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LONG-TERM OUTCOME OF SOFT TISSUE SARCOMAS TREATED WITH MESNA-DOXORUBICIN-IFOSFAMID-DACARBAZINE REGIMEN (MAID): A RETROSPECTIVE STUDY FROM A SINGE INSTITUTION

Mesna-Doxorubisin-İfosfamid-Dakarbazin (MAID) ile Tedavi Edilen Yumuşak Doku Sarkom Hastalarimizin Uzun Dönem Takip Sonuçları: Tek Merkez Deneyimi

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Our study was carried out in the medical oncology department of Çukurova University.

Abstract

Aim: Soft tissue sarcomas (STSs) account for 1% of cancers in the adult population. The treatment of choice is surgery but chemotherapy and/or radiotherapy are frequently used due to aggressive cancer behavior or incomplete surgery. Doxorubicin-based regimens are the most frequently used chemotherapy combinations but real-life data about the efficacy and safety of these agents in our country is limited. We aimed to present clinicodemographic and prognostic features of STS cases treated with mesna, doxorubicin, ifosfamide, dacarbazine (MAID regimen).

Materials and Methods: A total of forty-five STS cases who were diagnosed between 2007-2016 and treated with the MAID regimen as the initial therapy in Cukurova University were analyzed retrospectively. Associations between clinicodemographic parameters with overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan-Meier curves and with the log-rank test. Univariate-multivariate analyses were used to assess the prognostic values of parameters for OS-PFS.

Results: The median age of the patients was 49 and the most common STS subtypes were undifferentiated pleomorphic carcinoma (37.8%) followed by liposarcoma (17.8%) and leiomyosarcoma (13.3%). According to the AJCC TNM stages, 15.6% stage 1-2, 53.3% stage 3, and 31.1% stage 4 disease. The median PFS/OS were 17/39 months, respectively. The 5-year PFS/OS rates were 14%/32.5%, respectively. In univariate analyses, mitosis, necrosis, stage, and surgery were both prognostic for PFS-OS. However, in multivariate analysis, only stage was an independent prognostic factor both for PFS-OS.

Conclusion: Stage was the only independent prognostic factor for both PFS-OS in patients with STS who received the MAID chemotherapy as initial therapy.

Keywords: Soft tissue sarcoma, prognosis, doxorubicin.

Öz

Amaç: Yumuşak doku sarkomları (STS) erişkin kanserlerin %1 ini oluşturan agresif kanserlerdendir. Temel tedavisi cerrahi rezeksiyon olmakla beraber kemoterapi ve radyoterapide uygun hastalarda kullanılmaktadır. Doxorubisin temelli tedaviler en sık kullanılan kemoterapi rejimleridir ancak bu rejimlerle ilgili gerçek hayat verisi ülkemizde çok azdır. Bizde bu sebeple mesna-doxorubisin-ifosfamid-dakarbazin içeren MAID rejimi başlangıç tedavisi olarak alan STS olgularımızın yaşam sürelerini tespit etmek ve prognostik olabilecek klinikodemografik özellikleri ortaya çıkarmak istedik.

Materyal ve Metot: Çukurova Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Anabilim Dalı'nda 2007-2016 yılları arasında Yumuşak doku sarkomu tanısı alan ve başlangıç tedavisi olarak MAID rejimi uygulanan 45 hasta retrospektif olarak çalışmaya dahil edildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) ile klinikopatolojik parametreler arasındaki ilişkiler Kaplan-Meier eğrileri kullanılarak analiz edildi ve log-rank testi ile karşılaştırıldı. Tek değişkenli ve çok değişkenli analiz PFS ve OS için prognostik faktörleri tespit etmek amacıyla kullanılmıştır.

Bulgular: Median yaş 49 olup en sık görülen alt tip andiferansiye pleomorfik karsinom (%37,8) ardından liposarkom (%17,8), leiomyosarkom (%13,3) gelmektedir. Hastaların %15,6'sı evre 1-2, %53,3'ü evre 3 ve %31,1'i evre 4'tü. Median PFS ve OS 17 ay ve 39 ay olup 5 yıllık PFS ve OS oranları %14 ve %32,5 dur. Yaş, cinsyet ve grade in prognostik önemi saptanmamış olup univariate analizlere göre mitoz, nekroz, AJCC TNM evresi ve cerrahi hem PFS hem de OS için prognostiktir. Bununla beraber multivariate analizlere göre sadece AJCC TNM evresi hem PFS hem de OS için bağımsız prognostik faktördür.

Sonuç: Başlangıç tedavisi olarak MAID kemoterapisi alan olgularda PFS ve OS için tek bağımsız prognostik faktör AJCC TNM evredir.

Anahtar Kelimeler: Yumuşak doku sarkomu, prognostik faktörler, doxorubisin.

Introduction

Soft tissue sarcomas (STSs) develop from mesenchymal tissues and there are more than 50 subtypes with different outcomes[1]. The most common subtypes are undifferentiated pleomorphic sarcoma (UPS), gastrointestinal stromal tumor (GIST), liposarcoma (LPS), and leiomyosarcoma (LMS)[2]. The prognosis is generally poor and surgical treatment is the priority for the management of these patients.

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Local radiotherapy and systemic adjuvant chemotherapy are modalities used with respect to the risk factors to prevent local and systemic relapses[3, 4]. However relapse is seen in about 50% of the cases despite these multimodal treatments and novel therapeutic approaches and the median survival is 12-18 months in cases with relapse[5, 6].

The MAID regimen consists of uromitexan, doxorubicin, ifosfamide, and dacarbazine and is used both during adjuvant therapy and in cases with metastasis as recommended in the guidelines[7, 8]. Herein, we aimed to present the demographic findings, prognostic factors, treatment response rates, and survival times of our cases with STS who were treated using the MAID regimen.

METHODS

A total of 45 patients diagnosed with non-GIST STS and treated with the MAID regimen as the initial therapy were evaluated retrospectively between November 2007 and February 2016. Clinical, demographic, and histopathological data including age, sex, histological subtype, pathological features, and applied treatments were obtained from the patient archive files. The patients were staged according to the American Joint Committee on Cancer (AJCC) TNM 2017 8th edition STS system. Histologic grading was made according to Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system.

The MAID chemotherapy regimen was administered as follows: mesna 2500 mg/m^2/day by continuous intravenous (IV) infusion on days 1-4, adriamycin (doxorubicin) 20 mg/m^2/day by continuous IV infusion on days 1-3, ifosfamide 2000 mg/m^2/day by continuous IV infusion on days 1-3, and dacarbazine 250 mg/m^2/day by continuous IV infusion on days 1-4 with or without granulocyte colony-stimulating factor 5 µg/g/kg/day starting on day 5.

All procedures performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The participants were informed about the study and they provided written consents and ethical approval was obtained from the local ethical committee.

Statistical Analysis

Overall survival (OS) was defined as the time from the date of diagnosis to the time of death from any cause and censored at the date of last follow-up for survivors. Progression-free survival (PFS) was defined as the date of diagnosis to the time of recurrence or death and censored at the date of the last follow-up for survivors without recurrence. The associations between clinical and histopathological parameters with OS and PFS were analyzed using Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate cox-regression analyses were performed to determine the effects of probable prognostic factors, including mitosis, necrosis, AJCC TNM stage, and surgery on OS and PFS. Hazard ratios (HRs) were estimated from cox-regression analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All analyses were performed using the IBM SPSS v.21 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 45 patients (26 females (57.8%) and 19 males (42,2%)) with a median age of 49 (range 16-78) were included. The frequencies of

sarcoma subtypes were as follows: 17 (37.8%) undifferentiated sarcoma, 8 (17.8%) liposarcoma, 6 (13.3%) leiomyosarcoma, 5 (11.1%) synovial sarcoma, 4 (8.9%) malignant peripheral nerve sheath tumor (MPNST), 2 (4.4%) rhabdomyosarcoma, 2 (4.4%) fibrosarcoma, and 1 (2.2%) angiosarcoma. Five cases (11.1%) had grade I, 12 (26.5%) had grade II, and 28 (62.2%) had grade III disease. The number of mitotic figures in 10 representative high power fields were between 0 and 9 in 9 (20%) cases, between 10 and 19 in 11 (24.4%) cases, and more than 20 in 25 (55.6%) cases. In the pathological examination, necrosis was absent in 19 (42.2%) cases, less than 50% in 10 (22.25%) cases, and more than 50% in 16 (35.6%) cases. The median tumor diameter was 10 cm and the tumor diameter was greater than 5 cm in 39 (84.4%) cases. The disease stage was I-II in 7 (15.6%), stage III in 24 (53.3%), and stage IV in 14 (31.1%) of the cases. The majority of the tumors were localized to the extremities (62.2%). The remaining tumors were visceral (20%), truncal (8.9%), or retroperitoneal (8.9%). The clinical and pathological findings are shown in Table 1. Metastasis was detected at the time of diagnosis in 14 (31.1 %) cases and half of these metastases were in the lungs (50%). Metastatic site was liver in four (28.5%) cases and retroperitoneum in three (21.5%) cases. Surgical resection was performed in 36 (80%) cases and the surgical margin was found to be positive in five cases (13.9%). The MAID regimen was administered to 10 (22.2%) cases as neoadjuvant, 21 (46.6%) cases as adjuvant, and 14 (31.1%) cases in the metastatic setting. Patients with locally/locally advanced disease received 4 cycles as adjuvant and neadjuvant, whereas metastatic patients received an average of 6 cycles MAID regimen until progression or toxicity. Complete response in 4 (8.9%) patients, partial response in 8 (17.8%) patients, stable disease in 17 (37.7%) patients, and progressive disease in 16 (35.5%) patients were detected after administration of the MAİD regimen. Gemcitabine-docetaxel combination was administered as second line chemotherapy in 69.2% of the cases and pazopanib treatment was used as a third-line chemotherapy in 70% of the cases. Radiotherapy was applied to 19 (42.2%) cases.

The main side effects of the MAID chemotherapy included bone marrow suppression, nausea/vomiting, and alopecia; and the incidences of these side effects were 90%, 85%, and 70%, respectively. Grade III and IV bone marrow suppression, nausea/vomiting, and alopecia were detected in 35%, 20%, and 30% of the cases, respectively. Cardiac toxicity, liver damage, hematuria, and impaired renal function were rarely observed.

The median duration of follow up was 39 months (range 5-95). A total of 34 (75.6%) cases had progressive disease and 26 (57.8%) cases died during the study period.

Table 1. Baseline clinic and pathologic characteristics of 45 patients with soft tissue sarcomas

	N (%)
Age	
Median (range)	49 ± 15 (16-78)
<50	21 (46.7)
≥50	24 (53.3)
Gender	
Female	26 (57.8)
Male	19 (42.2)
Histological subtype	
Undifferentiated sarcoma	17 (37.8)
liposarcoma	8 (17.8)
Leimyosarcoma	6 (13.3)
Synovial sarcoma	5 (11.1)
MPNST	4 (8.9)
Rabdomyosarcoma	2 (4.4)
fibrosarcoma	2 (4.4)
Angiosarcoma	1 (2.2)
Grade	
1	5 (11.1)
2	12 (26.7)
3	28 (62.2)
Mitosis (*10)	
0-9	9 (20)
10-19	11 (24.4)
≥20	25 (55.6)
Necrosis	
No	19 (42.2)
< %50	10 (22.2)
≥ %50	16 (35.6)

Table 1. Baseline clinic and pathologic characteristics of 45 patients with soft tissue sarcomas (Continue)

Tumor size	
Median (range)	10 (4-20)
<5 cm	7 (15.6)
≥5 cm	38 (84.4)
AJCC TNM Stage	
1-2	7 (15.6)
3	24 (53.3)
4	14 (31.1)
Location	
Femur	21 (46.7)
Arm	3 (6.7)
Cruris	4 (8.9)
Sacrum	4 (8.9)
Viscera	9 (20)
Retroperitonium	4 (8.9)
Site of metastasis (n:14)	
Lung	7 (50)
Liver	4 (28.5)
Retroperitoneum	3 (21.5)
Surgery	
No	9 (20)
Yes	36 (80)
Surgical margin (n:36)	
Negative	31 (86.1)
Positive	5 (13.9)
Neoadjuvant chemoterapy	
No	35 (77.8)
Yes	10 (22.2)
Adjuvant Radiotherapy	
No	26 (57.8)
Yes	19 (42.2)
Response to MAİD regimen	
CR	4 (%8,9)
PR	8 (%17,8)
SD	17 (37,7)
PD	16 (35,5)
Second line treatment (n: 28)	
Gemcitabine+docetaksel	18 (69.2)
Irinotecan+vincristine	5 (19.2)
Pazopanib	3 (11.6)
Third line therapy (n:10)	
Pazopanib	7 (70)
Temozolamide	3 (30)
Progression	
No	11 (24.4)
Yes	34 (75.6)
Status	
Alive	19 (42.2)
Dead	26 (57.8)

MPNST; malignant peripheral nerve sheath tumor, AJCC; American Joint Committee on Cancer, PD; Progressive Disease, CR; Complete response, PR; Partial response, SD; Stabil disease, PD; Progressive disease

The median PFS and OS of the study population were 17 and 39 months and the rates of five year PFS and OS were 14% and 32.5%, respectively. The rates of five year OS were 66%, 30%, and 8% in cases with stage I-II, stage III, and stage IV disease, respectively. The rate of five year PFS was 20% in cases with non-metastatic disease.

The rates of overall response and disease control in cases with metastatic disease were 15% and 58%, respectively. The clinical and pathologic characteristics and PFS and OS rates in the study population are shown in Table 2. There was no association between age, sex, or grade and survival times (PFS: p=0.24, p=0.495, and p=0.178; OS: p=0.499, p=0.876, p=0.241, respectively). However, mitosis and necrosis rates were associated both with PFS (p=0.021, p=0.033, respectively) and OS (p<0.001, p<0.001, respectively). Although the median survival time has not been reached in cases with a tumor diameter less than 5 cm, mean PFS and OS times were longer than that in cases with a tumor diameter of more than 5 cm (p=0.007 and p=0.032, respectively). Similarly, the mean PFS and OS times were longer in cases with stage I-II disease than cases with stage III-IV disease (PFS: 72, 27, 15 months, p=0.001 and OS: 72, 54,8, 33,9 months, p= 0.029) (Figure 1). The median PFS was significantly longer and the median OS was insignificantly longer in cases with extremity sarcomas than those with sarcomas of other localizations (OS: 47 vs. 27 months, p=0.278 and PFS: 20 vs. 7 months, p=0.002, respectively). Both the median PFS and OS were significantly longer in cases who underwent surgical resection (PFS 18 vs. 6 months, p<0.001 and OS 47 vs. 12 months, p=0.014). The PFS and OS were shorter in cases who received radiotherapy in addition to chemotherapy compared with those who did not receive radiotherapy but the differences were not statistically insignificant (p=0.298, p=0.342, respectively).

The association of clinicopathological variables with PFS and OS are shown in Table 3. While an abundance of mitosis and necrosis and a higher AJCC TNM stage were associated with a shorter PFS and OS, a history of surgery was associated with longer PFS and OS in univariate analyses. Also, tumor size and localization were associated only with PFS; and response to first treatment was associated only with OS in univariate analyses. In the multivariate analysis, only the AJCC TNM stage was independent prognostic factor for both PFS (HR: 2.603; 95% CI: 1.257–

5.392. p= 0.010) and OS (HR: 2.242; 95% CI: 1.046–4.807. p= 0.038) and a higher AJCC TNM stage was associated with shorter PFS and OS.

Table 2. Overall and Progression-free survival times according to clinical and pathological parameters

			PFS			OS		
	Total(n)	**Total(%)**	**Mean**	**Median**	**p**	**Mean**	**Median**	***p***
Age								
<50	21	46.7	28.3	16	0.424	51.6	56	0.499
≥50	24	53.3	34	17		50.3	32	
Gender								
Female	26	57.8	29	16	0.495	50.1	47	0.876
Male	19	42.2	3.6	20		52.2	33	
Grade								
1	5	11.1	33.6	8	0.718	50.4	NR	0.241
2	12	26.7	37.4	16		60.4	NR	
3	28	62.2	27.2	17		48.7	27	
Mitosis								
0-9	9	20	41.6	19	**0.021**	70	NR	**<0.001**
10-19	11	24.4	50	NR		70	NR	
≥20	25	55.6	18.7	14		34.3	25	
Necrosis								
None	19	42.2	42	24	**0.033**	67.9	NR	**<0.001**
< %50	11	22.2	34.1	14		57.1	67	
≥ %50	15	35.8	14.7	16		24.4	24	
Tumor size								
<5 cm	7	30.1	64.8	NR	**0.007**	73.8	NR	**0.032**
≥5 cm	38	69.9	24.5	14		48.4	30	
AJCC TNM Stage								
1-2	7	15.6	72	NR	**0.001**	72	NR	**0.029**
3	24	53.3	27	17		54.8	33	
4	14	31.1	15	9		33.9	25	
Location								
Extremity	32	71.1	40.1	20	**0.002**	58.6	47	0.278
Other	13	28.9	14.8	7		41.7	27	
Surgery								
No	9	20	10.4	6	**<0.001**	26.1	12	**0.014**
Yes	36	80	36.3	18		59.5	47	
Radiotherapy								
No	26	57.8	36.7	16	0.298	58.5	56	0.342
Yes	19	42.2	21.4	17		44.4	30	
Response to first treatment								
PD	16	35.5	8.5	7	**<0.001**	32	23	**0.013**
No PD	29	64.5	43.5	24		63	67	
Overall	45	100	31.1	17		54.1	39	

AJCC; American Joint Committee on Cancer, PD; Progressive Disease

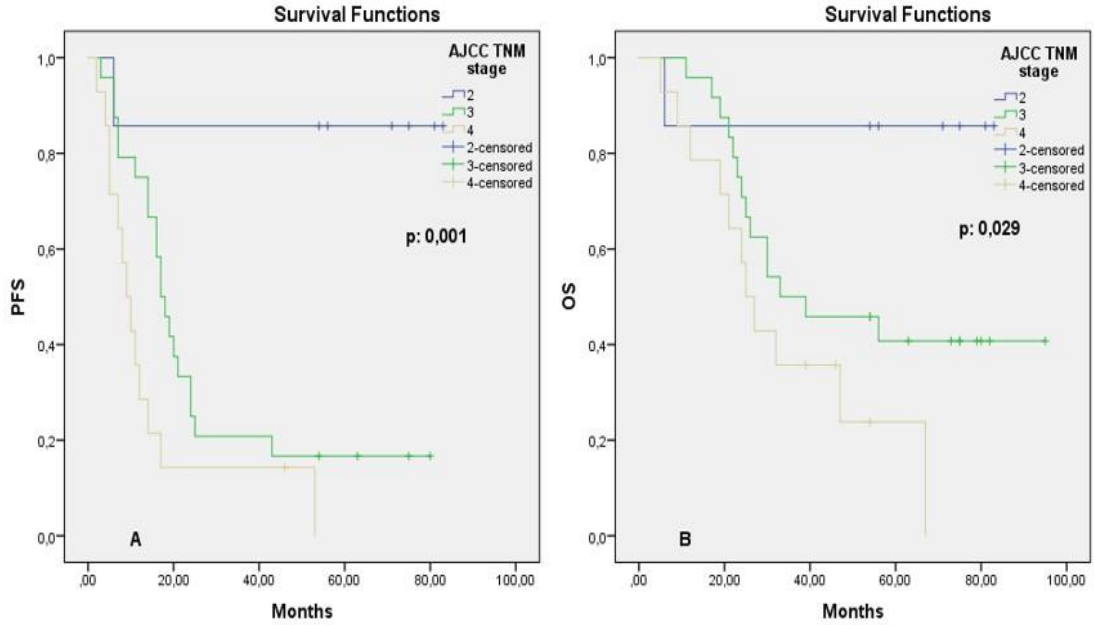

Figure 1. Kaplan-Meier curves for AJCC TNM stage. A: PFS, B: OS (AJCC: American Joint Committee on Cancer)

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for OS and PFS

OS	**Univariate**		**Multivariate**	
	HR	p	HR	p
Age (<50 vs ≥50)	0.769 (0.356-1.660)	0.503	-	-
Gender	1.062 (0.491-2.302)	0.877	-	-
Grade	1.632 (0.830-3.205)	0.155	-	**-**
Mitosis	3.688 (1.705-7.977)	**0.001**	1.739 (0.609-4.967)	0.302
Necrosis	3.043 (1.790-5.172)	**<0.001**	1.816 (0.832-3.962)	0.134
Tumor size (< 5 cm vs ≥ 5 cm)	6.598 (0.890-48.894)	0.065	-	-
AJCC TNM Stage	2.305 (1.228-4.327)	**0.009**	2.242 (1.046-4.807)	**0.038**
Location (extremity vs non-extremity)	1.392 (0.604-3.206)	0.437	-	**-**
Surgery (No vs Yes)	0.350 (0.145-0.843)	**0.019**	0.560 (0.225-1.397)	0.214
Response to first treatment (No PD vs PD)	1.897 (1.108-3.249)	**0.020**	1.438 (0.754-2.741)	0.270
PFS	Univariate		Multivariate	
	HR	p	HR	p
Age (<50 vs ≥50)	1.312 (0.666-2.584)	0.433	-	-
Gender	0.791 (0.399-1.569)	0.503	-	-
Grade	1.195 (0.695-2.053)	0.519	-	**-**
Mitosis	1.770 (1.056-2.968)	**0.030**	0.665 (0.328-1.348)	0.258
Necrosis	1.660 (1.098-2.512)	**0.016**	1.721 (0.948-3.125)	0.075
Tumor size (< 5 cm vs ≥ 5 cm)	5,599 (1,331-23,558)	**0.019**	2,068 (0.414-10,329)	0.376
AJCC TNM Stage	2.788 (1.605-4.841)	**<0.001**	2.603 (1.257-5.392)	**0.010**
Location (extremity vs non-extremity)	2.472 (1.215-5.030)	**0.013**	1.340 (0.569-3.158)	0.508
Surgery (No vs Yes)	0.244 (0.110-0.537)	**<0.001**	0.439 (0.175-1.097)	0.078
Response to first treatment (No PD vs PD)	1.564 (0.961-2.546)	0.072		

AJCC; American Joint Committee on Cancer, PD; Progressive Disease

DISCUSSION

The STSs are rare cancers of mesenchymal origin which are associated with aggressive behavior. Patients commonly die due to relapse or metastasis despite curative local treatments. Although new agents are in progress, the first-line chemotherapy is generally doxorubicin-based combinations. Herein, we present the factors predicting long term survival in patients with STSs who were treated using the MAID combination. While mitosis, necrosis, AJCC stage, and surgery were predictive for PFS and OS in univariate analysis, only AJCC stage was an independent predictive factor for PFS and OS in multivariate analysis in the present study.

The STSs have several subtypes with different biological properties and response rates to treatment options. However, it is difficult to design homogenous studies in patients with these subtypes of STSs due to the rarity of these neoplasias [9]. For these reasons, studies in patients with STSs have concurrently investigated different subtypes as in the present study, thus the outcomes of these studies are somehow conflicting. Neoadjuvant chemotherapy did not improve survival in 134 cases with high grade STSs irrespective of tumor diameter, grade, local recurrence, or adequacy of resection [10]. On the other hand, neoadjuvant MAID combination in addition to local radiotherapy improved the rate of 5 year freedom from distant metastasis, DFS, and OS in a study performed among 48 cases with high grade extremity sarcoma (75% vs. 44%, p=0,0016, 70% vs. 42%, p=0,0002, 87% vs. 58%, p=0,0003, respectively) [11]. Sarcoma meta-analysis collaboration (SMAC) covering 14 studies in localized resectable STSs with postoperative adjuvant chemotherapy including doxorubicin-based chemotherapies showed an increased rate of relapse-free survival and a decreased rate of recurrence but no effect on OS [12]. Han et al. reported a rate of 12.4% for ORR and 76.6% for DCR and a median DFS

and OS of 5 and 8 months, respectively, in cases with metastatic sarcoma treated using the MAID regimen [13]. In an intergroup phase III randomized study, the MAID regimen was associated with a better ORR than doxorubicin-dacarbazine (32% vs. 17%, respectively) and the median PFS was longer (6 vs. 4 months, respectively but grade III toxicity was more common in the MAID group (92% vs. 55%) [14]. Marshall et al. reported an ORR of 20% and a median OS of 20.1 months in cases with metastatic STSs treated with doxorubicin-based regimens [15]. These results suggest that the MAID regimen is recommended and a commonly preferred regimen in cases with STSs both as adjuvant therapy and in the metastatic settings. While the rate of OS was around 20% before the 2000s, the rate of OS was 81% in localized, 58% in locally advanced, 16% in metastatic disease, and 66% in the overall population with respect to the results of the 2014-2018 SEER database [16]. The ORR in the present study was similar to the results of published studies [13, 15]. However, the median PFS and OS were longer but the rate of 5-year OS was lower in the present study compared to similar studies in the literature [14, 16]. The reasons for these inconsistencies may be the late application of second-line treatments, unavailability of new drugs, and heterogeneous nature of the patients of the present study as in other sarcoma series.

Despite new developments and strategies in the recent years, the outcomes of STSs are not yet satisfying. For this reason, it is important to find out factors that predict survival and response to treatment in order to select high-risk patients who will benefit more from intensive chemotherapy regimens [17]. Although some classical factors are well-known to provide prognostic information, there is no widely accepted consensus about them. For example, while sex, mitosis, radiotherapy, and surgery have been found to be independent risk factors for OS by El-Jabbour et al.; older age (>56), extracompartmental location, grade, lower extremity involvement, and larger tumor diameter (>5cm) have been found as poor prognostic factors for OS by Keller et al. [18, 19]. In the present study, while age, sex, and grade were not predictive for OS, mitosis, necrosis, AJCC TNM stage, and surgery seemed to provide prognostic information with respect to the univariate analysis results. Tumor diameter and localization were found as prognostic only for PFS in univariate analyses. However, only the TNM stage was found as prognostic in multivariate analyses for both PFS and OS. The results of the present study in STS patients who underwent the MAID treatment should be validated in larger prospective studies in comparison with different treatment regimens.

The most important limitations of the present study are the retrospective nature, low number of the patients, and inclusion of heterogenous subtypes of STSs.

CONCLUSION

STSs are rare and aggressive cancers associated with a poor prognosis. Study groups are heterogenous in most of the previous studies due to the high number of subtypes. Herein, we aimed to present the long term results of our patients with STSs who were treated using the MAID regimen. Our cases had a lower rate of five-year OS despite a similar ORR with other studies. The only independent prognostic factor for PFS and OS was AJCC TNM stage in the present study and

this result highlights the importance of making the diagnosis at an earlier stage of the disease for better outcomes.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30
2. Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere AV, Péoc'h M, Istier L, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PloS one. 2011;6(8):e20294.
3. Borden EC, Baker LH, Bell RS, Bramwell V, Demetri GD, Eisenberg BL, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res. 2003;9(6): 1941-1956.
4. Colombo C, Randall RL, Andtbacka RHI, Gronchi A. Surgery in soft tissue sarcoma: more conservative in extremities, more extended in the retroperitoneum. Expert Rev Anticancer Ther. 2012;12(8):1079–87.
5. Crago AM, Brennan MF. Principles in the management of soft tissue sarcoma. Adv Surg. 2015;49:107–22
6. Koliou P, Karavasilis V, Theochari M, Pollack SM, Jones RL, Thway K. Advances in the treatment of soft tissue sarcoma: Focus on eribulin. Cancer Manag Res. 2018;10:207-16
7. Jain A, Sajeevan KV, Babu KG, Lakshmaiah KC. Chemotherapy in adult soft tissue sarcoma. Indian J Cancer. 2009;46(4):274-87
8. Ratan R, Patel SR. Chemotherapy for soft tissue sarcoma. Cancer. 2016;122(19), 2952-60.
9. Schöffski P, Cornillie J, Wozniak A, Li H, Hompes D. Soft tissue sarcoma: an update on systemic treatment options for patients with advanced disease. Oncol Res Treat. 2014;37(6): 355-62.
10. Gortzak E, Azzarelli A, Buesa J, Bramwell VHC, Van Coevorden F, Van Geel AN, et al. A randomized phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer, 2001:37(9):1096-103.
11. DeLaney TF, Spiro IJ, Suit HD, Gebhardt MC, Hornicek FJ, Mankin HJ, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys. 2003;56(4):1117-1127.
12. Sarcoma Meta-analysis Collaboration. (1997). Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet. 1997;350(9092): 1647-1654.
13. Han K, Sun Y, Zhang J, Tang L, Wang Z, Zhao H, et al. Retrospective clinical analysis of MAID protocol as first-line treatment on 137 metastatic soft-tissue sarcomas patients. The Chinese-German Journal of Clinical Oncology. 2012;11(2):117-120.
14. Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993;11:1276-1285.
15. Marshall S, Nakano K, Sugiura Y, Taira S, Ono M, Tomomatsu J, et al. Outcome for Advanced or Metastatic Soft Tissue Sarcoma of Nonextremities Treated with Doxorubicin-Based Chemotherapy: A Retrospective Study from a Single Cancer Institution. Sarcoma. 2018;8926598
16. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
17. Hoang NT, Acevedo LA, Mann MJ, Tolani B. A review of soft-tissue sarcomas: translation of biological advances into treatment measures. Cancer Manag Res. 2018;10:1089-114.
18. El-Jabbour JN, Akhtar SS, Kerr GR, McLaren KM, Smyth JF, Rodger A, et al. Prognostic factors for survival in soft tissue sarcoma. Br J Cancer. 1990;62(5):857-81.
19. Vraa S, Keller J, Nielsen OS, Sneppen O, Jurik AG, Jensen OM. Prognostic factors in soft tissue sarcomas: the Aarhus experience Eur J Cancer. 1998;34(12): 1876-82.