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The Impact of Neo-adjuvant and Adjuvant Chemotherapy in Treatment Outcome of Patients with High Risk Soft Tissue Sarcomas of the Extremities

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Abstract

Background: This prospective study assessed the efficacy of neoadjuvant and adjuvant chemotherapy on patients with high risk soft tissue sarcomasof the extremities.

Methods: Enrolled patients received the following neoadjuvant chemotherapy: doxorubicin (75 mg/m^2) on day1, ifosfamide (2.5 g/m^2/d) and mesna (20% of the ifosfamide dose) from days1 to 3, repeated every three weeks for a total of three cycles, followed by surgery and radiotherapy. Patients received an additional three cycles of adjuvant chemotherapy that was the same as the neoadjuvant protocol following completion of radiotherapy.

Results: There were 52 patients enrolled in the study, of which 50 were included in data analysis. Neoadjuvant chemotherapy was completed by 90% of enrolled patients and 88% completed all planned chemotherapy. A total of 96% of patients underwent surgery and 92% of these had R0 resections. Postoperative radiotherapy was administered to 96% of patients. The estimated three-year local-regional failure was 10%. Estimated three-year rate for distant disease-free survival was 66% and overall survival was 88%. One patient died with treatment secondary to leukopenic sepsis and respiratory failure. Grades 3-4 toxicities were experienced by 86% of patients of which 84% were grades 3- 4 hematologic toxicities and 38% were grades 3-4 non-hematologic toxicities.

Conclusion: The current protocol is feasible and associated with favorable distant disease-free survival, overall survival, and limb preservation. This protocol is tolerable and has a manageable toxicity level.

Keywords: Neo-adjuvant, Adjuvant chemotherapy toxicity, Survival, Soft tissue sarcomas

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Introduction

Soft tissue sarcomas (STS) are a rare, heterogeneous group of tumors that account for approximately 1% of

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all adult cancers.[1] While they may be found in nearly any site of the body, the upper and lower extremities are the most common locations, accounting for about 50% of all cases. High-risk STS of the extremities are large (>5 cm) and are intermediate or high grade.[1,2]

Management approaches for newly diagnosed primary sarcoma include wide local resection combined with preoperative or postoperative radiotherapy or wide local excision alone for small superficial lesions.[3-8] Management in this manner results in control of local tumors in 80% to 95% of patients, the majority of whom maintain good extremity function.[9,10] Patients with high-grade tumors >5 cm in size are at increased risk for distant treatment failure and death from metastatic disease. The risk of distant metastatic disease increases with an increase in size of the primary high-grade tumor.[10,11] The risk is 34% in patients with lesions 5.1 to 10 cm and increases to 43% for 10.1-15 cm and 58% for 15.1-20 cm lesions.[10] A potential role for adjuvant chemotherapy in these high-risk tumors has been investigated. While chemotherapy has established efficacy in reducing metastasis and prolonging survival in several specific subtypes of childhood STSs (rhabdomyosarcoma[12] and Ewing's sarcoma[13]), its value in treating most other histologic types of primary sarcoma remains controversial.

Many prospective trials of chemotherapy for STS conducted to date have had small sample sizes, suboptimal chemotherapy and involved a heterogeneous mix of tumor sites and grades. As a result, these trials have yielded variable results and have been difficult to interpret.

Despite these inconsistent data, neoadjuvant chemotherapy (NAC) has suggested several potential benefits including an ability to assess sarcoma response to a given chemotherapeutic regimen, earlier treatment of microscopic metastatic disease, and facilitation of tumor removal.[14,15]

Experience with neoadjuvant chemo-radiation (NCR) in STS has been reported by several groups. Eilber and colleagues published a regimen of intra-arterial doxorubicin infused over 24 hours for three days prior to radiation, followed by surgery.[16] Other single agents that have been studied with preoperative radiation include ifosfamide and gemcitabine.[17,18] Multi-agent chemotherapy regimens given preoperatively with radiation include mensa, doxorubicin, ifosfamide and dacarbazine (MAID) or ifosfamide, mitomycin, doxorubicin, andcisplatin (IMAP/MAP).[19-21] These strategies have shown promising results, including five-year overall survival (OS) rates up to 70%,[22-25] five-year local control rates up to 92%[19] and limb preservation rates up to 100%.[18] Toxicities of NCR typically include wound complications, many of which require additional surgery and long bone

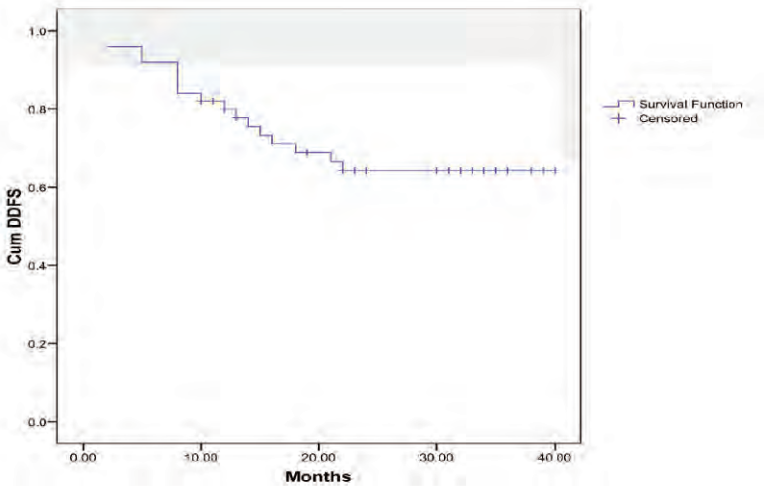

Figure 1. Kaplan-Meier curve of distant disease-free survival (DDFS).

fractures.[26]

The current study performed at Mansoura University Hospital assessed and evaluated the impact of NAC and adjuvant chemotherapy in the management of high risk STS of the extremities.

Patients and Methods

Eligibility criteria

Eligibility criteria consisted of the following: age 20-65 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; large (>8 cm), intermediate or high grade, deep extremity STS; adequate bone marrow (WBC >4,000/mL, platelets >120,000/mL, and hemoglobin >10 g/dL), renal (creatinine <1.3 mg/dL), and hepatic (bilirubin <1.2) levels; and normal cardiac function.

Exclusion criteria were as follows: distant or regional lymph-node metastases, local recurrence after prior treatment, previous malignancy, prior radiotherapy or chemotherapy, and diagnosis of Ewing's sarcoma or rhabdomyo sarcoma.

Patients who fulfilled the above eligibility criteria were made aware of the purpose and the design of the study and required to sign the informed consent.

Pretreatment evaluation

After a positive biopsy for STS, each patient gave a full medical history and underwent a physical examination, complete blood work, electrocardiogram, computed tomography(CT) scan and/or magnetic resonance imaging(MRI) of the primary lesion, and a CT scan of the thorax. Other tests (angiography, bone scan, CT scan of the brain, etc.) were performed only in the case of clinical suspicion.

Treatment schedule

Patients were treated with NAC, then local treatment (surgery and radiation therapy), followed by adjuvant chemotherapy with the same protocol as NAC.

Chemotherapy

Patients received a total of six cycles of chemotherapy, of which three cycles (range: 2–4 cycles) were administered preoperatively. The remaining three cycles (range: 2–4 cycles) were administered after patients completed radiation therapy. Chemotherapy was repeated every three weeks in the following manner: doxorubicin (75 mg/m^2) in a short intravenous (IV) infusion on day1, ifosfamide (2.5 g/m^2/d diluted in 500 mL of normal saline) administered over three hours on days 1 to 3, and mesna in a bolus IV injection at 20% of the ifosfamide dose, administered before,4, 8, and 12 hours after the ifosfamide infusions. IV hydration (1.5 to 2 L of fluids after chemotherapy) and antiemetics (5-hydroxytryptamine-3 antagonists) were routinely administered.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Patients	50 (100)
Age (yrs.), median (range, yrs.)	47(24-65)
Gender	
Male	29 (58)
Female	21 (42)
ECOG performance status	
0	19 (38)
1	27(54)
2	4(8)
Histology	
Fibrosarcoma	4(8)
Malignant fibrous histiocytoma	23(46)
Liposarcoma	7(14)
Leiomyosarcoma	6(12)
Synovial sarcoma	4(8)
Malignant peripheral nerve sheath	3(6)
Epithelioid sarcoma	3(6)
Primary location	
Shoulder	3(6)
Arm	10(20)
Forearm	2(4)
Buttocks	4(8)
Thigh	5(10)
Leg	26(52)
Tumor grade	
2	10 (20)
3	40(80)
Largest tumor diameter (cm)	
Median	18
Range	10-42

Surgery

All extremity lesions were to be treated with R0 resections. Biopsy was incisional or core needle. The resection was planned such that the biopsy site could be included in the resected specimen. If the tumor was close to or displaced major vessels or nerves, an attempt was made to remove adventitia or perineurium to obtain apathologically clear margin. Sections from the closest margin were examined by frozen section at the time of surgery to be confirmed as free of tumor. Giving special care to skin flaps, and the liberal use of muscle flaps, pedicled myocutaneous flaps, and free flaps was encouraged to fill dead space and cover bone and neurovascular tissue.

Radiation therapy

Postoperative 2-D radiotherapy(64 to 66 Gy in 32 to 33 fractions, 5 fractions per week) was administered to patients who underwent conservative surgery and had negative margins. In general, the entire compartment was not covered. The radiation therapy target area included the primary lesion and tissues that had involvement suggestive of microscopic disease. In addition to physical examination findings, MRI or CT scans obtained during evaluation were used to define the target volume. The field margins proximal and distal to the clinically or radiologically evident sarcoma were specified to be 7-9 cm. Radial margins were 2-3 cm, unless a facial or bony barrier to tumor spread in a given plane was present, in which case tighter radial field margins

Table 2. Type and frequency of toxicities.

Toxicity	No.	%
Hematologic grades 3-4		
Hemoglobin	26	52
WBC	42	84
Platelets	31	62
Neutrophils	41	82
Non-hematologicgrades 3-4		
Infection	19	38
Skin	15	30
Subcutaneous tissue	3	6
Diarrhea	3	6
Nausea and/or vomiting	6	12
Pain	1	2
Respiratory	1	2
Cardiac	1	2
Fever	1	2
Peripheral nerves	1	2
Vascular	2	4

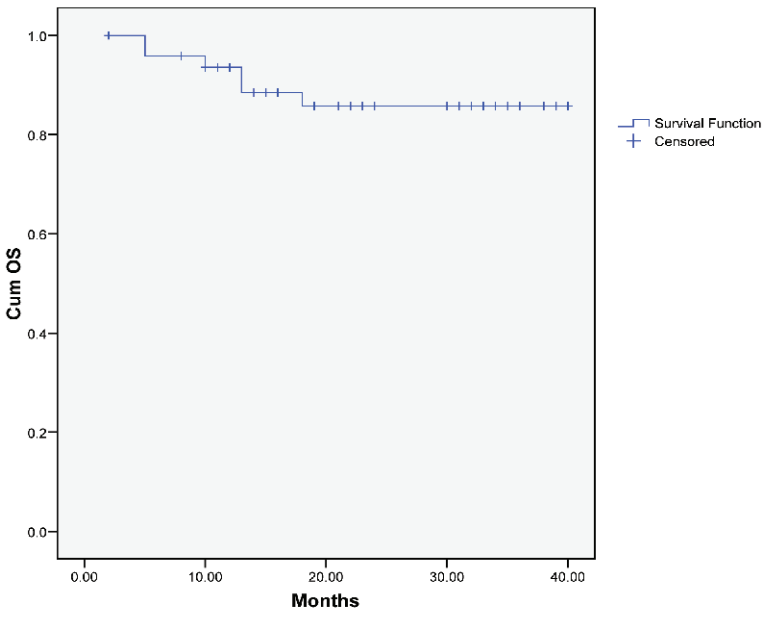

Figure 2. Kaplan-Meier curve of overall survival (OS).

were used to put the full dose on the facial or bony surface area proximate to the tumor. Every effort was made to avoid treating the full circumference of an extremity.

Evaluation of toxicity and follow up

After completion of NAC, clinical response was assessed by CT or MRI using the Response Evaluation Criteria in Solid Tumors Group (RECIST) criteria[27] and pathologic response of the operative specimens according to the percentage of viable tumor. Toxicities were graded according to World Health Organization criteria.[28] Physical examinations, routine chemistry, and X-ray of the thorax and bones underlying the primary site were performed every two months. ACT scan of the thorax and MRI or CT scan of the primary site was performed every six months for the first two years.

End points

The primary efficacy end point was local-regional failure (LRF), distant disease-free survival (DDFS) and OS. Secondary end point was treatment toxicity.

Statistical analyses

All time-to-failure end points for efficacy were calculated from the date of registration. Failure for each end point was defined as follows. OS was defined as death as a result of any cause. Time to LRF was defined as persistent local disease, or local or regional relapse. Time to distant metastases was defined as distant metastases.

Estimates for LRF, OS and DDFS rates were calculated with Kaplan-Meier.

Results

Patients

A total of 52 patients entered the study between January 2009 and April 2011. Two patients were ineligible (one had metastatic disease and one had ineligible histology), leaving 50 analyzable patients. Pretreatment characteristics are summarized in Table 1. The median age was 47 years, and ranged from 24 to 65 years. Males represented 58% of patients. There were 27 (54%) patients who had an ECOG performance status of 1. Malignant fibrous histiocytoma was the most common histological type with 46% of cases. Grade 3 tumors comprised 80% of tumors. The leg was the primary site in 52% of patients. Median tumor size as measured by MRI, CT, or clinical findings was 18cm (range: 10-42 cm). Median follow-up for all patients was 26 months (range: 2-39 months).

Treatment characteristics

Only 44 (88%) patients received all six cycles of NAC and adjuvant chemotherapy. There were 45 (90%) patients who received all three cycles of preoperative chemotherapy and 44 (88%) who received all three cycles of postoperative chemotherapy. The most frequent reason for patients not receiving chemotherapy was patient refusal secondary to toxicity. Forty-eight patients underwent surgery and two patients did not. Of these two patients, one had progressive primary tumor and was not a candidate for R0 resection. The other patient's primary tumor was controlled; however, he had progressive distant disease. Forty-six patients had R0 resections (of which three were amputations), and the other two patients had R1 resections. Postoperative radiotherapy was administered to 48 (96%) patients.

Treatment toxicity

Table 2 summarizes reported toxicity. Grades 3-4 toxicities were observed in 43 (86%) patients; 42 (84%) experienced grades 3-4 hematologic toxicities, and 19 (38%) experienced grades 3-4 non-hematologic toxicities. Observed grades 3-4 hematologic toxicities were as follows: leukopenia (n=42), thrombocytopenia (n=31) andanemia (n=26). The most common grades 3-4 non-hematologic toxicities were infectious (n=19), cutaneous (n=15), nausea and/or vomiting (n=6). Of 19 patients with grades 3-4 non-hematologic toxicities, 8 also had grade 4 leukopenia.

Of 48 patients who underwent surgery, 44 (88%) had no wound complications or had complications categorized as minor, and 4(8%) had complications considered serious or major that

either significantly delayed postoperative therapy (n=2) or in which serious tissue loss or amputation was threatened (n=2).

There were four amputations in this study; we considered two of them to be treatment-related. There were two patients who developed leukopenia associated sepsis that was attributed to infection at the biopsy site. In one patient, this occurred after an aspiration biopsy. The second patient underwent an incisional biopsy. Both patients developed progressive infection in their lower legs, which was associated with septicaemia and resulted in above-the-knee amputations. Two other patients had inadequate clinical responses to neoadjuvant treatment. One underwent a disarticulation and the other underwent an above-the-knee amputation. There was no viable tumor in either specimen.

One (2%) patient died from treatment in this protocol. She developed sepsis which was possibly related to her biopsy site. The patient underwent an amputation to control the sepsis but died secondary to widespread sepsis and pulmonary failure.

Response

Using RECIST criteria, 11 (22%) of 50 assessable patients had partial responses. Thirty-three (66%) were stable and 6 (12%) experienced disease progression on treatment.

Of 48 patients who underwent surgery, in 12 (25%)pathological results indicated no viable tumor in the resected specimen. There was less than 25% viable tumor in 18(38%) patients; 12 (25%) had evidence of 25% to 50% viable tumor; 2 (4%) had 51% to 75% viable tumor; and 4 (8%) had more than 75% viable tumor.

Of the 48 patients in which surgery was performed, 46 (92%) had R0 resections, of which 2 were amputations. In 2 patients who had positive microscopic margins (R1 resections), one achieved a complete response after adjuvant therapy; the other had local-regional recurrence and died as a result of the disease. The estimated three-year LRF was 10% (95% CI: 8.0%-25.2%). The estimated three-year rate for DDFS was 66% (95% CI: 51%-76.1%) and OS was 88% (95% CI: 65.3%-98.8%; Figures 1,2).

Discussion

The management of newly diagnosed sarcoma remains a challenge. Therapeutic goals consist of improving survival, avoiding local recurrence, maximizing function, and minimizing morbidity.[29]

Decision-making is more difficult in high risk tumors. It is estimated that approximately half of those who have high-risk tumors will ultimately die from metastatic disease that is present as microscopic foci at the time of diagnosis.[30] The timing and order of wide local resection, preoperative or postoperative radiotherapy, and preoperative or postoperative chemotherapy require a multidisciplinary approach.[20] Unfortunately, multimodal therapy differs considerably among major cancer centers.[31]

This study was done to evaluate the role of NAC and adjuvant chemotherapy in the management of high risk soft tissue sarcoma of the extremities at Mansoura University Hospital.

A retrospective study was done that compared the NAC of adriamycin, ifosfamide, and mensa to patients who underwent surgery without NAC. NAC was associated with improved disease-specific survival for this cohort of patients (P=0.02). This overall improvement appeared to be a result of the benefit of NAC on disease-specific survival for patients with tumors>10 cm. The three-year disease-specific survival for tumors>10 cm was 0.62 (95% CI: 0.53–0.71) for patients who did not receive NAC and 0.83 (95% CI: 0.72–0.95) for those administered NAC.[32]

William et al. studied high-grade STS≥8 cm in diameter of the extremities and bodywall. Patients received three cycles of NAC (modified mensa, doxorubicin, ifosfamide, and dacarbazine [MAID]), interdigitated preoperative radiation therapy of 44 Gy administered in split courses, and three cycles of postoperative chemotherapy (modified MAID). The estimated three-year rate for LRFwas 17.6% if amputation was considered as a failure and 10.1% if not. Estimated three-year rates were as follows: disease-free (56.6%), DDFS (64.5%), and OS (75.1%). In their study, 3 (5%) patients experienced fatal grade 5 toxicities of

myelodysplasias in 2 patients and infection in one patient. Another 53 (83%) experienced grade 4 toxicities, of which 78% had grade 4 hematologic toxicities and 19% experienced grade 4 non-hematologic toxicities. Surgery was performed in 61 patients, with 58 R0 resections, of which 5 were amputations. There were 3 R1 resections.[20]

In a study by Schmitt et al., patients with potentially curative high-risk STS (≥5 cm, deep/extra-compartmental localization, tumor grades II-III) were treated with four cycles of NAC (EIA, etoposide 125 mg/m2IVon days 1 and 4; ifosfamide 1500 mg/m2IVon days 1-4; doxorubicin 50 mg/m^2 on day 1; and pegfilgrastim 6 mg Subcutaneous on day 5), definitive surgery with intra-operative radiotherapy, adjuvant radiotherapy and four adjuvant cycles of EIA. Local recurrence occurred in 6% of patients, with distant metastasis in 24%. At two years, OS was 83% and DFS was 68%. Multivariate analysis failed to prove the effect of resection status or grade of histological necrosis on OS or DFS. Severe toxicities included neutropenic fever (8%), cardiac toxicity (4%), and CNS toxicity (8%) which lead to chemotherapy dose reductions in four subjects. No cases of secondary leukemia were observed thus far and the researchers recommended that this regimen only be used within a clinical study.[33]

Kelly et al. studied NCR prior to STS resection using a variety of chemotherapy regimens compared to neoadjuvant radiation without chemotherapy (NR) and surgery alone (SA). NCR did not improve the rate of margin-negative resections over SA or NR. Loco-regional relapse-free survival, distant metastases-free survival, and OS did not differ among the treatment groups. Patients with relapsed disease (OR 11.6; *P*=0.01), and tumor size >5 cm (OR 9.4; *P*=0.01) were more likely to have loco-regional recurrence on logistic regression analysis. Significantly increased OS was found among NCR-treated patients with tumors>5 cm compared to SA (three-year OS 69 vs. 40%; *P*=0.03). Wound complication rates were higher after NCR compared to SA (50 vs. 11%; *P*=0.003) but not compared to NR (*P*=0.36). Wet desquamation was the most common adverse event of NCR. They have concluded that NCR and NR are acceptable strategies for patients with STS. NCR is well-tolerated, but not clearly superior to NR.[34]

From previous trials and other non-mentioned trials to date, it had enrolled a heterogeneous population of soft tissue sarcoma subtypes due to the inability of single institutions to effectively conduct histology-specific studies. This increased the difficulty in selection of the best line of treatment. As certain soft tissue sarcoma subtypes are generally considered to be more chemotherapy-sensitive (i.e., synovial sarcoma, myxoid round cell liposarcoma), outcomes of neoadjuvant approaches in such histologies are of interest. Some retrospective attempts have been made to discern benefit. Data from 245 patients with high-risk liposarcoma of the extremities treated at UCLA and Memorial Sloan Kettering were analyzed based on whether patients received neoadjuvant or adjuvant ifosfamide-or doxorubicin-based chemotherapy, or no chemotherapy.[35]

On multivariate analysis, treatment with ifosfamide was independently associated with improved disease-specific survival (HR=0.3 compared with no chemotherapy, *P*=0.01). A similar analysis of 101 patients with high-risk synovial sarcomas also suggested a disease-specific survival benefit with ifosfamide over no chemotherapy (HR=0.3, *P*=0.007).[36] However, a retrospective report of 100 patients with synovial sarcoma treated with pre-operative ifosfamide and radiation followed by post-operative ifosfamide, doxorubicin and cisplatin reported an estimated five-year DFS rate of 50%, which was not suggestive of improved outcome compared with the overall STS population.[37]

To summarize, the use of NAC and adjuvant chemotherapy after surgery and radiotherapy in management of high-grade STS of the extremities is associated with favorable DDFS, OS, and limb preservation, as well as tolerable and manageable toxicities.

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