

The Use of Chemotherapy in Soft-Tissue Sarcomas

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the role of doxorubicin and ifosfamide in soft tissue sarcomas.
2. Identify the role of newer agents in soft tissue sarcomas.
3. Appreciate the role of adjuvant therapy in the management of soft tissue sarcomas.
4. Appreciate the role of neoadjuvant chemotherapy and radiotherapy in the management of soft tissue sarcomas.

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ABSTRACT

The treatment of advanced soft-tissue sarcomas is often palliative, although a subset of patients may be cured or have a long disease-free interval. This paper reviews the historical data over 30 years of treatment that has led to the use of ifosfamide and doxorubicin as the mainstay in the treatment of metastatic disease. These treatments have a high toxicity, relative to other

chemotherapeutic regimens, with median response durations on the order of months. Agents developed in the last few years, whose role in the treatment of sarcomas is still evolving, are discussed as well. Finally, we discuss the role of chemotherapy in combination with surgery and radiation in the adjuvant and neoadjuvant settings. *The Oncologist* 2002;7:348-359

INTRODUCTION

Soft-tissue sarcomas are rare tumors, accounting for approximately 1% of all cancers worldwide each year. The prognosis for patients with only localized disease is still sub-optimal. While local control can be obtained through the use of surgery and radiation, up to 50% of patients will eventually recur at distant sites, and the overwhelming majority of these will ultimately die from this cause. In terms of prognosis, the most important factor in terms of the occurrence of distant metastases and ultimate cure is the histological grade of the tumor (low, intermediate, or high), which often can be variable, depending upon the reviewing pathologist.

Low-grade sarcomas tend to recur locally and are usually dealt with by local means (i.e., surgery, radiation); high-grade tumors tend to recur systemically. While sarcomas can be further subdivided into dozens of subtypes [1], current treatment options are not dictated solely by the histological subtype of sarcoma. Rather, treatment(s) are dictated by tumor grade, size, and location of primary or metastatic disease. This review focuses on the agents and settings for which the use of chemotherapy in the treatment of soft-tissue sarcomas is important. Sarcomas of bone and primitive neuroectodermal tumors (PNETs or Ewing's sarcoma) are not addressed here, as their treatment is different. The agents

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are first discussed in terms of their utilization in the treatment of metastatic disease. This is done in a somewhat historical perspective that explains much of how today's therapies have come to exist and change over time, with a subsequent discussion of their use in other (i.e., adjuvant and neoadjuvant) settings.

METASTATIC DISEASE

Doxorubicin

The original phase II study evaluating doxorubicin in the treatment of cancer was published in 1972 [2]. Doses used in this study were between 60 and 75 mg/m² every 3 weeks, depending on the "risk" of the patient as determined by baseline blood counts. In this study, sarcomas had a 33% response rate to single-agent doxorubicin therapy, and this was the highest response rate of any tumor studied except for lymphoma. However, as most of the early studies were done, sarcomas were grouped together as a catchall for soft-tissue sarcomas, osteosarcomas, Ewing's sarcoma, Kaposi's sarcoma (KS), and, to some extent, even mesothelioma. Furthermore, the distinction between leiomyosarcomas of the abdomen (a traditional soft-tissue sarcoma) and gastrointestinal stromal cell tumors (GISTs, chemoresistant malignancies of different origin) was not known until recently, making a true analysis in modern pathologic terms more difficult. Removal of these tumors from the original data drops the response rate down to 20%. Subsequently, a dose-response relationship for doxorubicin was found. A follow-up study through the Southwest Oncology Group (SWOG) randomly assigned good-risk patients to a doxorubicin dose of 45, 60, or 75 mg/m² every 3 weeks [3]. Response rates for sarcomas were 18%, 20%, and 37%, respectively in a total of 79 patients, and thus, doxorubicin quickly became the standard of care for the treatment of sarcomas. With numerous clinical trials since then, the response rates for single-agent doxorubicin therapy have generally held up in the range of 20%-30% [1], along the lines of the original 1972 data [4].

Single-Agent DTIC Therapy and Combination with Doxorubicin

Decarbazine (DTIC) became available soon after doxorubicin and was rapidly tested in phase I and II settings. Initial trials were again performed by the SWOG and M.D. Anderson Cancer Center. Initial responses to its use as a single agent for sarcomas were promising. Out of the initial 138 patients, 18% had a partial (PR) or complete response (CR). Removal of the cases of KS leads to a more modest 15% response rate [5], with leiomyosarcomas accounting for a large percentage of the responding patients.

Subsequent studies, again done by the SWOG, looked at the combination of doxorubicin with DTIC against sarcomas. The first study combined DTIC with 60 mg/m² of doxorubicin, and an overall response rate of 47% was demonstrated; addition of vincristine in a subsequent study showed no additional response benefit except for a slight decrease in the percentage of patients experiencing progressive disease [4-7]. More importantly, these were the first trials to demonstrate a survival benefit, 10 months in those patients receiving combination chemotherapy compared with 6 months for those who did not.

As a follow-up, the Eastern Cooperative Oncology Group (ECOG) subsequently performed a randomized trial in which single-agent doxorubicin therapy in two regimens (70 and 75 mg/m²) was compared with doxorubicin (60 mg/m²) with DTIC [8]. The single-agent arms had response rates of 16% and 18%, while the combination had a response rate of 30%, with significantly higher grade 3 toxicity and no change in median survival. Similar data were obtained in a study of uterine sarcomas treated with similar doses of doxorubicin and DTIC; of note, those patients with more toxicity had a higher response rate as well (38% versus 20%) [9]. In light of all these data, some investigators felt multiagent chemotherapy with doxorubicin and DTIC was "indicated as part of the first-line treatment" [5, 10], while others felt that, because of the toxicity associated with the combination and a lack of survival benefit, single-agent doxorubicin therapy remained the standard of care [8, 11, 12].

Cyclophosphamide

Prior to the development of doxorubicin, the treatment of soft-tissue sarcomas was based upon the pediatric literature, where the predominant diagnosis was rhabdomyosarcoma. Rhabdomyosarcomas have a distinct biological course and impressive responsiveness to therapies, even in the metastatic setting. This treatment consisted of vincristine, actinomycin-D, and cyclophosphamide (VAC), which had a minimal (<10%) response rate in adult soft-tissue sarcoma. Because of the historical use of this regimen and the recent discoveries of doxorubicin and DTIC, a regimen known as CYVADIC was developed. This consisted of a lower dose of doxorubicin (50 mg/m²), to allow for the inclusion of cyclophosphamide (500 mg/m²), as well as DTIC and vincristine, and was tested in a phase II setting [13]. Patients included had a mixture of sarcomas, and the overall response rate was 47%. Those patients with soft-tissue sarcomas treated with CYVADIC had a 50% response rate and a 17% CR rate. Of importance, patients with a CR had a much longer long-term survival, with more than 20% of these patients alive after 5 years. Toxicity of the treatment was high but fairly similar to the doxorubicin and

DTIC (AD) combination, where the response rate was 47% [6, 7] in a previous study. Of note, beneficial effects from the addition of cyclophosphamide may have been negated by the lower doxorubicin dose, particularly with previous studies showing a steep dose-response curve for doxorubicin as one goes from 50 to 75 mg/m² [3]. Despite little or no evidence of the activity of single-agent cyclophosphamide or vincristine therapies [4, 14] and a similar benefit when comparing the phase II data from this trial with the aforementioned AD trial, for some this regimen became the treatment of choice in the early 1980s for soft-tissue sarcomas.

Soon thereafter, ECOG performed a phase III randomized study to best define the role of the historic regimens used to treat soft-tissue sarcomas, VAC (vincristine, actinomycin-D, and cyclophosphamide) versus vincristine, doxorubicin (50 mg/m²), and cyclophosphamide (VAdriC) versus doxorubicin alone (70 mg/m²) [15]. This study was useful in defining, in a phase III setting, the actual response rates of the various therapies, which had yet to be done, as well as defining the role of cyclophosphamide and vincristine administered in conjunction with other agents (Table 1). Response rates were highest for the doxorubicin alone arm. The historic VAC arm showed a minimal (12%) response rate in soft-tissue sarcomas. Reduction of the doxorubicin to 50 mg/m² to allow for inclusion of cyclophosphamide resulted in an inferior response rate. This could be due to complete inactivity of cyclophosphamide or relative inactivity of cyclophosphamide when compared with the advantage of doxorubicin dose intensification. With this study, one had to seriously question the advantage in adding any additional agents to doxorubicin.

The European Organization for Research and Treatment of Cancer (EORTC) subsequently reported a comparison of CYVADIC, given as above (every 4 weeks), with alternating CYV with ADIC (every 4 weeks) in an attempt to increase the duration of response and decrease toxicity [16]. The CYVADIC regimen proved to be superior in terms of response rate (38% versus 14%) and median duration of remission (62 versus 39 weeks, not statistically significant). More importantly perhaps, a subgroup analysis was done to

determine what prognostic factors would predict response. Karnofsky index (KI) was the single most important factor in predicting response. In those patients receiving continuous CYVADIC, the response rate of those with a KI \geq 90 was 57%, but in those patients with a KI of 50-80, it was only 17%. While this paradigm has been repeated throughout medical oncology, it is important to be reminded of the importance of performance status in predicting response to therapy. With these studies, the standard of care for many was still single-agent doxorubicin therapy at 75 mg/m².

Ifosfamide

Ifosfamide was first introduced in the 1960s as a chemical modification of cyclophosphamide with a shift of one of the 2-chloroethyl groups to provide a more effective DNA cross-linking distance [17], and would in effect change the management of soft-tissue sarcomas. Given differences in metabolism, a dose of approximately 3.5 g/m² of ifosfamide is felt to be equivalent to 1.0 g/m² of cyclophosphamide [18]. Initial studies demonstrated activity against tumors, but the dose-limiting toxicity of hemorrhagic cystitis would limit its use until the development of mesna in 1979 [19, 20]. Mesna is a thiol compound that detoxifies the acrolein metabolite of ifosfamide in the bladder only, without affecting its antitumor effect. With this, the new dose-limiting toxicity became leukopenia. An initial study used ifosfamide at 5-8 g/m² every 3 weeks in 42 heavily pretreated sarcoma patients and demonstrated a response rate of 38%, which was the first real promising development since the use of DTIC nearly 10 years before [21].

In light of this, the EORTC performed a randomized controlled trial in patients naive to alkylating agents; patients received either cyclophosphamide, 1.5 g/m², or ifosfamide, 5 g/m², every 3 weeks, which is approximately the equivalent dosing of the two alkylators [22]. This was the first study to look at the efficacy of cyclophosphamide alone and established its response rate as a meager 9%. Ifosfamide at this dose demonstrated a response rate of 18%; patients naive to chemotherapy had slightly higher response rates. The major toxicity was leukopenia, with 59% of patients on the

Table 1. ECOG randomized trial comparing three regimens in advanced soft tissue sarcoma, adapted from [15]

	Adr	VAdriC	VAC
Response rate (%)	30	21	12
Median survival (months)	9	8	10
Percentage of patients with moderate or worse gastrointestinal toxicity	42	60	50
Percentage of patients with moderate or worse hematologic toxicity	47	43	35

Regimens: Adr (doxorubicin 70 mg/m²); VAdriC (vincristine 1.4 mg/m², doxorubicin 50 mg/m², cyclophosphamide 750 mg/m²), and VAC (vincristine 1.4 mg/m², actinomycin-D 0.4 mg/m², cyclophosphamide 750 mg/m²).

cyclophosphamide arm and 31% of patients on the ifosfamide arm demonstrating grade 3 or 4 leukopenia. Patients in the ifosfamide arm had slightly more nausea and vomiting, but these were mostly grade 1 or 2. While there was no significant difference between the two arms in terms of time to progression and survival, this study was the first of many over the next 15 years or so to study the use of ifosfamide as both a single agent and in combination to treat soft-tissue sarcomas. In effect, this spelled the end of regimens that included cyclophosphamide, especially at the cost of doxorubicin dose reduction.

Based upon these data, the use of ifosfamide administered in different schedules was examined at the Dana-Farber Cancer Institute (DFCI). In a phase II study, patients received 8 g/m² of ifosfamide either via bolus (2 g/m² over 4 hours daily \times 4 days) or via a 4-day continuous infusion [23]. Nearly all the patients were pretreated with other chemotherapy. Response rates were 26% for those receiving bolus ifosfamide and 9% in those receiving it via continuous infusion. Three percent of patients had a CR. Because of the toxicity of the regimen, possibly complicated by the fact that many patients were heavily pretreated, only about 60% of patients were able to undergo full-dose therapy for at least two cycles. The bolus regimen did have a somewhat higher rate of central nervous system (CNS) toxicity (confusion, hallucinations) than the continuous infusion regimen.

Subsequent to this, the DFCI performed a phase I study looking at increasing doses of ifosfamide in a similar patient population. Twenty-nine patients received ifosfamide in doses ranging from 8-18 g/m² via a 4-day continuous infusion [24]. Twenty of the patients had sarcoma (both osteogenic and soft tissue) and were heavily pretreated. Seven of 20 (35%) had a PR, and two patients of 29 died during treatment. Autologous stem cell rescue was allowed but not needed due to a relatively low duration of prolonged neutropenia. Given this, the stage was set for combination therapies using ifosfamide in conjunction with other known active agents against sarcomas.

Combination Trials Using Ifosfamide

With the resultant data, the Dana Farber group sought to combine all agents with activity against sarcomas in the MAID regimen, consisting of doxorubicin (60 mg/m²), ifosfamide (7.5 g/m²), and DTIC (900 mg/m²) given over a 3-day continuous infusion [11]. Reports showed that continuous-infusion administration of doxorubicin and DTIC had less gastrointestinal and cardiac toxicity than did bolus dosing, with no change in efficacy [25, 26]. In this trial of patients without any prior therapy, 47% of patients responded, and 10% of patients had a complete response. Some patients were able to be rendered disease free after therapy and/or surgery,

with several long-term (2 year) survivors. Higher grade (3) tumors were more likely to respond than lower grade (1 or 2) tumors, as were less bulky tumors (<5 cm in size). Age and performance status did not correlate with response. Over the course of therapy, 74% of patients were hospitalized at some point for treatment-related toxicity, most of which was febrile neutropenia.

In July 1993, two randomized controlled studies were published in the *Journal of Clinical Oncology* looking to compare newer regimens with the previous standard, even though different groups still had different "standards." An intergroup study [27] published a randomized trial of MAID (doxorubicin 60 mg/m², ifosfamide 7.5 g/m², DTIC 1,000 mg/m², via continuous infusion) versus only the AD at the same doses (Table 2). Due to myelosuppression, the ifosfamide was subsequently decreased to 6 g/m² about half way through the study. Patients undergoing MAID had a higher response rate (32% versus 17%) and a longer time to progression (6 versus 4 months), but also a greater amount of grade 3 or higher toxicity (92% versus 55%) as well as more treatment-related deaths (4% versus 0.6%) than the AD group. Patients on the MAID arm were less likely to maintain full doxorubicin dose intensity after their first course than patients on the AD arm due to toxicity.

An ECOG study published in the same issue of that journal [28] presented a three-arm trial comparing the ECOG standard of care, doxorubicin alone (80 mg/m²) with MAI (doxorubicin 60 mg/m² and bolus ifosfamide 7.5 g/m²) and with another regimen, MAP (mitomycin 8 mg/m², doxorubicin 40 mg/m², and cisplatin 60 mg/m²). This latter regimen was developed at the Mayo Clinic and had some activity in a phase II trial [29] despite other studies pointing out the relative inefficacy of cisplatin as a single agent [30-32]. The data from these two trials are presented and compared in Table 2. The combination therapies did produce a higher response rate (MAI 34%, MAP 32%, and doxorubicin 20%), albeit at a cost of greater toxicity and no statistically significant survival advantage. Of note, younger patients in the ECOG study (less than 40) did have a much higher response rate on MAI than on doxorubicin alone (75% versus 7%), albeit with admittedly small numbers. The reason for this is not entirely clear, but may be partially accounted for by the fact that synovial cell sarcomas, which tend to occur in younger patients, may have a relatively higher response rate to ifosfamide [33]. These trials demonstrated a high rate of grade 3 and 4 myelotoxicity, but it should be noted that they were conducted before the advent of hematopoietic growth factors.

As the Europeans had their own phase II data supporting the use of ifosfamide [34], they too performed a phase III trial comparing their standard of care (doxorubicin alone, 75 mg/m²) with CYVADIC and with ifosfamide (5 g/m² over 24

Table 2. Phase III randomized trials using ifosfamide in the treatment of sarcomas

Regimen	ECOG			Intergroup		Adria	EORTC	
	Adria	MAI	MAP	AD	MAID		CYVADIC	AI
Doses*	Dox (80)	Dox (60) Ifos B (7.5)	Mito (8) Dox (40) Cis (60)	Dox (60) DTIC (1,000)	Dox (60) Ifos I (7.5/6) DTIC (1,000)	Dox (75)	Cy (500) Vinc (1.5) Dox (50) DTIC (750)	Dox (50) Ifos I (5)
Response rate (%)	20	34	32	17	32	23	28	28
Response rate (%) in younger patients (<40 years old)	7	75	50	NR	NR	NR	NR	NR
Survival (months)	8	12	8	13	12	12	13	12
Patients with severe/life-threatening toxicities (%)	21	70	33	55	92	13†	32†	15†
Treatment-related deaths (%)	2	3	1	0.6	4	NR	NR	NR

ECOG Trial [28]: published 1993, accrual 1987-1990.
 Intergroup Trial [27]: published 1993, accrual 1987-1989.
 EORTC Trial [34]: published 1995, accrual 1985-1990.

*Doses are shown in mg/m² in parentheses with ifosfamide (B) for bolus infusion (4 hours or less daily) and ifosfamide (I) for infusional (24-hour continuous daily infusion).

Abbreviations: Dox = doxorubicin; Ifos = ifosfamide; Cis = cisplatin; Mito = mitomycin-C; Vinc = vincristine; Cyclo = cyclophosphamide; DTIC = decarbazine; NR = not reported.

†Incidence of grade 4 leukopenia only; severity of all toxicity not reported in paper.

hours as a continuous infusion) and doxorubicin, 50 mg/m² [35]. They showed no statistically significant differences in response rate (Table 2) among any of the regimens used, with a significantly higher amount of grade III and IV myelosuppression in the combination regimens, concluding "combination chemotherapy cannot be recommended outside a controlled clinical trial with the exclusion of some subsets of patients." In retrospect, these trials had a total of eight different arms, all with slightly differing doses and infusion schedules, making it difficult to compare regimens across trials. Given the lack of single-agent efficacy of cyclophosphamide, vincristine, and cisplatin, the MAP and CYVADIC regimens became difficult to rationalize. Of note, the bolus regimen in one of the first trials performed [23] and in later works [36, 37] demonstrated that ifosfamide dosed via bolus infusion had a higher response rate than did ifosfamide given over prolonged (24-hour) infusion. Furthermore, neutropenia made raising the dose of doxorubicin higher than 50 mg/m² when given in conjunction with ifosfamide too difficult. Given the new proliferation of research as well as the lack of progress in the development of other novel agents, combinations of ifosfamide and doxorubicin were tested in detail.

First, the development of growth factor support (filgrastim) made it possible to elevate the doxorubicin dose to 75

mg/m² in conjunction with ifosfamide. The EORTC published a phase II trial showing a higher response rate (45%) than previously seen with lower doses [38, 39], which was in fact published prior to the publication of the EORTC phase III data, that used lower doses without filgrastim [35].

Over the next few years, further modifications of the doxorubicin/ifosfamide regimen, with or without the use of growth factors, came into being. Given a relative lack of data for the efficacy of single-agent DTIC therapy, its associated toxicity, and the difficulty seen in maintaining doxorubicin dose intensity when given in combination with other agents in the aforementioned randomized trials [27, 28, 35], newer trials looked to increase the use of ifosfamide and doxorubicin with the omission of DTIC. Phase II trials showed higher response rates with 10 versus 6 g/m² [37] of ifosfamide, leading investigators to postulate that even further dose escalation may be effective in the treatment of soft-tissue sarcomas. Several trials showed the benefit of ifosfamide dose escalation to 14 g/m² as a single agent in conjunction with growth factor (GM-CSF or G-CSF) support. A Spanish group gave ifosfamide, 14 g/m², over a 6-day continuous infusion [40] and the M.D. Anderson group gave the same dose via both bolus and continuous infusion [36]. Both trials showed activity, even in patients refractory to lower doses of ifosfamide.

Bolus infusion of single-agent, high-dose ifosfamide seemed to show a higher response rate against soft-tissue sarcomas than did continuous infusion (45% versus 19% in the M.D. Anderson study) [36]. Over the same period, numerous reports appeared showing the feasibility and activity of virtually every combination of ifosfamide and doxorubicin as well as every method of infusion (bolus versus continuous) [41–45]. While a formal phase III comparison study of the various ifosfamide and doxorubicin combinations has not been done, one could almost predict the results: higher doses yield higher response rates, more toxicity, and little (if any) change in overall survival. Comparing all phase II trials of the two-drug combinations is made difficult not only due to the regular bias found in such trials, but also because no two regimens are exactly identical in terms of doses, infusion method, number of pretreatment regimens, and inclusion of other sarcoma subtypes. This is best summarized in the title of a commentary in the *Annals of Oncology*: “Advanced soft tissue sarcoma: How many more trials with anthracyclines and ifosfamide?” [46]. This plethora of such trials reflects not the lack of desire to conduct studies of chemotherapy in the treatment of soft-tissue sarcomas but the lack of novel available approaches.

Which Regimen to Choose?

The take-home message of all these trials for metastatic sarcoma is as follows: both ifosfamide and doxorubicin work, they are the best single agents with activity in the treatment of soft-tissue sarcomas; there is a dose-response curve to both agents; bolus ifosfamide is probably better

than infusional; the toxicities are real and make treatment difficult; patients are more likely to respond to therapy earlier on in their course of treatment; and most, if not all patients, will ultimately relapse and die of their disease. In our practice, the most important question we ask is what is the performance status of the patient and how much therapy can they tolerate? One of the drawbacks of this therapy is that many patients often require inpatient administration of this therapy along with expensive growth factor support. Given that poorer performance status and advanced age bodes for greater toxicity, we tend to use single-agent doxorubicin therapy in the more frail (or offer best supportive care to those with a poor performance status). For those who are younger or more likely to respond, we tend to go with a modified version of an M.D. Anderson protocol, consisting of doxorubicin, 75 mg/m² via continuous infusion over 3 days, and bolus ifosfamide, 2.5 g/m² daily for 4 days with mesna [43]. Table 3 shows results of phase I and II studies from various groups using similar doses of these drugs. The toxicity is certainly real, but is usually manageable when given in conjunction with growth factors. Dose escalation of either agent beyond these doses is likely to carry excess toxicity without much additional benefit. The acute toxicities of ifosfamide, namely CNS toxicity, nausea, vomiting, and renal tubular acidosis, as well as the high requirements for intravenous hydration, administration of mesna, and electrolyte replacement require that, in many clinics, patients be admitted to the hospital for the administration of therapy. In our minds, patients will usually get

Table 3. Comparison of recent trials using doxorubicin and ifosfamide in chemotherapy-naïve patients

Regimen	AI 75/10 [43]	AI 90/10 [43]	Swiss phase I [42]	Italian feasibility [45]	Intergroup study, MAID arm [27]
Doses	Dox (75) Ifos B (10) G-CSF only after 1st NF	Dox (90) Ifos B (10) G-CSF all cycles	Dox (60-90) Ifos I (10-12) MTD: Ifos I (10) Dox (90) GM-CSF all cycles	Doxorubicin (60) Ifos I (12.5) G-CSF all cycles	Dox (60) Ifos I (7.5) DTIC (1,000)
Patients developing neutropenic fever (%)	94	100	87	57	NR See Table 2
Response rate (%)	69	59	55	50	32
Treatment-related deaths (%)	0	6	0	0	4
Grade 3/4 leukopenia (% of cycles)	89	87	58	59	NR See Table 2
Median survival	NR	NR	2 years	NR	12 months

The intergroup trial from Table 2 is used as a comparison.

*Doses are shown in mg/m² in parentheses with ifosfamide (B) for bolus infusion (4 hours or less daily) and ifosfamide (I) for infusional (24-hour continuous infusion).

Abbreviations: Dox = doxorubicin; Ifos = ifosfamide; MTD = maximum-tolerated dose; NR = not reported.

one best shot for a response once diagnosed with metastatic disease, so we elect to use this "best-chances" regimen up front. This is especially true for patients with limited metastases (lung only), when chemotherapy given in a multidisciplinary approach with surgery and/or radiation might allow, in some instances, either a cure or a moderate to long-term survival [27, 28, 35]. While the toxicities of this regimen are real, *Dr. Benjamin* summarized this best in the title of an earlier editorial in the *Journal of Clinical Oncology*: "Grade 3 nausea, vomiting, and myelosuppression or progressive, metastatic sarcoma?" [10]. Most patients will choose the former.

Relapses following chemotherapy or failure to respond offer different conundrums. Many patients will have a decline in performance status and elect best supportive care or hospice at that time. For those still able, we offer either high-dose ifosfamide (14 g/m²), DTIC, or usually, a phase I or II clinical trial. Unfortunately, most patients are in the condition that they choose best supportive care.

TUMOR HISTOLOGY

The importance of tumor histology in determining responsiveness to chemotherapy has been difficult to understand. Attempts to elucidate sensitivities based upon histology are difficult, particularly because of the lack of a sufficient number of patients with a particular sarcoma subtype even in the large, randomized aforementioned trials. As an example, while leiomyosarcomas represent a very large portion of tumors, it has long been known that those with liver metastases are much more chemoresistant than those with lung metastases [1]. In retrospect, the former most likely represent GISTs, which have recently been separated out from leiomyosarcomas as an entity and are very chemoresistant [47]. Further, uterine leiomyosarcomas have been reported to be relatively chemoresponsive [48]. Pathologists themselves often disagree as to the specific sarcoma subtype. Clearly, such differences in patient enrollment into trials could easily affect reported response rates. While there are subtle differences mentioned in this review, in general, we treat all advanced sarcomas in a similar fashion unless circumstances, such as performance status or age, dictate otherwise. GISTs that stain positive for c-kit are best treated with imatinib and are not discussed further [49, 50].

NEWER AGENTS

Gemcitabine

One of the reasons for the proliferation of trials using ifosfamide and doxorubicin is the lack of activity of any of the newer agents. Phase II studies of gemcitabine have shown limited response rates (about 15%) with up to 40% of

patients having prolonged stable disease [51-55]. Of note, a small phase II study in patients with uterine leiomyosarcomas showed a 50% response rate for gemcitabine in combination with docetaxol in patients who failed first-line therapy [56]. On this basis, this combination is useful for patients who fall into this scenario; single-agent gemcitabine therapy is appropriate for those patients who have failed first-line therapy, or even for first-line therapy in patients with leiomyosarcomas, where intensive treatment is contraindicated based upon hints of greater activity against this subtype in these trials [51-55].

Liposomal Doxorubicin

A phase II EORTC study compared liposomal doxorubicin with standard doxorubicin and found equivalent activity, around 10% for both arms [57]. A second study showed no responses at all [58]. The low response rate in the former study can probably be attributed to the inclusion of a large number of patients with GISTs, which are historically much less chemoresponsive. Liposomal doxorubicin is probably active and could be considered for treatment of soft-tissue sarcomas in those unable to tolerate intense up-front therapy, especially for those at risk of greater cardiotoxicity with standard doxorubicin. Its role in conjunction with ifosfamide is yet to be determined.

Taxanes

A Memorial-Sloan Kettering Cancer Center (MSKCC) phase II study looked at the use of paclitaxel in soft-tissue sarcomas [59]. Only two patients of 28 responded, including a single patient with angiosarcoma of the head, who had a sustained response. Subsequently, a retrospective review of all the patients treated at MSKCC over a 7-year time frame found that, of nine angiosarcoma patients treated with paclitaxel, eight (89%) had a "major" response [60]. Toxicities were as expected (neutropenia and neuropathy), but certainly this was far less than what would be expected with ifosfamide- and doxorubicin-based therapy, and with a much higher response rate. A specific study of paclitaxel in angiosarcomas will be incredibly difficult to do even in a cooperative group setting because of the rarity of this specific entity. Of importance, while prior studies have observed small differences in the response rates of the different regimens among the different sarcoma subtypes, this is by far the most impressive. While the exact role of paclitaxel in the treatment of angiosarcomas will be difficult to define due to the limitations in developing a large clinical trial, serious thought should be given to its front-line use in such instances. One phase II trial of docetaxel in pretreated soft-tissue sarcomas (none of which were angiosarcomas) showed a response rate of 15% [61], although a follow-up,

randomized phase II study showed a 0% response rate [62]. On this basis, we feel that docetaxel as a single agent is not effective in sarcomas other than angiosarcomas.

ET-743

ET-743 is a novel marine-derived antineoplastic agent that appears to bind to the minor groove of a DNA strand and probably inhibits DNA transcriptional activation, although its mechanism is complex [63]. In several phase II trials reported at the 2001 American Society for Clinical Oncology meeting, activity was seen in patients with both pretreated and untreated advanced soft-tissue sarcoma [64, 65]. Up to 18% of patients achieved a response. Dose-limiting toxicities included neutropenia and transaminitis in several patients, and there were several treatment-related deaths. Trials comparing ET-743 with more standard therapies are ongoing, with results anxiously awaited.

NEOADJUVANT CHEMOTHERAPY

High-grade, soft-tissue sarcomas that undergo local treatment by surgery alone have a local recurrence rate of as high as 70%-90%. Surgical resection with wide margins results in a lower recurrence rate, at the cost of removing wide margins of normal tissue, which is often not feasible depending on the location of the tumor [66, 67]. The addition of moderate doses of external beam radiation (50 Gy) allows for a more conservative surgery with an equivalent rate of local control and has become the standard of care [68]. Two prospective, randomized studies have shown the validation of such an approach. *Rosenberg et al.* showed equivalent disease-free survival in patients treated with a wide en bloc excision followed by external-beam radiation compared with those receiving amputation [69], and *Pisters et al.* showed improved local control for those patients treated with adjuvant brachytherapy [70]. It should be pointed out that the achievement of local control appears not to correlate with a patient's long-term survival and likelihood of developing metastases [71]. In this regard, the use of adjuvant therapy is discussed below.

The ability to deliver therapies prior to surgery has some theoretical advantages as well as disadvantages. First, a substantial number of patients may not be able to get postoperative chemotherapy or radiotherapy because of delayed wound healing, possibly resulting in recurrence before definitive local therapy [72]. It also may allow for smaller, less morbid surgeries in some instances. Preoperative chemotherapy could allow for the elimination of micrometastases before their progression, which may occur if chemotherapy is delayed due to surgical complications. Disadvantages potentially include delayed time to local control, if the preoperative treatment is ineffective, and in wound healing. The

M.D. Anderson Cancer Center published a retrospective review of their own in-house data showing no greater postoperative morbidity (wound complications, need for reoperation) in patients receiving neoadjuvant chemotherapy (of varying types) in conjunction with definitive local control [73]. More recent data demonstrated that the combination of ifosfamide (mean dose 10.2 g/m²) with 5,400 cGy of external-beam radiotherapy showed no greater toxicity than either individual modality given separately [74].

The Mayo Clinic group recently published their data using neoadjuvant IMAP (ifosfamide, mitomycin, doxorubicin, and cisplatin) in conjunction with GM-CSF for patients with high-grade, large, soft-tissue sarcomas [75]. This was based upon their earlier work with MAP chemotherapy in metastatic disease. Patients received chemotherapy followed by 4,500 cGy external-beam irradiation in conjunction with reduced-dose chemotherapy and an additional 1,000 cGy radiotherapy, either intraoperatively or postoperatively. Five-year survival was estimated at 80%, and 2-year freedom from metastases was approximately 85%. The Massachusetts General Hospital (MGH) in conjunction with the Radiation Therapy Oncology Group (RTOG) had similar data based upon the earlier work done at MGH with modified MAID [76]. Patients in this intergroup phase II trial received infusion ifosfamide (2.5 g/m² daily for 3 days), doxorubicin (60 mg/m²), and DTIC (675 mg/m²) every 3 weeks with split-course external-beam irradiation (4,400 cGy, 2,200 divided equally between each of the first two cycles of chemotherapy). Patients also received three courses of identical adjuvant chemotherapy following surgery. There was a large number of patients with grade 4 toxicity (neutropenia 66%, skin toxicity 12%, thrombocytopenia 29%) as well as a 7% infection rate. However, preoperative chemotherapy and radiotherapy were completed in 88% and 93% of patients, respectively, and wound healing was delayed (took longer than expected without infection) in 26% of patients. Impressively, 2-year survival was nearly 95%, which, based on past experiences in patients with high-grade sarcomas, is extremely promising. Currently, the RTOG has a similar trial under way that adds the antiangiogenesis compound, SU5416, to this regimen in a phase I/II study. While the RTOG and Mayo Clinic studies await maturity, based upon these data, we currently advocate an approach using combined chemoradiation prior to surgery in patients with intermediate- or high-grade, large tumors. For low-grade tumors, we defer chemotherapy unless systemic (metastatic) disease is present.

ADJUVANT THERAPY

Given the high risk of distant recurrence (>50%) for high-grade, large, soft-tissue sarcomas, investigators for years have been trying to assess the effects of adjuvant

chemotherapy following definitive (surgery \pm radiation) local treatment. Due to the rarity of sarcomas, a large prospective trial has been difficult to do, and smaller ones have been fairly inconclusive, leading to the conclusion, by most investigators, that limits adjuvant therapy to use in clinical trials only [77]. In 1997, an international collaborative group published a meta-analysis of more than 1,568 patients treated with adjuvant therapy for soft-tissue sarcoma [78]. All of the trials used doxorubicin as the basis of therapy, in doses totaling up to 480 mg/m². Depending on the dates of the study, different agents of those mentioned earlier in this review were used in conjunction with doxorubicin. Overall survival showed an absolute 4% survival benefit that did not reach statistical significance ($p = 0.12$). Recurrence-free intervals were also slightly better with chemotherapy, with hazard ratios for recurrence-free survival in all patients on the order of 0.70-0.75. An attempt to better classify these data by subgroup analysis showed only that men may benefit slightly more from adjuvant chemotherapy than women, as may patients with intermediate-sized tumors (5-10 cm) or those with a tumor in the extremity. One of the biggest criticisms of this analysis is that, while many of the trials used high doses of doxorubicin, because of the dates of the included trials, only 29 of the 1,568 patients received ifosfamide as part of their therapy.

In 2001, an Italian group published a trial utilizing epirubicin and ifosfamide in 104 patients given every 3 weeks for five cycles with G-CSF for patients with large (>5 cm), high-grade soft-tissue sarcomas [79]. The disease-free survival was 48 months in the treatment group compared with only 16 months in the control (no chemotherapy group); overall survival was 75 months versus 46 months, with an absolute overall survival benefit of 19% at 4 years. Of note, the 4-year metastasis-free survival was the same in both groups (albeit with small numbers) raising the question of whether or not this therapy was preventing local, but not distant, recurrence. Nevertheless, this trial shows a benefit of chemotherapy that is, by some standards, near that of what we see in the use of adjuvant therapy in colorectal cancer or breast cancer. Of note, a subsequent Austrian trial using more intense chemotherapy in the adjuvant setting did not show any benefit using adjuvant therapy [80]; however, with only 59 patients, this study was grossly underpowered to detect the differences one would expect. The drawback of this therapy is that it is highly toxic, expensive, and often requires inpatient administration. We feel that this latest trial, in conjunction with the aforementioned meta-analysis, does support the utilization of adjuvant therapy for those patients with large ($>5-8$ cm), intermediate- or high-grade sarcomas. While the idea of adjuvant treatment has become more accepted, an editorial accompanying this study states, quite appropriately, that because of the limited data,

it is still ethical to include a no-treatment control group in clinical trials [81]. Currently, we utilize ifosfamide and doxorubicin (in doses identical to those used in metastatic disease) for four cycles in those patients who have large, high-grade sarcomas who have already undergone resection with good performance status (ECOG 0-1) and have not received neoadjuvant therapy. For older patients or those with a worse postoperative performance status, we opt for single-agent doxorubicin therapy or no treatment. However, properly evaluated, these patients should undergo neoadjuvant therapy with a substantial portion of their therapy delivered up front, prior to definitive local therapy. Most importantly, the enrollment of patients into ongoing clinical trials will help definitively address many of these issues.

CONCLUSIONS

For advanced soft-tissue sarcomas, we usually recommend bolus ifosfamide and doxorubicin in combination with G-CSF as first-line treatment in younger patients with good performance status. While the goal is usually palliation, occasional long-term disease-free survival can be obtained with aggressive therapy (such as combining chemotherapy with surgical resection of metastases) in situations where the disease is limited. For those patients with poorer performance status or advanced age, we either modify the dose or use an alternative regimen (such as a taxane for angiosarcoma), if appropriate. For patients who fail initial therapy, agents such as gemcitabine, DTIC, or high-dose ifosfamide remain options, although we usually recommend clinical trials in such situations. In terms of neoadjuvant therapy, for patients presenting with large (>5 cm), intermediate- or high-grade lesions, we recommend neoadjuvant therapy with the MAID or IMAP regimens in conjunction with radiotherapy. We usually provide a total of three cycles of therapy up front, prior to surgery, and, if a good response is obtained at the time of surgery, an additional one to three cycles after. Given the high likelihood of complications, referral to specialty centers may be warranted. Ideally, most patients will thus receive chemotherapy preoperatively and will already have been evaluated. For those patients with large, high-grade lesions who do not receive preoperative therapy, but present after resection and radiation, we recommend four cycles of bolus ifosfamide and doxorubicin therapy as adjuvant, with the caveat that the benefits are still largely unknown. For those patients with worse performance status or advanced age, we either recommend four cycles of doxorubicin or observation. The recent development of imitinab in the treatment of GISTs has perked all oncologists' interests in the development of more refined therapy. Sarcomas, many with well-defined chromosomal translocations [1], are tumors primed for such interventions.

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