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ORIGINAL ARTICLE

Retrospective Comparison of the Efficacy of Therapeutic Agents in Metastatic Soft-Tissue Sarcomas

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OBJECTIVE

There are few agents used in soft-tissue sarcoma treatment. We compared the efficacy of therapies, aiming to identify the best therapy sequence, and reveal the factors affecting the risk of progression or death.

METHODS

Fifty-five patients were included in the study. Data such as age, gender, tumor primary site, histological type, tumor grade, the Ki67 percentage score, treatments, radiotherapy, and metastasectomy history, the dates of diagnosis, metastasis, progression, and death were retrospectively evaluated. Progression-free survival (PFS) and overall survival (OS) for therapies, and the risk factors for the progression or death were analyzed.

RESULTS

In the first-line, gemcitabine-docetaxel provided longer PFS than the doxorubicin-ifosfamide combination (7.4 months vs. 4.8 months, p=0.035), although this did not result in OS difference. In the second-line, the efficacy of trabectedin and pazopanib were similar, whereas trabectedin showed less activity in liposarcomas. In the third-line and beyond, trabectedin, pazopanib and eribulin showed similar PFS and OS. The only factor that affected the risk of death was metastasectomy (HR for death: 0.35, 95% CI: 0.18–0.66, p=0.001).

CONCLUSION

We found that agents used in soft-tissue sarcoma have similar efficacy, which is not affected by the previous therapies. However, it should be noted that soft-tissue sarcomas include many histological types, and to choose the optimal drug, the histological type must be one of the major factors considered. Furthermore, all patients should be evaluated for possible metastasectomy, which came out as the only factor reducing the risk of death in our study.

Keywords: Eribulin; pazopanib; sarcoma; trabectedin.

INTRODUCTION

Soft-tissue sarcomas are cancers originating from mesenchymal cells and contain many histological types. These rare tumors make up about 1% of adult cancers. Sarcomas can occur in any site, such as the extremities (the most common site), thorax, abdomen, and retroperitoneum. While surgery and radio-

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therapy constitute the primary treatment for the early-stage disease, for metastatic disease chemotherapy is the mainstay of treatment. Sarcomas are "immune cold" tumors. Unlike many other cancers, immunotherapy is ineffective in the treatment, except only in a small group with high microsatellite instability, showing some activity. Conventional chemotherapy is still the treatment of choice. It has been long known that sarcomas are anthracycline-sensitive tumors, and currently, the standard first-line treatment is doxorubicin monotherapy. Doxorubicin therapy provides a median of 7–8 months of progression-free survival (PFS). After progression, the treatment options include pazopanib, trabectedin, eribulin, gemcitabine-taxane, dacarbazine, and ifosfamide. Many criteria are evaluated to choose the optimal agent, including histology. Trabectedin appears to be more effective in leiomyosarcoma, while eribulin seems more effective in liposarcoma, and pazopanib is effective in non-liposarcoma histologies. However, there is no study comparing these three agents head-to-head.

Sarcomas have a poor prognosis. Despite intensive treatment, median overall survival (OS) in metastatic disease is <2 years; at 2–3 years, only 20% of patients are still alive. Besides new therapy options, optimal sequencing of the current agents may contribute to the patients' survival. In this retrospective study, we aimed to evaluate the treatment choices and responses, PFS, and OS of patients with metastatic soft-tissue sarcoma and determine the affecting factors for death.

MATERIALS AND METHODS

The medical records of patients between January 01, 2010, and May 01, 2022, in the Medical Oncology Clinic were reviewed to identify patients over the age of 18 who received chemotherapy with the diagnosis of soft-tissue sarcoma (excluding GIST, rhabdomyosarcoma, Ewing sarcoma, desmoids, and dermatofibrosarcoma protuberans, Kaposi sarcoma). Fifty-five eligible patients were included in the study. Age, gender, histological type, pathological grade, Ki67, primary site, treatments, radiotherapy, and metastasectomy history were evaluated. Best responses, PFS, and OS times were determined according to RECIST 1.1 criteria. The overall response rate (ORR) includes complete response (CR) and partial response (PR); and the disease control rate (DCR) includes CR, PR, and stable disease (SD). PFS is the time between initiation of therapy and progression or death; OS is the time between initiation of therapy and death. Treatment side effects were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) version 5.0.

Treatment regimens were doxorubicin-ifosfamide (60 mg/m^2 on day one, ifosfamide-mesna 2.5 g/m^2 per day IV on 1–3 days in every 3 weeks), gemcitabine-taxane (gemcitabine 900 mg/m^2 on days 1 and 8 plus docetaxel 75 mg/m^2 on day 8 in every 3 weeks), trabectedin (1.5 mg/m^2 iv infusion over 24 h through the central venous access port, in every 3 weeks), pazopanib (800 mg daily), and eribulin (1.4 mg/m^2 iv on days 1 and 8 in every 3 weeks). Pazopanib was given to non-liposarcoma histologies.

Statistical Analysis

Statistical analysis was performed using SPSS 23 statistical software. Factors that may be related to death and progression were evaluated with the logistic regression test, and PFS and OS were evaluated with the Kaplan–Meier test, with comparisons made with the log-rank test.

RESULTS

Fifty-five patients with metastatic soft-tissue sarcoma were included in the study. The median age was 54 (minimum-maximum: 19–79). There were 31 women and 24 men. At diagnosis, 21 patients had metastatic disease, and 34 had early-stage disease. Twenty-nine patients (52.7%) received adjuvant chemotherapy. About 50.9% (28 patients) of the whole group received doxorubicin as adjuvant therapy. The demographic and clinical characteristics of the patients are listed in Table 1. The distribution of the patients according to the second and third-line therapies is given in Table 2.

First-line Treatment

The median PFS of 24 patients receiving doxorubicin-ifosfamide was 4.8 months (SD 1.41, 95% confidence interval [CI]: 2.10–7.63), of 29 patients receiving gemcitabine-docetaxel was 7.4 months (SD 0.23, 95% CI: 6.99–7.93, p=0.035). In the doxorubicin group, the median number of treatment cycles was 4, and the ratio of patients who received six cycles was 34.8%; in the gemcitabine-docetaxel group, the median number of cycles given was 6, and the ratio of patients who received six cycles was 69%. Reasons for discontinuation were intolerance in 5 (33.3%), progression in 10 (66.7%) in the doxorubicin-ifosfamide group; intolerance in 2 (22.2%); and progression in 7 (77.8%) in the gemcitabine-taxane group.

There was no difference in OS between the groups. The median OS of the doxorubicin-ifosfamide group

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Table 1 Demographic and clinical characteristics of the patients

	n	%
Median age (min-max)	54.7 (19–79)	
Sex		
Female	31	56.4
Male	24	43.6
Primary site		
Uterus	9	16.4
Retroperitoneal	19	34.5
Trunk	4	7.3
Extremity	23	41.8
Adjuvant chemotherapy	29	52.7
Doxorubicin-ifosfamide	28	96.6
Dacarbazine-platinum	1	3.4
ECOG score		
0	9	16.4
1	34	61.8
2	12	21.8
Histology		
Leiomyosarcoma	22	40
Liposarcoma	10	18.2
Undifferentiated pleomorphic sarcoma	7	12.7
Malignant peripheral nerve sheath tumor	6	10.9
Others*	10	18.2
1st line treatment		
Doxorubicin-ifosfamide	24	43.6
Gemcitabine-taxane	29	52.7
Dacarbazine	1	1.8
Dacarbazine-platinum	1	1.8
Later line treatments		
Trabectedin	17	30.9
2nd line	8	47.1
≥3rd line	9	52.9
Pazopanib	34	61.8
2nd line	18	52.9
≥3rd line	16	47.1
Eribulin (≥3rd line)	5	9.1
Metastasectomy		
Yes	23	41.8
No	32	58.2

*: Synovial sarcoma (3), desmoplastic round tumor (2), myxofibrosarcoma (2), fibrosarcoma (1), pleomorphic malignant fibrous histiocytoma (1), angiosarcoma (1). ECOG score: Eastern Cooperative Oncology Group performance score

was 31.7 months (SD 3.93, 95% CI: 24.0–39.4), and the gemcitabine-docetaxel group was 22.4 months (SD 1.01, 95% CI: 20.4–24.4, p=0.90) (Fig. 1).

Second-line Treatment

Treatment responses were 50% disease control for trabectedin and 66.7% for pazopanib. Median PFS of pazopanib was 7.6 months (SD 3.99, 95% CI: 0.00–15.43), median PFS of trabectedin was 3.7 months (SD 3.04, 95% CI: 0.00–9.65, p=0.92). When liposarcoma histologies were excluded, the median PFS of three patients in the trabectedin arm was 7.2 months. Trabectedin seemed to be less effective in liposarcomas than other histologies. The PFS of the second-line treatments was compared according to the given first-line treatment, and no difference was found between the groups (p=0.49) (Table 3). The median OS was 14.1 months for pazopanib (SD 4.64, 95% CI: 5.05–23.27), and 30.6 months for trabectedin (SD 13.68, 95% CI: 3.80–57.46, p=0.15) (Fig. 2).

≥Third-line Treatments

Treatment responses were 55.6% disease control for trabectedin, and 50% for pazopanib. All five responses were progressive disease for eribulin. The median PFS for pazopanib was 5.8 months (SD 1.70, 95% CI: 2.53–9.19), 2.7 months for trabectedin (SD 0.99, 95% CI: 0.78–4.68), and 4.2 months for eribulin (SD 1.60, 95% CI: 1.11–7.41). The median OS for pazopanib was 8.5 months (SD 1.16, 95% CI: 6.21–10.78), 5.8 months for trabectedin (SD 0.99, 95% CI: 5.63–6.02), and 12.3 months for eribulin (SD 3.99, 95% CI: 4.54–20.19). There was no difference in PFS and OS between groups (p=0.62 and p= 0.95, respectively) (Fig. 3).

Toxicity

When the toxicity of the agents was evaluated, the frequency was 67.6% (all were grade 1 or 2) for pazopanib, 100% (grade 3–4 68.8%) for trabectedin, and 40% (all grade 1–2) for eribulin. Grade 3–4 side effects were seen in patients receiving trabectedin; those were cytopenias, nausea-vomiting, and elevated liver enzymes. Treatment-related death was not observed.

OS

The median OS at the metastatic stage was 26.6 months (SD:4.45, 95% CI: 17.89–35.36) for all patients. In non-L histologies (other than leiomyosarcoma and liposarcoma), OS was significantly worse than L-sarcomas (median OS 23.4 months versus 26.2 months, p=0.017). Logistic regression analysis showed no significant correlation between gender, primary site, ECOG performance score, histological type, Ki67 value, first-line treatment regimen, and risk of death. With metastasectomy (OR:0.18. p=0.56), longer second-line treatment PFS (OR:0.91. p=0.082), and longer ≥third-line treatment PFS (OR:0,89. p=0.057), there was a decrease in the risk of death, but statistical significance was not reached. Twenty-three patients (41.8 %) had metastasectomy; all were pulmonary metastasectomies. In the survival anal-

Table 2 Distribution of patients according to the second and ≥ third-line treatments

	Sex-median age	ECOG score	Histology	Metastasectomy
2nd line pazopanib	Female: 9 (50%) Male: 9 (50%) Median age: 51.6 (SD: 17.7. 19–79)	ECOG 0: 2 (11.1%) ECOG 1: 12 (66.7%) ECOG 2: 4 (22.2%)	Leiomyosarcoma 5 (27.8%) Undifferentiated pleomorphic sarcoma 5 (27.8%) Others* 8 (44.6%)	Yes: 6 (33.3%) No: 12 (66.7%)
2nd line trabectedin	Female: 3 (37.5%) Male: 5 (62.5%) Median age: 58.5 (SD:13.2. 37–75)	ECOG 0: 1 (12.5%) ECOG 1: 4 (50%) ECOG 2: 3 (37.5%)	Leiomyosarcoma 3 (37.5%) Liposarcoma 5 (62.5%)	Yes: 3 (37.5%) No: 5 (62.5%)
≥3rd line pazopanib	Female: 11 (68.8%) Male: 5 (31.3%) Median age: 57.3 (SD: 15.2. 25–74)	ECOG 0: 2 (12.5%) ECOG 1: 8 (50%) ECOG 2: 6 (37.5%)	Leiomyosarcoma 8 (50%) Undifferentiated pleomorphic sarcoma 2 (12.5%) Others **6 (37.8%)	Yes: 4 (25%) No: 12 (75%)
≥3rd line trabectedin	Female: 5 (55.6%) Male: 4 (44.4%) Median age: 55.5 (SD: 10.4. 40–72)	ECOG 0: 4 (44.4%) ECOG 1: 5 (55.6%)	Leiomyosarcoma 5 (55.6%) Liposarcoma 3 (33.3%) Malignant peripheral nerve sheath tumor 1 (11.1%)	Yes: 6 (66.7%) No: 3 (33.3%)
≥3rd line eribulin	Female: 4 (80%) Male: 1 (20%) Median age: 55.4 (SD: 11.4. 43–69)	ECOG 1: 5 (100%)	Leiomyosarcoma 2 (40%) Liposarcoma 2 (40%) Synovial sarcoma 1 (20%)	Yes: 4 (80%) No: 1 (20%)

*: Synovial sarcoma, desmoplastic round tumor, myxofibrosarcoma, fibrosarcoma, pleomorphic malignant fibrous histiocytoma, angiosarcoma. ECOG score: Eastern Cooperative Oncology Group performance score

ysis, a significant difference was found between the OS of the patients who had and did not have metastasectomy. The median OS was 51.9 months for the metastasectomy group (SD: 16.59, 95% CI: 19.37–84.42), and 22.4 months for the non-metastasectomy group (SD: 1.63, 95% CI: 19.26–25.67, p=0.003) (Fig. 4). In Cox regression analysis, the hazard ratio for death was 0.35 for the metastasectomy group (95% CI: 0.18–0.66, p=0.001).

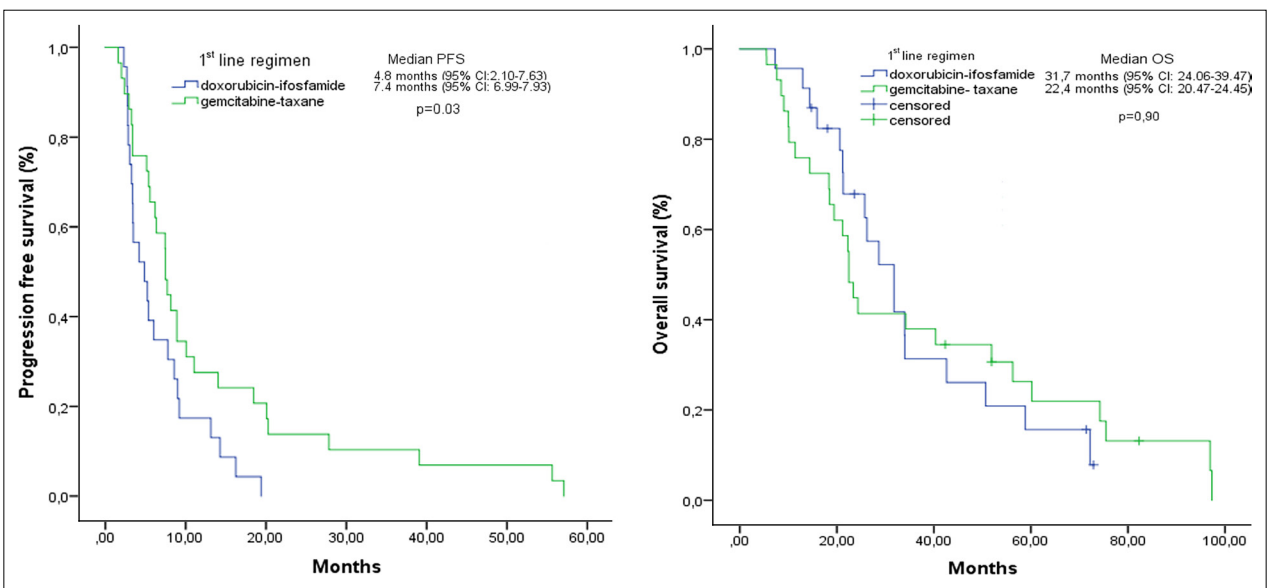

Fig. 1. PFS and OS graphics of first-line therapies.
PFS: Progression-free survival; OS: Overall survival.

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Table 3 PFS of second-line treatments stratified according to the first-line regimen

1st line treatment	2nd line treatment	Median			
				95% CI	
		Estimate	Std. Error	Lower bound	Upper bound
Doxorubicin	Pazopanib	5.23	7.40	0.00	19.73
	Trabectedin	3.70	0.87	1.98	5.41
	Overall	5.23	2.28	0.75	9.71
Gemcitabine-taxane	Pazopanib	10.76	4.24	2.44	19.08
	Trabectedin	7.20	4.51	0.00	16.05
	Overall	10.76	3.15	4.58	16.95
Overall	Overall	7.20	3.52	0.28	14.11

*log-rank p=0.49. PFS: Progression-free survival; CI: Confidence interval; Std.: Standard

DISCUSSION

At present, anthracycline is the preferred first-line therapy in metastatic soft-tissue sarcoma. When doxorubicin is used alone, it provides a 14% response rate. Although the response rate is increased (26%) when used in combination with ifosfamide, and there is a PFS benefit, the survival benefit of the combination regimen could not be demonstrated.[1] Moreover, the higher toxicity of the combination regimen limits its use. In a study evaluating treatment with doxorubicin (including patients using it alone or in combination), median PFS and OS were 8.7 months and 20.1 months, respectively.[2] A combination regimen could still be preferred to obtain a better tumor response in patients with a high tumor burden. Some experts prefer the gemcitabine-taxane regimen in the first-line, especially in uterine leiomyosarcoma. In a retrospective review, the gemcitabine-docetaxel regimen provided an ORR of 18% for sarcoma (24% for leiomyosarcoma). At 12 months 51%, and at 24 months, 15% of patients were still alive. This suggested that the combination regimen was as effective as doxorubicin.[3] When single-agent doxorubicin was compared to the gemcitabine-taxane regimen in the GeDDis trial, no difference in PFS or OS was observed, 46% of patients in both groups were progression-free at 24 weeks, with doxorubicin being better tolerated. As a result, the gemcitabine-taxane combination is typically not employed in the first-line setting for anthracycline-sensitive histologies. Still, it could be preferred for patients not suitable for anthracycline therapy.[4]

While the second and after-line treatment options are determined according to many criteria, including histology, options include ifosfamide, gemcitabine-taxane, dacarbazine, pazopanib, trabectedin, and eribulin. In the phase 3 PALETTE study, pazopanib was compared with placebo as second-line therapy for histologies other than liposarcoma in patients who progressed on anthracycline therapy. The pazopanib arm had a significantly better median PFS (4.6 vs. 1.6 months) in the study. OS was the same for both treatment arms (12.5 vs. 10.7 months). There was PR in 6%, and SD in 67% of the pazopanib arm.[5] Trabectedin appears to have activity in leiomyosarcomas and liposarcomas (particularly the round cell/myxoid subtype), and perhaps other histologies. In the ET743-SAR-3007 trial, patients with metastatic leiomyosarcoma or liposarcoma who had progression after anthracycline-based chemotherapy were randomly assigned to trabectedin versus dacarbazine. Approximately three-fourths of those enrolled had leiomyosarcoma, and the remaining one-third had liposarcomas. In the trial, relative to dacarbazine, trabectedin demonstrated improved PFS but similar OS (median PFS 4.2 versus 1.5 months; median OS 13.7 versus 13.1 months).[6,7] Another agent eribulin has the most significant activity in dedifferentiated or pleomorphic liposarcoma. Eribulin's efficacy over dacarbazine in advanced liposarcoma and leiomyosarcoma was observed in a phase III trial, with both drugs showing similar PR rates ([4%] in the eribulin arm vs. [5%] in the dacarbazine arm) or SD rates ([52%] vs. [48%] in the dacarbazine arm); similar median PFS: 2.6 months; but the eribulin arm having significantly improved OS in comparison with the dacarbazine arm (median 13.5 months vs. 11.5 months, hazard ratio 0.77 [95% CI 0.62–0.95]; p=0.0169).[8]

Head-to-head comparisons of these agents are unknown. In a retrospective study evaluating second-line gemcitabine-taxane and pazopanib, ORR was better for the chemotherapy arm (26.7% vs. 6.5%), but OS was not different for the two groups (14.2 months vs. 12.6 months, p=0.362).[9] In a study revealing a real-life experience from Japan, the DCR at 8 weeks was 58.5%, and the median OS was 12.6 months. There was no comparison between the efficacies of therapies.[10] Another retrospective study evaluating second-line therapies in synovial sarcoma reported an ORR of 9.4% and a DCR over 6 months of 34.3%. This study also did not reveal any preference for any agent.[11] An abstract in ESMO 2017 presented data analyses from PALETTE and SAR 3007; in a sample size of 372 pa-

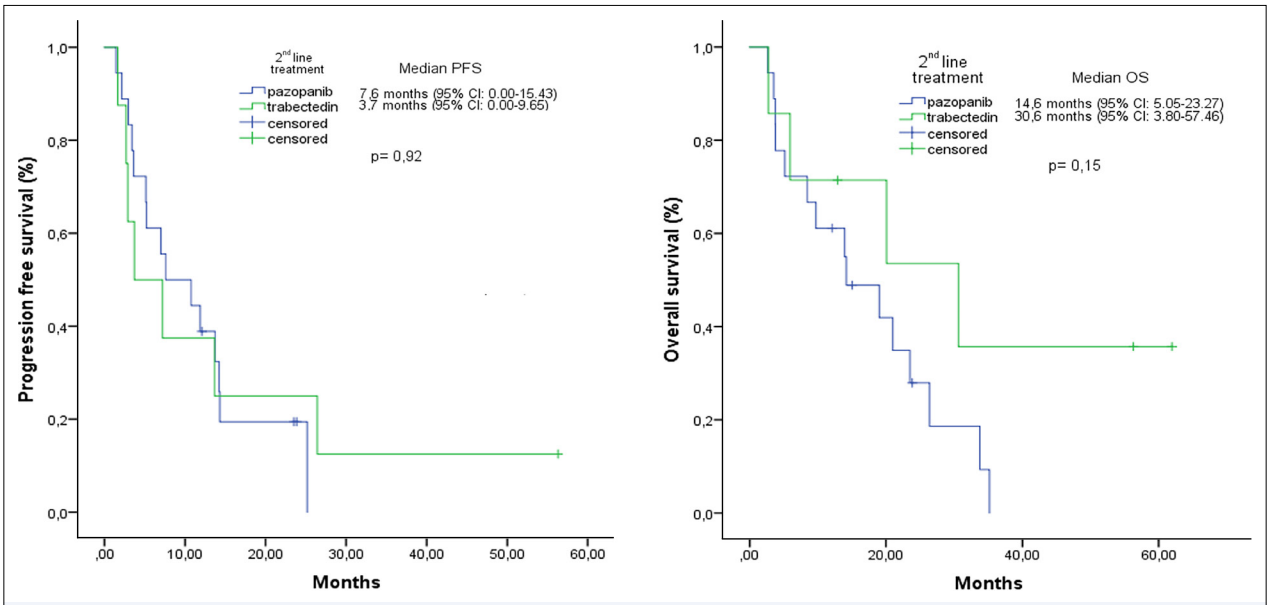

Fig. 2. PFS and OS graphics of second-line therapies.
PFS: Progression-free survival; OS: Overall survival.

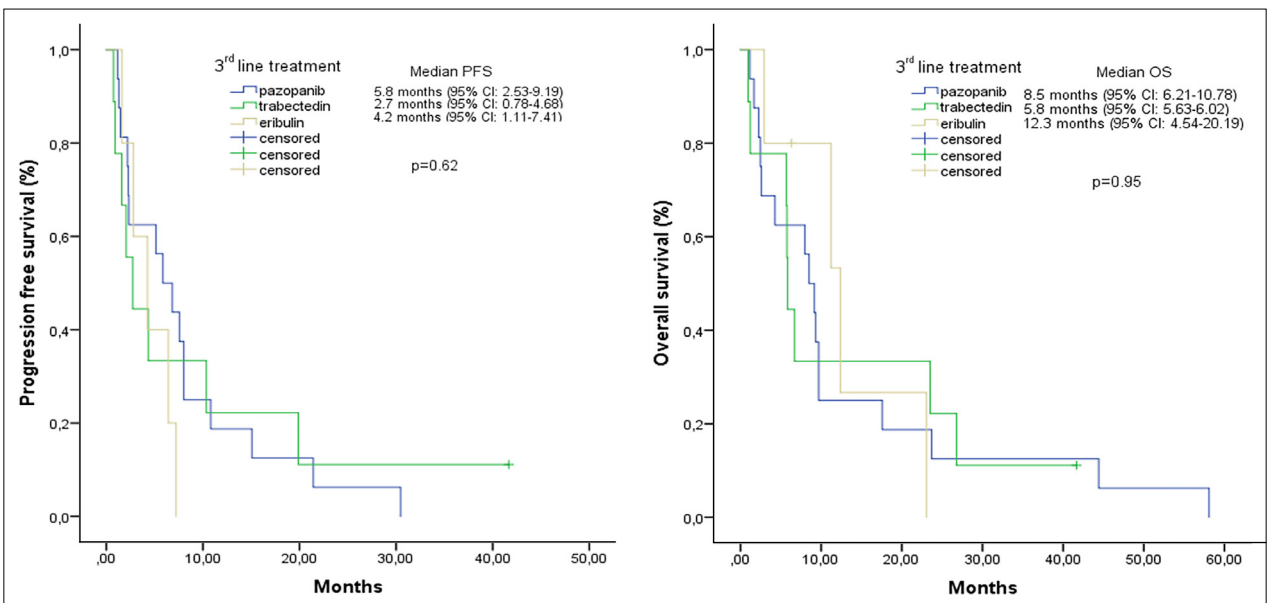

Fig. 3. PFS and OS graphics of ≥ third-line therapies.
PFS: Progression-free survival; OS: Overall survival.

tients with leiomyosarcoma, there was no difference in PFS or OS between pazopanib and trabectedin.[12] A study evaluating immune-related markers as a potential indicator of response to pazopanib, trabectedin, and eribulin in soft-tissue sarcoma showed PFS and OS of the three agents did not differ. In this study, in the low neutrophil-to-lymphocyte ratio group, pazopanib had statistically significant shorter OS; in the low platelet-to-lymphocyte ratio group, pazopanib was associated with shorter OS, and eribulin was associated with longer OS. PFS was the same in all immune-related marker subgroups.[13] A study from Japan comparing trabectedin and eribulin after pazopanib therapy showed that trabectedin had a median OS of 9.1 months and eribulin had 13.8 months. The researchers did not observe any difference between agents in terms of OS.[14]

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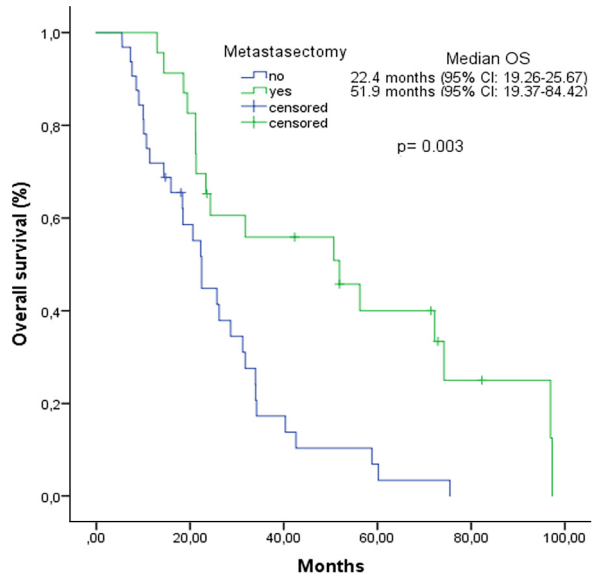

Fig. 4. OS graphic for metastasectomy versus non-metastasectomy groups.
OS: Overall survival.

In our study, unlike the GeDDis study, the median PFS of gemcitabine-taxane as first-line was found to be longer. Still, OS was not different between the treatment groups. It could be due to the lower median number of cycles in the doxorubicin group. Furthermore, malign peripheral nerve sheath tumors are considered chemoresistant and have a poor response to therapies. Six patients in our study, all treated with doxorubicin in first-line, may be the reason for shorter PFS in this group. Treatment intolerance was higher in the doxorubicin-ifosfamide group than in the gemcitabine docetaxel group as expected. There was no difference between the efficacy of the following therapies, according to the given first-line treatment. When trabectedin and pazopanib in the second-line and trabectedin, pazopanib, and eribulin in the latter lines were compared, no difference in response rates, PFS, and OS was found between the treatment groups. When side effects were evaluated, pazopanib seemed to be better tolerated than trabectedin in our study. Besides L-histology (liposarcoma or leiomyosarcoma), the only variable that was shown to affect OS time was metastasectomy. Pulmonary metastasectomy has long been known to provide a survival benefit in soft-tissue sarcomas. In a meta-analysis published in 2012, the 5-year OS rate was 25% in patients with pulmonary metastasectomy.[15] In another study, the median OS of 45.3 months was reported in the metastasectomy group.[16] Similarly, in our study, the median OS of 51.9 months was reached in this group. Even in the presence of multiple metastases, metastasectomy can be performed safely and should be preferred.[17]

Limitations of the Study

The limitations of our study are the small number of subjects in groups, the variety between the groups in terms of histological types, and the retrospective nature of the study. Sarcomas are a heterogeneous group comprising approximately 70 histological types, and we recognize that combining all these histologies in one basket is not optimal. However, the rarity of the disease makes it challenging to design an ideal trial. Furthermore, the number of metastatic sites is not reported. One possible reason for the prolonged survival achieved in the metastasectomy group could be lesser tumor burden in this group.

CONCLUSION

Various agents are used in the treatment of soft-tissue sarcomas and there is no randomized controlled trial comparing those therapies head-to-head. We retrospectively analyzed that our patients' data and found all three drugs (trabectedin, pazopanib, and eribulin) showed similar efficacy. We think that prospective studies will contribute to answering questions such as what is the optimal therapy sequence and whether there is a predictive biomarker to choose the proper drug. Not surprisingly, we found metastasectomy as the only factor reducing the risk of death, consistent with the literature. Surgical resection of metastases as much as possible and effective chemotherapies undoubtedly prolongs the survival of sarcoma patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (no: 2022-16/51, date: 08/11/2022).

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Authorship contributions: Concept – B.C., B.O., A.B.Ş., S.S., E.Ç., E.Çu., A.D.; Design – B.C., S.S., E.Ç., B.O., A.B.Ş., E.Çu., A.D., T.E.; Supervision – E.Çu., A.D., T.E.; Funding – B.C., S.S., E.Ç.; Materials – B.C., S.S., E.Ç., B.O., A.B.Ş.; Data collection and/or processing – B.C., S.S., E.Ç., B.O., A.B.Ş.; Data analysis and/or interpretation – B.C., S.S., E.Ç., B.O., A.B.Ş., A.D., E.Çu.; Literature search – B.C., S.S., E.Ç., B.O., A.B.Ş., A.D., E.Çu.; Writing – B.C., S.S., E.Ç., A.D., E.Çu.; Critical review – E.Çu., A.D., T.E.

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