Advances in Neoadjuvant Chemotherapy in Soft Tissue Sarcomas

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Opinion statement

The use of adjuvant chemotherapy in soft tissue sarcomas (STS) continues to be an area of controversy; however, the group of investigators favoring the use of an anthracycline- and ifosfamide-based regimen for high-risk (American Joint Committee on Cancer stage III) extremity STS is steadily increasing. The historic 5-year survival rate of approximately 50% in this high-risk group treated with local therapy alone represents a poor standard of care, thus there is a need to incorporate systemic therapy early in the management of these patients. Published data from the meta-analysis of doxorubicin-based adjuvant chemotherapy trials and the prospective randomized data with epirubicin and ifosfamide from the Italian Sarcoma Group are frequently used as rationale for this approach. In a rare and heterogenous group of diseases, such as STS, physicians run into negative studies for various reasons that have little to do with the efficacy of the treatment being tested. The wisdom may be in capitalizing further on a positive lead as opposed to nihilism. It is appropriate to acknowledge that the chemotherapeutic agents have limited efficacy and are toxic, especially when used at full therapeutic doses. Selecting patients in whom there is some evidence of benefit, justifying the poor quality of life from receiving chemotherapy, becomes very important. This rationale, with the lessons learned from osteosarcoma research, forms the basis for neoadjuvant chemotherapy for STS. Until we reach the day when we have identified critical tumorigenic targets and their effective inhibitors for most of these tumors, we are obligated to use the available therapeutic armamentarium in the best possible sequence.

Introduction

Soft tissue sarcomas (STS) are rare but anatomically and histologically heterogeneous neoplasia, accounting for less than 1% of all cancers worldwide each year. This is because of the ubiquitous locations of the soft tissues and the nearly 40 recognized histologic subtypes of STS. An estimated 8300 new patients will be diagnosed with STS in the United States in 2003 and approximately 3900 patients will succumb to these diseases, which include adults and children [1]. STS is malignant tumors that may arise in any of the mesodermal tissues of the extremities (60%), trunk and retroperitoneum (30%), or head and neck (10%). These tumors rarely arise in the gastrointestinal tract or gastrointestinal stroma, and a small percentage of these tumors are called gastrointestinal stromal tumors. Malignant gastrointestinal stromal tumors arise most commonly from the stomach or small intestine.

The prognosis of patients with adult STS depends on several factors, including the patient's age, size, histologic grade, and stage of the tumor [2–5]. Factors associated

with a poorer prognosis include age older than 60 years, tumors larger than 5 cm, or high-grade histology [6]. Although low-grade tumors are often curable with local therapy alone, high-grade sarcomas are associated with higher local failure rates and increased metastatic potential [7]. In an analysis of prognostic factors in 1041 patients with localized STS of the extremities, investigators observed that the independent adverse prognostic factors for distant recurrence and disease-specific survival differ from those factors identified for subsequent local recurrence [8]. More specifically, significant independent adverse prognostic factors for local recurrence were age older than 50 years, microscopically positive surgical margins, and the histologic subtypes fibrosarcoma and malignant peripheral nerve tumor. For distant recurrence, intermediate tumor size, high histologic grade, deep location, leiomyosarcoma, and nonliposarcoma histology were independent adverse prognostic factors. For disease-specific survival, large tumor size, high grade, deep location, histologic subtypes leiomyosarcoma and malignant peripheral nerve tumor, microscopically positive surgical margins, and lower extremity site were adverse factors. For postmetastasis survival, only large tumor size (> 10 cm) was an adverse prognostic factor.

Local control can be effectively obtained through the use of surgery and radiation in 70% to 90% of patients; however, up to 50% of patients will eventually recur at distant sites and most of these patients will ultimately die from this cause. The 5-year survivals of patients with resectable STS varies from more than 90% for American Joint Committee on Cancer (AJCC) stage I to II tumors to approximately 50% for AJCC stage III tumors. This review focuses on these high-risk tumors for which the use of adjuvant/neoadjuvant chemotherapy is important.

Treatment

Adjuvant chemotherapy

- Investigations over the past couple of decades have only generated a limited number of active chemotherapeutic agents in STS. Therefore, the use of the available agents should be optimized with regards to dose-intensity and schedule of administration to achieve the best response and maximum possible improvement in disease-free and overall survival. For many years, several investigators around the world have been trying to assess the effects of adjuvant chemotherapy after definitive (surgery plus radiation) local treatment. Because of the rarity and heterogeneity of sarcomas, large prospective trials have been difficult to perform, and smaller trials have lacked the power to arrive at a definitive conclusion, leading most researchers to consider adjuvant chemotherapy as an investigational approach [9]. In 1997, the Medical Research Council published a meta-analysis of more than 1568 patients treated with adjuvant therapy for STS [10]. All the trials used doxorubicin as the basis of therapy in doses up to 480 mg/m^2. Only 29 of 1568 patients received ifosfamide as part of their therapy. Recurrence-free intervals were better with chemotherapy, with hazard ratios for recurrence-free survival in all patients ranging from 0.70 to 0.75 (*ie*, the risk of distant relapse was reduced by 25%–30% in treated patients). Overall survival showed a 4% absolute survival benefit in favor of chemotherapy that did not reach statistical significance ($P = 0.12$). Subset analysis failed to show that the effects of chemotherapy differed by primary site, although the best evidence for an effect of adjuvant chemotherapy was seen in patients with intermediate-sized tumors (5–10 cm) or patients with a tumor in the extremity where a 7% improvement in overall survival was noted in favor of chemotherapy ($P = 0.029$).
- A North American attempt to conduct a large prospective trial of postoperative chemotherapy with the MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) regimen failed because of insufficient patient accrual. It was not until 2001, when the Italian Sarcoma Group published their trial using epirubicin and ifosfamide administered every 3 weeks for five cycles with granulocyte colony-stimulating factor for patients with large (> 5 cm) high-grade STS of the extremities [11••]. The trial had been planned for 200 patients, but it was interrupted after an accrual of 104 patients when an

interim analysis showed a significant survival advantage for the group treated with chemotherapy. The disease-free survival time was 48 months in the treatment group compared with only 16 months in the control (no chemotherapy). The overall survival time was 75 months versus 46 months, with an absolute overall survival benefit of 19% at 4 years ($P = 0.03$). This trial shows proof of concept by demonstrating statistically significant improvement in local control, disease-free survival, and overall survival benefit of adjuvant chemotherapy for appropriately selected high-risk primary or locally recurrent extremity STS when a dose-intensive anthracycline and ifosfamide combination is used.

Neoadjuvant chemotherapy

- The role of neoadjuvant chemotherapy in STS has been an active area of clinical investigation for the past 5 to 10 years. Most of the studies have been small retrospective reviews of single institution experience with neoadjuvant chemotherapy in high-risk STS. High risk is generally defined as large tumors (> 5 cm) and high-grade histology. Table 1 is a list of some of these selected neoadjuvant clinical trials. The rationale for neoadjuvant (preoperative) chemotherapy for patients with large/bulky high-grade sarcoma, especially patients with tumors of the extremity, is based on the lessons learned from the osteosarcoma literature combined with some evidence of efficacy based on the meta-analysis and the randomized trial by the Italian Sarcoma Group described earlier in this paper. Besides the theoretical consideration of early treatment of micrometastases, there are several pragmatic reasons that favor preoperative over postoperative treatment. A reduction in the size of a large lesion may permit surgical resection with less morbidity. Compliance may be better with preoperative therapy and the problem of a small number of patients not being able to get postoperative chemotherapy because of delayed wound healing can be avoided [12]. It is possible that a response to preoperative therapy may provide important prognostic information. Disadvantages potentially include delayed time to local control, if the preoperative treatment is ineffective, and potential delay in wound healing. Investigators from the MD Anderson Cancer Center (Houston, TX) published a retrospective review of their own in-house data addressing the postoperative morbidity in patients receiving neoadjuvant chemotherapy in conjunction with definitive local control [13•]. Of 309 patients who were treated at the University of Texas MD Anderson Cancer Center for definitive surgical management of primary STS, 105 patients receiving neoadjuvant chemotherapy were compared with 204 patients undergoing primary surgical resection. The analysis included 201 patients with STS of the extremities (71 neoadjuvant therapy and 130 primary surgery) and 108 patients with STS of the retroperitoneal/visceral sites (34 neoadjuvant therapy and 74 primary surgery). The incidence of surgical complications was not different for neoadjuvant patients compared to surgical patients with extremity sarcomas (34% vs 41%) and retroperitoneal/visceral sarcomas (29% vs 34%).
- The Mayo Clinic (Rochester, MN) group published their data using neoadjuvant IMAP (ifosfamide, mitomycin, doxorubicin, and cisplatin) in conjunction with granulocyte macrophage colony-stimulating factor (GM-CSF) for patients with high-grade large STS [14•]. Thirty-nine patients with primary extremity or limb girdle high-grade STS were treated with two cycles of preoperative IMAP plus GM-CSF, followed by preoperative irradiation and subsequent limb-sparing surgery. The two sequential monthly cycles of IMAP involved intravenous ifosfamide 2500 mg/m^2 and mesna 2500 mg/m^2 on

Table 1. Neoadjuvant chemotherapy regimens for high-risk soft tissue sarcomas

Study	Neoadjuvant treatment	Patients, *n*	Treatment outcomes LRFS,%	DMFS, %	DFS, %	OS, %
Azzarelli *et al.* [20]	Two cycles of A/I	47	75 (4 years)	69 (4 years)	—	91 (4 years)
Casper *et al.* [21]	Two cycles of A/C/DTIC	29	—	28 months	—	35 months
Pisters *et al.* [22]	Three cycles of CyADIC	76	83 (5 years)	52 (5 years)	46 (5 years)	59 (5 years)
Gortzak *et al.* [23]	Three cycles of A/I vs surgery alone	134	—	—	56 vs 52 (5 years)	65 vs 64 (5 years)
Edmonson *et al.* [14•]	Two cycles of IMAP/ GM-CSF and RT	39	—	85 (2 years)	—	80 (5 years)
Delaney *et al.* [24]	Three cycles of MAID and RT	48	92 (5 years)	75 (5 years)	70 (5 years)	85 (5 years)
Grobmyer *et al.* [25]	A/I vs surgery alone	487	90 vs 78 (2 years)	61 vs 64 (2 years)	—	—
Kraybill *et al.* [15]	Modified MAID and RT	64	79 (3 years)	—	55 (3 years)	75 (3 years)
Schlemmer *et al.* [26]	Four cycles of A/I and RHT	47	50 (5 years)	53% (5-year)	—	57 (5 years)

A/C/DTIC—doxorubicin, cyclophosphamide, and dacarbazine; A/I—doxorubicin and ifosfamide; CyADIC—cyclophosphamide, doxorubicin, and dacarbazine; DFS—disease-free survival; DMFS—distant metastasis-free survival; GM-CSF—granulocyte macrophage colony-stimulating factor; IMAP—ifosfamide, mitomycin, doxorubicin, and cisplatin; LRFS—local recurrence-free survival; MAID—mesna, doxorubicin, ifosfamide, and dacarbazine; OS—overall survival; RHT—regional hyperthermia; RT—radiotherapy.

day 0, followed by identical doses of these agents plus intravenous mitomycin 4 mg/m^2, doxorubicin 40 mg/m^2, and cisplatin 60 mg/m^2 on day 1. GM-CSF 250 μg/m^2 was administered subcutaneously every 12 hours for 4 days beginning 6 days before the chemotherapy and 14 more days beginning the day after chemotherapy was completed. At the beginning of the third month, external beam irradiation was administered daily 5 days each week for five consecutive weeks to total preoperative doses of 4500 cGy. This regimen was accompanied by reduced doses of MAP (mitomycin 6 mg/m^2, doxorubicin 30 mg/m^2, and cisplatin 45 mg/m^2) chemotherapy intravenously on days 0, 21, and 42 of the radiation therapy segment. Approximately 1 month after preoperative irradiation ended, each patient had complete surgical excision with curative intent, using limb-sparing techniques when possible. Radiation to total doses of 5500 to 6500 cGy was accomplished by delivery of an additional 1000 to 2000 cGy to the tumor bed through intraoperative electron beam, brachytherapy, or external beam irradiation at the completion of surgery. Chemotherapy toxicity grade 3 or higher consisted primarily of vomiting (23%), leukopenia (54%), and thrombocytopenia (77%). An estimated 5-year overall survival rate was approximately 80% and freedom from metastasis at 2 years was approximately 85%. The favorable outcome of patients treated on this regimen is encouraging for the continuing investigations of neoadjuvant chemotherapy in the multimodality treatment of STS.

- The Massachusetts General Hospital (Boston, MA) in conjunction with the Radiation Therapy Oncology Group (RTOG) has similar data based on the earlier work done at Massachusetts General Hospital with modified MAID [15]. This work was presented during the 2001 American Society of Clinical Oncology annual meeting and was updated at the 2003 American Society of Clinical Oncology annual meeting. Patients were treated with two cycles of

ifosfamide (2.5 g/m^2 daily for 3 days), doxorubicin (60 mg/m^2), and dacarbazine (675 mg/m^2) every 3 weeks with split-course external beam irradiation (4400 cGy, with 2200 cGy divided equally between the first two cycles of chemotherapy). Patients also received three courses of identical adjuvant chemotherapy after surgery. Grade 4 toxicity (neutropenia 66%, skin toxicity 12%, and thrombocytopenia 29%) and a 7% infection rate were observed. However, preoperative chemotherapy and radiotherapy were completed in 88% and 93% of patients, respectively, and wound healing was delayed in 26% of patients. The 3-year survival rate was 75%, which appears promising, based on past experience in patients with high-grade sarcomas.

- Investigators at the University of California at Los Angeles have studied neoadjuvant chemotherapy in combination with radiation therapy since 1975. A total of 496 patients with localized intermediate and high-grade extremity STS have been treated with one of five different protocols. The first three protocols included doxorubicin and variable doses of radiation therapy. The fourth protocol included doxorubicin, cisplatin, and radiation. The fifth protocol incorporated ifosfamide with doxorubicin, cisplatin, and radiation therapy. All of the patients underwent surgery within 4 to 8 weeks of initiation of neoadjuvant therapy. Patients with 95% or higher tumor necrosis had improved outcomes at 5 and 10 years compared to patients with less than 95% necrosis. The 5- and 10-year local recurrence rates were 6% and 11%, respectively, for good responders compared to 17% and 23%, respectively, for poor responders. The 5- and 10-year survivals for good responders were 80% and 71%, respectively, compared to 62% and 55%, respectively, for poor responders. The group of patients achieving 95% or higher tumor necrosis improved to 48% with the protocol containing ifosfamide compared to 13% for all of the other protocols combined, which did not include ifosfamide [16••].
- Although most of the studies discussed earlier in this paper involved patients with STS of the extremities, retroperitoneal STS presents a different set of therapeutic challenges. Only approximately 40% of patients with localized retroperitoneal sarcoma are able to undergo complete surgical resection. Of the patients undergoing complete resection, approximately 50% will develop local recurrence. This significant local failure rate suggests a potentially important role for adjuvant therapy (*ie*, preoperative or postoperative) in patients with retroperitoneal STS. However, the role of radiation therapy in the treatment of retroperitoneal STS is not clearly defined. Two-year local control rates of 70% have been reported with the addition of postoperative radiotherapy. The challenge of irradiation of the retroperitoneum/abdomen is the normal tissue tolerance limitation in delivering therapeutic doses (50–65 Gy). Furthermore, most retroperitoneal STS are bulky (> 10–15 cm), which requires larger radiation fields, implying increases in radiation toxicity. Preoperative radiotherapy is favored over postoperative radiotherapy for patients with retroperitoneal STS because preoperative radiotherapy may facilitate complete surgical resection, allow the tumor bed to be precisely anatomically outlined for radiation planning, and because the radiosensitive normal viscera/bowel is displaced outside the treatment field by the tumor, the toxicities may be minimized. Therefore, most of the investigations involving retroperitoneal STS have used preoperative radiation therapy [17–19]. Preoperative chemoradiation is being studied for retroperitoneal STS in phase I/II settings. The RTOG has initiated a multi-institutional intergroup phase II trial of preoperative chemotherapy, followed by preoperative radiotherapy and surgical resection with an intra- or postoperative radiation boost (RTOG S0124) for patients with intermediate- or high-grade retroperitoneal STS. Patients with localized and potentially resectable T2 G2/3 retroperitoneal/pelvic STS will be treated with four

cycles of A/I (doxorubicin 75 mg/m^2 and ifosfamide 10 mg/m^2), followed by external beam radiotherapy (45–50.4 Gy) before undergoing surgical resection. Postoperatively, patients will receive a radiation boost by intraoperative or postoperative electron beam/brachytherapy/external beam radiotherapy. The results of this intergroup trial will provide important information regarding the feasibility and toxicities of this treatment approach in a multi-institutional setting.

Conclusions

- The use of adjuvant or neoadjuvant chemotherapy for STS continues to remain controversial and generate debate. Our assessment of the literature is that modern dose-intensive anthracycline and ifosfamide combination is the most active regimen for this disease. When this regimen is used in appropriately selected patients at high risk for metastases and death, the disease-free and overall survivals show significant improvement, which was published by the Italian Sarcoma Group. Based on this premise and lessons learned from the osteosarcoma model, we favor neoadjuvant use of this regimen for AJCC stage III STS. The oncology community at large awaits the time when we have defined appropriate targets controlling tumorigenesis for these tumors and identified their effective inhibitors that may provide a better therapeutic outcome with less morbidity. However, until that day, we are obligated to use our current therapeutic armamentarium to the best of our ability.

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