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The Role of Chemotherapy in the Treatment of Bone and Soft-tissue Sarcomas

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OVERVIEW

Sarcomas are rare, mesenchymal tumors of the soft tissue and bone that exhibit a marked heterogeneity in their clinical presentation, biologic behavior, and histologic features. Approximately 10,400 new cases are diagnosed annually, 7800 of which arise from the soft tissues (50–60% of which involve the extremities) and 2600 from bones.[1] Although the incidence of extremity sarcomas is similar to that of Hodgkin's disease, they are responsible for more than twice as many deaths each year. Major advances in the treatment of these tumors have been limited by an inability to accumulate sufficient numbers of similar patients to perform prospective randomized clinical trials with results that can achieve statistical significance.

Until the 1970s, surgery was the accepted method for the primary management of most soft-tissue and bone sarcomas of the extremities. However, surgery alone, especially wide resection, was associated with a high incidence of local recurrences. Even when local control was achieved, more than 50% of patients with soft-tissue sarcoma and 80% of patients with skeletal sarcoma (osteogenic and Ewing's sarcoma) eventually developed distant metastasis and died, usually within 2 years.[2–11] Nonsurgical treatment modalities (i.e., radiation therapy and chemotherapy) were subsequently found to exhibit reproducible anti-tumor effects against these neoplasms. Initially used only in the treatment of metastatic disease, they were later used as a part of combined-modality therapy in the adjuvant (postoperative) setting, and then as preoperative (neoadjuvant, induction) therapy in an attempt to preserve limb function and/or increase long-term survival.[2–11] The routes of chemotherapy administration have included intravenous (IV) bolus, continuous IV infusion, and local (regional) drug delivery directly to the tumor via a feeding artery.[12]

SOFT-TISSUE SARCOMA

Despite the development of successful therapeutic modalities for local tumor control (e.g., limb-sparing surgery and radiation therapy), 40–50% of patients, particularly those with high-grade, large, deep tumors, will have local recurrences and die from metastases that were not apparent at presentation.[3] An additional 10% of patients will have metastases (usually lung) at the time of initial diagnosis. Consequentially, chemotherapy was used initially to treat metastatic disease and, more recently, in an attempt to increase survival after local treatment and to also maximize the number of candidates for limb-sparing surgery.[13,14]

Chemotherapy Development

Only two single agents, Adriamycin and ifosfamide, have shown a reproducible response that is greater than 20% for soft-tissue sarcomas.[15] The largest experience with single-agent chemotherapy in this disease is with Adriamycin. A steep dose–response relationship has been found for Adriamycin. This was first demonstrated in the Southwest Oncology Group (SWOG) study in the 1970s, in which a dose of 75 mg/m^2 given every 3 weeks was shown to have a superior response rate to doses of 60 mg/m^2 and 45 mg/m^2.[16] Further evidence of a dose response has come from other studies of Adriamycin administered alone, as well as in conjunction with ifosfamide.[17,18] Unfortunately, Adriamycin also has an associated dose-limiting cardiotoxicity. The cardiotoxicity has been reduced without altering the drug's effectiveness by administering it as a continuous IV infusion over 72–96 h via a central venous catheter rather than by bolus dosing.[19,20] To obtain an optimal response it appears to be important to achieve a dose intensity of at least 70 mg/m^2 every 3 weeks.[15]

Analogues of Adriamycin have been developed in an attempt to reduce the potential for cardiotoxicity that exists at higher cumulative doses. Epirubicin has been the most extensively studied. The EORTC Sarcoma Group compared equitoxic doses of Adriamycin 75 mg/m^2 and Epirubicin 150 mg/m^2 (given as a single bolus or fractioned over 3 days).[21] An overall response rate of 18% was obtained. No difference was seen between the three study arms; however, myelosuppression was greater for Epirubicin than for Adriamycin. The incidence of cardiotoxicity was similar for both agents. Unfortunately, none of the currently available anthracycline analogues shows any advantage over Adriamycin for patients with soft-tissue sarcomas, and early studies of the new liposomal Adriamycin derivatives have shown variable activity.[22]

Alkylating agents have also been studied extensively, but only ifosfamide has shown activity equivalent to that of Adriamycin.[15] Prior to the availability of ifosfamide, cyclophosphamide was used widely as a component of the CyVADIC regimen, largely on the basis of its reported activity in pediatric sarcomas (especially rhabdomyosarcoma). Since the introduction of ifosfamide there has been considerable debate over its activity compared with that of cyclophosphamide. In the 1980s the EORTC performed a randomized trial comparing a 24-h continuous infusion of cyclophosphamide 1.5 g/m^2 versus ifosfamide 5 g/m^2 (chosen to produce a comparable degree of myelosuppression).[23] The response rate for ifosfamide in previously untreated patients with sarcoma was 25% versus 13% for cyclophosphamide.

In addition, ifosfamide showed activity in previously treated patients and in patients who were resistant to cyclophosphamide. There were no responses observed in patients crossed over to cyclophosphamide, indicating an incomplete cross-resistance between the two agents. Leukopenia was much less common in patients who received ifosfamide, suggesting that further dose escalation would be possible.

Both the dosage and scheduling appear to be important factors for the use of ifosfamide in soft-tissue sarcomas. Doses of less than or equal to 8 g/m^2 demonstrated clinical activity in numerous studies in the 1980s.[24] But it was only in the 1990s that a dose–response activity relationship was recognized and fully evaluated.[25,26] There appeared to be further anti-tumor activity of high-dose ifosfamide (12–14 g/m^2) in patients who did not respond to lower doses or who relapsed after standard dose ifosfamide-containing regimens.[24,26–28] Several dose-intensified studies have shown higher clinical response rates than conventional dose regimens. When ifosfamide is used as a single-agent therapy, several experts recommend that a dose of $\geq$ 10 g/m^2 be the minimum needed to obtain an optimal response for patients with soft-tissue sarcomas. It was only with the availability of mesna (M), which protects against urothelial toxicity (i.e., hemorrhagic cystitis), that the clinical use of this agent has become practical. The scheduling of ifosfamide also appears to be important. Studies by Antman *et al.* and Patel *et al.* have suggested that a 2–4 h IV bolus schedule appears to have approximately twice the response rate as a continuous IV infusion.[26,29] Results of a recent EORTC randomized trial that compared two different dose schedules of ifosfamide (5 g/m^2 over 24 h vs. 3 g/m^2 over 4 h, day 1–3), demonstrated an advantage for the IV bolus intensive regimen in terms of response (10% vs. 25%).[30] This same group also evaluated ifosfamide given at 12 g/m^2 as a 72-h continuous IV infusion q 4 weeks,

which yielded an overall response rate of only 14%.[31]

Ifosfamide has been shown to have significant activity against synovial cell sarcoma.[27] With the availability of mesna, it is much safer to use, but it still has dose-limiting myelosuppression, renal and central nervous system (CNS) toxicity.[32] Vigorous hydration with electrolytes and bicarbonate/acetate must be utilized to prevent severe metabolic acidosis and reduce the risk of significant neurotoxicity. CNS toxicity usually presents as a metabolic encephalopathy that may include confusion, blurred vision, mutism, auditory or visual paranoid hallucinations, seizures, and rarely, coma.[29] The exact mechanism for this toxicity is not known, but it may be related to the accumulation of chloracetaldehyde, one of ifosfamide's metabolites. Patients who are particularly prone to renal and CNS toxicity include those with a poor performance status, low serum albumin level (< 3 g/dl), renal dysfunction (as indicated by a prior nephrectomy, clinical or subclinical renal tubular dysfunction, or previous treatment with cisplatinum), and bulky pelvic disease, as well as those over the age of 65.[32]

Neurotoxicity is usually self-limited. Methylene blue (50 mg IV) and diazepam (5 mg IV) have been reported to rapidly reverse the encephalopathy; however, methylene blue should not be given to patients who are glucose-6-phosphate dehydrogenase (G6PD)-deficient.[33,34] Both these agents can be given prophylactically in subsequent cycles in order to prevent neurotoxicity (i.e., methylene blue 65 mg tablets qid). Hematologic toxicity in terms of myelosuppression has been ameliorated through the use of the hematopoietic growth factors G or GM-CSF, but patients still can develop dose-limiting thrombocytopenia.[35] This may be better controlled in the future with the use of new thrombopoietin agents.

Dacarbazine (DTIC) has also been used extensively for soft-tissue sarcomas, but it has a response rate under 20% as a single agent.[15] Emesis, a major side-effect, can be reduced when the drug is given as a continuous IV infusion. Its use with ifosfamide and Adriamycin in the MAID regimen has been questioned since it may contribute to increased toxicity with minimal additional efficacy. There is some evidence that DTIC has particular activity against non-gastrointestinal leiomyosarcoma.[36]

Most other agents have had disappointingly low response rates for soft-tissue sarcoma. Methotrexate has minimal activity, and 5-fluorouracil and its derivatives are inactive.[17,18] Vincristine, which was initially incorporated in combination regimens because of its activity in pediatric soft-tissue sarcomas, has a low response rate. The newer taxanes have minimal, if any, activity.[37,38] A recent study shows a synergistic effect for cisplatinum when given with epirubicin, and several preliminary reports suggest that gemcitabine may also have activity.[39,40]

Combination Therapy in the Treatment of Advanced Disease

Given the modest results of single-agent chemotherapy in the treatment of soft-tissue sarcomas, several combination chemotherapy regimens have been explored.[15,18] There is still controversy as to whether single-agent Adriamycin or a multi-agent regimen that includes Adriamycin is better for the treatment of advanced disease.[41,42] In the 1980s, Adriamycin (A) and DTIC (D) was the most commonly recommended combination regimen. ECOG and GOG studies showed higher response rates for the AD combination, but because there was no survival advantage and greater gastrointestinal toxicity for AD, both groups concluded that Adriamycin alone was preferable.[15,18] In a SWOG study, AD had reduced toxicity (i.e., cardiac, nausea, and vomiting) compared with a 96-h IV infusion to bolus, and still equivalent tumor activity and survival.[19] Several other studies have shown no advantage for adding other agents (i.e., cytoxan, vincristine, actinomycin-D).[15] It was felt that these agents simply reduced the dosage of Adriamycin that could be safely used.

Based on its activity in refractory and relapsed soft-tissue sarcoma, ifosfamide with mesna has been studied in combination with Adriamycin and Adriamycin/DTIC. In the late 1980s the MAID regimen was pioneered at the Dana Farber Cancer Institute (DFCI). MAID was a logical modification of the CyVADIC regimen; it eliminated the inactive vincristine and replaced cyclophosphamide with ifosfamide.[43] Studies from the DFCI using MAID reported a response rate of approximately 50% (10% complete response). In Europe, substitution of epirubicin for Adriamycin yielded similar results.[15,17,18] Although the MAID regimen has been used extensively in the 1990s for the treatment of soft-tissue sarcoma, it is a highly toxic therapy with severe life-threatening myelosuppression. Furthermore, adjusting the dosage of the regimen components has not significantly decreased toxicity or improved efficacy.

The effect of adding DTIC to this regimen has been unclear, since its single-agent activity is less than that of the other two components and it may be increasing toxicity without improving response. There have been three randomized trials of Adriamycin (A) with or without ifosfamide (I); EORTC, ISSG (Intergroup), and ECOG (Table 3.1).[44–46] The ECOG and ISSG studies both showed a significant increase in response rate for the AI regimen. However, in all three studies there was significantly more myelosuppression (including fatal

Table 3.1 Combination chemotherapy regimens containing Adriamycin and ifosfamide for soft-tissue sarcomas – randomized studies

Study	*Regimen*	*No. of patients*	*% CR*	*% OR*	*Median survival (months)*
ISSG Antman	A (60 mg/m^2), D (1 g/m^2)	170	2	17 $p = 0.005$	13 $p = NS$
	A (60 mg/m^2), D (1 g/m^2) I (7.5 g/m^2 → 6.0 g/m^2)	166	4	32	12
EORTC Santoro	A (75 mg/m^2)	240	4	23	12
	A (50 mg/m^2), I (5 g/m^2)	231	6	28 $p = NS$	12 $p = NS$
	ACDV–A (50 mg/m^2)	134	8	28	13
ECOG Edmonson	A (80 mg/m^2)	90	2	20	9
	A (60 mg/m^2) I (7.5 g/m^2)	88	3	34 $p = 0.03$	12 $p = NS$
	A (40 mg/m^2) P (60 mg/m^2), Mi (8 mg/m^2)	84	7	32	9
EORTC Steward	A (75 mg/m^2), I (5 g/m^2)	104	10	45	15
	+GM–CSF (molgramostim)	134			
EORTC Tursz	A (50 mg/m^2), I (5 g/m^2)	128	3	$p = NS$	
	A (75 mg/m^2), I (5 g/m^2) +GM–CSF (sargramostim)			21	

I = ifosfamide, C = cytoxan, A = Adriamycin, D = DTIC, NS = not significant, CR = complete response; V = vincristine, P = cisplatinum, Mi = mitomycinC, OR = objective response

sepsis) for AI, with no significant advantage in survival. Furthermore, in the middle of the ISSG trial, the MAID group protocol was amended to reduce the starting dose of ifosfamide from 7.5 g to 6 g/m^2.[44] There was also a significant decrease in the delivered dose of Adriamycin by the fourth cycle (from 60 to 51 mg/m^2). Patients with low- to intermediate-grade tumors responded less frequently to MAID (18%) than to AD (29%). A univariate analysis demonstrated a significant survival advantage for the two-drug arm AD in patients greater than 50 years old and those with low- to intermediate-grade tumors. This advantage for AD has been hypothesized to be due to the lower dose intensity of Adriamycin in the three-drug arm and to the fact that patients who failed on the AD arm subsequently received ifosfamide, which provided a secondary benefit.

The focus of research has now shifted to the two most active chemotherapy agents Adriamycin and ifosfamide, with dose intensification utilizing hematopoietic growth factors.[41,47–50] This approach is based on the hypothesis that their previous use at less than full doses in combination regimens with other agents (i.e., the MAID regimen) may have compromised their activity. An EORTC study utilizing GM-CSF support with high-dose Adriamycin showed the highest response rate (45%; 10% CR) so far seen by this cooperative group for advanced soft-tissue sarcomas (10% above their standard AI regimen).[35] This was followed by a larger phase III randomized trial comparing this higher-dose Adriamycin regimen with their conventional dose regimen (Adriamycin 50 mg/m^2 and ifosfamide 5 g/m^2).[41,51] The response rates, progression free interval, and overall survival were found to be similar for the two study arms. Unfortunately, some have concluded from these results that the activities of dose-intensified Adriamycin and ifosfamide regimens are disappointing. However, the dose and scheduling of ifosfamide in this trial was suboptimal. Furthermore, the predominant histologic subtype of the patients was leiomyosarcoma (38%), which is inherently more chemotherapy-resistant. Therefore, with a smaller overall number of possible chemotherapy-responsive sarcoma patients, the chance of detecting a small but significant difference between the two treatment arms was markedly reduced.

Recently, Patel and colleagues at M.D. Anderson Cancer Center (MDACC) escalated the doses of Adriamycin and ifosfamide further and have obtained the highest reported response rates to date.[47,48] They conducted two pilot studies to evaluate the feasibility and activity of Adriamycin at either 75 mg/m^2 or 90 mg/m^2 combined with ifosfamide at 10 g/m^2 (2 g/m^2 for 5 days) with G-CSF support. The overall objective response rate in 79 evaluable patients was 65%. There was no further benefit in improved response with the higher adriamycin dose arm, but about 50% of patients experienced Grade 3–4 thrombocytopenia within the first two cycles, and virtually all patients by cycle three. Results of time to progression and survival analysis are still pending. This higher dose therapy is felt to be feasible only for selected patients (i.e., age less than 65, ECOG performance status 0–1, no prior chemotherapy, and radiation therapy to less than 20% of the bone marrow). Bokemeyer *et al*. kept the dose of Adriamycin at 75 mg/m^2 and escalated the doses of ifosfamide to 14 g/m^2 with G-CSF and peripheral blood stem cell support.[49] This resulted in a 50% response rate with 22% complete responses.

These preliminary data appear to reflect a real improvement over previous experience with the MAID regimen. At present, the highest reported response rate for soft-tissue sarcoma is with a high-dose Adriamycin–ifosfamide regimen; however, it is associated with severe (although short-lived) myelosuppression, including significant cumulative thrombocytopenia. Whether the improved response rate will translate into a significant survival advantage is not yet known.[41] New growth factors (e.g., thrombopoietin) could further reduce the hematologic toxicity and enhance dose intensity. An improved response rate may be more important for early-stage disease (i.e., in the neoadjuvant or adjuvant setting) for young, good-performance status patients with a high-grade, borderline resectable lesion, or patients with pulmonary metastases who are borderline candidates for metastectomy. A significant response could facilitate subsequent surgery and/or radiation therapy, and render the patient disease-free.

For palliation, particularly in older or poor-performance status patients and in those with low- to intermediate-grade tumors, Adiamycin and Adriamycin/DTIC regimens seem preferable. Toxicity can be reduced by giving this regimen as a continuous IV infusion.

Adjuvant Chemotherapy

Although the role of adjuvant chemotherapy is well established in the treatment of rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma, its use in soft-tissue sarcomas remains controversial and unresolved.[52–56] Published articles range from retrospective reviews of outcome at single institutions, to prospective nonrandomized studies, to formal randomized trials.

Most of these studies have enrolled few patients (less than 100); have used different patient inclusion criteria and had an imbalance between the two arms with respect to pathologic grade, histologic subtype, and anatomic site; or utilized different drugs, doses, and schedules (some with suboptimal delivery and a delayed start). Several have an extremely short follow-up period, while others included patients with good risk factors (i.e. small, [less than 5 cm], low-grade tumors). For these reasons it is hard to draw meaningful conclusions concerning the validity of their results.

The resection of pulmonary metastases and the use of preoperative chemotherapy may also affect overall survival. Furthermore, it is difficult to detect small, but potentially clinically important, differences in survival, when only moderately effective chemotherapy regimens are used. Several single-arm studies show adjuvant chemotherapy to be beneficial when compared with historical controls; however, in nearly all the prospective randomized trials with an observation arm, there is no difference in overall survival. Both the treated and observation (control) arms do better than previous historical controls. Most studies show a trend toward longer disease-free survival but no significant increase in overall survival.

Twelve randomized studies have used the most active agent, Adriamycin, either alone or in combination (Table 3.2). Two (Fond Bergonie-Bordeaux and the Rizzoli Institute) showed a significant overall survival advantage for the patients receiving adjuvant chemotherapy; however, both of these studies were quite small. The remainder of these studies showed no increase in overall survival. None of the studies included ifosfamide, either alone or in combination.

A 5-year follow-up of a National Cancer Institute (NCI) study utilizing cytoxan, Adriamycin (total dose 530 mg/m^2), and methotrexate (CAM) showed a significant increase in disease-free and overall survival rates for the subset of patients with extremity sarcomas. However, at re-evaluation 2 years later (7.1 years median follow-up), overall survival was no longer significantly better for patients who had received adjuvant chemotherapy.[57] There was no significant benefit of chemotherapy for truncal and head and neck sarcomas. In patients with retroperitoneal disease, the control group fared better than the chemotherapy group. Cardiotoxicity, for the chemotherapy arm, was significant (14% congestive heart failure and greater than 50% abnormal MUGA scans). In the NCI's most recent study, with reduced total Adriamycin (350 mg/m^2), the

Table 3.2 Randomized adjuvant trials in soft-tissue sarcomas

			% DFS		% OS	
Study	*Regimen*	*No. of patients*	–	+	–	+
EORTC	ACVD	468	61	61	68	74
Extremities		233	52	67	74	79
Fond Bergonie	ACVD	59	16	57 $p < 0.01$	53	87 $p < 0.01$
Extremities		36	NA	NA	NA	NA
Mayo Clinic	AVDAd	61	68	65	70	70
Extremities		48	67	88 $p = 0.08$	83	63
MD Anderson	ACVAd	47	83	76	NA	NA
Extremities		43	35	54 $p < 0.05$	46	65
NCI	ACM	31	49	77 $p = 0.075$	58	68
Nonextremity/nonretroperitoneal		22	47	92 $p < 0.01$	61	82
Trunk		15	NA	NA	100	47 $p = 0.06$ ↑
Retroperitoneal		67	54	75 $p < 0.05$	60	82
Extremities						
Scandinavian	A	181	56	62	70	75
Extremities		155	NA	NS	NS	NS
Pooled DFCI/MGH, ISSG, ECOG	A	168	53	66	65	68
Extremities		72	64	79	70	79
GOG	A	156	47	59	52	60
UCLA	A	119	54	56	74	78
Extremities						
Rizzoli	A	77	45	73 $p < 0.05$	70	91 $p < 0.05$
Extremities						

DFS = disease free survival, OS = overall survival, (–) = observation, (+) = chemotherapy; NS = not significant, A = Adriamycin, C = cyclophosphamide, V = vincristine, D = dacarbazine, Ad = actinomycin D, M = methotrexate.
Modified from Mazanet R, Antman KH. Sarcomas of soft tissue and bone. Cancer. 1991;68:463–73.

disease-free and overall survival was found to be similar to that of the initial regimen, but cardiotoxicity was reduced.

An updated report by the Rizzoli Institute at greater than 10 years median follow-up showed a significant increase in disease-free survival ($p = 0.015$) and overall survival ($p = 0.04$) for adjuvant chemotherapy.[58] This study has been criticized because of an imbalance of large pelvic and thigh tumors between the control and chemotherapy groups.

An update of the large, randomized trial from the EORTC (median follow-up 80 months) reconfirmed that there was no difference in overall survival for CyVADIC adjuvant chemotherapy (63% versus 56%, $p = 0.64$).[59] Rates of relapse-free survival (56% versus 43%, $p = 0.007$) and local recurrence (17% versus 31%, $p = 0.004$) were significantly reduced. The reduction in local recurrence was apparent only for head, neck, and trunk sarcomas. Interestingly, only 68% of entered patients (317 of 468) were found to be eligible, and chemotherapy was not started for a median of 6 weeks after surgery (maximum 13 weeks).

There have been four published meta-analyses of the randomized adjuvant studies utilizing Adriamycin-based chemotherapy for soft-tissue sarcomas.[53,56] Three analyzed only the published data and showed a significant advantage in disease-free and overall survival rates for patients receiving adjuvant chemotherapy.[53] These meta-analyses have been criticized because the data are abstracted from narrative text and tables instead of from the raw data, and they did not include the most recent results from the EORTC and Rizzoli Institute. They also suffer from a number of other possible flaws (i.e., biases due to the exclusion of unpublished trials; inappropriate postrandomization patient exclusions; variable follow-up time; and a fixed

time-point analysis with deferring definitions of end points), all of which could contribute to overestimates of the treatment effect and significance.

Tierney *et al*. of the MRC Cancer Trials Office and the Sarcoma Meta-Analysis Collaboration, published an individual patient data meta-analysis (IPD-MA) of updated outcomes of 1568 patients from 14 randomized trials of Adriamycin-based adjuvant chemotherapy versus observation control (Table 3.3).[56] The median follow-up period was 9.4 years. Soft-tissue sarcomas of all sites, sizes, grades, and histologies were included. Only 59% of the histologic subtypes and 25% of the grades had been reviewed at the time of its publication. This IPD-MA showed a significant improvement for adjuvant chemotherapy with respect to time to recurrence (local and distant) and disease-free survival, but only a trend for benefit in overall survival. Of further interest, for the subset of patients with extremity soft-tissue sarcoma ($n = 886$), there was a significant absolute benefit in overall survival at 10 years (7%, $p = 0.029$). This finding must still be viewed cautiously since it was not included as part of the initial randomization and analysis, and there can be inherent dangers in the later evaluation of subsets. In addition, this IPD-MA may not be fully relevant for present medical practice, because it did not include adjuvant studies containing ifosfamide or using hematopoietic growth factors to maintain dose intensity.

Recently, Frustaci *et al*. reported on the Italian Cooperative Soft-Tissue Sarcoma Group's randomized adjuvant trial of 104 patients with high-risk (i.e. high-grade, deep, and greater than 5 cm) extremity soft-tissue sarcomas utilizing high doses of epirubicin and ifosfamide with G-CSF support.[60,61] At a median follow-up of 24 months (range 5–57 months), there was a significant difference in favor of the chemotherapy arm for both disease-free ($p = 0.001$) and overall ($p = 0.005$) survival. At interim analysis, after only half of the planned number of patients had been randomized, the investigators decided to stop accrual, even though follow-up was short. No evaluation of toxicity was reported. Nonetheless, these data, the first from a randomized trial evaluating aggressive chemotherapy with an ifosfamide-containing adjuvant regimen, are encouraging. Follow-up is ongoing, and the study will need to be confirmed with a larger number of patients by another multi-institutional group.

Since the survival of patients with high-grade extremity soft-tissue sarcomas is already 50–70% at several centers, it will be increasingly difficult to show a statistically significant difference in randomized adjuvant trials.[62] More patients will be needed to show small differences in survival. Patients with low-grade sarcomas should not be given adjuvant chemotherapy, because of their inherently low rate of metastatic spread and excellent prognosis. In addition, small (less than 5 cm), superficial, high-grade primary extremity sarcomas should not be included, since recent studies also suggest that these patients have an excellent survival.[5,63] Despite their limitations the IPD-MA and the Italian study indicate that adjuvant therapy is beneficial for select patients with extremity soft-tissue sarcoma. Future randomized trials should include only patients at high risk for metastases (i.e., large, high-grade, deep-seated lesions) with a reasonable likelihood of local control (radical resection or resection with uninvolved margins and radiotherapy). The recent NCCN Practice Guidelines recommend considering adjuvant chemotherapy with an aggressively dosed ifosfamide/Adriamycin regimen for patients with Stage IIB or IIIB extremity sarcomas who have undergone optimal resection, with or without radiation therapy.[5]

Table 3.3 Adjuvant chemotherapy of adult soft-tissue sarcoma: meta-analysis of individualized data

	Absolute benefit (at 10 years)		*Hazard ratio*	p-*Value*
	+	–		
Recurrence-free interval				
Local	6% (75 → 81%)		0.73	0.016
Distant	10% (60 → 70%)		0.70	0.0003
Survival				
RFS	10% (45 → 55%)		0.75	0.0001
OS	4% (50 → 54%)		0.89	0.12
	7% (extremity)		0.80	0.029

Tierney JF. Lancet. 1997;350:1647–54.
(–) = Observation, (+) = adjuvant chemotherapy.
RFS = recurrence-free survival; OS = overall survival

Neoadjuvant Chemotherapy

Neoadjuvant (induction) chemotherapy for soft-tissue sarcomas of the extremities evolved as a result of studies initially performed for osteogenic sarcoma. Routes of administration have included IV bolus, continuous IV infusion, and intra-arterial regional therapy, with or without concomitant radiation therapy.[12,64] They have also included isolated limb perfusion.[65] Neoadjuvant therapy has primarily been utilized for patients with large primary or recurrent sarcomas, usually with the goal of permitting a limb-sparing operation in patients in whom amputation may otherwise have been necessary or for converting a marginally resectable tumor to one that can be adequately resected with preservation of extremity function. Although initial local tumor control and limb-salvage rates appear very good, most studies have enrolled only small numbers of patients and have a short follow-up. Therefore, the effect of neoadjuvant therapy on disease-free and overall survival rates is not fully known. There have been no prospective randomized trials comparing preoperative and postoperative chemotherapy for patients with soft-tissue sarcoma. Nevertheless, patients with large, deep-seated, high-grade lesions of the extremities are a high-risk group that is an optimal target population for investigating the effectiveness of multimodality treatment strategies.

There have been several representative early reports of the use of IV preoperative chemotherapy for extremity sarcomas with Adriamycin-based regimens. Pezzi *et al.* from M.D. Anderson summarized a 7-year experience (1979–1985) with preoperative Adriamycin-based systemic therapy (an average of four cycles), with or without radiation therapy, in 46 patients with large tumors (median 10.6 cm).[66] The clinical response rate was 23%. Limb-sparing surgery could be performed in 67% of patients, but the local recurrence rate was 34%, and overall survival (median of 28 months follow-up) was 62%. In a study by Casper *et al.* from MSKCC, which entailed administration of two cycles of preoperative CyVADIC to 22 patients with large extremity soft-tissue sarcomas (median 10 cm), there was only one partial clinical response, and just 10% of patients had greater than 90% tumor necrosis.[67] Median 3-year disease-free survival was 36%, overall survival at 3 years was 45%. There was no survival advantage between this study group and a historical control group of patients with surgery alone or surgery plus post-operative Adriamycin. Possible explanations for the lower response rate could have been a lower Adriamycin dose (60 mg/m^2), as well as administration of fewer cycles of preoperative chemotherapy.

Pisters *et al.* reported on 76 patients with large high-grade extremity sarcomas treated at M.D. Anderson between 1986 and 1990 who received a median of three preoperative cycles of IV Adriamycin/DTIC (+/–) cyclophosphamide or other Adriamycin-based regimens.[68] Limb-sparing surgery was able to be performed in 91% of these patients. Five-year actuarial disease-free survival was 46%, and overall survival was 54% (median follow-up 85 months).

Much of the pioneering work utilizing preoperative chemotherapy for extremity soft-tissue sarcomas has been conducted by the University of California at Los Angeles (UCLA) group.[69,70] Their experience entails five sequential trials over a 20-year period (Table 3.4). They initially utilized a preoperative continuous infusion of intra-arterial Adriamycin 90 mg (30 mg/day for 3 days), a suboptimal dose, followed by varying amounts of preoperative radiation therapy in three sequential studies. Utilizing 3500 cGy produced a low local recurrence rate, but a high incidence (25%) of complications. When the dosage was decreased to 1750 cGy the complication rate (including bone fractures) decreased, but the local recurrence rate increased. The protocol was again modified in 1984 to incorporate an intermediate radiation dose of 2800 cGy (350 cGy/day for 8 days). In addition, the preoperative Adriamycin dose was randomized to be given either as an intra-arterial or IV infusion. Ninety-nine percent of patients were able to undergo a limb-sparing procedure, and the local recurrence rate was only 8%. Complications occurred in 14% of patients, which was less than with the higher dose of radiation. At a median follow-up of 36 months there was no significant difference between the IV and the intra-arterial groups in the limb salvage, local recurrence or complication rate; percentage of histological necrosis; or disease-free survival. This study has been cited by some as evidence for the lack of efficacy of intra-arterial chemotherapy. However, the dosage of Adriamycin was suboptimal, and at the time of initial randomization the two treatment groups were not stratified for tumor size and grade. The intra-arterial group contained a greater percentage of patients with large (>10 cm), high-grade tumors. Several other investigators have attempted to reproduce the UCLA group results using intra-arterial Adriamycin.[12] The results appear to be similar, with a fairly high complication rate. On the basis of these findings it was concluded that Adriamycin is not the proper drug for intra-arterial use because of problems with musculocutaneous necrosis.

The UCLA group then investigated the use of intravenous cisplatinum 120 mg/m^2 over 4 h with Adriamycin 60 mg/m^2 given via continuous infusion over 48 h followed by radiation 2800 cGy. The limb-sparing and local recurrence rates remained about the same, but the complication rate was reduced.

Table 3.4 UCLA – neoadjuvant chemoradiation protocols for soft tissue sarcoma

Protocol	*Years*	*Chemotherapy*	*Radiation dose (cGy)*	*Percentage median tumor necrosis*	*Percentage pathologic CR necrosis*	*Percentage local recurrence*	*Percentage overall grade III tumors*
Pilot	1973	ADR 90 mg IA over 3 days)	+3500	–	–	–	–
1	1974–80	ADR 90 mg IA over 3 days	3500	70	12	9	56
2	1981–84	ADR 90 mg IA over 3 days	1750	45	4	20	61
3	1984–87	ADR 90 mg IA or IV over 3 days	2800	60	6	14	70
4	1987–90	CDP 120 mg/m^2 IV over 4 h (two cycles) ADR 60 mg/m^2 IV over 48 h	2800	70	15	12	71
5	1990–93	IFOS 14 g/m^2 IV over 7 days CDP 120 mg/m^2 over 4 h ADR (75 mg/m^2 IV over 48 h (one cycle)	2800	98	34	2	85

Adr = Adriamycin; IFOS = ifosfamide; CDP = _; CR = ?

In an attempt to augment the pathologic complete response rate, the UCLA group next added two cycles of high-dose ifosfamide at 14 g/m^2 to the neoadjuvant chemotherapy and radiation regimen.[69] Radiation (2800 cGy) was given during the second cycle of ifosfamide, and this was then followed by one cycle of cisplatinum/Adriamycin. When retrospectively compared with the previous sequential trials at UCLA, this regimen resulted in a markedly improved complete pathologic response of 34% vs. 7.4%, the combined complete response rate for all prior trials. At a median follow-up of 27 months, local failure was 2% and overall survival was 87%, with 98% of patients undergoing a limb-salvage procedure. These results are impressive despite the fact that this is fairly toxic, requiring significant replacement of blood components for cytopenias and hospitalizations for febrile neutropenia. Whether, with longer follow-up, the improved complete pathologic response rate will translate into an improved overall survival (as hypothesized) is not yet known.

Investigators at MGH have combined three preoperative cycles of a MAID-type chemotherapy with radiation (4400 cGy) in a neoadjuvant regimen for large (>8 cm), high-grade extremity soft-tissue sarcomas.[71] At a short median follow-up of 13 months, local control was 100%, disease-free survival 84%, and overall survival 93%. When compared with a historically matched control group from the same institution, the results of this study group were significantly better. Based on these data, a Phase II Intergroup (ECOG and RTOG) study is now seeking to confirm these results in a multi-institutional setting.

Our group evaluated a short course of combination regional/systemic chemotherapy consisting of two preoperative cycles of intra-arterial cisplatinum (120 mg/m^2 over 2 h) and continuous IV infusion Adriamycin (60 mg/m^2 over 72 h) in 24 patients with large, high-grade, unresectable/borderline resectable soft-tissue sarcomas of the extremities.[72] This regimen was utilized based on its known activity in osteogenic sarcoma, and on the fact that, although cisplatinum has low-single agent activity for soft-tissue sarcoma, it appears to have a synergistic effect when given with Adriamycin. With this neoadjuvant regimen, 92% of patients were able to undergo limb-sparing surgery, and the local control rate was 87%. After surgery, four adjuvant cycles of IV cisplatinum/Adriamycin were given. Postoperative radiation was used only for patients with positive margins or massive contamination from previous inadequate surgery. At a median follow-up of 76 months, disease-free survival was 66% and overall survival 83%. No patient developed major cardiac or renal dysfunction; however, 29% of these patients developed significant peripheral neuropathy that was probably due to cumulative cisplatinum.

A new protocol, initiated in 1995, adds one cycle of IV ifosfamide at 9 g/m^2 (2.25 g/m^2 per day for 4 days) combined with Adriamycin to the preoperative regimen (Figure 3.1). The dose of Adriamycin for all cycles has

been increased to 75 mg/m^2, with G-CSF support afterwards. Postoperatively, three cycles of ifosfamide and Adriamycin at the same dose are given.[73] Thus far, the incidence of severe peripheral neuropathy has been significantly reduced; however, it is too early to determine whether this regimen will be superior in terms of local control, disease-free, and overall survival.

Hyperthermic isolated limb perfusion with melphalan and tumor necrosis factor has been used in patients with large soft-tissue extremity sarcomas that are close to bone, nerve, and/or blood vessels and in whom amputation would otherwise be necessary (see Chapter 4). A high limb-salvage rate (>80%), has been reported.[65,74] This is, however, a localized treatment when used alone, and there has been no control of or reduction in the recurrence of systemic disease.

In conclusion, neoadjuvant chemotherapy for large, high-grade soft-tissue sarcomas of the extremities is feasible and associated with good local control and survival. Limb-sparing surgery is possible in the overwhelming majority of these patients. More aggressive regimens appear to reduce local recurrence and result in a high complete pathologic response rate. The best regimen, in terms of specific drugs, drug/dose sequence, and route is not known at this time; also unknown is whether radiation therapy is necessary for all patients. However, neoadjuvant chemotherapy should be considered for patients who have traditionally been thought to be at high risk for local recurrence (i.e., patients with large, deep-seated, high-grade, extremity sarcomas). We believe that amputation should rarely be performed for large, high-grade, extremity soft-tissue sarcomas without first considering a trial of neoadjuvant therapy.

Unfortunately, we are still faced with limitations in the options for chemotherapy with only a small number of modestly active agents. For the future, more multicenter, prospectively randomized studies utilizing new, more effective chemotherapeutic agents, are needed.

OSTEOSARCOMA

Although osteosarcoma is a rare tumor, it is the most common malignant tumor of bone in adolescents and young adults. Approximately 1000 new cases occur each year in the United States.[6,7] It is more prevalent in males and has a strong predilection for the distal femur, proximal tibia, and proximal humerus. About 80% of patients have localized disease at the time of diagnosis. The most common sites of metastasis are the lung and other bone.[6,7,9,10]

Prior to 1970 the primary treatment of nonmetastatic osteosarcoma of the extremities consisted of surgical extirpation (usually amputation) and/or high-dose radiation therapy of the primary tumor. The 5-year disease-free survival rate was no more than 20%; lung metastases were the most common reason for treatment failures. Early investigations of chemotherapy for osteosarcoma were unrewarding, and it was considered a chemoresistant tumor.[75,76]

By the early 1970s, and continuing through the 1980s reports began to emerge of effective drugs for the treatment of osteosarcoma, i.e., Adriamycin, high-dose methotrexate with calcium leucovorin rescue, cisplatinum, and, more recently, ifosfamide.[8,77–91] It was demonstrated that these agents could eradicate overt metastatic disease and improve disease-free survival,

Study design

- Preoperative chemotherapy – three cycles, q21 days
  - Cycle 1: Ifosfamide 2.25 g/m^2 IV qd over 2 h, days 1–4
    Adriamycin 75 mg/m^2 CIV over 72 h
  - Cycles 2, 3: Adriamycin 75 mg/m^2 CIV over 72 h
    Cisplatinum 120 mg/m^2 IA over 4 h
- Surgery – Limb-sparing or amputation
- Postoperative chemotherapy – three cycles, q21 days
  - Cycles 4, 5, 6: Ifosfamide 2.25 g/m^2 IV qd over 2 h, days 1–4
    Adriamycin 75 mg/m^2 CIV over 72 h

All cycles of chemotherapy are supplemented with G-CSF support at 5 μg/kg SQ, starting 24 h after chemotherapy is finished.

Figure 3.1 WHC/WCI neoadjuvant chemotherapy for extremity soft tissue sarcoma #2 (W94-3)

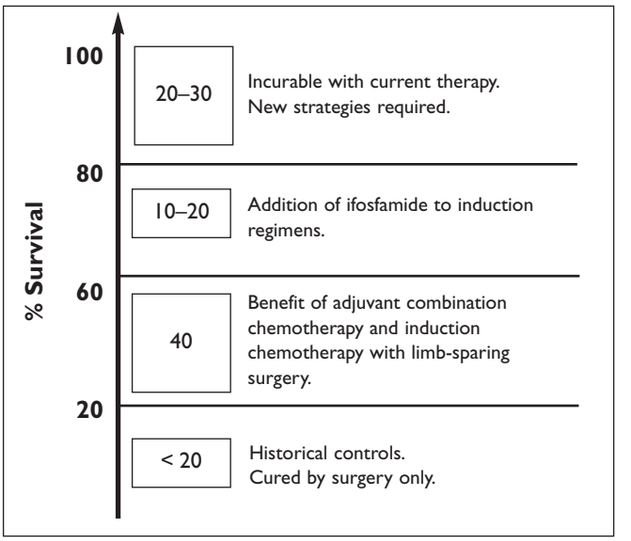

Figure 3.2 Development of treatment of patients with nonmetastatic osteosarcoma.

and they have been incorporated into modern chemotherapy protocols in varying combinations. To a large extent the major advances made over the past three decades in the treatment of osteosarcoma are a consequence of the development of effective chemotherapy. The introduction of these agents into multidisciplinary treatment strategies has allowed for more conservative and limb-sparing procedures to be performed and improved overall patient survival.[6–10]

Chemotherapy Development

There has been a wide variation in reported response rates to methotrexate (e.g. 0–80%), leading several investigators to question its effectiveness. The activity of methotrexate appears to be dose-dependent, given that dose escalation has been associated with responses in patients previously unresponsive to lower doses.[78] It has the significant advantage of being nonmyelosuppressive, but it is expensive and needs to be used with care and appropriate monitoring, especially in older patients. Rosen and others believe the variable response rates reported with methotrexate are directly related to improper drug administration.[79,90] Several recent studies have shown that, in order for methotrexate to be effective in osteosarcoma, one must achieve a minimum peak serum concentration of greater than 1000 μmol (10^{-3} M) at the completion of a 4-h infusion (700 μmol after a 6-h infusion). To achieve these drug levels it is necessary to give a dose of at least 8–12 g/m^2. Furthermore, excessive amounts of IV hydration should not be administered during the first 24 h, in order to limit urine output to less than 1400 ml/m^2.[78–85]

Recently, Guo *et al*. have shown a high frequency (~65%) of decreased reduced folate carrier (RFC) expression in osteosarcoma biopsy samples, suggesting that the impaired transport of methotrexate is a common mechanism of intrinsic resistance in osteosarcoma.[92] In addition, increased dihydrofolate reductase (DHFR) expression was found to be significantly higher in metastatic or recurrent tumor specimens but not in primary tumors.[92] This may be a mechanism of acquired methotrexate resistance or reflect a possible difference between primary and metastatic tumors. These findings could help explain why higher doses of methotrexate with minimum peak serum levels (producing prolonged drug exposure) are required in order to obtain a good histologic response.

There also appears to be a steep dose–response rate for Adriamycin; i.e., doses ≥ 70 mg/m^2 have more activity than lower doses.[77] Whether carboplatinum can be substituted for cisplatinum is still controversial. Carboplatinum has reduced renal and ototoxicity but produces more myelosuppression and may be less active than cisplatinum.[93–95] Initial reports indicated that the combination of bleomycin, cyclophosphamide, and dactinomycin (BCD) was effective in the treatment of metastatic disease, and in several early preoperative studies this regimen was given with other known active agents. Subsequent studies failed to confirm the activity of BCD when given alone; consequently it is not included in most modern chemotherapy regimens.[96]

Ifosfamide appears to have significant activity for the treatment of both primary and recurrent osteosarcoma. It also has a clear dose-dependent response curve (with responses occurring at doses of 12–18 g/m^2 in patients who had failed with previous doses below 10 g/m^2).[24–26,87–89] Further enhancements in patient outcome will most likely come from the inclusion of ifosfamide into newer combination regimens, and with the development of novel agents.

How best to combine these drugs is still unknown. There is still heated debate over what constitutes optimum chemotherapy. While most institutions utilize an intensive multi-agent regimen, some have questioned the merits of prolonged and complicated schemes over regimens that include fewer drugs given over a shorter time period.

A recently completed study by the European Osteosarcoma Intergroup (EOI) explored whether the intensive use of two active agents, cisplatinum and Adriamycin, administered in six cycles over 18 weeks is better than a more complex, multi-agent modified Memorial Sloan Kettering Cancer Center (MSKCC) T10-like regimen given over 44 weeks.[97] There was poor patient compliance and a reduction in dose intensity with the multidrug regimen. The shorter, two-drug combination was found to have equivalent survival outcomes to that observed with the modified T10 program; the 5-year progression free and overall survival rates for both groups being only 44% and 55%, respectively. Unfortunately, these results are somewhat lower than that achieved in other previous studies. The EOI has since shown that the cisplatinum/Adriamycin regimen can be safely intensified with G-CSF support.[98] Therefore, in its new study, the EOI will test the concept of dose density by randomizing patients to an induction cisplatinum/Adriamycin regimen given every 3 weeks for two cycles or to the same regimen given every 2 weeks for three cycles with G-CSF support.

Adjuvant Chemotherapy

Once chemotherapy had been found to be effective against metastatic disease, investigations were initiated to determine the efficacy of these agents in destroying micrometastases, which are thought to be present in the majority of patients at the time of initial primary surgery (i.e., adjuvant or postoperative chemotherapy).[99] Five-year survival figures of 1286 patients

collected from the world literature between 1946 and 1971 showed a mean survival rate of 19.7% (range 16–23%).[6,7] Eighty percent of patients developed metastases despite amputation, suggesting the presence of micrometastatic disease in the majority of cases.[75,76]

In the 1970s, early uncontrolled adjuvant trials of single- and multi-agent chemotherapy regimens documented relapse-free survival rates of 35–60%.[99,100] However, the contribution of adjuvant chemotherapy was then questioned by researchers from the Mayo Clinic, where the outcome with surgery alone was found to be improved (13% disease-free survival for patients treated in the 1960s compared with 42% for patients in the 1970s).[101,102] Furthermore, a randomized adjuvant chemotherapy trial at the Mayo Clinic of moderate-dose methotrexate (considered inadequate by today's standards) versus surgery alone indicated no benefit for adjuvant chemotherapy. The relapse-free survival of the surgery-alone group was 44%, more than twice what was expected on the basis of the historical experience.

The exact role of adjuvant chemotherapy was then heatedly debated.[101,103–106] Some felt that an increased survival for osteosarcoma patients had occurred over time. They believed that this was related solely to diagnostic advances in staging, the earlier detection of metastases, and to improvements in surgical techniques and supportive care.[101,102] Prospective randomized controlled trials conducted by the Multi-Institutional Osteosarcoma Study Group (MIOS) and the UCLA group resolved this controversy when they confirmed the significant favorable impact of adjuvant chemotherapy on outcome.[107–109] They also corroborated the poor prognosis for patients treated with surgery alone (Table 3.5).

Adjuvant chemotherapy has been shown to reduce the number of pulmonary metastases and to delay their appearance, thus possibly facilitating surgical removal.[110–115] It has also changed the natural history of this neoplasm; more patients develop extrapulmonary metastases (e.g., to the skin, brain, and/or heart).[112–115] The majority of trials of adjuvant chemotherapy now report event-free survival rates of 45–65%.[99–100,103–109] Even with the increased use of preoperative chemotherapy to induce tumor necrosis, intensive adjuvant chemotherapy is still believed to be needed.

Induction Chemotherapy

At the same time that advances were evolving with chemotherapy, improved techniques of primary surgical resection were being developed that reduced the need for amputation. These new limb-sparing procedures required that surgery be delayed 2–3 months for the manufacture of a custom-made endoprosthesis. In the mid-1970s Rosen *et al.* at MSKCC designed a strategy to use induction (neoadjuvant) chemotherapy to treat patients who were awaiting manufacture of their prosthesis.[116]

The induction therapy approach had other potential benefits as well. It not only was felt to be an early defense against the possible presence of pulmonary metastases but also had the theoretical advantage of being able to reduce the emergence of drug-resistant tumor cells.[116–120] It was also thought to help downstage a tumor by reducing the size of an accompanying soft-tissue mass and forming a surrounding reactive rim that would confine the tumor within a calcified periosteum. This could lead to better tumor demarcation and permit successful tumor removal with a

Table 3.5 Adjuvant chemotherapy for osteosarcoma – randomized studies.

Study	*Drug regimen*	*No. of patients*	*Percentage RFs*	*Percentage OS*
Mayo Clinic	HDMTX = VCR vs. no adjuvant therapy	38	40 p = NS 44 (6 years)	
MIOS[102]	BCD + HDMTX + ADRIA + CDDP vs. no adjuvant therapy	36 random. 165 nonrandom	63 p = 0.001 12 (2 years)	71 p = 0.04 48
UCLA[103]	BCD = HDMTX + VCR + ADRIA (+ intra-arterial ADRIA + XRT) vs. no adjuvant therapy	59	55 p = 0.004 20	80 p = 0.04 48

RFS = relapse free survival, OS = overall survival, NS = not significant, HDMTX = high-dose methotrexate, VCR = vincristine, BCD = bleomycin, cytoxan, dactinomycin-D, ADRIA = Adriamycin, CDDP = cisplatinum, XRT = radiation therapy.

limb-sparing resection.[12,119] In addition, it provided an opportunity to test chemotherapy sensitivity *in vivo* on the basis of the initial histologic response and then to customize or tailor adjuvant chemotherapy.[120]

When intensive multi-agent regimens are used, induction chemotherapy trials have often produced better relapse-free survival rates (42–82%) than those reported for patients undergoing immediate surgery followed by adjuvant chemotherapy.[12,118–132] Most modern induction protocols include a multidrug regimen, given for 6–18 weeks, followed by resection of the primary tumor and 3–8 months of adjuvant IV chemotherapy. Drugs used in these regimens include cisplatinum and Adriamycin with or without high-dose methotrexate. Recent trials incorporating ifosfamide appear to have further increased tumor necrosis and improved patient survival.[125,126,129,130] Nevertheless, patients need to be followed closely, since a small number may be completely insensitive to induction chemotherapy and the tumor may continue to progress. These patients need to be identified early so that they can be either switched to another chemotherapeutic regimen or have immediate surgical resection.

In conjunction with improvements in surgical technique and prosthetic devices, there has been a growing enthusiasm for limb-sparing surgery by orthopedic surgeons, which has also led to the more frequent use of induction chemotherapy. However, a number of key questions regarding induction chemotherapy remain, among which the most important are the following:

Histologic Assessment of Chemotherapy Response

The response of osteosarcoma to preoperative chemotherapy may be assessed by clinical, laboratory, radiologic, and pathologic parameters. Clinical responses are noted with a decrease in pain, swelling, and heat.[133] On laboratory analysis there can be a reduction of an elevated alkaline phosphatase.[134,135] With plain radiography and computerized tomography scan, one can see a reduction or complete disappearance of any associated soft-tissue mass, revisualization of the fat planes between muscle bundles, healing of pathologic fractures, and organized deposition of calcium within the neoplastic bone (calcified periosteum) (Figures 3.3 and 3.4).[136–139] An arteriogram can offer a less subjective means of assessing a tumor response; this can be manifest by a diminution or a disappearance of tumor vascularity and stain.[137,140,141] Other techniques undergoing further evaluation include technetium-99 methylene diphosphonate functional imaging, gallium, thallium-201, and nuclear magnetic resonance scans.[142–145]

Despite the utility of these various findings, the histologic appearance of the resected primary tumor specimen after induction chemotherapy has emerged as the gold standard for evaluating and measuring a therapeutic response. Several pathologic grading systems for assessing the effect of induction chemotherapy have been developed, all of which are based on the degree of tumor cellularity and necrosis found within the resected specimen.[146–149] Grading systems can be imprecise, subjective, and prone to sampling errors. Nevertheless, with careful attention to adequate and precise sectioning from many sites of the surgical specimen, a determination of response can be assessed which appears to correlate with patient outcome.[147–149]

The Huvos grading system has served as a model for other systems.[146] A Grade III and IV response is characterized by an extensive or complete destruction of cells within the primary tumor and is associated with better survival (Figure 3.5). While a Grade I or II response is indicative of minimal destruction of tumor; these patients are more likely to develop distant metastases and have a poor survival. Unfortunately, the percentage of tumor necrosis is difficult to evaluate, and most investigators have not graded tumor necrosis in a similar fashion as first proposed by Huvos and Rosen.[146] This ambiguity and variable definition of a good pathologic response (between 60% and 95% necrosis) amongst institutions and cooperative groups makes comparisons between different induction chemotherapy studies difficult.[6,7,12]

Furthermore, of particular concern was an updated report from MSKCC suggesting a further modification of the Huvos system. With larger patient accrual and longer follow-up, it was apparent that there was a greater difference in event-free survival in patients with a Grade III and IV response than between patients with a Grade II and III.[121,150] Thus, it was felt that only patients with a Grade IV response should be considered as having a favorable prognosis, and if therapy were to be changed based on the degree of tumor necrosis following induction chemotherapy, it would be applied to all patients with less than Grade IV necrosis. For the future, an international standardized definition for a good pathologic response to induction chemotherapy is needed.

Tailoring Adjuvant Therapy

The concept of tailoring adjuvant therapy on the basis of the histologic response of the primary tumor to induction chemotherapy was first proposed by Rosen *et al*. and tested in the MSKCC T10 protocol.[120] This was formulated on the hypothesis that the responsiveness of the primary tumor to chemotherapy will predict that

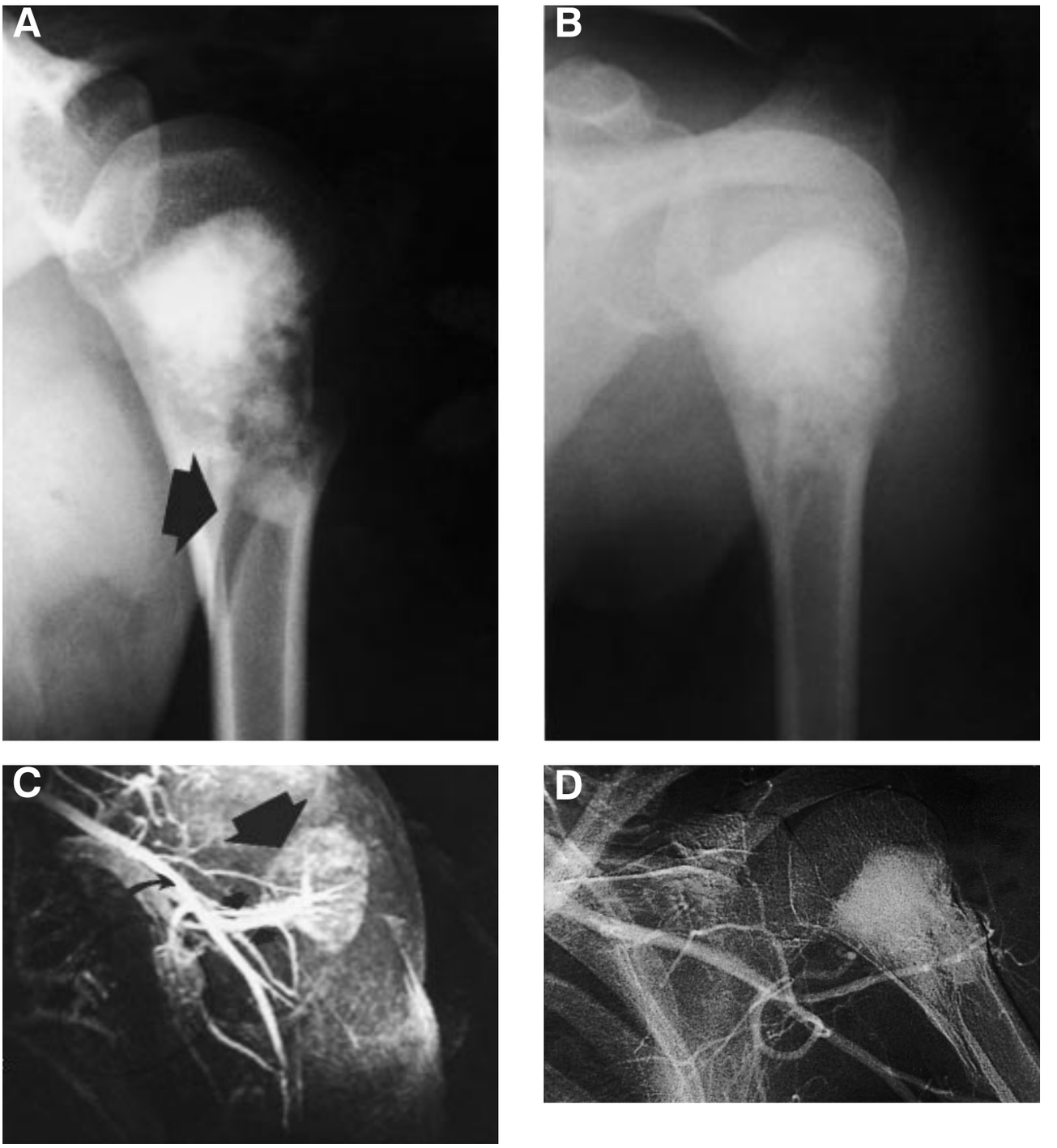

Figure 3.3 Pathological fracture through a sclerosing osteosarcoma of the proximal humerus treated by induction chemotherapy. (**A**) Initial radiograph of the proximal humerus showing a sclerotic lesion within the medullary canal with a slightly displaced pathological fracture at the base (solid arrow). (**B**) Radiograph showing complete healing of the pathological fracture following three cycles of induction chemotherapy (consisting of Adriamycin, cisplatinum, and ifosfamide). (**C**) Prechemotherapy angiogram showing marked vascularity of the tumor corresponding to the plain radiographs seen in (**A**). The axillary artery (curved arrow) gives rise to the circumflex vessels (small arrows) that feed the main tumor blush (large arrow). Most tumors of the proximal humerus have this vascular pattern. (**D**) Post-induction chemotherapy angiogram corresponding to Figure 3.3B showing complete avascularity of the tumor. This patient underwent a successful limb-sparing procedure with a modular proximal humeral replacement. There was 98–100% tumor necrosis (Huvos grade III to IV response). This patient remains free of disease at 24 months.

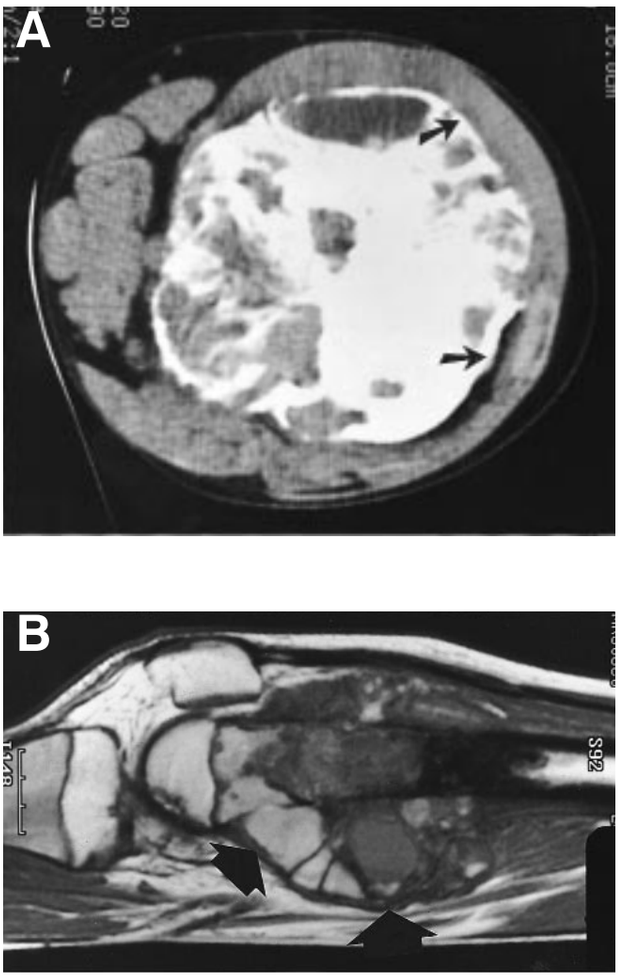

Figure 3.4 Typical radiographic response following induction chemotherapy. (**A**) CT scan of an extremely large tumor of the distal femur following induction chemotherapy. Note the complete sclerosis and rimming of the lesion (small arrows). A smooth rimming border is characteristic of a very high rate of tumor necrosis and an excellent chemotherapy effect. This patient underwent limb-sparing surgery with a distal femoral replacement in lieu of an initially planned high above-knee amputation. The amputation was initially considered due to the large size of the tumor. A vascular graft was not required. (**B**) MRI of the same patient shows a very typical black rimming response around the periphery of the tumor (solid arrows). MRI is not as reliable as CT in determining the response to chemotherapy. Although a solid black line around the periphery corresponds with the smooth cortical rimming seen on CT, this indicates the attempt of reossification and healing of the "tumor" defect.

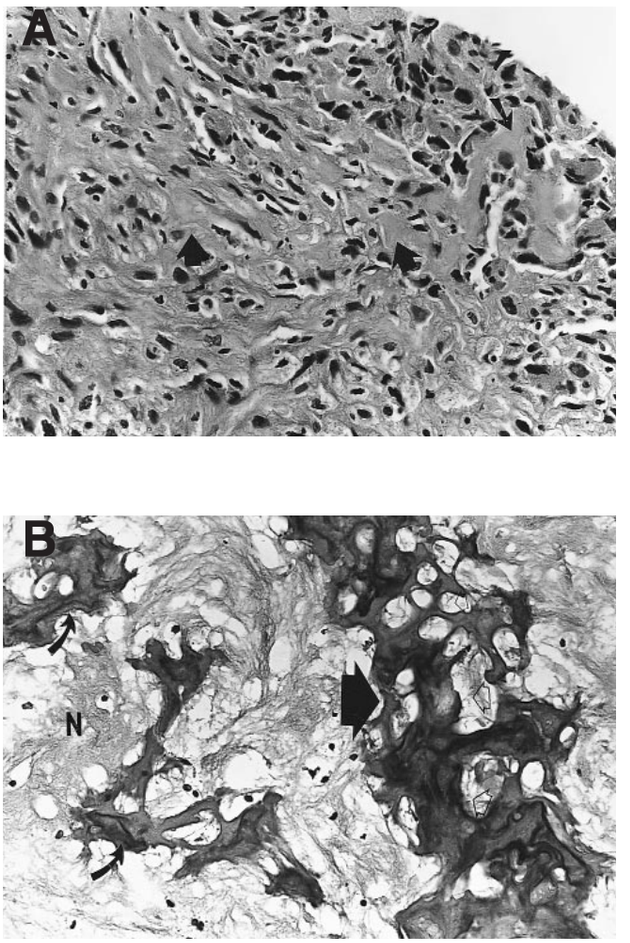

Figure 3.5 Histological effect of induction chemotherapy. (**A**) Osteosarcoma of the distal femur prior to chemotherapy. This photomicrograph shows completely viable tumor with early osteoid (solid arrows) formation. Note the pleomorphism and hyperchromatism. (**B**) Post-induction chemotherapy. This was obtained following a limb-sparing resection of the tumor. This section is representative of the entire tumor. Note that the stroma is completely necrotic (N) with several small, pignotic, dead nuclei seen. The remaining osteoid cells (large curved arrows) are present. There are no viable cells within the lacunae of the osteoid matrix. This is a very typical appearance of a good killing effect by the chemotherapeutic agents. The stroma cells die and are replaced by a fibrovascular stroma but the osteoid matrix remains. Clinically, an osteosarcoma with a good response to chemotherapy may shrink no more than 20–25%. This is explained because the remaining osteoid does not resolve (hematoxylin and eosin stain; original magnification × 100).

of micrometastases. Thus, a good-responding patient receives the same drugs after surgery as before surgery, while the postoperative regimen of a patient who has responded poorly to induction chemotherapy is changed. Early results by Rosen *et al*. from the T10 protocol reported an excellent disease-free survival rate for poor-responding patients as well, suggesting that they could be salvaged with a modified adjuvant (postoperative) treatment.[120]

The T10 protocol was a model for many trials launched in the 1980s, virtually all of which featured induction chemotherapy and the individualization of postoperative therapy on the basis of the pathologic responsiveness of the primary tumor.[117–120] Unfortunately, later studies from several groups, including the Children's Cancer Study Group (CCSG), German–Austrian–Swiss Cooperative Osteosarcoma Study Group (COSS-82), and the Rizzoli Institute, failed to confirm an improved prognosis for poor responders treated with alternative postoperative chemotherapy regimens.[118,119,123,127] Furthermore, an update of the MSKCC T10 protocol, reported by Meyers *et al*., indicated that Rosen's promising preliminary results were not sustained over time. With longer follow-up the efficacy of tailored treatment was not demonstrated.[121]

However, a recent study by Benjamin *et al*. from MDACC suggests that the addition of postoperative ifosfamide significantly improved the 5-year disease-free survival of poor-responding patients over that seen in their previous treatment regimens (67% vs. 34%, respectively, $p = 0.015$).[126] Other recent studies incorporating ifosfamide have documented better survival rates, and it appears that there may be further benefits if this agent is added to induction therapy as well.[125,128–130,132]

Duration of Induction Chemotherapy

There is considerable variability in the duration of induction chemotherapy. Most studies use an arbitrary time of 6–18 weeks with the administration of two to six cycles of chemotherapy. Some investigators have attempted to adjust surgical intervention to the time of maximal response to induction chemotherapy. Longer-duration chemotherapy regimens may be associated with a higher proportion of good histologic responses; however, as the duration of induction chemotherapy is prolonged, the value of using its effect on histologic response as a predictor of patient outcome may be lost. Thus, regimens of longer duration may result in a better histologic response, but this may not translate into improved patient survival. Meyers *et al*. have suggested that the rate of a good histologic response may be related to the duration of induction chemotherapy, but that the duration of chemotherapy does not correlate with relapse-free survival.[131]

Induction/Adjuvant Chemotherapy versus Adjuvant Chemotherapy

Some investigators have felt that the superior results obtained with induction chemotherapy may simply reflect the use of more intensive multi-agent chemotherapy (i.e., cisplatinum and ifosfamide) and may be unrelated to the timing (preoperative versus postoperative) or route of administration of chemotherapy (IV versus IA).[7,151] They have argued that equally intensive adjuvant chemotherapy regimens need to be tested against induction chemotherapy in a prospectively randomized fashion. Retrospectively, it appears that patients treated with induction chemotherapy have fared better than patients treated with immediate surgery and postoperative adjuvant chemotherapy. However, the majority of induction chemotherapy trials have been single-institutional studies, which inherently are known to yield better results because of patient selection. By contrast, the majority of adjuvant chemotherapy trials have been multi-institutional or cooperative group studies (Table 3.6).

The Pediatric Oncology Group (POG) performed a randomized trial of induction versus adjuvant chemotherapy.[151] Patients were randomized to immediate surgery or to presurgical treatment with two cycles (10 weeks duration) of high-dose methotrexate, cisplatinum, and Adriamycin. Except for timing, postsurgical chemotherapy (methotrexate, cisplatinum, Adriamycin, and BCD), given over 44 weeks, was the same in both arms.

The survival rate for the group receiving induction chemotherapy was no better than that of the adjuvant chemotherapy alone group (Table 3.7). Whether induction chemotherapy improved the limb salvage rate has not yet been reported. Poor responders in the induction arm were not crossed over to other agents; thus, the strategy of salvage therapy was also not evaluated.

Table 3.6 Updated chemotherapy trials for non-metastatic osteosarcoma (with >50 patients)

	Composite 5-year disease free survival
Adjuvant (mostly multi-institutional, cooperative groups)	46–61%
Neoadjuvant + adjuvant (mostly single institutions)	49–80%
POG #8651 – randomized trial	Same – no difference

Table 3.7 POG #8651 – 100 evaluable patients

Chemotherapy regimen	*% 5-year survival*	
	Disease free	*Overall*
Induction adjuvant	63.2	79.7
	$p = 0.60$	$p = 0.41$
Adjuvant	65.5	
		75.3

Goorin A *et al.*, Med Ped Oncol. 1996;27:263a.

Some have cited this study as a reason not to give induction chemotherapy since there was no improvement in patient survival. On the other hand, the results suggest that induction chemotherapy may have improved the limb-salvage rate and extremity function without compromising overall survival, as was initially feared.

Intra-arterial Chemotherapy

To improve the results of induction IV systemic chemotherapy, to further downstage tumors, and to augment the rate of successful limb-sparing procedures, several investigators began to administer induction chemotherapy via the IA route.[12] This allows for a higher concentration of chemotherapy to be delivered to the primary tumor, with possible improved penetration of drug across the cell membrane.[152–154] Pharmacologic studies have confirmed an increased regional drug concentration, drug uptake, and tumor destruction when the IA route is utilized.[133,152–154] Furthermore, the concentration of chemotherapy reaching the systemic circulation after initial intra-arterial passage has been found to be similar to that attained via the IV route and therefore should be enough to destroy any microscopic pulmonary metastases.[133,152–154]

Initial IA studies utilized Adriamycin, but this treatment was complicated by erythema and ulceration of the underlying skin and subcutaneous tissue, with extensive necrosis of normal tissue. A complete histologic response in the primary tumor was rarely obtained.[155–157] Because of the potential for normal tissue destruction, preoperative IA Adriamycin was not endorsed or accepted.[12]

Cisplatinum is an alternative drug for IA use. Jaffe *et al.* established the use of IA cisplatinum as a single agent for the treatment of osteosarcoma in the pediatric population.[153,158] When this drug was given alone, at least four courses were required to achieve an optimum effect. In a study comparing cisplatinum and high-dose methotrexate, a greater proportion of patients were found to respond to IA cisplatinum, with a significantly higher number of pathologic good responders (≥ 90% tumor necrosis).[159] Unfortunately, there was still a high rate of metastases (almost 50%).

Others have given IA cisplatinum concurrently with different IV systemic agents.[12,160–169] Small single-institution studies suggest that this allows for more limb-sparing procedures to be performed and does not substantially increase the risk of local recurrence or the development of metastatic disease. Such an approach has been associated with a higher tumor necrosis rate, perhaps making it possible to convert a marginal resection to a wide resection and to allow for a safer surgical procedure to be performed.[169] Relapse or disease-free survival (DFS) rates for single-institution IA studies appear to be similar to those using IV induction chemotherapy (with DFS rates in the 43–89% range).[12]

To date, the use of IA chemotherapy has been limited to centers with excellent angiographic support and facilities. There is a need to determine whether the cost, complexity, time commitment, and morbidity associated with this approach are justifiable. A prospective randomized study from the Rizzoli Institute reported that patients who received induction IA cisplatinum had a significantly higher proportion of good histologic responses than those who received similar doses of IV cisplatinum.[124] There did not appear to be any differences between the two groups in the number of limb-sparing operations, and the follow-up period was too short to determine a difference in survival (Table 3.8).

In a second study (COSS-86) investigating the use of more intensive preoperative chemotherapy, Winkler *et al.* compared the effects of cisplatinum given by IA tourniquet infusion or by IV infusion (Table 3.8).[132] Following cycles of IV Adriamycin and methotrexate, cisplatinum was administered over 1 h with concomitant IV low-dose ifosfamide (6 g/m^2). These authors confirmed the results of previous researchers by showing that the amount of drug available to act against micrometastatic disease was not compromised by regional therapy. They found an identical systemic availability for cisplatinum; plasma, ultrafilitrate, and urinary concentrations were similar, regardless of the route used. There was also no correlation between the deposition of cisplatinum in tumor tissue and the mode of cisplatinum administration or the histologic response. When pharmacokinetic data showed equal systemic drug availability for both routes, the dose was reduced from 150 to 120 mg/m^2. Additionally, the IV cisplatinum infusion was extended from 1 to 5 h in order to decrease ototoxicity.

The original efforts to randomize patients onto this study were not successful, and randomization was abandoned in favor of central allocation (with an

Table 3.8 IV vs. IA cisplatinum neoadjuvant chemotherapy for osteosarcoma

	IV	*IA*	p-*Value*
Rizzoli Inst. Regimen – HD–MTX, ADR, CDP 120 mg/m²/CI 72 h IV or IA			
Histologic good response (no. of patients)	46% (18/39)	78% (31/40)	0.004
COSS-86 Regimen – HDMTX, ADR, IFOS, CDP 120–150 mg/m² IV or IA			
Limb-salvage surgery	28% (20/72)	54% (30/56)	0.007
Local recurrence	4% (3/68)	0% (0/56)	NS
10-year DFS	70%	63%	0.453 NS
10-year OS	75%	67%	0.335 NS

Bacci G *et al*. J Chemother. 1992;4:189–95.
Fuchs N *et al*. Ann Oncol. 1998;9:893–9.
NS = not significant.

attempt to balance for patient age and sex, tumor site and size). Furthermore, all high-risk patients who received only one IA treatment were included in the comparison. Limb-salvage surgery was possible more often after IA than after IV treatment (Table 3.8). There were fewer local recurrences in the IA group, but the difference did not reach statistical significance. There was no significant correlation between the route of administration and survival, although outcomes were slightly poorer for patients treated intra-arterially. This study has been cited as a fully prospective, randomized trial, but when the original plan for randomization was discarded, a selection bias could have been introduced despite the efforts of each study center to try to obtain balanced groups.

Any further benefits of IA induction chemotherapy will require prospective randomized investigation. Thus far, it has not appeared to make a significant difference in terms of disease-free and overall survival. It is also possible that future studies with more intensive multi-agent IV chemotherapy (i.e., high-dose ifosfamide) could negate any IA effect.

Incorporation of Ifosfamide into Induction Multi-agent Regimens

For many years the main strategy used to improve survival in osteosarcoma patients was to modify the postoperative chemotherapy regimen of those with a poor histologic response to induction chemotherapy. As mentioned previously, except for more recent regimens that contain ifosfamide, the effect of conventional salvage treatment is questionable.

An obvious alternative to salvage chemotherapy is to use new active agents up-front during induction chemotherapy. Miser *et al*. achieved excellent long-term results by incorporating ifosfamide concomitantly with Adriamycin into a 14-week induction regimen that included high-dose methotrexate.[129] Cisplatinum was added postoperatively only for poor histologic responders. Seventy-six percent of patients had ≥ 95% tumor necrosis; relapse-free and overall survival rates at 6 years were 73% and 88%, respectively. Bacci *et al* have shown independently that adding ifosfamide to an induction chemotherapy regimen significantly improved the limb-salvage, histologic response, and disease-free survival rates when compared with their previous study in which ifosfamide was given only after surgery (Table 3.9).[130]

Patel *et al*. are attempting to improve the survival of osteosarcoma patients known to have a poor prognosis (e.g. patients with the chondroblastic subtype or with metastases at presentation) using an intensive multi-agent induction regimen that includes cisplatinum, Adriamycin and high-dose ifosfamide with peripheral blood stem cell and G-CSF support.[170]

SUMMARY

The prognosis for patients with osteosarcoma of the extremities has markedly improved over the past three decades. More than two-thirds of patients who present with nonmetastatic disease are now cured (Figure 3.2). These advances are mainly due to the use of intensive multi-agent chemotherapy. The impact of adjuvant chemotherapy is now indisputable, and it has become part of standard treatment. It is not yet clear which combination or duration schedule of chemotherapy is the best (among cisplatinum, Adriamycin, and high-dose methotrexate), but it does appear that the addition of ifosfamide further improves overall patient survival.

Limb-salvage surgery is now an accepted practice by orthopedic oncologists for the majority of osteosarcoma patients. Many centers also administer induction

Table 3.9 Addition of ifosfamide to neoadjuvant chemotherapy for osteosarcoma

	OS-3: HDMTX, CDP, ADR + post-op IFOS	*OS-4: HDMTX, CDP, ADR, pre and post-op IFOS*	p-*Value*
Limb salvage	83%	95%	0.004
Total necrosis	17%	32%	0.005
Good response	55%	83%	
Local recurrence	5%	6%	NS
2-year disease-free survival	68%	85%	0.003

Bacci G *et al*. Acta Oncol. 1998;37:41–8.

chemotherapy in order to enhance limb-salvage opportunities, although its role in further improving patient survival remains uncertain. The question of a possible advantage of IA over IV cisplatinum remains unresolved because of a lack of properly randomized prospective studies. However, any positive effect of the IA route may be nullified by the inclusion of ifosfamide into new IV induction regimens. The benefit of tailoring adjuvant chemotherapy on the basis of the histologic response of the primary tumor to induction chemotherapy has not been fully substantiated. New markers are needed that can conclusively predict the histologic response and prognosis of patients at diagnosis, prior to induction chemotherapy, such that patients can be stratified into high- and low-risk subgroups.[171–177]

Finally, despite the enormous progress that has been made, we are still faced with limitations in the options for chemotherapy because of the small number of modestly active chemotherapeutic agents. There is a need for new drugs and strategies to treat those patients already known to have a poor prognosis (e.g., chondroblastic subtype, metastases at presentation) earlier in the course of their treatment.[178–180]

Table 3.10 New developments and strategies for sarcoma therapy

(1) *Chemotherapy*
- (a) Dose intensification with hematopoietic growth factor and/or PBSC support
- (b) Reversing multidrug resistance
  MDR Inhibitor (e.g., PSC-833, Incel)

(2) *Angiogenesis inhibitors*

(3) *Growth factor manipulation*
Liposarcoma – ligand activation of PPAR
Troglitazone – stimulates adipose differentiation
Osteogenic sarcoma – Somatuline → decrease IGF-I
Herceptin

(4) *Immune modulation*
L-MTP-PE
Immunotoxins
Nonmyeloblative allogeneic transplant

(5) *Utilizing oncogene products*
Modifying tumor suppressor genes
Antisense oligonucleotides
Vaccines to tumor-specific fusion peptides

New Developments and Approaches for Sarcoma Treatment

In the future, therapy for sarcomas should be enhanced by advances in pharmacology, cell biology, immunology, and molecular genetics that will lead to more efficacious, specific, and less toxic treatments (Table 3.10).

Higher doses of ifosfamide have already been incorporated into many front-line regimens.[47–50,170] The resultant cumulative thrombocytopenia could be ameliorated with more specific growth factors (i.e., thrombopoietin) and/or stem cell infusion. New platinum analogs may prove to have equal or more activity than cisplatinum, and be less toxic. With the identification of one of the mechanisms of primary drug resistance being mediated through p-glycoprotein, new strategies have evolved to reverse the multi-drug resistant phenotype with inhibitor agents (e.g., cyclosporin, PSC-833, Incel).[181]

Cell biologic studies have further elucidated several growth factors and receptors that play critical roles in sarcoma cell proliferation and differentiation. In preadipocytes it has been shown that stimulation of the peroxisome proliferator activated receptor-gamma (PPAR-γ) induces terminal differentiation. Troglitazone, an oral antidiabetic agent and a PPAR-γ ligand, is being evaluated in order to promote differentiation in patients with incurable liposarcomas.[182,183]

Insulin-like growth factor (IGF-1) has been found to be a potent mitogen for osteosarcoma cells *in vitro*, and growth hormone (GH) is a major regulator of IGF-1.[184] In a murine osteosarcoma model, modulation of the GH/IGF-1 axis by hypophysectomy reduced local growth and inhibited metastases.[185] The Pediatric NCI Group is utilizing a somatostatin analog to block GH release (indirectly reducing IGF-1 production) in order to prevent the development of lung metastases in osteosarcoma patients who have received adjuvant chemotherapy.[186]

Recently, the over-expression of the Her-2-neu (human epidermal growth factor 2) receptor has been identified in tissue samples from approximately 40% of osteosarcoma patients. It was found to be associated with a poorer histologic response to chemotherapy and decreased event-free survival.[176,177] In breast cancer the results of clinical trials of an antibody that targets this receptor, Herceptin (rhuMAB HER2, recombinant humanized anti-HER2 monoclonal antibody), used as a single agent or in combination with chemotherapy, have been encouraging. Furthermore, there appears to be synergy when herceptin is used with cisplatinum.[187] These findings have led to new Phase II single-agent trials for patients with refractory or recurrent osteosarcoma and, in combination with chemotherapy, for newly diagnosed patients who have poor prognostic factors.

Since several types of sarcomas are known to be quite vascular and the majority of recurrences are systemic, the role of angiogenesis inhibitors in controlling sarcoma growth is of great interest. Interferon alpha has been shown to have weak antiangiogenic effects and only minimal activity.[48,188] However, new compounds, including the matrix metalloproteinase inhibitors, vitaxin (monoclonal antibody to endothelial cell integrin), anti-VEGF (vascular endothelial growth factor), endostatin, and thalidomide, are being evaluated not only to prolong disease stabilization but also to reduce tumor growth.[48] The ultimate goal is to use these agents in the adjuvant setting.

Translational research in immunotherapeutic technology has also advanced. Kleinerman *et al.* have shown that the biologic response modifier L-MTP-PE (liposome-encapsulated muramyl tripeptide phosphatidylanolanine), a component of *Mycobacterium*, can activate pulmonary macrophages to a tumoricidal state and prevent or reduce the incidence of lung metastases in both canine and human studies.[189,190] A current Intergroup (CCSG and POG) trial is evaluating whether the addition of this biologic response modifier, given after adjuvant chemotherapy, will improve relapse-free survival.

Most human sarcoma cells express class I and/or II MHC and HLA class I and II antigens that can be recognized by cytotoxic CD8+ and CD4+ T cells.[191] On the basis of initial promising results in renal cell cancer by the National Heart, Lung and Blood Institute (NHLBI) Transplant Group, our institution and the NHLBI will be investigating the use of nonmyeloblative allogeneic transplantation followed by donor lymphocyte infusion in order to elicit an anti-tumor immune response through a donor graft versus sarcoma effect.[192,193]

Cytogenetic analyses of sarcomas have identified distinct chromosomal translocations that appear to encode for tumor-specific fusion proteins associated with certain histologic subtypes (e.g., synovial sarcoma – t(X;18), SYT/SSX1; Ewing's sarcoma – t(11;22), EWS/FLI-1).[194] These characteristic and consistent genetic changes not only transform cells to the malignant phenotype but also could result in tumor-specific antigens that are potential targets for immune-based therapy (e.g., immunotoxins, vaccines, and antisense oligonucleotides against the fusion RNA).[191,194] In addition, tumor suppressor genes (i.e., p53, Rb1) have been found to play critical roles in sarcoma growth inhibition. Reintroduction of wild-type genes such as p53 *in vivo* could lead to complete tumor regression or sensitization of resistant tumors to existing chemotherapy.[194]

CONCLUSIONS

The prospects for further understanding the clinical and molecular behavior of this complex group of rare tumors appear promising. Most likely, therapy will become more individualized based on the biology and chemosensitivity of different sarcoma subtypes. Such a development would be analogous to what has occurred in the treatment of non-Hodgkin's lymphomas. It is hoped that the dramatic surgical advances that have been made in limb salvage will be surpassed by significant discoveries in the control of systemic disease.

As we enter a new millennium, the treatment of patients with sarcomas will require collaboration among a variety of different health professionals and researchers. An interdisciplinary team approach will be necessary in order to advance the goals of local tumor control, limb salvage with optimum extremity function, minimal morbidity from treatment, and improved long-term survival.

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