

## Phase I Trial of Preoperative Doxorubicin-Based Concurrent Chemoradiation and Surgical Resection for Localized Extremity and Body Wall Soft Tissue Sarcomas

Peter W.T. Pisters, Shreyaskumar R. Patel, Victor G. Prieto, Peter F. Thall, Valerae O. Lewis, Barry W. Feig, Kelly K. Hunt, Alan W. Yasko, Patrick P. Lin, Marc G. Jacobson, Michael A. Burgess, Raphael E. Pollock, Gunar K. Zagars, Robert S. Benjamin, and Matthew T. Ballo

From the Multidisciplinary Sarcoma Center and the Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted January 7, 2004; accepted May 13, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Peter W.T. Pisters, MD, Department of Surgical Oncology, Box 444, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030-4009; e-mail: ppisters@mdanderson.org.

© 2004 by American Society of Clinical Oncology

0732-183X/04/2216-3375/\$20.00

DOI: 10.1200/JCO.2004.01.040

### A B S T R A C T

#### Purpose

The primary objective of this phase I trial was to define the maximum-tolerated dose of continuous-infusion doxorubicin administered with standard preoperative radiation for patients with localized, potentially resectable soft tissue sarcomas of the extremities or body wall.

#### Patients and Methods

Twenty-seven patients with radiographically resectable intermediate- or high-grade soft tissue sarcomas were treated. Preoperative external-beam radiation was administered in 25 2-Gy fractions (total dose, 50 Gy). Concurrent continuous-infusion doxorubicin was administered by an initial bolus (4 mg/m<sup>2</sup>) and subsequent 4-day continuous infusion (12.5, 15.0, 17.5, or 20.0 mg/m<sup>2</sup>/wk). Radiographic restaging was performed 4 to 7 weeks after chemoradiation, and patients with localized disease underwent surgical resection.

#### Results

Chemoradiation was completed as an outpatient procedure in 25 patients (93%). The maximum-tolerated dose of continuous-infusion doxorubicin combined with standard preoperative radiation was 17.5 mg/m<sup>2</sup>/wk; at this dose level, seven (30%) of 23 patients had grade 3 dermatologic toxicity. Macroscopically complete resection (R0 or R1) was performed in all 26 patients who underwent surgery. Among 22 patients who were treated with doxorubicin 17.5/mg/m<sup>2</sup>/wk with concurrent radiation and subsequent surgery, 11 patients (50%) had 90% or greater tumor necrosis, including two patients who had complete pathologic responses.

#### Conclusion

Preoperative doxorubicin-based chemoradiation appears safe and feasible. The maximum-tolerated dose of continuous-infusion doxorubicin with standard preoperative radiation was 17.5 mg/m<sup>2</sup>/wk. Pathologic response rates with this regimen are encouraging.

*J Clin Oncol* 22:3375-3380. © 2004 by American Society of Clinical Oncology

### INTRODUCTION

Over the past two decades there has been continued interest in approaches that deliver concurrent or sequential chemotherapy plus radiation for patients with a variety of solid tumors, including soft tissue sarcomas (STS). Chemoradiation for locally advanced STS of the extremities and body wall capitalizes on the radiosensitizing properties of the chemotherapeutic agents (eg, doxorubicin and ifosfamide). Theoretical advantages include increasing the therapeutic

ratio of external-beam radiotherapy (EBRT) and, in some instances, providing synchronous treatment of the primary tumor and potential micrometastatic disease.

The majority of published reports of doxorubicin-based concurrent chemoradiation for STS have been pilot studies that used bolus intraarterial or intravenous (IV) doxorubicin.<sup>1-4</sup> While this approach allows administration of standard doses of doxorubicin that may have maximum systemic activity, it may not provide optimal chemotherapy-associated radiosensitization

since the duration of concurrent treatment may be as short as 1 or 2 days. In contrast, lower-dose continuous-infusion chemotherapy during radiotherapy would provide prolonged radiosensitization and may have radiobiologic advantages. Although it is commonly employed for other solid tumors, lower-dose continuous-infusion chemoradiation has not been used for patients with STS.

To our knowledge, there are no published data on the dose of continuous-infusion doxorubicin that can be used throughout a course of standard preoperative EBRT (50 Gy delivered in 2-Gy fractions). This phase I trial was designed to determine the maximum-tolerated dose (MTD) of continuous-infusion doxorubicin that can be given concurrently with standard preoperative EBRT for patients with localized, potentially resectable STS of the extremities or body wall.

## PATIENTS AND METHODS

### Eligibility

Patients with localized, potentially resectable, intermediate- and high-grade clinical stage T2 STS of an extremity or the body wall (American Joint Commission on Cancer [6th edition]<sup>5</sup> stages IIB and III) were eligible for this phase I trial. Patients with primary untreated and locally recurrent disease were eligible. Histologic or cytologic confirmation of histologic grade was required. Determination of resectability was based on pretreatment magnetic resonance imaging (MRI) or computed tomography (CT) scans and multidisciplinary consultation between a sarcoma surgeon and radiation oncologist.

Pretreatment evaluation included a complete history and physical examination, baseline assessment of organ function, chest x-ray, chest CT, and cross-sectional imaging (MRI or CT) of the primary tumor site. Additional eligibility criteria included a Karnofsky performance status  $\geq 70$ , an absolute granulocyte count  $> 1,500/\text{mL}$ , platelet count  $\geq 100,000/\text{mL}$ , serum creatinine  $\leq 1.8 \text{ mg/dL}$ , serum alanine transaminase and aspartate transaminase concentrations  $\leq 3\times$  normal, and total bilirubin

$\leq 1.5 \text{ mg/dL}$ . Patients with a history of prior radiotherapy in the region of the primary tumor or those in whom the anticipated radiation field would include the perineum, scrotum, or vagina were not eligible. Patients with prior doxorubicin exposure were eligible only if the total prior doxorubicin dose was less than  $450 \text{ mg/m}^2$ .

The institutional review board of The University of Texas M.D. Anderson Cancer Center (Houston, TX) approved the trial. Written informed consent was obtained from all patients before initiation of therapy. There was no industry funding for this protocol.

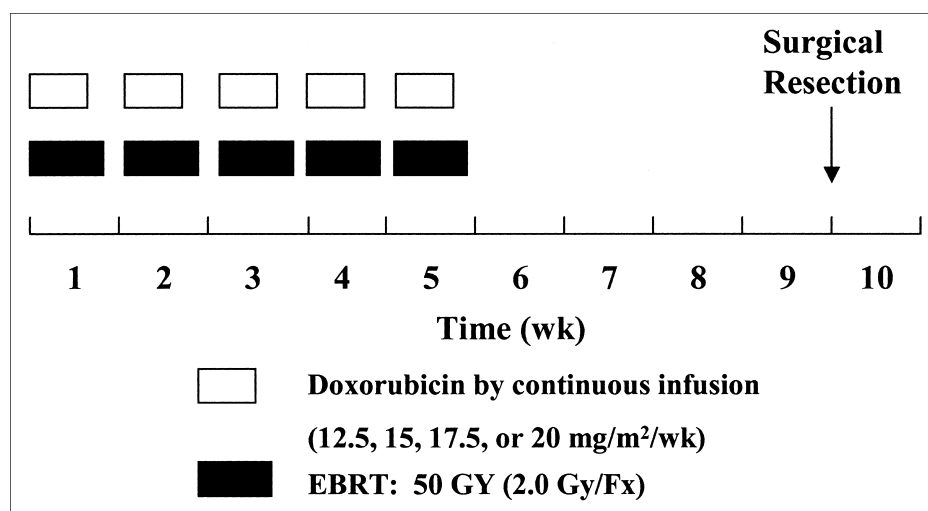
### Chemoradiation Treatment

The treatment schema is summarized in Figure 1. Standard preoperative EBRT was administered up to a dose of 50 Gy using 2-Gy daily fractions (5 days/wk for 5 weeks). Three-dimensional CT-based treatment planning was used with multiple fields to ensure uniform dosimetry. Margins of 5 to 7 cm were utilized whenever possible in the longitudinal dimension. In the transverse and radial dimensions, the margin was permitted to be smaller in order to spare at least one third of the circumference of an extremity. Dosimetry was flexible to a 7% variation from the dose prescribed to the isocenter.

Doxorubicin  $4 \text{ mg/m}^2$  was administered as a 15 to 30 minute IV bolus on days 1, 8, 15, 22, and 29 (ie, the first day of each week of treatment). Each bolus was followed by a continuous IV infusion of doxorubicin for 4 days, on days 1 to 4, 8 to 11, 15 to 18, 22 to 25, and 29 to 32. The half-life of doxorubicin is approximately 24 hours and thus it was felt that a 4-day doxorubicin infusion that was discontinued on Thursday would allow for 5 days of radiosensitization. The doxorubicin doses to be used were 12.5, 15.0, 17.5, and  $20.0 \text{ mg/m}^2$  per week, referred to as levels 1, 2, 3, and 4. The trial design specified that patients would be treated in cohorts of three patients, with each successive cohorts' dose level determined by the continual reassessment method<sup>6</sup> (CRM), starting with the first cohort treated at  $15.0 \text{ mg/m}^2/\text{wk}$ .

### Toxicity Evaluation and Response Assessment

Evaluation during chemoradiation included daily assessment of toxicity and weekly history, physical examination, assessment of body weight and performance status, complete blood count, and



**Fig 1.** Treatment schema for phase I trial of doxorubicin-based chemoradiation for extremity and superficial body wall soft tissue sarcoma. EBRT, external-beam radiotherapy; Fx, fraction.

**Table 1.** Criteria for Grading Chemoradiation-Related Cutaneous Toxicity

Grade	Clinical Features
1	Faint or dull erythema, or epilation, or dry desquamation, or decreased sweating
2	Tender or bright erythema, patchy or moist desquamation
3	Confluent moist desquamation (other than skin folds) or pitting edema
4	Ulceration, hemorrhage, or necrosis

NOTE. Modified from Radiation Therapy Oncology Group toxicity criteria (now supplanted by Common Toxicity Criteria version 3.0).

laboratory assessment of electrolytes and organ functions. Cutaneous treatment-related toxicities were graded according to the Radiation Therapy Oncology Group toxicity scale (Table 1). Non-cutaneous toxicities were graded according to National Cancer Institute Common Toxicity criteria (Version 2). Both radiation and doxorubicin were suspended for Radiation Therapy Oncology Group grade 4 cutaneous toxicity. Patients were assessed daily, and radiotherapy (without doxorubicin) was resumed when the treating radiation oncologist considered it safe to do so.

Restaging MRI or CT scans were performed 4 to 6 weeks after chemoradiation. For patients with measurable disease, the radiographic response to preoperative chemoradiation was evaluated by a single radiologist (M.J.F.) by comparing pretreatment and restaging (preoperative) MRI or CT scans. Radiographic responses were classified using the Response Evaluation Criteria in Solid Tumors.<sup>7</sup>

#### **Surgical Resection, Classification of Wound Complications, and Pathologic Evaluation**

Resection of the postchemoradiation tumor mass was performed approximately 4 to 7 weeks following completion of preoperative chemoradiation. For patients with measurable disease, the surgical procedure consisted of wide local excision of the residual tumor mass with a wide (> 2 cm) soft tissue margin wherever possible. When, in the judgment of the operating surgeon, the maintenance of this margin would result in unacceptable compromise of neurovascular function, a smaller margin was permitted.

Wound complications were classified using the definitions developed and used in the Canadian Sarcoma Group SR2 trial of preoperative versus postoperative radiation for extremity STS.<sup>8</sup> Major wound complications were defined as those that required (1) secondary operation under general or regional anesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skin grafts); (2) an invasive procedure not requiring general or regional anesthesia (mainly aspiration of seroma); (3) readmission for wound care such as IV antibiotics; or (4) persistent deep packing of the wound for 120 days or longer.

Standardized pathologic evaluation of the resected specimen was performed. The tumor size was calculated after resection by measuring the maximum dimension (craniocaudad, medial-lateral, or anterior-posterior) of the tumor. The percentage tumor necrosis was estimated and assigned a semiquantitative value of less than 10%, 10% to 49%, 50% to 89%, 90% to 99%, or 100%. Pathologic complete response was defined as 100% tumor necrosis. A microscopically positive surgical margin was defined as tumor extending to the inked margin of the specimen.

#### **Statistical Analyses**

For dose-finding purposes, a dose-limiting toxicity (DLT) was defined as grade 3 or greater treatment-related cutaneous toxicity (Table 1). The MTD of doxorubicin that could be combined with standard preoperative EBRT was defined as the dose chosen by the CRM<sup>6</sup> with a target mean dose-limiting toxicity (DLT) probability of 0.30. This was based on the belief that a 30% rate of cutaneous toxicity would be clinically acceptable and not substantially different from that seen with preoperative EBRT alone.

The CRM is a practical Bayesian statistical methodology for conducting phase I trials that chooses dose levels for successive cohorts of patients based on the accumulated dose-response information from patients already treated in the trial.<sup>6,9</sup> For this trial, the CRM was implemented with a cohort size of three patients and a maximum of 10 cohorts (30 patients), and was based on the exponential dose-response model with  $\text{Pr}(\text{DLT dose level } j) = (p_j)^{\exp(a)}$ , for  $j = 1, 2, 3, 4$ . The random parameter "a" was assumed to follow a Gaussian prior with mean 0 and variance 1.80, and the fixed prior DLT probabilities at the four dose levels were assumed to be  $P_1 = .05$ ,  $P_2 = .20$ ,  $P_3 = .40$ , and  $P_4 = .80$ . The first cohort was treated at dose level 2, and the dose of each successive cohort was that for which the mean posterior DLT probability was closest to the target of .30. Tumor maximum diameter was compared between the groups of patients who did ( $n = 7$ ) and did not ( $n = 20$ ) suffer a DLT, using a Wilcoxon rank sum test.

## RESULTS

### **Patients and Treatment**

Thirty patients were registered for this study. Treatment was initiated in 27 patients with extremity or body wall STS believed to be resectable based on pretreatment staging evaluation. Three patients were registered and but were not treated with the protocol therapy owing to pretreatment neutropenia below the protocol threshold (one patient), patient noncompliance with initial protocol treatment (one patient), and presence of a tumor that was considered too large for safe administration of preoperative radiation after radiation simulation (one patient).

The clinicopathologic characteristics of the 27 treated patients are summarized in Table 2. The median patient age was 50 years (range, 18 to 83 years). Twenty-five patients (93%) had extremity STS; two patients (7%) had STS of the body wall. The median pretreatment (radiographic) tumor size was 13.5 cm (range, 3.0 to 24 cm). The most common histologic subtypes were malignant fibrous histiocytoma (eight patients, 30%) and unclassified high-grade sarcoma (eight patients, 30%).

### **Chemoradiation Feasibility and Toxicity**

Preoperative chemoradiation was completed as planned in all 27 patients. Chemoradiation was completed on an outpatient basis in 25 patients (93%). Two patients (7%) required hospital admission during chemoradiation for toxicity-related reasons: one with a large right proximal medial thigh unclassified sarcoma had confluent moist des-

**Table 2.** Clinicopathologic Factors for 27 Patients Receiving Preoperative Doxorubicin-Based Chemoradiation for Extremity and Body Wall STS

Factor	No. of Patients	%
<b>Age, years</b>		
Median	50	
Range	18-83	
< 60	18	67
≥ 60	9	33
<b>Sex</b>		
Male	13	48
Female	14	52
<b>Tumor presentation</b>		
Primary	26	96
Locally recurrent	1	4
<b>Anatomic site</b>		
Upper extremity	1	4
Lower extremity	24	89
Trunk	2	7
<b>Tumor grade</b>		
High	23	85
Intermediate	4	15
<b>Tumor size (radiographic) before chemoXRT, cm</b>		
Median	13.5	
Range	3.0-24.0	
Mean	12.2	
<b>Tumor size (pathologic) at surgery, cm*</b>		
Median	10.9	
Range	2.0-22.0	
Mean	10.8	
<b>Microscopic surgical margins*</b>		
R1 (positive)	3	12
R0 (negative)	23	88
<b>Histology</b>		
Malignant fibrous histiocytoma	8	30
Unclassified sarcoma	8	30
Liposarcoma	6	22
Synovial sarcoma	3	11
Rhabdomyosarcoma	1	4
Alveolar soft part sarcoma	1	4

Abbreviations: STS, soft tissue sarcoma; chemoXRT, chemoradiation; R1, macroscopically complete resection with microscopically positive surgical margins; R0, macroscopically complete resection with microscopically negative surgical margins.  
\*n = 26; one patient completed chemoradiation but declined subsequent surgery.

quamation (grade 3 skin toxicity) intertriginous area of the groin and lateral perineal area during the final week of chemoradiation, and one patient was admitted for catheter-related sepsis. In addition, one patient required hospital admission in the postchemoradiation preoperative period for catheter-related sepsis 1 week after completing chemoradiation.

The frequencies of grade 3 and 4 toxicities observed during preoperative chemoradiation are outlined in Table 3. Although the protocol specified an initial doxorubicin starting dose of 15.0 mg/m<sup>2</sup>/wk (level 2), the first patient

entered in the protocol was erroneously started at level 1 (12.5 mg/m<sup>2</sup>/wk). This patient completed preoperative chemoradiation at this dose without identifiable toxicities. The remaining patients were treated at the 15.0 and 17.5 mg/m<sup>2</sup>/wk dose levels, per the CRM. Few treatment-related toxicities were observed at the 15.0 mg/m<sup>2</sup>/wk doxorubicin dose. Among 23 patients treated at the 17.5 mg/m<sup>2</sup>/wk doxorubicin dose level, seven patients experienced grade 3 dermatologic toxicity (confluent moist desquamation). There was no definable relationship between maximum tumor size and skin toxicity ( $P = .34$  by Wilcoxon rank-sum test). Hematologic toxicities at this dose level were mild, with only three patients experiencing grade 3 neutropenia. No patients experienced neutropenic fever during or following preoperative chemoradiation. Based on the CRM, 17.5 mg/m<sup>2</sup>/wk was determined to be the MTD of doxorubicin that could be combined with standard-dose preoperative EBRT.

### **Radiographic and Pathologic Response to Chemoradiation**

The radiographic response of the primary tumor to chemoradiation was assessable in all 27 patients. All patients had stable disease; there were no patients with a radiographic partial response or disease progression 4 to 8 weeks following preoperative chemoradiation. The histologic responses to chemoradiation in the 26 patients that underwent complete tumor resection are summarized in Table 4. Among 22 patients who received the 17.5 mg/m<sup>2</sup>/wk doxorubicin dose level followed by surgical resection, 11 patients (50%) had 90% or greater tumor necrosis, including one patient who had complete pathologic response.

### **Surgical Resection**

Twenty-six (96%) of the 27 patients entered completed chemoradiation and underwent subsequent surgical resection of the residual tumor mass. One patient refused surgical resection of the residual tumor mass; he has experienced gradual regression of the postchemoradiation tumor mass and currently has no radiographically definable disease 33 months following completion of chemoradiation.

Macroscopically complete surgical resection with microscopically negative surgical margins (R0) was performed in 23 patients (88%); three patients (12%) underwent macroscopically complete resection with microscopically positive surgical margins (R1). Operative procedures included wide local resection in 25 patients; one patient with recurrent sarcoma in an above knee amputation stump underwent more proximal amputation. Primary closure was performed in 13 patients. Reconstructive surgery with rotational or free tissue transfer techniques was utilized for wound closure in the remaining 13 patients.

Major wound complications were noted in six patients (23%). Three of these patients experienced wound complications requiring hospital readmission; two of these pa-

**Table 3.** Grade 3 or 4 Toxicities of Preoperative Doxorubicin-Based Chemoradiation by Doxorubicin Dose in 27 Patients

Doxorubicin Dose, mg/m <sup>2</sup> /week	No. of Patients With Grade 3 or 4 Toxicity							
	Nausea	Vomiting	Diarrhea	Anorexia	Stomatitis	Neutropenia	Thrombocytopenia	Dermatologic
12.5 (n = 1)	0	0	0	0	0	0	0	0
15.0 (n = 3)	0	0	0	1	0	0	0	0
17.5 (n = 22)	2	0	0	7	1	3	0	7

tients underwent reoperation for wound debridement or soft tissue coverage. No patient underwent amputation for management of treatment-related wound complications.

## DISCUSSION

The present report demonstrates the feasibility of preoperative doxorubicin-based chemoradiation and surgical resection for patients with extremity and body wall STS. The MTD of continuous-infusion doxorubicin that could be combined with standard preoperative EBRT (50 Gy in 25 fractions) was 17.5 mg/m<sup>2</sup>/wk. The toxicity profile observed with preoperative doxorubicin-based chemoradiation was acceptable, with approximately one third of patients treated at the highest dose level experiencing grade 3 chemoradiation-associated skin reactions. In addition, three patients (11%) experienced grade 3 neutropenia—but none with associated fever. A weekly doxorubicin dose of 17.5 mg/m<sup>2</sup> should be considered for future trials of infusional doxorubicin-based chemoradiation.

To our knowledge, this is the first report of a study evaluating low-dose continuous-infusion doxorubicin combined with and given throughout a course of standard preoperative EBRT. Prior reports of doxorubicin-based chemoradiation included pilot or phase I trials that utilized a higher dose (20 to 30 mg/m<sup>2</sup>) and bolus administration of

doxorubicin (alone or with ifosfamide and/or cisplatin) combined with a shorter and higher dose-per-fraction radiation schedule (28 or 35 Gy in 2- to 3-Gy fractions).<sup>1-4,10</sup>

Our chemoradiation approach differs from the reports that utilized bolus doxorubicin dosing in that we sought to promote continuous radiosensitization throughout radiotherapy. The toxicity profile of our approach utilizing lower-dose continuous-infusion doxorubicin appears generally comparable to the toxicity profiles reported in the trials that used bolus IV chemotherapy during radiotherapy.<sup>1-4</sup> However, given the differences in doxorubicin dose and schedule as well as the shorter and higher dose-per-fraction radiation schedule utilized in most prior studies, direct comparison of the toxicity profiles in these studies and in our study is difficult. Randomized trials would be required for an objective comparison of the toxicities of these approaches.

Eilber et al<sup>10</sup> have demonstrated that a pathologic complete response following preoperative doxorubicin-based chemoradiation is associated with improved local recurrence-free and overall survival. In the current report, 11 (50%) of 22 patients treated at the 17.5 mg/m<sup>2</sup>/wk doxorubicin dose who underwent surgery had 90% or greater treatment-associated tumor necrosis, and two patients had complete pathologic responses. This rate of significant pathologic response is encouraging in light of the finding of Eilber et al. In addition, the 88% R0 resection rate appears favorable considering the relatively high-risk nature of the patient population (median tumor size > 10 cm). This rate is also greater than the 67% R0 resection rate observed in another study from our institution in which surgery is the initial form of STS treatment.<sup>11</sup> Whether this favorable R0 resection rate is a consequence of patient selection or whether it is treatment-related is impossible to determine in a single-arm phase I trial.

Preoperative radiation is known to be associated with an increased risk for major wound complications after surgery.<sup>8</sup> We observed major wound complications in six (23%) of 26 patients. This incidence of major wound complications is similar to that observed with preoperative radiation without chemotherapy<sup>12,13</sup> and appears comparable to the wound complication rates observed in the Canadian Sarcoma Group randomized prospective trial of preoperative versus postoperative radiotherapy, in which a 35% incidence of major wound complications was observed in the patients randomly assigned to preoperative radiation.<sup>8</sup>

**Table 4.** Pathologic Findings and Responses in 26 Patients Who Underwent Surgical Resection Stratified by Doxorubicin Dose

Pathologic Finding	No. of Patients by Doxorubicin Dose		
	12.5 mg/m <sup>2</sup> /wk (n = 1)	15 mg/m <sup>2</sup> /wk (n = 3)	17.5 mg/m <sup>2</sup> /wk (n = 22)
Tumor size, cm			
Range	8.0	8-15	3.0-24.0
Microscopic margins			
Positive	0	1	2
Negative	1	2	20
Pathologic response, %*			
< 10	0	0	4
10-49	0	1	4
50-89	0	2	4
90-99	0	0	9
100 (complete response)	1	0	1

\*Percentage tumor necrosis estimated on final pathology.

Thus, the risk for wound complications after preoperative chemoradiation does not appear to be higher than that after preoperative radiation alone. Nevertheless, the issue of treatment-related wound complications is one that should be considered in all future trials of preoperative radiotherapy and/or chemoradiation for STS.

The use of the CRM in this trial offered significant advantages over older sequential-cohort phase I designs. In particular, the CRM allowed for a better estimate of the targeted toxicity rate of 30% and permitted more patients to be treated at the target dose. In addition, this design permitted us to make preliminary observations on the efficacy of this regimen since all but four patients were treated with the MTD of continuous-infusion doxorubicin.

In summary, the overall toxicity profile of preoperative doxorubicin-based chemoradiation was considered to be acceptable, and 90% or greater tumor necrosis was

found in 50% of patients. The encouraging pathologic response rate and favorable R0 resection rate suggest that further studies of doxorubicin-based chemoradiation should be considered. Future phase II studies of standard preoperative EBRT combined with continuous-infusion doxorubicin should be performed using a weekly doxorubicin dose of 17.5 mg/m<sup>2</sup>.

---

### Acknowledgment

We gratefully acknowledge review of the manuscript by Xuemei Wang and the editorial assistance from Melissa Burkett.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## REFERENCES

1. Eilber FR, Giuliano AE, Huth JF, et al: Intravenous (IV) vs. intraarterial (IA) Adriamycin, 2800 Gy radiation and surgical excision for extremity soft tissue sarcomas: A randomized prospective trial. *Proc Am Soc Clin Oncol* 9:309, 1990 (abstr 1194)
2. Levine EA, Trippon M, DasGupta TK: Preoperative multimodality treatment for soft tissue sarcomas. *Cancer* 71:3685-3689, 1993
3. Wanebo HJ, Temple WJ, Popp MB, et al: Preoperative regional therapy for extremity sarcoma. A tricenter update. *Cancer* 75:2299-2306, 1995
4. Temple WJ, Temple CLF, Arthur K, et al: Prospective cohort study of neoadjuvant treatment in conservative surgery of soft tissue sarcomas. *Ann Surg Oncol* 4:586-590, 1997
5. Pollock RE, Baker LH, Blumenstein B, et al: Soft tissue sarcoma, in Greene F, Page D, Fleming ID, et al (eds): *AJCC Cancer Staging Manual*. New York, NY, Springer-Verlag, 2002, pp 193-200
6. O'Quigley J, Pepe M, Fisher L: Continual reassessment method: A practical design for phase I clinical trials in cancer. *Biometrics* 46:33-48, 1990
7. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
8. O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomized trial. *Lancet* 359:2235-2241, 2002
9. Goodman SN, Zahurak ML, Piantadosi S: Some practical improvements in the continual reassessment method for phase I studies. *Stat Med* 14:1149-1161, 1995
10. Eilber FC, Rosen G, Eckardt J, et al: Treatment-induced pathologic necrosis: A predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. *J Clin Oncol* 19:3203-3209, 2001
11. Zagars GK, Ballo MT: Sequencing radiotherapy for soft tissue sarcoma when resection is planned. *Int J Radiat Oncol Biol Phys* 56:21-27, 2003
12. Bujko K, Suit HD, Springfield DS, et al: Wound healing after preoperative radiation for sarcoma of soft tissues. *Surg Gynecol Obstet* 176:124-134, 1993
13. Peat BG, Bell RS, Davis A, et al: Wound-healing complications after soft-tissue sarcoma surgery. *Plast Reconstr Surg* 93:980-987, 1994