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Original Article

The timing of targeted therapy initiation in metastatic sarcoma as an adjuvant to first-line chemotherapy or a second-line agent

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Abstract: 58 cases of metastatic sarcoma were reviewed retrospectively in order to compare the efficacy and safety of concurrent (n=24, group A) versus sequential (n=34, group B) use of chemotherapy and targeted therapy in metastatic sarcoma. Progression-free survival (PFS) 1 was defined as the duration between initiation of first-line treatment to disease progression or recurrence. PFS' was defined as the duration between initiation of first-line treatment to the failure of chemotherapy and targeted therapy, and overall survival (OS) was defined as the duration between initiation of first-line treatment to the date of last follow-up or death. The results revealed that patients in group A possessed a higher tumor burden compared to those in group B (P=0.049). Survival curves revealed that the median PFS1 (15.2 vs. 5.4 months, P=0.000), median PFS' (15.2 vs. 10.8 months, P=0.049), and median OS (42.3 vs. 25.3 months, P=0.041) of subjects in group A were remarkably longer than those of group B. Subgroup analysis showed that patients in group A experienced more favorable PFS1 (15.2 vs. 3 months, P=0.000), PFS' (15.2 vs. 5.8 months, P=0.003), and OS (35.2 vs. 15.7 months, P=0.011) than those in group B, with findings especially prominent in patients with tumor burden ≥ 10 cm in comparison to patients with tumor burden < 10 cm (P ≥ 0.05). All grades of leukopenia, thrombocytopenia, fatigue, and oral mucositis were more frequently diagnosed in patients of group A compared to those of group B. However, there were no significant differences between the rates of Grade 3-4 adverse events between the two groups. This investigation suggests that the concurrent use of targeted therapy and chemotherapy may be useful and safe as a first-line treatment in patients with metastatic sarcoma who possess a high tumor burden.

Keywords: Sarcoma, chemotherapy, targeted therapy, concurrent, metastatic

Introduction

Sarcomas form a rare group of mesenchymal malignancies that possess strong predilections for recurrence and metastasis [1]. They account for 12-15% of all pediatric tumors [2], but make up less than 1% of all adult tumors [3]. Approximately 80% of all sarcomas are of soft tissue origin, while the remaining 20% originate from bone [4]. Sarcomas are treated with a combination of surgery, chemotherapy and radiotherapy, which have resulted in an overall improved prognosis over the last four decades [5, 6]. Nevertheless, prognosis of those who have developed metastasis remains poor and 5-year survival rate ranges from 10% to 30% [7-9].

Metastatic sarcoma is typically treated with chemotherapy. Typical chemotherapeutic agents utilized in managing this disease comprise of doxorubicin, ifosfamide, methotrexate, cisplatin, etoposide, gemcitabine and docetaxel [10, 11]. There is a lack of established second-line rescue agents upon failure of first-line chemotherapeutic agents in metastatic sarcoma [12]. Evidence has highlighted the efficacy of targeted therapy in chemo-resistant sarcoma, which works by inhibiting specific tumor signaling pathways. Molecular-targeting drugs such as sunitinib [13], sorafenib [14], regorafenib [15], pazopanib [16], apatinib [17], and anlotinib [18] have been widely used as monotherapy agents in patients who show little response to chemotherapy.

Both targeted therapy and chemotherapy appeared to confer synergistic effects [19]. Clinical trials demonstrated that bevacizumab combined with chemotherapy significantly improved patient outcomes compared to usage of chemotherapy only for NSCLC [20], ovarian cancer [21], and cervical cancer [22]. Moreover, a growing body of research indicated that the concurrent use of targeted therapy and chemotherapy may result in better clinical outcomes compared to the use of chemotherapy alone for metastatic sarcoma [23, 24]. Therefore, it is of clinical interest to explore a reliable treatment strategy for metastatic sarcoma that includes both of these treatment modalities.

However, the optimal timing of administering targeted therapy for this disease is unclear. This retrospective study aimed to compare the efficacy and safety profiles between two treatment regimens - concurrent application of chemotherapy and targeted therapy versus the sequential application of chemotherapy followed by targeted therapy in metastatic sarcoma. The results may shed light on the future clinical decision-making and prospective for future randomized, multicenter clinical trials.

Patients and methods

Study population

The medical records of metastatic sarcoma patients who were treated in our department between January 2016 and June 2018 were extracted and reviewed retrospectively. Patients with the following characteristics were included in the study: (1) histopathologically diagnosed sarcoma; (2) patients who were given chemotherapy combined with targeted therapy as a first-line treatment (group A) or those who were given first-line chemotherapy followed by second-line targeted therapy (group B); (3) patients with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0-2; (4) patients with lesions that were able to be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients who were diagnosed with other primary malignancy or possessed incomplete clinical data were excluded from the study. This study was approved by the Medical Ethics Committee of the Shanghai Jiaotong University Affiliated Sixth People's Hospital (Approval NO. 2020-YS-147).

Treatment and evaluation

The patients were grouped based on the timing of initiation of targeted therapy. In group A, patients were treated concurrently with chemotherapy and targeted therapy. Treatment was administered every 3 weeks until disease progression was detected. In group B, patients were first treated with chemotherapy as a first-line agent. Upon occurrence of disease progression, patients were then initiated with second-line targeted therapy. Treatment was then continued until re-detection of disease progression. Patients received one of the following regimes of targeted therapy: apatinib administered 500 mg once per day, anlotinib administered 12 mg once per day for 14 days and then discontinued for 7 days, sorafenib administered 400 mg twice per day, and pazopanib administered 800 mg once per day orally.

The RECIST 1.1 was used to determine tumor burden, which was defined as the sum of baseline target lesion diameters. Computed tomography (CT) or magnetic resonance imaging (MRI) scans were used to assess tumor response to treatment every two cycles. Tumor responses were classified as stable disease (SD), partial response (PR), complete response (CR), and progressive disease (PD) based on RECIST 1.1. The National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to grade treatment toxicity. Dose reduction was carried out for patients who developed grades 3 or 4 adverse events.

Statistical analysis

All statistical analyses were carried out with the SPSS statistical software (Version 19.0, IBM Corp.). As depicted in **Figure 1**, the interval from the start of first-line treatment to the date of last follow-up or death of any cause was defined as the overall survival (OS). Progression-free survival (PFS) 1 was determined as the duration between initiation of first-line treatment to first detection of disease progression or to death from any cause. PFS2 was defined as the duration spanning the start of second-line treatment to the second progression of the disease or death from any cause in group B. PFS' was defined as the duration between initiation of first-line treatment to failure of chemotherapy and targeted therapy or death from any

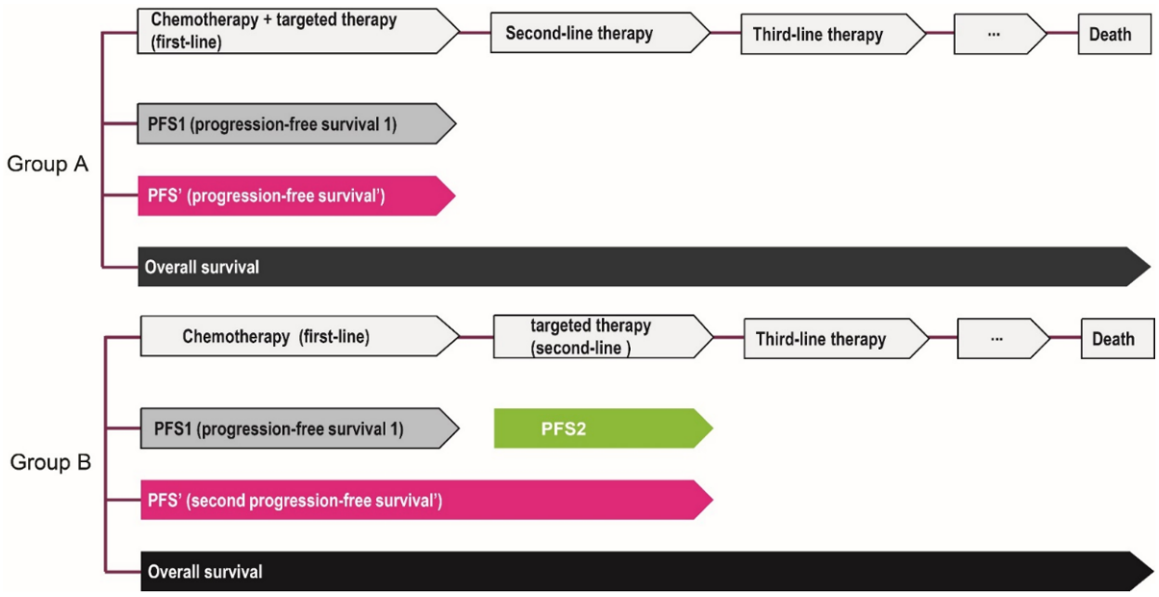

Figure 1. Endpoints overview.

cause. In group A, PFS'=PFS1. In group B, PFS'=PFS1 + PFS2. The disease control rate (DCR) was determined to be the total percentage of patients who achieved CR, PR, and SD. The objective response rate (ORR) was determined to be the total percentage of patients who achieved CR and PR. The Chi-square test or Fisher's exact test was used to analyze categorical data. The Kaplan-Meier method was used to estimate survival. The log-rank test allowed for intergroup comparison of survival. Statistical significance was granted when $P < 0.05$.

Results

Patient characteristics

This study included a total of 58 patients who possessed stage IV sarcomas. There were 24 and 34 patients in group A and B, respectively. As shown in **Table 1**, approximately 41% of all patients were female in both groups. The majority of patients had already undergone surgery. Most of patients did not receive radiotherapy. Half of the patients were less than 18 years of age, possessed tumors of bone origin and had the tumors in their extremities. There were no obvious variances between the groups with respect to gender, age, surgery history, radiotherapy history, targeted therapy, ECOG-PS, primary site, and histology. However, patients in group A had a higher baseline tumor burden than those in group B (58.3% vs. 32.4%, P=0.049).

Efficacy

In group A, 1 patient achieved CR, 8 patients achieved PR, 13 patients achieved SD, and 2 patients showed PD. In group B, there were 0 CR, 5 PRs, 22 SDs, and 7 PDs (**Tables 2** and **3**). Overall treatment response rates in groups A and B were 37.5% and 14.7%, respectively (P=0.046). Disease control rates of groups A and B were 91.7% and 79.4%, respectively (P=0.204) (**Table 3**).

The survival curve revealed that the median PFS1 of group A was markedly longer in contrast to that of group B (15.2 vs. 5.4 months, P=0.000, **Figure 2A**). The median PFS2 in group B was 5.2 months. Moreover, the median PFS' of group A was also remarkably longer compared to that of group B (15.2 vs. 10.8 months, P=0.049, **Figure 2B**). Analysis of overall survival analysis yielded similar findings (42.3 vs. 25.3 months, P=0.041, **Figure 2C**).

Group A and Group B were then further subgrouped according to degree of tumor burden. We found that patients who had a tumor bur-

Table 1. Baseline characteristics of the patients

Characteristic	Group A (%)	Group B (%)	*P* value
Gender			0.97
Female	10 (41.7)	14 (41.2)	
Male	14 (58.3)	20 (58.8)	
Age/year			0.419
< 18	11 (45.8)	12 (35.3)	
≥ 18	13 (54.2)	22 (64.7)	
Surgery history			0.692
Yes	18 (75.0)	27 (79.4)	
No	6 (25.0)	7 (20.6)	
Radiotherapy history			0.808
Yes	5 (20.8)	8 (23.5)	
No	19 (79.2)	26 (76.5)	
Targeted chemotheray			0.781
Apatinib	5 (20.8)	8 (23.5)	
Anlotinib	7 (29.2)	12 (35.3)	
Sorafenib	5 (20.8)	8 (23.5)	
Pazopanib	7 (29.2)	6 (17.7)	
Tumor burden			0.049
<10 cm	10 (41.7)	23 (67.6)	
≥ 10 cm	14 (58.3)	11 (32.4)	
Eastern Cooperative Oncology Group performance status			0.897
0	13 (54.2)	19 (55.9)	
1	11 (45.8)	15 (44.1)	
Primary site			0.531
Extremity	10 (41.7)	17 (50.0)	
Other sites	14 (58.3)	17 (50.0)	
Histology			0.531
Bone sarcoma	10 (41.7)	17 (50.0)	
Soft tissue sarcoma	14 (58.3)	17 (50.0)	

Note: Data are presented as percentages.

den ≥ 10 cm in group A demonstrated better PFS1 (15.2 vs. 3 months, P=0.000, **Figure 2D**), PFS' (15.2 vs. 5.8 months, P=0.003, **Figure 2E**), and OS (35.2 vs. 15.7 months, P=0.011, **Figure 2F**) compared to the same cohort of patients in group B. However, among patients with tumor burden < 10 cm, we observed no significant difference in PFS1 (**Figure 2G**), PFS' (**Figure 2H**), or OS (**Figure 2I**) between the two groups (P ≥ 0.05).

Safety

None of the patients in either group required a dose reduction or temporary discontinuation of chemotherapy. 4 (16.7%) patients in group A and 5 (14.7%) patients in group B required targeted therapy dose reduction for toxicity management, which did not differ significantly between groups. There was no treatment-associated death in both groups. Commonly encountered adverse events (AEs) are shown in **Table 4**. The incidences of all grades of leukopenia (P=0.031), thrombocytopenia (P=0.033), fatigue (P=0.028), and oral mucositis (P=0.011) were significantly more common in patients of group A compared to those of group B. Nevertheless, there was no significant differences of the rates of Grade 3-4 adverse events between the two groups (P ≥ 0.05, **Table 4**).

Discussion

Patients with metastatic sarcoma often demonstrate poor prognoses. Chemotherapy, which works by inhibiting cell division, is the first-line

Table 2. Efficacy data by histologic category

Histological subtypes	Group A				Group B			
	CR	PR	SD	PD	CR	PR	SD	PD
Synovial sarcoma	0	1	1	0	0	3	1	0
Leiomyosarcoma	0	1	2	0	0	0	0	0
Liposarcoma	0	0	1	1	0	0	1	1
Fibrosarcoma	0	0	0	0	0	0	2	0
Ewing's sarcoma	0	0	0	0	0	0	1	0
Undifferentiated sarcoma	0	2	2	0	0	0	0	0
Angiosarcoma	0	1	1	0	0	0	2	0
Undifferentiated pleomorphic sarcoma	0	1	0	1	0	0	1	0
Rhabdomyosarcoma	0	1	0	0	0	1	2	3
Osteosarcoma	1	1	5	0	0	1	10	3
Chondrosarcoma	0	0	1	0	0	0	2	0

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Overall response to treatment

Tumor Response	Group A (n=24)	Group B (n=34)	*P* value
CR	1	0	-
PR	8	5	-
SD	13	22	-
PD	2	7	-
ORR	9 (37.5%)	5 (14.7%)	0.046
DCR	22 (91.7%)	27 (79.4%)	0.204

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

treatment of choice for this disease as recommended by the National Comprehensive Cancer Network [25]. There is a lack of established second-line therapies [12]. The VEGF/VEGFR signal pathway, often targeted by therapeutic agents, is a crucial pathway in sarcoma [26]. Preclinical studies have shown that anti-angiogenic agents were able to reduce abnormal tumor vascularization, resulting in enhanced drug delivery and efficacy [27]. Pazopanib combined with topotecan demonstrated significant antitumor activity in contrast to use of any of these agents alone in treating sarcoma mouse models [28]. Moreover, several studies highlighted the benefits of combining anti-angiogenic agents and chemotherapy, which may represent a feasible and tolerable regimen in treating metastatic sarcoma [29, 30]. Likewise, our results also showed that a concurrent application of chemotherapy and targeted therapy allowed patients to achieve a significantly improved ORR and PFS in contrast to the sequential use of chemotherapy followed by targeted therapy, despite the higher average tumor burdens of patients in the concurrent application group. Nevertheless, further studies should be done to determine the optimal timing of administering targeted therapy in relation to chemotherapy.

In the present study, the survival curves revealed that the median PFS1 (15.2 vs. 5.4 months, P=0.000), median PFS' (15.2 vs. 10.8 months, P=0.049), and median OS (42.3 vs. 25.3 months, P= 0.041) of the concurrent application group were notably longer compared to those in the sequential application group. Furthermore, subgroup analysis showed that patients in the concurrent application group gained more benefits in terms of PFS1 (15.2 vs. 3 months, P=0.000), PFS' (15.2 vs. 5.8 months, P=0.003), and OS (35.2 vs. 15.7 months, P=0.011) in comparison with those of the sequential application group, especially in the subpopulation of patients of both groups with a tumor burden of ≥ 10 cm compared to those with a tumor burden of < 10 cm (P ≥ 0.05).

Both chemotherapy and targeted agents possess different toxicity profiles. Chemotherapeutic agents that interact with DNA and cause cell death are non-selective and can damage both cancer cells and normal tissues [31]. The most common adverse effects of chemotherapeutic agents are alopecia, nausea and vomiting, as well as myelosuppression [32]. There are several other organs that may also be affected by conventional chemotherapy [33, 34]. Targeted drugs, on the other hand, act more specifically on cancerous cells and spare normal cells. The most commonly seen side effects of these medications include hypertension, oral mucositis, hypothyroidism, proteinuria and fatigue [35]. In our study, the concurrent application of chemotherapy and targeted therapy increased the incidences of all grades of leukopenia (P=0.031), thrombocytopenia

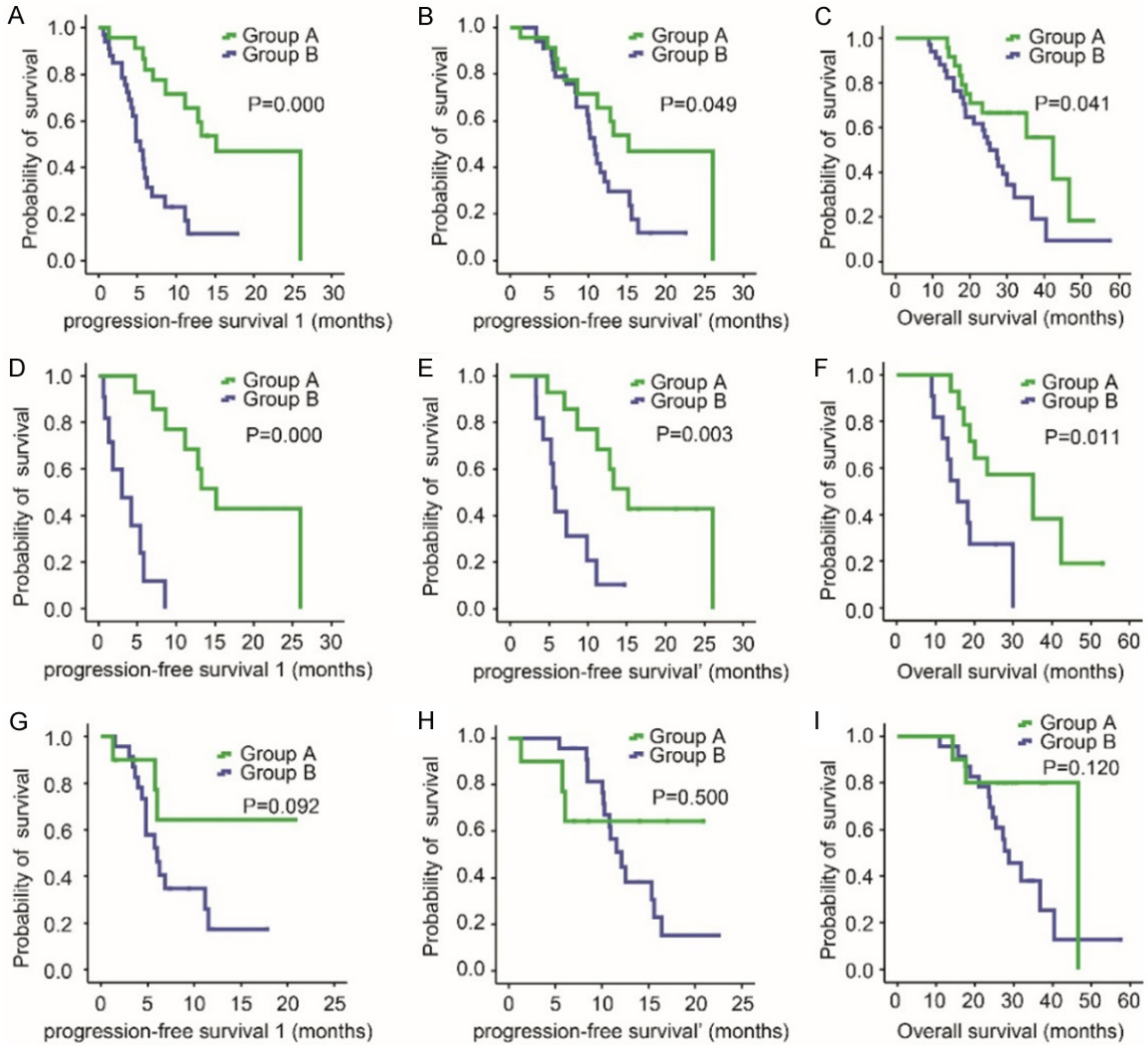

Figure 2. Kaplan Meier survival curves. A. Progression-free survival1 in overall samples; B. Progression-free survival' in overall samples; C. Overall survival in overall samples; D. Progression-free survival1 in the subpopulation with tumor burden ≥ 10 cm; E. Progression-free survival' in the subpopulation with tumor burden ≥ 10 cm; F. Overall survival in the subpopulation with tumor burden ≥ 10 cm; G. Progression-free survival1 in the subpopulation with tumor burden < 10 cm; H. Progression-free survival' in the subpopulation with tumor burden < 10 cm; I. Overall survival in the subpopulation with tumor burden < 10 cm.

(P=0.033), fatigue (P=0.028), and oral mucositis (P=0.011). However, there were no significant differences between the occurrences of Grade 3-4 adverse effects between the groups. Patients in the concurrent application group appeared to tolerate the regimen well, with toxicities that were able to be managed.

This is the first study of its kind to compare the efficacy and safety of concurrent versus sequential application of chemotherapy and targeted therapy. Our findings suggest that concurrent application of the two modalities may yield more favorable outcomes without increasing rates of Grade 3-4 adverse events, even in patients who possess a higher tumor burden. However, we also acknowledge the existence of a number of limitations in this research. The small sample size and retrospective design inevitably weakens the strength of this study. Our study is underpowered to perform subgroup analyses based on the histological subtype of sarcoma. The heterogeneity of treatment regimens may also have influenced the results.

In conclusion, this study demonstrated that concurrent application of chemotherapy and

Table 4. Adverse events

Adverse event	All grades No. (%)			Grade > 2 No. (%)		
	Group A n=24	Group B n=34	*P* value	Group A n=24	Group B n=34	*P* value
Leukopenia	22 (91.7)	23 (67.6)	0.031	4 (16.7)	5 (14.7)	0.559
Anemia	13 (54.2)	15 (44.1)	0.451	2 (8.3)	2 (5.9)	0.552
Thrombocytopenia	18 (75.0)	16 (47.1)	0.033	3 (12.5)	5 (14.7)	0.564
Nausea/vomiting	17 (70.8)	24 (70.6)	0.984	1 (4.2)	2 (5.9)	0.630
Fatigue	20 (83.3)	19 (55.9)	0.028	2 (8.3)	4 (11.8)	0.514
Diarrhea	10 (41.7)	14 (41.2)	0.970	0	0	-
Weight loss	9 (37.5)	16 (47.1)	0.469	0	0	-
Transaminase increase	8 (33.3)	15 (44.1)	0.408	0	0	-
Triglyceride elevation	7 (29.2)	10 (29.4)	0.984	0	0	-
Proteinuria	7 (29.2)	13 (38.2)	0.474	2 (8.3)	3 (8.8)	0.664
Hypertension	9 (37.5)	17 (50.0)	0.346	1 (4.2)	2 (5.9)	0.630
Pneumothorax	4 (16.7)	7 (20.6)	0.491	1 (4.2)	1 (2.9)	0.661
Hand-foot syndrome	6 (25.0)	9 (26.5)	0.900	2 (8.3)	2 (5.9)	0.552
Hypothyroidism	5 (20.8)	9 (26.5)	0.621	0	0	-
Alopecia	22 (91.7)	32 (94.1)	0.552	0	0	-
Oral mucositis	18 (75.0)	14 (41.2)	0.011	2 (8.3)	1 (2.9)	0.370

targeted therapy significantly improved the PFS and OS in metastatic sarcoma with tumor burden ≥ 10 cm, without increasing the rates of Grade 3-4 adverse events. We propose that the concurrent application of chemotherapy and targeted therapy may be a safe and reliable first-line treatment regimen for metastatic sarcoma with high tumor burden. However, further prospective studies are necessary to strengthen the evidence underlying the potential clinical benefits of the proposed treatment regimen.

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Disclosure of conflict of interest

None.

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