

Improved Survival in Primary Nonmetastatic Pediatric Osteosarcoma of the Extremity

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A prospective study using a dose-intensified neoadjuvant intra-arterial chemotherapy regimen was designed to improve survival rates of young patients with primary, nonmetastatic osteosarcoma of the extremity. Arteriography was implemented to individualize duration of therapy by serially assessing change in tumor neovascularity. Intravenous doxorubicin and intra-arterial cisplatin were administered repetitively at 3-week intervals until $\geq 90\%$ reduction in tumor neovascularity was achieved. Surgery was delayed until this good arteriographic response was documented. After resection, prediction of tumor neovascularity was compared with tumor necrosis. Since 1987, 62 eligible patients younger than 22 years old were treated with an average of four neoadjuvant courses. Toxicities were manageable. Fifty-four (87%) patients had a good histologic response. The rate of limb preservation surgery was 93.5% (58/62). Accuracy and sensitivity of serial arteriography in predicting histologic response were 92% and 98% respectively, and greatly assisted surgical planning. With an average followup of 91 months, estimated Kaplan-Meier survival at 10 years was 93% and event-free survival was 86%. Osteosarcoma survival rates were significantly improved by the use of this regimen compared with previously reported results. Serial arteriography succeeded in individualizing duration of neoadjuvant therapy and led to a higher rate of good histologic response.

Level of Evidence: Therapeutic study, level II-1 (prospective cohort study). See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

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Patients with osteosarcoma treated with immediate amputation of the extremity without further treatment have a survival rate of less than 20% at 5 years. With the advent of adjuvant chemotherapy, patient survival improved to the 40% to 50% range. Neoadjuvant multiagent regimens were developed in the late 1980s and increased survival to the 60% to 70% range. However, since these advances in tumor therapy for young patients diagnosed with osteosarcoma, there has been little improvement in survival reported for this patient population.

Local control of osteosarcoma primarily is a surgical problem, but histologic response to neoadjuvant therapy is the single most important prognostic factor for long-term survival in nonmetastatic osteosarcoma of the extremity.^{7,12,22} Modern intravenous-based multiagent preoperative chemotherapy regimens, even combined with modern imaging techniques, fail to adequately guide the surgeon as to how well the patient is responding to therapy. It is unfortunate if a patient goes through a standard neoadjuvant chemotherapy protocol for 12 weeks, but at the time of definitive surgery has a poor histologic response. The outcome for these patients uniformly is less favorable.

In an attempt to design an ideal protocol to treat osteosarcoma, a series of steps were taken. First, a multidisciplinary team was formed in the mid-1980s between two institutions composed of pediatric oncologists, orthopedic oncologists, and interventional radiologists at the Institute for Limb Preservation at Presbyterian/St. Luke's Medical Center and the Children's Hospital, both in Denver. Second, doxorubicin and cisplatin, two of the most efficacious drugs against osteosarcoma, were selected for the neoadjuvant therapy. Doxorubicin was administered intravenously and cisplatin was administered intra-arterially. Additional drugs with overlapping toxicities that would interfere with maximum dosing were excluded. Third, serial arteriography was chosen as the method used to monitor tumor response during preoperative therapy. Response as measured by arteriography served to individualize duration of the neoadjuvant treatment. This approach was

based on pilot studies conducted in Houston, Texas, at the MD Anderson Cancer Center.^{11,20}

We hypothesized first, that survival rates would be improved by the use of a dose-intensive, repetitive chemotherapy regimen of intravenous doxorubicin and intra-arterial cisplatin, and second, that serial arteriography could be used to individualize the duration of neoadjuvant therapy leading to a higher rate of good histologic response. The primary objective was to evaluate the efficacy of this protocol. In addition, there were four secondary research questions in the study design. 1) Can tumor necrosis be predicted using serial arteriography? 2) Does individualization of duration of neoadjuvant therapy based on tumor neovascularity improve good histologic response rates? 3) Does this therapy impact the ability to perform limb preservation surgery? 4) What are the toxicities of such a dose-intensive regimen?

MATERIALS AND METHODS

This was a single-arm prospective study of the treatment of patients newly diagnosed with osteosarcoma. Patients were entered into our protocol if they had 1) histologically proven, previously untreated, high-grade osteosarcoma of an extremity; 2) no evidence of metastatic disease; 3) residual primary tumor with tumor neovascularity demonstrable on arteriogram; 4) no previous cancers; 5) age younger than 22 years; and 6) normal cardiac function. The study began in July 1987 and ended in January 2003. Closed-needle biopsy was the recommended diagnostic procedure; however, open incisional biopsies were acceptable. Tests used to establish the stage as nonmetastatic were radiographs and magnetic resonance imaging (MRI) scans of the entire primary involved bone, computed tomography (CT) scans of the chest, and a total body bone scan. Pretreatment evaluations included echocardiogram, hemogram, and blood chemistries. An indwelling central venous catheter was placed in each patient before treatment was instituted. The protocol was approved by the two institutional review boards.

Preoperative chemotherapy was administered every 3 weeks and consisted of a 48-hour to 72-hour continuous intravenous infusion of 90 mg/m² of doxorubicin followed the next day by intra-arterial cisplatin (Fig 1). The dose and duration of cisplatin were 120 mg/m² for 6 hours for primary tumors smaller than or equal to 10 cm in maximum dimension at diagnosis and 160 mg/m² for 24 hours for tumors larger than 10 cm. All arteriograms and intra-arterial chemotherapy were administered at Presbyterian/St. Luke's Medical Center in Denver, Colorado. Intra-arterial catheterization for administration of cisplatin was done under intravenous conscious sedation. Anesthesia generally was used for patients younger than 10 years. For the intra-arterial therapy, the tip of the catheter was positioned in the affected extremity to infuse all vessels feeding the neoplasm. The catheter was placed proximal to the tumor and as far away from arterial side branches and skin perforators as possible. The cisplatin was infused in a heparinized solution using a volumetric and pulsatile

jet infusion pump (Gianturco-Wallace Chemo-Pulser Pump, Cook, Inc., Bloomington IN). The patient was restricted to bed rest with hourly monitoring of the distal limb color, temperature, and pulses during the cisplatin administration. The infusions of cisplatin were accompanied by vigorous intravenous hydration, hypertonic saline diuresis, and close monitoring of intake, output, and electrolytes.

The number of preoperative chemotherapy cycles administered ranged from three to five, based on arteriographic response. Neoadjuvant therapy was discontinued and the patient proceeded to surgery when one of four criteria was achieved: 1) $\geq 90\%$ reduction in tumor neovascularity (good response); 2) initial response followed by plateau of effect (partial response); 3) no response or progressive disease; or 4) completion of five preoperative chemotherapy courses, regardless of response. Evidence of arteriographic response consisted of reduction in tumor neovascularity as determined by a decrease in the size, displacement, or number of vessels, and/or diminished tumor stain on serial studies (Fig 2). The multidisciplinary team reached consensus prospectively on the arteriographic response. An optimal window for definitive surgery was determined based on the expected hematologic recovery once maximum arteriographic response was reached.

All patients were re-evaluated radiographically before surgery. Magnetic resonance imaging of the entire involved bone was used to plan the extent of the definitive resection. If the neurovascular structures appeared to be free of tumor and the patient would be expected to retain adequate limb function, a limb-preservation procedure was recommended. In addition, the prediction of a good arteriographic response to therapy was instrumental in selecting patients who would be candidates for limb-preservation surgery. Amputation was reserved for patients who were thought to be at high risk for local recurrence because of previous attempts at excisional biopsy, massive size of tumor, involvement of the neurovascular bundle, or a poor arteriographic response. Previous pathologic fracture did not compromise the ability to do limb preservation surgery. All patients were treated prophylactically with systemic antibiotics at the time of definitive resection.

Percentage of tumor necrosis was determined after definitive surgery according to the method reported by Huvos et al.¹⁹ Patients with few or no viable tumor cells ($\geq 90\%$ tumor necrosis) were deemed good responders. All others were considered poor responders.

Postoperative chemotherapy was initiated 2 to 3 weeks after surgery. The agents used and the duration of postoperative chemotherapy were dependent on the patient's histologic response. Good responders continued the same agents (cisplatin and doxorubicin), both administered intravenously. When the maximum dose of doxorubicin had been reached, etoposide was substituted for doxorubicin. Ifosfamide or carboplatinum was substituted for impending cisplatin-induced ototoxicity or nephrotoxicity. Postoperative chemotherapy was administered every 4 weeks for four cycles to good responders. Alternative chemotherapy incorporating high-dose methotrexate, etoposide, and ifosfamide was administered to poor responders for a total of 1 year from diagnosis.

PREOPERATIVE CHEMOTHERAPY			
IV DOX IA CDDP Week 0	IV DOX IA CDDP Week 3	IV DOX IA CDDP Week 6	IV DOX IA CDDP Week 9*
Definitive Surgery Week 13**			

POSTOPERATIVE CHEMOTHERAPY FOR PATIENTS WHO WERE GOOD RESPONDERS			
IV DOX IV CDDP Week 17	IV DOX IV CDDP Week 21	IV ETOP IV CDDP Week 25†	IV ETOP IV CDDP Week 29

POSTOPERATIVE CHEMOTHERAPY FOR PATIENTS WHO WERE POOR RESPONDERS			
IV MTX Leucovorin Week 17	IV MTX Leucovorin Week 18	IV IFOS MESNA Week 19	IV MTX Leucovorin Week 23
IV MTX Leucovorin Week 35	IV MTX Leucovorin Week 36	IV IFOS MESNA Week 37	IV MTX Leucovorin Week 41
IV MTX Leucovorin Week 29	IV MTX Leucovorin Week 30	IV IFOS MESNA Week 25	IV IFOS MESNA Week 43
IV MTX Leucovorin Week 47	IV MTX Leucovorin Week 48	IV IFOS MESNA Week 49	IV IFOS MESNA Week 31

Key: *The number of preoperative cycles of chemotherapy was variable, depending on arteriographic response. Patients had 3 to 5 cycles.
 **Definitive surgery occurred 4 weeks after the last neoadjuvant chemotherapy cycle; ie, week 10 to 16.
 †Etoposide was substituted for DOX when the total DOX dose equaled 540 mg/m².
 IA = Intra-arterial; IV = Intravenous; CDDP = Cisplatin 120 mg/m² for 6 hours or 160 mg/m² for 24 hours; DOX = Doxorubicin 90 mg/m² for 48 hours; MTX = Methotrexate 12 g/m² for 4 hours; IFOS = Ifosfamide 2.4 g/m²/day for 5 days.

Fig 1. The neoadjuvant chemotherapy schema is shown. The postoperative protocol was determined according to histologic response and modified for toxicity. Reprinted and adapted with permission from Springer-Verlag © 2003 from Wilkins RM, Cullen JW, Odom L, et al: Superior survival in treatment of primary nonmetastatic pediatric osteosarcoma of the extremity. *Ann Surg Oncol* 10:501, 2003.

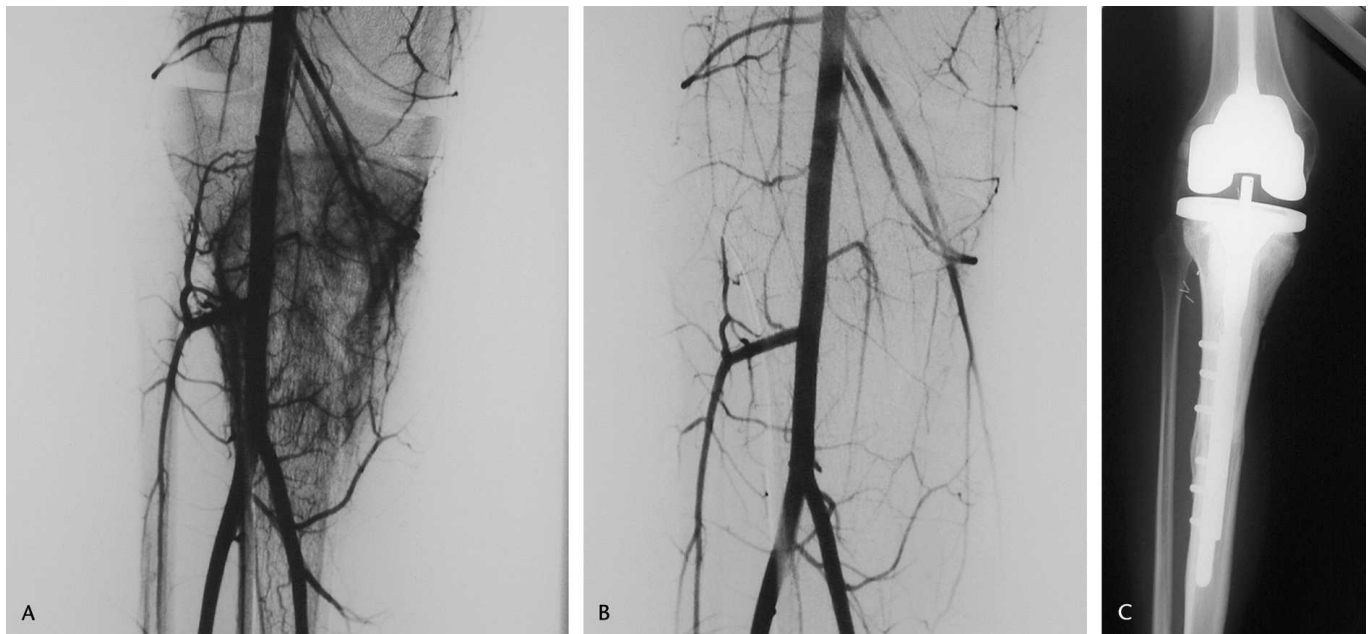


Fig 2A–C. (A) An AP baseline arteriogram shows prominent (3+) hypervascularity in an osteosarcoma of the proximal tibia. (B) The final arteriogram after three neoadjuvant cycles of intravenous doxorubicin and intra-arterial cisplatin shows no evidence of remaining tumor neovascularity. This patient was predicted to be a good responder and histopathologic analysis reported > 95% tumor necrosis. (C) Thirteen years after his allograft prosthetic composite he continues to function well.

At the completion of postoperative chemotherapy, plain radiographs of the primary disease site, chest CT scan, and a total body bone scan were obtained along with an echocardiogram, audiogram, and appropriate laboratory studies. Chest radiographs were done every 2 months. Chest CT scans were done at 6-month intervals unless indicated sooner by the chest radiograph. Beginning in 1993, audiograms were required 1 year after completion of chemotherapy. In addition, echocardiograms were done 1 year after completion of therapy and every 3 to 5 years thereafter. The National Cancer Institute standard toxicity scales^{9,10} were used to assess adverse effects of chemotherapy. Grade III and IV toxicities were recorded and tabulated.

Postoperative patient satisfaction and limb function were measured using a modified patient-based Musculoskeletal Tumor Society (MSTS) Functional Evaluation System.¹³ Questionnaires were administered at every followup visit and were completed by the patient or, in cases of young children, by the parent or guardian in the waiting room. The surgeon completed a corresponding clinical evaluation to record complications, range of motion, and the presence or absence of recurrent osteosarcoma. These data were then entered into the electronic database.

Efficacy of the treatment regimen was judged by the determination of the good histologic response rate, survival and event-free survival. Kaplan-Meier methodology was applied to calculate projected survival and event-free survival. An adverse event was defined as recurrence or death from osteosarcoma or its treatment. Patients who died from other causes were censored at that time in regard to survival. Patients were stratified by tumor size, ≤ 10 cm versus > 10 cm. The log-rank test was used

to compare patients with large versus patients with small primary tumors for survival and event-free survival. Correlation was made between > 90% decrease in tumor neovascularity by arteriography and > 90% tumor necrosis by histology. Sensitivity and specificity of arteriographic prediction of necrosis were calculated using the typical formulas. Histology was assumed to represent the “gold standard” and the arteriogram was assumed to represent the experimental test. Accuracy was defined as the percentage of patients for whom there was agreement between histology and arteriogram.

RESULTS

Sixty-seven consecutive patients younger than age 22 were diagnosed with nonmetastatic high-grade osteosarcoma of an extremity at one of the two institutions. Of the 67 eligible patients, three declined to participate. Two additional patients were inevaluable: one patient successfully completed four preoperative cycles and was predicted to be a good responder, but the parents refused surgery or further chemotherapy, opting instead for alternative treatment. The second patient received two courses of neoadjuvant therapy then withdrew for psychosocial issues unrelated to therapy. Therefore, 62 patients were available for evaluation of response and survival. There were 43 boys and 19 girls with an average age of 14 years (range, 5 to 21 years). Sites of involvement included the femur

($n = 40$), tibia ($n = 14$) humerus ($n = 5$), fibula ($n = 2$), and ulna ($n = 1$).

This individualized, dose-intensified regimen was highly efficacious. At 10 years, the Kaplan-Meier estimate of overall cancer survival was 93.2% [95% confidence interval (CI); 85.2, 100] and the event-free survival was 86.4% (95% CI; 77.6, 95.3). The 10-year survival and event-free survival for patients with tumors > 10 cm ($n = 30$) were 87.7% and 81.2%, respectively. This compared with 96.9% and 90.6% for patients with small tumors ($n = 32$). This difference was not significant ($p = 0.44$ survival and $p = 0.40$ event-free survival). Of the eight patients who developed metastatic disease, six were good responders (six of 54 patients) and two were poor responders (2 of 8 patients). Because of the small number of poor responders ($n = 8$), the study lacked statistical power to compare outcomes for good and poor responders. Kaplan-Meier estimated 5-year and 10-year survival and event-free survival are presented in Table 3. All patients had clinical and arteriographic evidence of response from administration of neoadjuvant chemotherapy as demonstrated by initial symptomatic relief of pain at the primary disease site and a decrease in tumor neovascularity on serial arteriograms. Three patients were inevaluable for arteriographic response because of minimal baseline tumor neovascularity. Fifty-four patients (87%) had a good histologic response ($\geq 90\%$ tumor necrosis). These patients went on to receive four months of postoperative therapy with the same agents (doxorubicin and cisplatin), all intravenously. Eight poor responders required alternative postoperative therapy, consisting of high-dose methotrexate, ifosfamide, and etoposide. The duration of therapy for poor responders was 12 months from the beginning of neoadjuvant therapy. Eighty-seven percent (54 of 62 patients) remained continuously disease free with a mean followup of 91 months (range, 25–204). One patient died from causes unrelated to cancer or therapy. There were no local recurrences. Eight patients developed lung metastasis; three of these patients have died and one had stable disease after further therapy. The four remaining patients have been off therapy without evidence of disease 48, 51, 71, and 96 months from the date of last relapse.

Serial arteriograms were highly predictive of tumor necrosis, demonstrating an accuracy of 92%. The sensitivity and specificity rates were 98% and 50%, respectively. In five cases arteriographic prediction did not correlate with the final pathology: four poor responders were predicted to have $\geq 90\%$ tumor necrosis, and in one case the arteriographic response was interpreted to be poor but histologic necrosis proved $> 90\%$.

The number of intra-arterial cycles varied based on patient response as judged by the change—or lack of change—in tumor neovascularity on serial arteriography.

Patients received an average of four neoadjuvant courses (range, 3–5 courses). Twenty-five patients (40.3%) had 3 cycles. Of these, 22 achieved $> 90\%$ decrease in tumor neovascularity. After an initial response, one patient had a plateau of effect, one had progressive tumor neovascularity, and one declined a fourth cycle. Thirty patients (48.4%) received four cycles of neoadjuvant therapy. Of these, 28 achieved $> 90\%$ decrease in tumor neovascularity. Two patients had a plateau of effect from the third to the fourth arteriogram. Seven patients (11.2%) received five intra-arterial cycles. Five patients of the seven achieved $> 90\%$ decreased tumor neovascularity. One patient had a plateau of effect and one had progressive tumor neovascularity on the fifth arteriogram.

Limb preservation procedures were done in 93.5% (58 of 62 patients). Primary amputations were necessary because of tumor proximity to the neurovascular bundle (2 patients), pre-existing fibrous dysplasia (1 patient), and extensive growth anticipated due to young age at diagnosis (1 patient). Because most of the lesions occurred around the knee, the most common limb preservation surgery consisted of wide local resection and endoprosthetic replacement. Skeletally immature children estimated to have greater than 4 cm of extremity growth received either a modular endoprosthesis (32 patients) or, later in the series, the “growing” prosthesis (3 patients) (Repiphysis, Wright Medical Technology, Arlington, TN).²⁸ Other limb preservation reconstructions included intercalary (7 patients), osteochondral allograft (6 patients), or allograft prosthetic composite (6 patients), depending on the location of the primary tumor and the extent of resection required. Two patients had wide resection with a soft tissue reconstruction only. Secondary amputations were necessary in four patients because of persistent infection that occurred after cessation of postoperative chemotherapy. The MSTS scores were available from 61 patients and averaged 71% at last followup. Patients who had limb preservation averaged 72% compared with 65% for those with amputations ($n = 8$).

The majority of toxicities were manageable and tolerable. There were no toxic deaths. Tables 1 and 2 describe the grading criteria for cardiotoxicity and ototoxicity, respectively. One patient with Grade 3 cardiotoxicity (1.6%) developed overt congestive heart failure. Her cardiac function has returned to normal on medications now 30 months later. The neoadjuvant protocol was modified in another patient because of an abnormal echocardiogram after the first dose of doxorubicin. Etoposide was substituted for doxorubicin in this patient and the echocardiogram later returned to normal. Since 1993, echocardiograms were required 1 year after completing therapy and every 3 to 5 years thereafter. Among 37 patients evaluable for late cardiotoxicity, there have been five patients with Grade 1

TABLE 1. Grading Criteria for Cardiotoxicity⁷

Grade	Echocardiography Left Ventricular Shortening Fraction
0	> 30%
1	< 30–24
2	< 24–16%
3	< 15% responsive to therapy
4	Refractory congestive heart failure

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echocardiographic changes and the one patient with Grade 3 toxicity referred to above. The remaining 31 patients have maintained normal cardiac function. Ototoxicity was minimal. Before 1993, one patient required a hearing aid. After 1993, audiograms were required to evaluate ototoxicity objectively after the completion of chemotherapy. Among 33 evaluable patients, there was no Grade 4 and only one Grade 3 ototoxicity. Twenty-six patients had minimal changes on audiogram and six remained normal throughout therapy and followup. Initially, painful mucositis followed most doxorubicin infusions and patients frequently required intravenous hydration, narcotics, and nutritional support. In 1993 the protocol was changed to infuse doxorubicin for 48 hours instead of 72 hours and severe mucositis became less frequent. After this change, 10 of 37 patients (27%) developed Grade 3 or 4 mucositis at any time during therapy, usually during later cycles. Myelosuppression was common and cumulative. After granulocyte colony stimulating factor became available in 1991, it was prescribed for all subsequent cycles after an initial cycle of neutropenia. Occurrences of febrile neutropenia and bacteremia were infrequent and treatable. Six patients developed painful myocutaneous inflammation in the area of the tumor bed after 24-hour intra-arterial cisplatin infusion. Four of these patients had superficial epidermal sloughing at the site of inflammation, which went on to heal. One patient required a skin graft. No patient experienced a subsequent episode. The area of inflamma-

TABLE 2. Grading Criteria for Ototoxicity⁸

Grade	Audiogram Findings
0	Within normal limits
1	20–40 db loss > 4 KHz
2	> 40 db loss > 4 KHz
3	> 40 db loss at 2 KHz
4	> 40 db loss < 2 KHz

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TABLE 3. Survival and Event-Free Survival

	5 Year	95% CI	10 Year	95% CI
All Patients— Cancer Survival	96.6%	(92, 100)	93.2%	(85.2, 100)
All Patients—EFS	86.4%	(77.6, 95.3)	86.4%	(77.6, 95.3)
Tumor Size > 10 cm—Survival	96.4%	(89.6, 100)	87.7%	(70.1, 100)
Tumor Size > 10 cm—EFS	81.2%	(66, 96.4)	81.2%	(66, 96.4)
Tumor Size ≤ 10 cm—Survival	96.9%	(90.8, 100)	96.9%	(90.8, 100)
Tumor Size ≤ 10 cm—EFS	90.6%	(80.5, 100)	90.6%	(80.5, 100)

EFS = Event-free survival; CI = Confidence interval

tion was excised at the time of definitive tumor resection and the ability to perform a limb preservation procedure was never compromised. There were no other arterial catheter-related untoward effects.

DISCUSSION

The administration of neoadjuvant chemotherapy with delayed definitive surgery has become the standard approach in newly diagnosed osteosarcoma.^{1–3,6,14,15,17,22–24,26,29} Typically, four or more drugs were alternated during the neoadjuvant phase of therapy. The duration of neoadjuvant therapy has been empirically set in each protocol, with definitive surgery done from weeks 8 to 16 in various protocols. Only Carasco et al¹¹ individualized the duration of neoadjuvant therapy based on tumor response. The percent tumor necrosis induced by neoadjuvant therapy has been found to be the most important prognostic factor in the treatment of nonmetastatic osteosarcoma of the extremity.^{7,12,22} We hypothesized that the percent tumor necrosis could be maximized by using the two most active agents repetitively. The activity of these agents could be improved through intensification of dose and duration. The dose of doxorubicin was increased to 90 mg/m² every 3 weeks. The dose of cisplatin was increased to 120 mg/m² in 6 hours every 3 weeks for tumors < 10 cm and further increased to 160 mg/m² in 24 hours for larger tumors. The dose of cisplatin delivered to the tumor was increased an estimated fourfold to fivefold using the intra-arterial rather than the intravenous route.^{20,25} In addition, a unique pulsatile jet infusion pump was used to interfere with normal flow dynamics within the arteries to prevent layering of the drug. This improved distribution of the cisplatin into the tumor vascular bed. We also hypothesized that tumor necrosis could be predicted by assessing change in tumor neovascularity on serial arteriography. If we were correct with this assumption, the duration of neoadjuvant therapy

could be individualized based on arteriographic response, thus improving the rate of good histologic response. The literature supports the concept that a higher rate of good histologic response would lead to an improved rate of survival. In a multivariate analysis of 1702 patients, Bielack et al⁷ found that histologic response was the most important prognostic factor for osteosarcoma of the extremity ($p < 0.0001$). Provisor et al²² reported 8-year survival and event-free survival rates of 87% and 81% for good responders versus 52% and 46%, respectively, for poor responders ($p < 0.0001$).

Overall conclusions from this study are limited by four factors. First, this was a single-arm study with no direct comparison group. Second, the study was carried out in a specific patient population, excluding patients with axial skeletal lesions or metastatic disease. Third, there was a relatively small number of patients treated. Fourth, although patients were cared for in three different oncology programs, all intra-arterial therapy was conducted at a single institution. This last limitation was somewhat mitigated by the participation of 14 different interventional radiologists. Nonetheless, a highly committed multidisciplinary team maintained consistency throughout the study.

No unexpected toxicities occurred in this study, and those encountered compared favorably to reports in the literature. For example, Goorin et al¹⁸ reported three toxic deaths in 106 patients, while we had none. Goorin's protocol called for a total dose of 390 mg/m² of doxorubicin and two patients died from doxorubicin-induced cardiomyopathy. Our protocol called for a total dose of 540 mg/m² of doxorubicin administered at 90 mg/m² per dose as a 48 to 72 hour continuous infusion. We had one case of cardiomyopathic congestive heart failure that was successfully treated medically. In addition, Goorin reported one case of hearing loss while using a total dose of 480 mg/m² of cisplatin. One of our patients had clinical hearing loss and one had Grade 3 hearing loss by audiogram with total doses of cisplatin reaching 840 mg/m².

The rate of successful limb preservation surgery (93.5%) was remarkable and compares favorably with rates reported by Provisor et al (43%)²² and Rha et al (83%).²⁴ Improvement of limb preservation rates depends on controlling local progression during neoadjuvant therapy. In this study, no patient had progression of the tumor compared to baseline. All patients had at least an initial response. Plateau of effect or worsening of tumor neovascularity after an initial response led to early surgical intervention in four patients (6.4%). This compares with local disease progression rates of 13.3% (6 of 45 patients)¹⁸ and 10.2% (21 of 206 patients).²² Ultimate local control is not determined by the effectiveness of the neoadjuvant therapy alone, but also by the success of definitive surgery. There were no local recurrences in this study

among the 58 patients who had limb preservation surgery. Again, this compares favorably with rates of local recurrence reported by Fuchs et al (3.6%, 6 of 65 patients),¹⁷ Provisor et al (4.5%, 4 of 88 patients),²² Bacci et al (6.3%, 7 of 111 patients),⁴ and Brosjo (10–11%).⁸ Local progression during neoadjuvant therapy and local recurrence following definitive surgery may be minimized by administering highly effective neoadjuvant therapy, monitoring tumor response arteriographically during each cycle, and intervening with early surgery for plateau responders.

The assessment of change in tumor neovascularity by arteriography at the time of each intra-arterial cycle allowed therapy to be individualized for each patient. Patients who were poor arteriographic responders (< 90% decrease in tumor neovascularity) had early definitive surgery and were switched to alternative therapy if tumor necrosis proved to be < 90%. Additionally, the arteriograms were successful in individualizing duration of therapy based on response. If the protocol had empirically mandated three neoadjuvant cycles, 59.6% of patients would have potentially been under treated. Conversely, empirical administration of four cycles would have resulted in over treating 40% of patients and under treating 11%. Finally, administration of five neoadjuvant cycles, regardless of response, would have over treated at least 89% of the patients. It appears that duration of neoadjuvant therapy can be based on arteriographic response. This improves the chances of achieving a good histologic response and avoids unnecessary toxicity for rapid responders. Although authors of many studies^{1,2,11,14,15,17,21,23,24,27,29} incorporated intra-arterial cisplatin into the antineoplastic regimen, duration of neoadjuvant cisplatin was the same for all patients except for the study by Carrasco et al.¹¹

Serial arteriography was highly accurate and sensitive in predicting good histologic response as shown by our accuracy rate of 92% and sensitivity of 98%. Authors of five previous papers reported the accuracy and sensitivity of using arteriography to predict histologic response in osteosarcoma. A total of 176 patients were assessed preoperatively with arteriography. The composite accuracy rate for the world literature was 82% and sensitivity was 95%. Therefore, our data further add to the growing evidence that arteriography can be used to predict histologic response in osteosarcoma.

The intensified use of cisplatin and doxorubicin was successful compared with previous studies. Intra-arterial administration of cisplatin and the use of the pulsatile pump increased the dose delivered to the tumor bed. In previously reported studies using intra-arterial cisplatin, the dose and duration of infusion were not adjusted for tumor size. Cisplatin was alternated with other agents and was not given repetitively as in our study. Only two cycles of intra-arterial cisplatin were administered in each study,

except in the study of Rha et al,²⁴ who used three cycles. In our study, the average number of intra-arterial cycles was four, with 40% of patients having three and 11% having five cycles of intra-arterial cisplatin. Therefore, our total dose of cisplatin ranged from 360 mg/m² to 760 mg/m² during the neoadjuvant phase. Additionally, other studies used one or two doses of doxorubicin at 60 to 75 mg/m² compared with 90 mg/m² for three to five doses in our study. This intensification of neoadjuvant therapy, combined with individualization based on arteriographic response, contributed to the highest good histologic response rate ever reported. Our good histological response rate was 87% compared with 62%¹⁸ and 28%²² in studies in which intra-arterial cisplatin was not used, and 64% to 80%^{5,14} in studies in which intra-arterial cisplatin was used. Most importantly, this excellent good histologic response rate translated into improved rates of survival and event-free survival. The 10-year survival and event-free survival for patients with tumors < 10 cm was 96.9% and 90.6%, respectively. There was no statistical difference in outcome between large and small tumors. Our 10-year actuarial estimated survival was 93.2% for all patients and the event-free survival was 86.4%. This compares with the outcomes in nonmetastatic patients reported by Goorin¹⁸ of event-free survival at 5 years of 65% and of nonmetastatic osteosarcoma of the extremity in Provisor et al's report²² of 53% at 8 years. In the published reports that included intra-arterial cisplatin in the neoadjuvant treatment, event-free survival rates varied from a low of 26% at 5 years in 40 patients⁵ to a high of 63% at 10 years in 50 patients.²⁹

An explanation for improved survival rates with this protocol would be speculative. The improved local control rate can be attributed to the intensification of the cisplatin delivered directly to the tumor. The excellent histologic response rate can be attributed to dose intensification and individualized duration of neoadjuvant therapy. However, relapse and ultimate demise in patients with osteosarcoma is usually due to pulmonary metastasis. One might legitimately question the ability of this protocol to decrease the incidence of metastatic disease to the lung. Because the cure rate for patients without metastasis treated with immediate amputation and no further therapy is approximately 20%, it has been postulated that 80% of patients have micrometastases at diagnosis.¹⁶ Perhaps the incidence of metastasis is enhanced by inappropriate surgical manipulation of the viable primary tumor. When a biopsy is done by an experienced orthopedic oncologist and administration of neoadjuvant therapy is expedited, the likelihood of metastasis at the time of surgery may be reduced because much less viable tumor is disturbed. By intensifying the individualizing therapy to reach maximum response, the metastatic risks may be decreased further.

Neoangiogenesis factors are produced by tumors and are necessary for the development of metastatic nodules. Certain factors may promote local angiogenesis and inhibit distant neovascularity needed for metastatic development. Such inhibitory factors may be advantageous if the tumor is left undisturbed until it becomes mostly necrotic. In our study, 87% had > 90% necrosis at the time of definitive surgery. This markedly reduced the risk of spreading viable tumor cells through surgical manipulation.

A comparison of our results with other studies is difficult because of the varied patient populations. Some authors reported on patients up to age 40 years, others included axial lesions, and others had small number of patients with metastatic disease. It will be important to confirm these results by comparing them with the best intravenous regimen available in a multi-institutional trial.

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