence, the hazard ratio was 0.65 (95% CI, 0.53–0.80), representing a 9% ARR. Finally, for overall recurrence, the hazard ratio was 0.67 (95% CI, 0.53–0.82), signifying a 10% ARR [34]. At the time the abstract was presented at the Connective Tissue Oncology Society meeting, the large EORTC adjuvant trial had not been included in the meta-analysis update. Because this is one of the largest adjuvant trials to date, and has thus far not shown a trend toward improved overall survival, this is likely to have a significant impact on the meta-analysis results. Another smaller study by the Italian Sarcoma Group examining adjuvant chemotherapy in extremity STSs reported a survival advantage in patients who had high-grade sarcomas of the extremities treated with a regimen of epidoxorubicin, ifosfamide, and mesna [35]. After a longer follow-up period with a median follow-up of 89.6 months, however, the overall disease-free survival and overall survival were not found to be statistically significant. Of note, however, compared with the original published data, the differences in median time to progression (31.2 months), median survival (not reached versus 48.6 months), and survival at 4 years (69.8% versus 52.2%) continued to suggest an advantage for the treatment group [36].

Perhaps even the small potential benefit of adjuvant chemotherapy would be worth attempting if it were not for the substantial and well-documented short-term and long-term toxicities of chemotherapy. Short-term side effects and toxicities from single-agent and combination regimens include alopecia, myelosuppression with possible infection, nausea, vomiting, diarrhea, mucositis, and neurologic compromise. The most notable long-term toxicities include cardiomyopathy, which increases with the increasing cumulative dose of anthracycline, the possibility of secondary leukemias, and nephrotoxicity.

Outside of a clinical trial, adjuvant chemotherapy in the care of STS needs to be discussed with patients on an individual basis. We await the final updated published results of the Sarcoma Meta-Analysis Collaboration and of the EORTC adjuvant trial. Despite the larger number of patients included in the adjuvant trials, however, the inclusion of such a heterogeneous group of patients within one study makes broad treatment recommendations difficult.

**Neoadjuvant chemotherapy**

There has been much attention given to the use of neoadjuvant therapy in the care of STS, especially in high-risk extremity STS. There are several
Theoretic advantages that neoadjuvant therapy could lend to patient management. First, by treating a patient who has visible disease, one has an in vivo tumor response model, using radiologic imaging and pathologic response after resection as a means to evaluate disease response. Furthermore, by potentially shrinking a tumor and enabling less morbid operations, for example, there is a better possibility of limb salvage in STSs of the extremity and less opportunity for viable tissue to spread at the time of resection. Finally, by documenting which patients respond to chemotherapy, patients who do not respond adequately are spared further cytotoxic therapy in the postoperative setting or additional chemotherapeutic agents can be added for synergistic or additive cytotoxic effects.

The theoretic disadvantage to neoadjuvant chemotherapy is the peri- and postoperative complications that could potentially be caused by chemotherapy, and the resulting myelosuppression and wound healing limitations. There has been one retrospective study evaluating this specific hypothesis by Meric and colleagues [37], in which 309 patients who presented to a single institution for definitive surgical management of primary STS were retrospectively reviewed. One hundred five patients who received neoadjuvant chemotherapy before surgery were compared with 204 patients who underwent surgery first. There was no evidence to support neoadjuvant chemotherapy increasing postoperative morbidity.

Despite evidence supporting that neoadjuvant chemotherapy does not have a negative impact during the postsurgical period, there has been little evidence to support the use of neoadjuvant chemotherapy in STSs [38–40]. A prime example of the underwhelming outcome of neoadjuvant therapy was an EORTC randomized controlled trial comparing neoadjuvant doxorubicin and ifosfamide in high-risk adult STS. This study failed to show any differences in 5-year disease-free survival (56% versus 52%) or overall survival (65% versus 64%). The study closed early because of poor patient accrual; therefore, it was underpowered [40]. Treatment-induced pathologic necrosis was examined in an interesting article by Eilber and colleagues [41] to determine whether pathologic necrosis correlated with local recurrence and overall survival in patients who received neo-adjuvant therapy for high-grade extremity sarcomas. A total of 496 patients who had intermediate- and high-grade extremity sarcomas received one of five different protocols using radiation with doxorubicin alone; doxorubicin and cisplatin; or doxorubicin, cisplatin, and ifosfamide. The 5- and 10-year local recurrence rates for patients found to have 95% or greater pathologic necrosis were significantly lower (6% and 11%, respectively) than those for the patients with less than 95% pathologic necrosis (17% and 23%, respectively). The patients who achieved 95% or greater pathologic necrosis increased to 48% with the addition of ifosfamide as compared with 13% in all other neoadjuvant protocols combined. A separate retrospective analysis evaluated the impact of neoadjuvant chemotherapy on the extent of the surgical procedure in 65 patients and the hypothesis that radiographic response to neoadjuvant chemotherapy
predicts improved local control and survival. In patients who had stage II and III limb and retroperitoneal STS, only 8 patients (13%) showed a response significant enough to allow their operation to be reduced, and in another six cases (9%), there was actually disease progression, and therefore an increase in the extent of the operation. Of nine extremity sarcoma cases that were thought to require amputation before preoperative therapy, none were able to proceed with limb-sparing operations [42]. One encouraging study published by the Radiation Therapy Oncology Group (RTOG) evaluated patients who had high-grade STS 8 cm or greater in diameter of the extremities and body wall. Patients received three cycles of neoadjuvant mesna, adriamycin, ifosfamide, and DTIC (MAID), interdigitated with preoperative radiation, and then three cycles of postoperative MAID. Although only 59% of patients in this multi-institutional trial actually were able to finish all six cycles of chemotherapy, 22% of 59 assessable patients had partial responses by RECIST criteria, 64% had stable disease, and 8 patients (14%) had progressive disease. There was substantial toxicity in this trial. There were three deaths (5%) associated with treatment, and 84% of patients experienced grade 4 toxicity. The investigators concluded that outside of a clinical trial, the use of this particular regimen was not recommended [43].

New strategies

With the introduction of small-molecule inhibitors like imatinib (Gleevec) and the enormous success they have had in patients who have metastatic gastrointestinal stromal tumors (GISTs), there has been a shift away from developing further cytotoxic therapies for sarcoma or combining different cytotoxic chemotherapeutics and a turn toward molecularly targeted therapies. Furthermore, in the recent GIST adjuvant trials, imatinib has thus far been quite impressive in the postoperative setting, albeit with many as of yet unanswered questions, leading investigators to explore the concept of using more molecularly targeted therapeutics for adjuvant treatment or maintenance therapy in STS [44,45].

Targeting angiogenesis

The humanized antivascular endothelial growth factor (VEGF) antibody, bevacizumab (Avastin), when used in combination with chemotherapy, has been shown to be beneficial in tumor response rates and in overall survival in metastatic colorectal cancer, breast cancer, and lung cancer [46–48]. Many STSs can overexpress VEGF [49,50]; therefore, this is thought to be a viable target and is being evaluated currently in ongoing trials. A recent article by Zhou and colleagues [51] reported on significant responses in an Ewing’s sarcoma mouse xenograft model when treated with DC101 antibody, an inhibitor of VEGF-2. A phase II study evaluating doxorubicin
and bevacizumab in patients who had STS found no higher rate of response beyond that seen with single-agent doxorubicin; however, 65% of patients had stable disease lasting four cycles or longer, prompting the investigators to conclude that further study is warranted. There was substantial cardiac toxicity noted in the trial, with 6 of 17 patients developing cardiac toxicity of grade 2 or more [52].

Sorafenib (Nexavar) is an effective inhibitor of several receptor tyrosine kinases involved in tumor-angiogenesis, including Raf-1, VEGFR-2 and VEGFR-3, platelet-derived growth factor receptor (PDGFR), Flt-3, and c-Kit [53]. It has recently been approved for the treatment of advanced renal cell carcinoma because of these properties, and there are several ongoing phase II studies evaluating its use in locally advanced and metastatic STSs.

Similarly, sunitinib (Sutent), which has been approved for second-line therapy in GIST, is being evaluated in several ongoing phase II studies in STSs, alone or in combination with other chemotherapeutics like ifosfamide.

Thalidomide (Thalomid), an immunomodulatory and antiangiogenic drug, has been evaluated in phase II trials of uterine leiomyosarcomas and found to have little impact on disease response and overall survival [54]. It has been used extensively and with good results in AIDS and non–AIDS-related Kaposi’s sarcoma [55,56], but its use is often limited by side effects, including deep venous thrombosis.

**Apo 2L/Tumor necrosis factor–related apoptosis-inducing ligand**

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) receptor 2 (TR-2) is a member of the tumor necrosis factor (TNF) gene superfamily of receptors. TRAIL is the natural ligand for TR-2, and its binding to the receptor initiates an intracellular caspase cascade and induces apoptosis through engagement of death receptors in several transformed human cell lines [57]. Ewing’s sarcoma cell lines have been shown to express high levels of TR-1 and TR-2 by immunohistochemistry [58]. Furthermore, in vitro models have shown TRAIL to induce apoptosis in multiple sarcoma subtypes with activity enhanced with concurrent chemotherapy [59–61]. A phase I study evaluating Apomab, a human DR5 agonist antibody, in patients who had advanced cancer was reported in abstract form at the 2007 ASCO meeting. At the time of the presentation, there was one minor response seen in a patient who had colorectal cancer. There are several phase II trials currently evaluating these drugs in patients who have sarcoma [62].

**Mammalian target of rapamycin inhibitors**

Mammalian target of rapamycin (mTOR) is a member of the phosphatidylinositol 3’ kinase-related kinase family, which can regulate protein translation, cell cycle progression, and cellular proliferation [63,64]. Rapamycin’s
antitumor activity is thought to occur through cell cycle arrest in the G1 phase [64]. In early phase I studies, there seemed to be demonstrable responses in patients who had sarcoma [65]. There are currently three different drugs inhibiting the mTOR pathway that are being evaluated: RAD-001 (everolimus), CCI-779 (temsirolimus), and AP23573 (deforolimus). Several phase II trials have been recently completed with results pending, and a phase III maintenance study of AP23573 is about to commence in sarcoma. An update of the phase II trial of AP23573 in patients who have advanced sarcomas was reported at ASCO 2006 meeting. Clinical best response (partial and stable disease) was reported in 30% of bone sarcomas, 36% of leiomyosarcomas, 22% of liposarcomas, and 22% of other sarcomas. For each cohort, treatment was defined as active if the proportion of patients with clinical best response for at least 16 weeks was more than 25% [66,67].

**Ecteinascidin-743**

Ecteinascidin-743 (ET-743 [Yondelis]) is a novel chemotherapeutic originally derived from the Caribbean sea squirt, *Ecteinascidia turbinata*, and now produced synthetically. It is a tertahydroisoquinolone alkaloid that binds the minor groove of DNA and blocks cell cycle progression in the G2 and M phases and blocks the organization and assembly of the microtubular cytoskeleton [68,69]. Preclinical studies have shown in vitro activity of ET-743, and in vivo studies have shown tumor response in a xenograft model [69–72]. A phase I trial using a continuous 24-hour infusion schedule showed promise in liposarcoma and osteosarcoma [73]. The most common toxicities included bone marrow suppression and liver function abnormalities. Two phase II studies in patients who had been pretreated with doxorubicin and ifosfamide or combination therapy reported objective response rates in 8% and 6% of patients, with an additional 35% and 50% of patients achieving stable disease for longer than 2 months [74–77]. In a phase II front-line study, one complete and five partial responses were achieved in 35 assessable patients for an overall response rate of 17.1%, with an overall clinical benefit of 20% [78]. Because of encouraging results, specifically in patients who have liposarcoma, 51 patients who had advanced pretreated myxoid liposarcomas and were treated in a compassionate use program at five separate institutions were evaluated retrospectively. ET-743 was given as a 24-hour infusion or as a 3-hour infusion every 21 days. Two patients had complete responses defined by RECIST, and 24 patients had partial responses, with an overall response rate of 51%. Median progression-free survival was 14.0 months, and progression-free survival at 6 months was 88% [79].

**Insulin-like growth factor-1 inhibitors**

Small-molecule insulin-like growth factor-1 receptor (IGF-1R) inhibitors have recently been shown to be clinically active in patients who have
Ewing’s sarcoma in phase I studies and in preclinical studies [80], and there are several phase II studies being initiated at the present time to evaluate this class of drugs in sarcoma. IGF-1R is a tyrosine kinase cell surface receptor that has approximately 70% homology with the insulin receptor [81]. IGF-1R has been linked to autocrine and paracrine control of sarcoma growth, and inhibition of the receptor reduces growth, increases apoptosis of sarcoma cells in vivo and in vitro, and is thought to reduce the metastatic potential of tumors [81–85]. In a preclinical study evaluating NVP-AEW541, an IGF-1R kinase inhibitor, impairment of the IGF-1R was found to contribute substantially to control of malignancy in musculoskeletal tumors, especially in Ewing’s sarcoma cell lines [86].

The future

Despite considerable attention to musculoskeletal tumors over the last 20 to 30 years, little has changed for the treatment of STS, with clinicians still reaching for doxorubicin as a front-line agent based on literature first reported in 1973 [87]. It is difficult to perform well-powered randomized controlled studies in rare tumors, and there is active interest in developing avenues by which investigators can expedite the approval of new drugs that are found to be effective in phase II trials. With continued research into the molecular biology and genetic aberrations associated with the many different subtypes of sarcoma, investigators should be able to identify new targets for therapeutic intervention. Given the recent encouraging results reported in the interim analysis of the adjuvant imatinib study in GIST at the ASCO 2007 meeting, perhaps focusing efforts on finding molecularly targeted agents that can be used in the adjuvant setting would prove more encouraging than the cytotoxic adjuvant studies performed thus far.

Summary

STSs are a heterogeneous group of connective tissue tumors, with more than 50 different subtypes. Given the heterogeneity, and the relative small numbers of patients, performing large adequately powered clinical trials in which one can glean any overall broad treatment decisions based on outcome is difficult at best. There is controversy on which chemotherapeutic agents to use in the adjuvant and metastatic settings, or even if to use chemotherapy in the adjuvant setting. In the metastatic setting, doxorubicin and ifosfamide have remained the standards of care for more than 20 years. With the introduction of what can be considered more targeted agents, however, we might be entering a new era of sarcoma management, and figuring out how to use these agents best is likely to remain a challenging therapeutic question in the years to come.
References


