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ORIGINAL ARTICLE

The effect of adjuvant chemotherapy on the survival of patients with high-risk soft tissue sarcomas: Single center experience

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Summary

Purpose: *To evaluate the effect of adding adjuvant ifosfamide/doxorubicin combination chemotherapy (CTX) to adjuvant radiotherapy (RT) on the survival in patients with surgically treated high-risk soft tissue sarcomas (STSs).*

Methods: *The study included 69 patients (group A) receiving adjuvant RT and 74 patients (group B) receiving adjuvant CTX after adjuvant RT.*

Results: *The median relapse-free survival (RFS) was 18.2 months (95% CI, 11.9-43.4) in group A and 27.2 months (95% CI, 17.6-36.8) in group B (p=0.004). The median overall survival (OS) was 45.6 months (95% CI, 26.4-64.8) in group A and 110.1 mo (95% CI, 44.3-175.8) in group B (p=0.007). Receiving adjuvant CTX was an independent predictive factor for both RFS [HR: 0.482, (0.307-0.757), p=0.002) and OS (HR: 0.549, [0.348-0.867], p=0.010).*

Conclusions: *There are conflicting literature data regarding the survival benefit of adjuvant CTX for surgically treated STSs. However, appropriate patient selection may provide a significant survival benefit in RFS and OS with CTX in the adjuvant treatment of high-risk STSs.*

Key words: *adjuvant chemotherapy, high-risk, ifosfamide/doxorubicin, soft tissue sarcomas, survival*

Introduction

Soft tissue sarcomas (STSs) are extremely rare tumours, which account for less than 1% of all adult malignancies [1]. Standard treatment for localized and high-risk STSs consists of surgery and adjuvant radiotherapy (RT) [2,3]. RT can be applied both in the pre-operative and post-operative periods [4]. A recent meta-analysis indicated that RT reduced local recurrence (LR) and improved overall survival (OS) of retroperitoneal STSs, and reduced LR of STSs located in other regions [5]. The survival benefit of chemotherapy (CTX) as an adjuvant treatment for STSs is inconsistent due to adjuvant STS trials that studied the effectiveness of CTX, providing conflicting findings. For example, the multi-centre randomized European Organisation for Research and Treatment of Cancer (EORTC) 62931 study on macroscopically resected grade II-III STSs observed no benefit in terms of relapse-free survival (RFS) and OS with adjuvant CTX (doxorubicin/ifosfamide combination) [6]. In

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contrast, the Italian Sarcoma Group (ISG) study on high-risk surgically treated STSs reported significant disease-free survival (DFS) and OS benefits of five cycles of doxorubicin/ifosfamide combination in the adjuvant setting [7]. According to a meta-analysis performed by the Sarcoma Meta-analysis Collaboration (SMAC), doxorubicin used alone or in combination with other chemotherapeutic agents for adjuvant purposes significantly improved RFS with CTX and appeared to improve OS [8]. A study based on data from the French Sarcoma Group observed significantly better metastasis-free survival and OS in grade III cases with adjuvant CTX [9]. In a pooled analysis of two randomized studies conducted by the EORTC, doxorubicin-based adjuvant CTX was associated with improved RFS only in male patients and those older than 40 years [10]. In the same analysis, RFS and OS in R1 resected tumours with adjuvant CTX were significantly better than without adjuvant CTX [10]. Due to these conflicting data, treatment guidelines cannot strongly recommend adjuvant CTX in surgically treated STSs. In the current study, we aimed to retrospectively investigate the effect of adjuvant doxorubicin/ifosfamide combination on OS and RFS in patients with high-risk surgically treated STSs.

Methods

Data on non-pediatric patients (>15 years) who underwent curative-intent surgery for STSs between 1990 and 2019 in our hospital, a tertiary referral center, were retrospectively evaluated. Patients diagnosed with stage II/grade III and stage III/grade II-III STSs were identified as a high-risk group. Patients diagnosed with high-risk STSs who had completely resected, marginally resected, or R1 resected tumours and received adjuvant RT were included in the study. The exclusion criteria were as follows: neoadjuvant CTX; post-operative macroscopic residual cancer (R2 resection); stage I, grade I or stage II with grade II tumours; histopathological subtypes (e.g. rhabdomyosarcomas, uterine leiomyosarcomas, dermatofibrosarcoma protuberans, GISTs, carcinosarcomas and Ewing sarcomas) requiring different treatment approaches; patients who did not receive adjuvant RT; and patients who received adjuvant CTX other than doxorubicin/ifosfamide combination. Patients with insufficient data in terms of histopathological evaluations or treatment modalities were also excluded from the study.

Data on patient age, sex, histological tumour subtype, tumour location, grade, stage, resection type (R0 or R1/marginal), and adjuvant treatment modality (RT or RT / CTX sequential therapy) were collected. Also, disease recurrence locations, dates of relapse and death were recorded. Patients with surgically treated high-risk STSs and who received adjuvant RT were divided into two groups according to their status of receiving adjuvant CTX. Group A was formed from patients who received only adjuvant RT. Group B consisted of patients who received adjuvant CTX (ifosfamide 7,500–9,000 mg/m^2 and doxorubicin 60 mg/m^2, every 21 days) after adjuvant RT. The main patient and tumour characteristics, RFS and OS of the two groups were compared.

Statistics

Descriptive statistics were used to show the distribution of the main characteristics in the population. The differences of the groups in terms of categorical and ordinal parameters were evaluated using Chi-Square and Mann-Whitney *U* tests, respectively. Overall survival (OS) was defined as the time interval between the histological diagnosis and time of death or last follow-up. Relapse-free survival (RFS) was defined as the time interval between surgery and local recurrence or distant metastasis. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. The Cox regression model was carried out using multivariate analyses. Variables that may influence sur-

Table 1. Main patient and tumour characteristics of study population (n=143)

Characteristics	*n (%)*
Sex	
Female	58 (40.6)
Male	85 (59.4)
Age, median (range)	49.9 (17.4-86.4)
Pathological subtype	
Pleomorphic sarcoma	46 (32.2)
Liposarcoma	24 (16.8)
Synovial sarcoma	22 (15.4)
MPNST	15 (10.5)
Leiomyosarcoma	11 (7.7)
Fibrosarcoma	6 (4.2)
Angiosarcoma	3 (2.1)
Others	16 (11.2)
FNCLCC grade	
Grade II	15 (10.5)
Grade III	128 (89.5)
Tumor location	
Extremity	117 (81.8)
Non-extremity	26 (18.2)
Stage	
Stage II	29 (20.3)
Stage III	114 (79.7)
Resection type	
Complete resection	112 (78.3)
R1/Marginal	31 (21.7)
Adjuvant treatment modality	
RT	69 (48.3)
RT / CTX	74 (51.7)

FNCLCC: Federation Nationale des Centres de Lutte Contre le Cancer; MPNST: Malignant peripheral nerve sheath tumor; RT: radiotherapy; CTX: chemotherapy

vival were included in the univariate analysis. These variables were sex, age (categorized as lower than median or higher than median), grade, stage, tumour location (extremity or non- extremity), resection type (complete or R1/marginal), and adjuvant treatment modality (RT or RT and CTX in a sequential manner). Variables associated with survival with a p value <0.20 in the univariate analysis were included in the multivariate regression analysis. The analyses were done using SPSS software (SPSS for Windows, version 24.0. Chicago, SPSS Inc.). All statistical tests were two-sided, and p <0.05 indicated statistical significance.

Results

Of 461 patients who underwent curative-intent surgery, 143 were eligible for inclusion the study. The median follow-up time was 30.6 months (range: 1.4-304.4).

Patient and tumour characteristics

The main patient and tumour characteristics of the 143 patients with a median age of 49.9 years (17.4-86.4), most of whom were males (85/59.4%), are shown in Table 1. The most common histological subtypes were pleomorphic sarcomas (46/32.2%), liposarcomas (24/16.8%), synovial sarcomas (22/15.4%) and malignant peripheral nerve sheath tumours (15/10.5%). Most of the patients had a grade III tumour (128/89.5%) and stage III disease (114/79.7%). The majority of the tumours were located in extremities (117/81.8%). Complete resection (112/78.3%) was performed in most of the patients.

Group A and group B had 69 and 74 patients, respectively. There were more male patients in group A (49/71% vs. 36/48.6%) than in group B (p=0.010). There were more older patients in group A (median, 53.2 vs. 48.4, p=0.001) than in group B, and the proportion of stage III patients in group A was lower than that in group B (72.5% vs. 86.5%, p=0.040). There was no statistically significant between-group difference in the tumour grade, tumour location, complete resection, or recurrence rates. The results of a comparative evaluation of the main patient and tumour characteristics of the two groups are displayed in Table 2.

All 74 patients who received adjuvant CTX received at least one cycle of CTX. The median number of cycles was 4 (range: 1-6), and 65 (87.8%) patients received 3-6 cycles of adjuvant CTX. Dose reduction was not required in 49 (66.2%) patients, and 46 (62.2%) patients were able to complete adjuvant CTX within the planned time. In 39 (52.7%) patients, there was no grade III-IV CTX-related toxicity. There were no treatment-related deaths.

Table 2. Comparative main patient and tumour characteristics according to treatment groups

Characteristics	*Group A (n=69)* *n (%)*	*Group B (n=74)* *n (%)*	*p*
Sex			
Male	49 (71.0)	36 (48.6)	0.010
Female	20 (29.0)	38 (51.4)	
Age, median (range)	53.2 (17.4-86.4)	48.4 (19.4-70.4)	0.001
FNCLCC grade			
Grade II	9 (13.0)	6 (8.1)	0.417
Grade III	60 (87.0)	68 (91.9)	
Tumor location			
Extremity	56 (81.2)	61 (82.4)	1.0
Non-extremity	13 (18.8)	13 (17.6)	
Stage			
Stage II	19 (27.5)	10 (13.5)	0.040
Stage III	50 (72.5)	64 (86.5)	
Resection type			
Complete resection	51 (73.9)	61 (82.4)	0.231
R1 / Marginal	18 (26.1)	13 (17.6)	
Recurrence ratios			
All recurrences	43 (62.3)	36 (48.6)	0.130
Local recurrence	19 (27.5)	19 (25.7)	0.851
Distant metastasis	33 (47.8)	25 (33.8)	0.092

FNCLCC: Federation Nationale des Centres de Lutte Contre le Cancer.

Survival

The median RFS was 18.2 months (95% CI, 11.9-43.4) in group A and 27.2 months (95% CI, 17.6-36.8) in group B (p=0.004). Figure 1 presents a graph comparing RFS in the two groups according to the adjuvant treatment modality. The univariate analysis revealed no difference in RFS according to the following variables: sex, age (lower than median vs. higher than median), tumour grade (II vs. III), tumour location (extremity vs. non-extremity), tumour stage (II vs. III) or resection type (complete vs. R1/marginal) (Table 3). The 60-month RFS rates were 37.9% and 9.2% for complete and R1/marginal resected tumours, respectively.

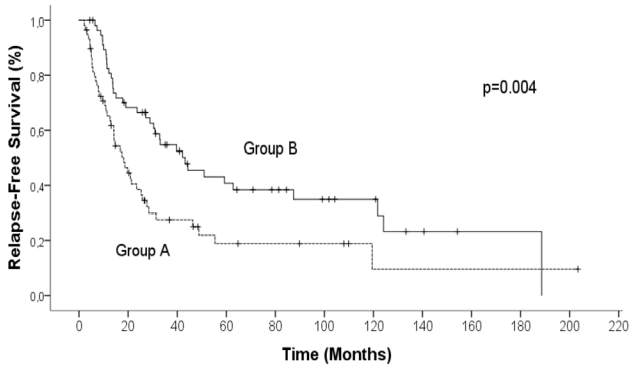

Figure 1. Relapse-free survival of 69 patients treated with adjuvant RT (Group A) and 74 patients treated with adjuvant RT / CTX (Group B).

The median OS was 45.6 months (95% CI, 26.4-64.8) in group A and 110.1 months (95% CI, 44.3-175.8) in group B (p=0.007). Figure 2 shows a graph comparing OS in the two groups according to the adjuvant treatment modality. Also, in the univariate analysis, age (lower than median vs. higher than median) and resection type (complete vs. R1/marginal) affected OS. The univariate analysis revealed no difference in OS according to the following variables: sex, grade (II vs. III), tumour location (extremity vs. non-extremity), or stage (II vs. III).

Table 3 presents the results of the univariate analysis including factors that may affect RFS and OS.

The results of the multivariate Cox regression analysis, which included factors that affected (p <0.2) RFS and OS in the univariate analysis, are shown in Table 4. The adjuvant treatment modality

Table 3. Results of univariate analysis ıncluding factors that may affect RFS and OS

Factor (*n, %*)	*RFS* *Median (Range)* *(95% CI)*	*p*	*OS* *Median (Range)* *(95% CI)*	*p*
Sex				
Male (85, 59.4%)	23.5 (14.8-32.2)	0.421	49.5 (43.1-56.0)	0.392
Female (58, 40.6%)	31.4 (11.4-51.4)		90.7 (37.2-144.3)	
Age				
≥49,9* (72, 50.3%)	23.7 (11.7-35.7)	0.521	47.9 (30.5-65.3)	0.037
<49,9* (71, 49.7%)	30.4 (15.0-45.8)		99.5 (26.6-172.4)	
FNCLCC grade				
Grade II (15, 10.5%)	55.4 (0.0-124.0)	0.688	165.9 (12.5-319.2)	0.424
Grade III (128, 89.5%)	27.2 (18.6-35.8)		52.8 (41.1-64.6)	
Tumor location				
Extremity (117, 81.8%)	28.9 (20.2-37.6)	0.409	58.5 (9.1-107.8)	0.321
Non-extremity (26, 18.2%)	21.0 (16.5-25.5)		50.1 (32.1-64.6)	
Stage				
Stage II (29, 20.3%)	28.5 (15.3-41.8)	0.597	159.1 (5.5-312.8)	0.253
Stage III (114, 79.7%)	27.2 (16.6-37.8)		52.7 (39.3-66.1)	
Resection type				
R1 / Marginal (31, 21.7%)	28.9 (14.4-43.4)	0.138	47.4 (22.9-72.0)	0.024
Complete resection (112, 78.3%)	27.2 (17.6-37.8)		75.8 (22.8-128.8)	
Adjuvant treatment modality				
RT (69, 48.3%)	18.2 (11.9-43.4)	0.004	45.6 (26.4-64.8)	0.007
RT / CTX (74, 51.7%)	27.2 (17.6-36.8)		110.1 (44.3-175.8)	

RFS: relapse-free survival; OS: overall survival; CI: confidence interval; *, median age; FNCLCC: Federation Nationale des Centres de Lutte Contre le Cancer; RT: radiotherapy; CTX: chemotherapy. Bold numbers denote statistical significance.

Table 4. Multivariate Cox regression analysis results including factors that may affect RFS and OS

Factor (n, %)	*HR for RFS 95% CI)*	*p*	*HR for OS (95% CI)*	*p*
Age*				
≥49,9 (72, 50.3%)	N/E		Reference	0.035
<49,9 (71, 49.7%)			0.614 (0.390-0.967)	
Resection type				
R1 / Marginal (31, 21.7%)	Reference	0.065	Reference	0.009
Complete resection (112, 78.3%)	0.627 (0.382-1.029)		0.505 (0.303-0.844)	
Adjuvant treatment modality				
RT (69, 48.3%)	Reference	0.002	Reference	0.010
RT / CTX (74, 51.7%)	0.482 (0.307-0.757)		0.549 (0.348-0.867)	

HR: Hazard ratio; RFS: relapse-free survival; OS: overall survival; CI: confidence interval; *, median age; RT: radiotherapy; CTX: chemotherapy; N/E: not evaluated.

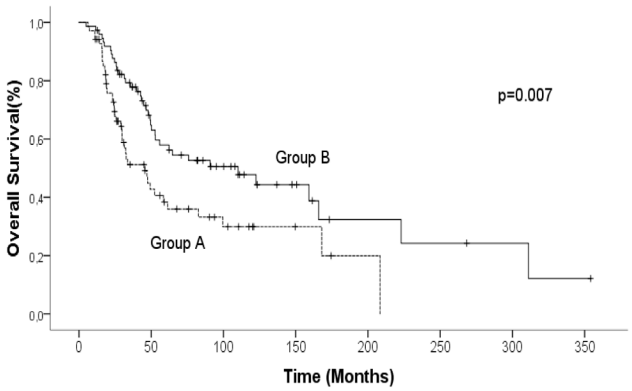

Figure 2. Overall survival of 69 patients treated with adjuvant RT (Group A) and 74 patients treated with adjuvant RT / CTX (Group B).

was the only independent predictive factor of RFS in the multivariate analysis. Age, resection type and adjuvant treatment modality were independent predictive factors for OS.

Discussion

In our study, we found that RFS and OS benefit was obtained with adjuvant ifosfamide/doxorubicin combination CTX in a highly homogeneous and high-risk patient population who were surgically treated and diagnosed with stage II-grade III and stage III-grade II / III soft tissue sarcoma.

In the EORTC 62931 study, which is one of the main studies on the adjuvant treatment of STSs, ifosfamide/doxorubicin combination did not benefit either OS or RFS in the adjuvant treatment of STSs [6]. The findings of the EORTC 62931 study were critical, given that it was a large study, and the results augmented the uncertainty about the benefit of adjuvant CTX in STSs treatment [6]. In our study, we observed a significant survival benefit in terms of both OS and RFS in high-risk patients. Our study differed from the EORTC 62931 study in terms of the composition of the study population. In the EORTC 62931 study, patients diagnosed with grade II and III STSs were included, regardless of the disease stage [6]. Although grade I patients were excluded from the EORTC 62931 study, after central evaluation, 7% of patients receiving CTX were found to have grade I disease. In contrast to the EORTC 62931 study, in which 74% of the patients received RT, all the patients in our study received RT [6]. Another difference between the two studies was in the chemotherapeutic doses used. Although the total dose of doxorubicin administered in the EORTC 62931 study was higher than that in our study, the dose of ifosfamide was lower [6]. As no studies have compared the efficacy of different doses of chemotherapeutics used in STSs adjuvant therapy, we cannot conclude that differences in the dose administered affect survival. According to a review by Benjamin, the following factors may affect the findings of the EORTC 62931 study on the survival of STSs patients: the number of non-extremity tumours, insufficient surgical resection, the inclusion of low-grade tumours, and low ifosfamide doses and application densities [11]. The SMAC meta-analysis demonstrated RFS benefit and a better OS trend with adjuvant CTX in the treatment of STSs [8]. However, 6 of the 14 trials included in this meta-analysis studied the efficacy of single-agent doxorubicin, not combination [8]. In another meta-analysis, Pervaiz et al observed a non-significant reduction in mortality with doxorubicin-based adjuvant CTX, as well as a significant decrease in mortality with ifosfamide/doxorubicin combination therapy (HR: 0.56, 95% CI, 0.36-0.85; p=0.01) [12]. The existence of stud-

ies with doxorubicin monotherapy in the SMAC meta-analysis is a weakness of this meta-analysis. However, some other weaknesses of the SMAC meta-analysis (N=1,568 patients) included the inclusion of patients with low-grade tumours (5%), tumours smaller than 5 cm (18%), and a low level of RT (47%) [8]. Neither the patient population in the EORTC 62931 study nor the SMAC meta-analysis appear to be homogeneous enough to assess the efficacy of adjuvant CTX in STSs.

In the ISG study, in which patient recruitment was stopped early due to the early demonstration of a clear DFS benefit, patients diagnosed with high-risk STSs received adjuvant doxorubicin (60 mg/m^2)/ifosfamide (9 g/m^2) combination [7]. This study demonstrated a significant benefit in terms of both OS (median 75 vs. 46 months, p=0.03) and DFS (median 48 vs. 16 months, p=0.04) among those who received adjuvant CTX as compared to those who did not receive adjuvant CTX [7]. The patient recruitment criteria in the ISG study were quite similar to those in our study. In another large study (N=1,513), using data from the French Sarcoma Group database, the researchers evaluated the effect of adjuvant CTX on survival in operated STSs [9]. This study did not observe an OS benefit in those with grade II tumours (HR: 0.8 [0.6-1.1], p=0.15) but found a significant OS benefit in those with grade III tumours (HR: 0.6 [0.5–0.8], p=0.0002) as compared to OS in a control group [9]. Based on the findings of a recently published prospective single-arm non-randomized phase II study (N=150), the researchers asserted that adjuvant CTX for patients with high-risk operated STSs treated with post-operative RT and CTX (similar to group B in our study) provided a survival benefit as compared to historical control groups [13]. Finally, in a prospective study from MSKCC (N=5,436) multi-agent neoadjuvant or adjuvant CTX conferred a survival benefit in high-risk patients with tumours of >5 cm and in those receiving RT [14]. To evaluate the efficacy of adjuvant CTX in STS patients in a comprehensive manner, a sample group with a high-risk of recurrence and treated with RT, which is the standard adjuvant therapy for high-risk STSs, should be included. The present study included a high-risk population that received adjuvant RT. We found a statistically significant survival benefit in terms of both RFS and OS in patients who received adjuvant CTX.

The majority of the patients underwent at least 3 cycles of CTX. In a prospective study involving high-risk patients by Gronchi et al, 3 cycles of epirubicin/cyclophosphamide combination given before surgery was compared adding 2 post-operative courses of the same combination CTX to the same treatment scheme [15]. The probabilities of OS in 5-year post-treatment were 0.68 (95% Cl, 0.60-0.75) and 0.71 (95% Cl, 0.63-0.77), demonstrating non-inferiority of 3 cycles to 5 cycles CTX [15]. Long-term follow-up results of this study population, with a median follow-up of 117 months, confirmed this non-inferiority [16]. Although CTX was administered in the pre-operative period in this study, this study suggested that the CTX density in our study might be sufficient to evaluate the efficacy of the treatment.

A long-term prospective study by Brennan et al, based on data from 10,000 patients, revealed prognostic features in patients with STSs who underwent surgery [17]. According to this study, tumour location, grade, and size were the primary prognostic factors affecting survival [17]. In our study, we evaluated various factors (age, sex, stage, grade, location, resection type and adjuvant treatment modality) that may predict survival. Receiving adjuvant CTX was the only independent predictive factor of RFS, with statistical significance. Although not statistically significant, R0 resection seemed to provide a RFS benefit. The small number of patients in our study may explain the latter finding. In our study, young age, R0 resection and adjuvant CTX were independent predictive factors for OS. As our study was retrospective, there may exist patient selection bias. Although the patients in group B were relatively younger than those in group A, there were more grade III and stage III patients in group B than in group A. So, the relapse risk in group B appeared to be higher than that in group A, although the median RFS and median OS of group B patients were significantly longer than that of group A patients. Also, distant metastasis was less common in group B than in group A, although this finding did not reach statistical significance. We speculate that these findings are evidence for the protective effect of adjuvant CTX for distant metastasis.

Numerous prognostic nomograms have been developed for STSs [18]. However, data in support of the predictive value of these nomograms for adjuvant CTX in the treatment of STSs are lacking. Previous research showed that the Sarculator, one of these nomograms, could determine variation in perioperative CTX results in patients with high-risk STSs and provide an improved prognostic classification [19]. The application of these nomograms in different STSs patient populations may yield more accurate results in evaluating the effectiveness of adjuvant CTX for STSs. Another critical factor that requires investigation is the possibility that the benefit of adjuvant CTX may differ according to different histological subtypes. The number of each

histological subgroup in our study was insufficient to draw a firm conclusion in this regard.

In conclusion, although our study was retrospective and had a small number of patients, it showed that adding CTX to RT in the adjuvant therapy provided a survival benefit in terms of OS and RFS in highly homogeneous and high-risk surgically treated STS patients. There is a need for randomized prospective controlled studies with homogeneous histological subgroups and clear prognostic and predictive classification to evaluate the efficacy of adjuvant CTX in STSs.

Conflict of interests

The authors declare no conflict of interests.

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