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Evaluating the Role of Interdigitated Neoadjuvant Chemotherapy and Radiation in the Management of High-Grade Soft-Tissue Sarcoma:

The Johns Hopkins Experience

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Abstract

Objectives—High-grade soft-tissue sarcoma (STS) has a poor prognosis. The goal of this study was to review treatment outcomes of patients with high-grade STS treated with interdigitated neoadjuvant chemotherapy (CT) and radiation at our institution.

Materials and Methods—Patients with high-grade STS (1997 to 2010) were planned for treatment with 3 cycles of neoadjuvant CT, interdigitated preoperative radiation therapy (44 Gy administered in split courses with a potential 16 Gy postoperative boost), and 3 cycles of postoperative CT. Cancer control outcomes at 3 years were analyzed.

Results—Sixteen patients with high-grade STS were evaluated. Median age was 53 years, the median longest tumor diameter was 14.6 cm, and median follow-up was 33 months. All 16 patients received 2 or 3 cycles of neoadjuvant CT and all patients completed neoadjuvant RT. The estimated 3-year rate for local control was 100%, disease-free survival 62.5%, and overall survival 73.4%.

Conclusions—Patients with high-grade STS treated with interdigitated neoadjuvant CT and radiation before surgical resection had excellent rates of local control, along with disease-free survival and overall survival similar to previously published reports. This combined-modality approach continues to have a role in the treatment of patients with high-grade STS.

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Keywords

sarcoma; interdigitated; neoadjuvant

Ideal management of patients with high-grade soft-tissue sarcoma (STS) has been a challenge for surgical, medical, and radiation oncologists. Because of the variety of histologic subtypes of the disease, the rarity of the disease, and the poor prognosis of many patients, treatment modalities have often focused on aggressive combination therapies.¹

Surgery is an essential component of treatment, with a role for neoadjuvant and/or adjuvant radiation therapy in improving local control (LC). The role of chemotherapy (CT), in either a neoadjuvant and/or adjuvant setting is somewhat controversial, although regimens including doxorubicin have shown promising though conflicting results in multiple studies.² Over the past 2 decades there has been a single institutional patient series and a phase II multi-institutional study looking at the role of interdigitated neoadjuvant CT and radiation therapy before surgery for high-grade STS. Results showed improvements in LC, disease-free survival (DFS), and overall survival (OS) compared with historical controls.

In 2003 a group of researchers from Massachusetts General Hospital published their findings on a series of patients treated with a program of aggressive CT interdigitated with radiotherapy for patients with large, high-grade sarcomas.³ This study treated patients with neoadjuvant modified mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) CT, with split-course radiation therapy to 44Gy, followed by resection and postoperative adjuvant MAID CT. The actuarial 5-year LC, DFS rate, and OS rates for MAID patients were 92%, 70%, and 87%, respectively, compared with retrospectively matched patients treated with radiation and surgery with results of 86%, 42%, and 58%.

On the basis of these results, the Radiation Therapy Oncology Group initiated a phase II trial (RTOG 9514) to evaluate the efficacy and toxicity of a modified MAID regimen in similar patients in a multi-institutional setting.^{4, 5} Updated results showed estimated 5-year rates of LC (77.8%, including amputation as a local failure), DFS (56.1%), and OS (71.2%).

Our hospital serves as a specialized referral center for patients with sarcoma, and we have treated STS patients using a variety of techniques over the past few decades. A retrospective study of patient outcomes from individuals with high-grade extremity or trunk STS treated with interdigitated neoadjuvant CT and radiation before surgery was conducted to review whether there remains a role for such an aggressive combined-modality therapy for these patients.

MATERIALS AND METHODS

Patient Selection

The records of all high-grade extremity or trunk STS patients treated with interdigitated neoadjuvant CT and radiation at our institution between 1997 and 2010 were identified using institutional tumor registries. Patients were 18 years and older with large (> 6 cm), high-grade (grade 2 or 3 in a 3-tier grading system) primary STS of the extremity or trunk.

All patients had imaging workup including CT and/or magnetic resonance imaging of the primary tumor region along with a diagnostic core needle or incisional biopsy of their tumor, with all pathology reviewed at our institution.

Patient Treatment Plan: (CT, Radiation Therapy, Surgery)

Patients selected were planned for treatment as per the RTOG 9514 protocol consisting of 3 cycles of neoadjuvant CT (modified mesna, doxorubicin, ifosfamide, and dacarbazine [MAID]), interdigitated preoperative radiation therapy (RT; 44Gy administered in split courses), surgical resection, and a planned 3 cycles of postoperative CT (modified MAID). The modified MAID CT regimen was planned with mesna (2500mg/m²/d IV continuous infusion days 1 to 4), doxorubicin (20mg/m²/d IV continuous infusion days 1 to 3), ifosfamide (2500mg/m²/d IV continuous infusion days 1 to 3), and dacarbazine (225mg/m²/d IV continuous infusion days 1 to 3). CT dose reduction, use of granulocyte macrophage colony-stimulating factor, and exclusion of dacarbazine or change in postoperative CT regimen was performed in select patients at the treating medical oncologist's discretion. Radiation therapy was given to a total dose of 44Gy in split courses of 22Gy between the first and second cycles and between the second and third cycles of preoperative CT (Fig. 1). Treatment-utilized CT and/or magnetic resonance imaging to define target volumes, and external beam radiation with photons was given in 2 Gy daily fractions for 11 fractions during each split course. All patients were planned for R0 resections, with incisional biopsy sites resected within the surgical specimen. A postoperative external beam radiation boost of up to 16Gy was permitted for patients with positive margins.

Postoperative Pathologic Evaluation

All tumor specimens were evaluated by experienced musculoskeletal pathologists. Tumor size, margin status, and World Health Organization grade were reported. The percentage of histologic necrosis was also estimated and reported during the pathology review of the surgical specimen for all except 1 patient. Surgical resections were defined as R0 if margins were microscopically negative, R1 if all gross disease was removed with microscopically positive margins, and R2 if there was a grossly positive margin.

Study Endpoints and Statistical Analysis

All measured outcome time points for patients were calculated from the date of original confirmatory biopsy. LC was defined as absence of persistent local disease, absence of extremity amputation, and absence of local disease relapse. DFS was defined as survival with an absence of persistent local disease, amputation, local relapse, distant relapse, or death. OS was defined as patient death from any cause. Estimated cancer control outcomes at 3 years (LC, DFS, and OS) were calculated using the Kaplan-Meier method. Wound complications were graded by severity as per RTOG 9514 (category 1: minor issues not causing delay of postoperative CT or if indicated postoperative radiation; category 2: complications causing delay of postoperative CT including major infections without limb loss or major tissue loss; category 3: presence or threatened limb loss or major tissue loss).⁴

RESULTS

Patient Population

Sixteen patients with high-grade extremity or trunk STS were treated with interdigitated neoadjuvant CT and radiation at our institution during the study period. Patient characteristics are detailed in Table 1, with the median age at diagnosis of 53 years (range, 24 to 68), and the median primary tumor diameter in the longest dimension was 14.6 cm. Overall, 15 of 16 patients had a primary tumor with the longest dimension > 8 cm, which was part of the inclusion criteria of both the MGH and RTOG 9514 studies. Median follow-up was 33 months (range, 13 to 165 mo). All 16 patients received neoadjuvant CT (13 patients received 3 cycles, and 3 patients had 2 cycles of CT as per medical oncologist discretion) and all patients completed neoadjuvant RT to 44 Gy.

Treatment Outcomes

The estimated 3-year rate for LC was 100%, DFS 62.5%, and OS 73.4%. Table 2 outlines various clinical factors and patient outcomes between our patient data and that previously published by the MGH group and from the RTOG 9514 study. Fifteen of 16 patients had surgical pathology reports that detailed treatment response to neoadjuvant CT and radiation, and among these there were 9 patients with 95% necrosis, 4 patients with 20% to 50% necrosis, and 2 patients with < 20% necrosis.

Wound complication rates were measured using the criteria for the RTOG 9514 study, and from our group of 16 patients, 14 (88%) had either no or minor wound complications (10 with no wound complications and 4 patients with category 1 minor complications). There were 2 patients with category 2 wound complications leading to a delay in the start of postoperative CT. In addition, no patients had category 3 wound complications. The limb salvage rate in this group of patients was 100%, with no patients requiring amputation for an inability to potentially perform an R0 resection, from local recurrence, or from serious wound complications.

DISCUSSION

Management of patients with high-grade STS remains a challenge and identifying an optimal treatment regimen for this aggressive disease is important. The initial promising results of MGH investigators led the RTOG to study incorporating MAID CT and interdigitated radiation therapy for high-grade STS patients. The MGH study detailed improvements in LC, DFS, and OS compared with their own institutional control patients.³ The RTOG study was the first prospective phase II trial incorporating this regimen, and it published initial results in 2006,⁴ with longer follow-up data published in 2010.⁵

With our institution serving as a tertiary center for sarcoma management, select patients over the past 2 decades have been treated with a planned regimen as per the RTOG 9514 study with minor modifications in postoperative CT regimens. In light of these previously published results, we examined our patient cohort retrospectively to shed light on the potential continued use of this approach in future patients. Although median patient age and median tumor size was similar across all 3 studies, the percentage of patients having high-

grade disease (grade 3 in a 3-tier grading system) was different. The MGH study had 48% of patients with grade 3 in both their control and MAID group, the RTOG study had 80%, and at our institution 100% of patients had grade 3 histology. As it was discussed in the RTOG 9514 study, the fact that all of our patients were grade 3, and the vast majority in the RTOG study were as well, compared with 48% of patients in the MGH study, may in part explain the decreased rates of DFS and OS seen in these more recent data.

Again, this treatment regimen was selected for patients in whom a potential R0 resection could be performed. As detailed in Table 2, our institution had excellent LC (100% LC at 3 y), with no amputations or local recurrences in any patient during follow-up. With larger groups of patients, the MGH study showed an R0 resection rate of 81% (controls) and 85% (MAID group), whereas the RTOG study had an R0 rate of 91%. As interdigitated neoadjuvant CT and radiation is designed to both initiate systemic therapy while attempting a limb sparing local R0 resection, in our cohort of patients this goal was achieved by selectively using this approach when indicated (15 patients had R0 resection, and 1 patient had an R1 resection and was treated with a postoperative RT boost of 16 Gy).

In terms of treatment toxicity, we compared our wound complication rates to the RTOG 9514 study using that publication's category (1 to 3) definitions for this outcome. In the RTOG study, of the 61 patients who underwent surgery after interdigitated neoadjuvant CT and radiation, 54 (89%) of patients had no wound complications or minor complications. In our smaller study, 14 patients (88%) similarly had either no or minor wound complications (10 with no wound complications as per these criteria and 4 patients with category 1 minor complications). In the RTOG study there were 5 patients (8%) with category 2 complications (with delayed postoperative CT) and 2 patients (3%) with category 3 complications in which serious tissue loss or amputation was threatened. At our institution, we had 2 patients (13%) with category 2 complications (delayed start of postoperative CT), and no patients with category 3 complications. Thus, the wound toxicity results in this cohort of patients were consistent with results published for patients in the RTOG 9514 phase II trial. In terms of limb salvage rates, 5 patients in the RTOG study required amputation (3 related to planned treatment where an R0 resection was felt unable to be successfully performed, and 2 related to posttreatment toxicity) with an overall amputation rate of 9.4% based on an initial 53 patients having extremity sarcomas. In the MGH MAID group, 1 patient underwent amputation for a wound complication, and another 2 patients underwent salvage amputation for local recurrence, with an overall amputation rate of 6.3%. Although we had a smaller number of patients, there were no amputations necessary in our patient group with a limb salvage rate of 100%.

One of the aims of such an aggressive treatment regimen is to achieve LC with surgery, and to determine treatment effect of neoadjuvant CT and radiation at the time of surgery on the pathology specimen. In the RTOG 9514 study, 27% of patients had no viable tumor seen on pathology, and in our study 56% (9 patients) had 95% necrosis. The RTOG also showed 37% of resection specimens with <25% viable tumor, 25% of specimens with 25% to 50% viable tumor, and 10% of specimens with > 50% viable tumor. The other groups in our study showed 19% (3 patients) with 20% to 50% necrosis, 13% (2 patients) with < 20% necrosis, and 6% (1 patient) where there was no information on necrosis available. These tissue

effects may play a role in improving LC of disease, or may simply reflect the biological nature of a particular patient's tumor response.

However, in all of these studies, there still remain a large proportion of patients who have distant metastases. In light of the excellent rates of LC with this treatment regimen, the rate of distant disease likely continues to play the largest role in patient overall mortality. Thus, as has been a challenge in sarcoma, significant improvements in systemic therapy continue to be needed. Recent testing of new ifosfamide formulations is either ongoing (clinicaltrials.gov NCT01710176) or completed (with disappointing interim results for a phase III palifosfamide trial: PICASSO 3). Pazopanib, a multitargeted tyrosine kinase inhibitor, with proven activity in STS is being combined with standard cytotoxic agents to evaluate both safety and efficacy in patients (NCT01418001). Also, other approaches including immune checkpoint blockade with ipilimumab administered with the TKI dasatinib (NCT01643278) are being assessed in early phase I trials as well. Although interdigitated neoadjuvant CT and radiation therapy as per the RTOG 9514 protocol is an aggressive therapy, future use of this regimen could undergo modifications such as using novel combinations of adjuvant chemotherapies, the addition of targeted agents, or the use of immunotherapy.^{6, 7} For select patients with high-grade extremity or trunk STS, this combined-modality approach may continue to offer potential benefit as a therapy option in the future (Figs. 2, 3).

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012; 62:10–29. [PubMed: 22237781]
2. Tierney JF, Mosseri V, Stewart LA, et al. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. *Br J Cancer*. 1995; 72:469–475. [PubMed: 7640234]
3. DeLaney TF, Spiro IJ, Suit HD, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2003; 56:1117–1127. [PubMed: 12829150]
4. Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol*. 2006; 24:619–625. [PubMed: 16446334]
5. Kraybill WG, Harris J, Spiro IJ, et al. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *Cancer*. 2010; 116:4613–4621. [PubMed: 20572040]
6. Page DB, Yuan J, Wolchok JD. Targeting cytotoxic T-lymphocyte antigen 4 in immunotherapies for melanoma and other cancers. *Immunotherapy*. 2010; 2:367–379. [PubMed: 20635901]
7. Kasper B, Gil T, D'Hondt V, et al. Novel treatment strategies for soft tissue sarcoma. *Crit Rev Oncol Hematol*. 2007; 62:9–15. [PubMed: 17141519]

FIGURE 1.

Interdigitated neoadjuvant chemotherapy and radiation treatment program. MAID indicates modified mesna, doxorubicin, ifosfamide, and dacarbazine; RT, radiation therapy. Reprinted with permission from DeLaney et al.³ Copyright [Elsevier], [Oxford, UK]. All permission requests for this image should be made to the copyright holder.

FIGURE 2. Disease-free survival (DFS): Kaplan-Meier estimate of DFS. Each notch indicates a censored patient.

FIGURE 3.
Overall survival (OS): Kaplan-Meier estimate of OS. Each notch indicates a censored patient.

TABLE 1

Patient Characteristics

Characteristics	n (%) or Value
Male	11 (69)
Female	5 (31)
Median age at diagnosis	53 (range, 24–68)
Median follow-up (mo)	33 (range, 13–165)
Primary tumor location (upper extremity)	4 (25)
Primary tumor location (lower extremity)	9 (56)
Primary tumor location (trunk)	3 (19)

TABLE 2

Comparison of Patient Characteristics and Outcomes Between Studies

Study	MGH Controls	MGH MAID Group	RTOG 9514	Our Institution
Patients (N)	48	48	64	16
Median age (y)	52	49	45.5	53
Median largest tumor diameter (range) (cm)	12.0 (8–27)	14.2 (8–35)	15.0 (8.2–55)	14.6 (6.3–27)
Tumor grade 2 (n [%])	25 (52)	25 (52)	13 (20)	0 (0)
Tumor grade 3 (n [%])	23 (48)	23 (48)	51 (80)	16 (100)
Surgery margins R0 (n [%])	39 (81)	41 (85)	58 (91)	15 (94)
Surgery margins R1 + (n [%])	9 (19)	7 (15)	6 (9)	1 (6)
LC (n [%])	5 (86)	5 (92)	5 (77.8)	3 (100)
DFS (n [%])	5 (42)	5 (70)	5 (56.1)	3 (62.5)
OS (n [%])	5 (58)	5 (87)	5 (71.2)	3 (73.4)

MGH controls and MGH MAID group,³ RTOG 9514.^{4,5}

R1 + indicates R1 resection, R2 resection, limb amputation, or surgery not performed; DFS, disease-free survival; LC, local control; MAID, modified mesna, doxorubicin, ifosfamide, and dacarbazine; OS, overall survival.