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Research Article

ICE Regimen in Adult Advanced/Relapsed Soft Tissue Sarcoma Patients; is it More Effective in Early Use? Retrospective Analysis of Single Center Study

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Abstract

Objectives: To analyze the efficacy and tolerability of the ICE regimen and prognostic factors for survival in patients with advanced or relapsed soft tissue sarcomas treated with the ICE regimen (ifosfamide, carboplatin and etoposide).

Methods: The records of 28 patients diagnosed with advanced or relapsed soft tissue sarcoma who were treated with the ICE regimen at our center between 2008 and 2020, were evaluated retrospectively.

Results: The most common histopathological subtype were pleomorphic sarcoma (9/32.1%). After a median follow-up duration of 8 months, the median PFS and OS were 6 months (95% confidence interval (CI), 3.6–8.3) and 9.3 months (95% CI, 4.7–13.9), respectively. A multivariate analysis for overall survival revealed the ICE treatment line (HR:4.8, 95% CI 1.7–12.8, p: 0.002), tumor site (HR: 0.12, 95% CI 0.03–0.4, p: 0.001) and response to ICE regimen (HR: 0.09, 95% CI 0.01–0.49, p: 0.005) to be independent prognostic factors. The group that received 1–2 chemotherapy regimens prior to the ICE regimen recorded better OS than the group received more than two chemotherapy regimens (22.8 months vs 5 months, p: 0.006).

Conclusion: The ICE regimen may be particularly effective when used for early treatment after doxorubicin-based therapy in patients with advanced or relapsed soft tissue sarcomas.

Keywords: Chemotherapy, ICE regimen; soft tissue sarcoma

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Soft tissue sarcomas (STS) constitute 1% of all cancers, and are of mesenchymal origin, with more than 70 different histological types.[1] In recent years, despite major advances in the field of oncology, there are still limited systemic treatment options for the treatment of soft tissue sarcomas.[2] In this area, where treatment agents are limited, chemotherapy agents play an important role in the management of advanced or relapsed soft tissue sarcomas.[2,3] Should doxorubicin be applied alone or in combination with ifosfamide? Although the subject is controversial, the combination of doxorubicin and ifosfamide is a commonly used treatment regimen in advanced stage sarcomas.[4] The objective response rates with this combination in first line treatment are 23–48%.[5-7] Treatment options after a failure to respond to first line therapy are more limited, and the prognosis is much worse. The second line treatment for

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advanced or relapsed soft tissue sarcomas includes high-dose ifosfamide, gemcitabine with docetaxel, pazopanib and trabectedin, the latter two of which have entered the treatment algorithm in the last decade.[8] Soft tissue sarcomas are a highly heterogeneous disease with different histopathological, molecular features and clinical behaviors, and while new treatment options may be beneficial in some subgroups of patients, they show limited benefit in a significant proportion of STS patients. Accordingly, the treatment of STS has come to be managed based on the histological type in recent years. For example, gemcitabine-based treatments are preferred in leiomyosarcoma, while trabectedine is preferred in myxoid liposarcoma.[9] Furthermore, in some histological types, the efficiency of tyrosine kinase inhibitors has been demonstrated.[3] In general, chemotherapy agents show efficacy in both specific and non-specific histology subtypes.[9] Furthermore, chemotherapeutic agents can be considered a suitable treatment option in patients who are not candidates for targeted therapy agents, or who do not respond to targeted therapy. Due to the limited number of effective treatment agent options for the treatment of advanced soft tissue sarcomas, more effective systemic treatments are needed.

The ICE regimen consists of three chemotherapy agents, given in different dosages and with different mechanisms of action (ifosfamide, carboplatin, etoposide), and has shown promising results in the treatment of many recurrent and refractory malignant solid tumors, in both childhood and adulthood.[10-17] There have been few studies evaluating ICE chemotherapy in patients with adult advanced or relapsed soft tissue sarcomas. While the effectiveness of the ICE treatment regimen in soft tissue sarcomas in childhood has been demonstrated in many studies, its effectiveness in adults has not been fully established.[8-10,18]

In the present study we analyze the efficacy and tolerability of the ICE regimen (ifosfamide, carboplatin and etoposide) and the prognostic factors for survival in patients with advanced/relapsed soft tissue sarcomas treated with this regimen.

Methods

The medical records of patients with advanced or relapsed STS undergoing treatment with the ICE regimen in our center between 2008 and 2020 were evaluated retrospectively. All patients had been treated previously with anthracyclines and ifosfamide for advanced or relapsed STS of different histological sub-types, or as adjuvant therapy in the early stage of disease. Patients younger than 18 years of age and those with bone sarcomas, gastrointestinal stromal tumors and angiosarcoma, were excluded from the study.

Included in the analysis were patients with histologically confirmed soft tissue sarcoma, with advanced or relapse disease, with distant metastases or with locally advanced disease. All patients had measurable disease and adequate hematological (absolute neutrophil count greater than 1,500/ml, platelet count greater than 100,000/ml), hepatic (AST and ALT less than three times normal and bilirubin <1.5 mg/dl) and renal (serum creatinine <1.5 mg/dl and creatinine renal clearance >60 ml/min) function, and an Eastern Cooperative Oncology Group performance status of 0–1. The demographic and clinical characteristics of the patients, their histopathological features and details of their treatments were recorded.

A total of 13 clinical variables were evaluated, based on previously published clinical trials, being patient age (>50/≤50), gender, histologic subtype (non-adipose/adipose), tumor size (>10 cm/≤10 cm), tumor grade (1–2/3), tumor site (extremity/non-extremity), stage at diagnosis (stage 1–2/3–4), ICE treatment line (1–2nd line/>2nd line), response to ICE regimen, region of relapse (locally/distant), surgical history, and presence of adjuvant chemotherapy and radiotherapy. The study was approved by the local ethics committee.

Treatment Plan

The patients were treated with the ICE regimen (ifosfamide, carboplatine, etoposide) administered i.v. over 2–5 hours on day 1–5 of a 21-day cycle. The ICE regimen comprised ifosfamide 1800 mg/m^2 (2-hour infusion), with the same dosage of mesna (24-hour infusion) on days 1–5; carboplatin 400 mg/m^2 (1-hour infusion) on days 1 and 2; and etoposide 100 mg/m^2 (1-hour infusion) on days 1–5. Thus, the total dosages were ifosfamide 9000 mg/m^2, carboplatin 800 mg/m^2 and etoposide 500 mg/m^2. Each cycle was repeated after 3 weeks, or after hematologic recovery, as previously described. For all patients, a 5 µg/kg/day (subcutaneously, five day) of granulocyte colony stimulating factor (G-CSF) was administered in a primer prophylaxis for 5 days after chemotherapy, and repeated in the following courses.

Dose reductions and treatment delays were made for grade 3 or 4 toxicities, based on the judgement of the treating physician. The treatment continued every 3 weeks until disease progression, unacceptable toxicity or patient refusal. Assessments of tumor response were based on radiological reports and reviews of imaging (contrast-enhanced computed tomography (CT) scans or magnetic resonance imaging (MRI). Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) after every third cycle of treatment. The side effects were evaluated after each treatment cycle, based on the Common Terminology Criteria for Adverse Events (CTCAE), 4th Edition.

Definitions

PFS was defined as the period from the beginning of treatment until documented progression or death; OS was defined as the period from the first day of treatment until the date of the last follow-up or death; the response rate was classified as follows: complete response was defined as no evidence of measurable disease; partial response was defined as a 30% or more reduction in the product of the perpendicular diameter of the primary lesion, with no evidence of new lesions; stable disease (SD) was defined as no significant change (<20% increase or <30% decrease) in tumor size; and progressive disease was defined as an increase in tumor size greater than 20%. The objective response rate (ORR) was defined as the sum of the partıal response (PR) and the complete response (CR). Disease control was defined as the sum of PR, CR and SD (stable disease), maintained for at least 3 months. The parameters identified as prognostic factors for advanced soft tissue sarcoma in previous studies were included in the analysis.

Statistics

PASW Statistics (Version 18.0. Chicago: SPSS Inc.) was used for the statistical analyses. A univariate analysis was performed with independent samples using a t-test, a Chi-square test and a Fisher's exact test. For the survival analysis, the Kaplan-Meier method was used and a log-rank test was performed for the evaluation of the differences between groups. A multivariate analysis was performed using the Cox model. The parameters identified as prognostic factors for advanced or relapsed soft tissue sarcoma in the univariate analysis were entered into the Cox model. A P value of <0.05 was accepted as statistically significant.

Results

Patient Characteristics

A total of 28 patients treated with the ICE regimen in our centers between 2008 and 2020 were evaluated retrospectively. All patients had previously been treated with anthracycline and ifosfamide for advanced or relapsed soft tissue sarcoma, or as adjuvant therapy in early stage disease. The tumor characteristics and clinical features of the patients are reported in Table 1. The median age was 38 years (range 15–65) and the median ECOG was PS 1. The patients were 71.4% (20/28) male and 28.6% (8/28) female. The distribution of histological subtypes was as follows: pleomorphic sarcoma (9/32.1%), leiomyosarcoma (7/25%), liposarcoma (3/10.7%), fibrosarcoma (3/10.7%), synovial sarcoma (3/10.7%) and others (3/10.7%). Of the total, 11 (39.3%) patients were identified with ≥10 cm tumors at diagnosis; 8 (28.6%) of all patients had moderately differentiated sarcomas (grade 1–2), and poorly differentiated tumors (grade 3) were observed in 71.4% (n=20/28) of the patients. The majority of sarcomas were localized in the trunk (14/50%) followed by the extremities (10/35.7%).

Some 75% (21/28) and 64.2% (18/28) of patients, respectively, underwent surgery and radiotherapy prior to the application of the ICE regimen, and 72.2% (13/18) of the patients had undergone adjuvant radiotherapy. Surgery was performed for curative purposes in 60.7% (17/21) of the patients. The proportion of patients receiving adjuvant chemotherapy was 72.2% (13/18). The median number of previous chemotherapy regimens undertaken by those with advanced or relapsed disease was 2.3 (range 1–4). All patients had undergone previous anthracycline and ifosfamide treatment (IMA). Previous therapies were doxorubicin and ifosfamide (IMA regimen), gemcitabine and docetaxel, pazopanib and cyclophosphamide and etoposide (orally). The patients had undergone a median of 3.5 ICE cycles (range 1–12) for advanced or relapsed soft tissue sarcomas. The ICE regimen was given as the first- and second-line treatment in 60.7% (17/28) patients, and as another treatment line in 39.3% (11/28) of patients.

Survival Analysis and Response Rates

The median follow up time was 8 months (range 1–98); the median PFS was 6 months (95% CI: 3.6–8.3 months); and the median OS was 9.3 months (95% CI: 4.7–13.9). One year PFS and OS rates were 28.6% and 32.1%, respectively. The median PFS was 10 months (95% CI,1–20.9 months) and 6 months (95% CI, 3.1–8.8 months) in patients who received 1–2 lines of therapy, and in patients who had received >2 previous lines of therapy prior to the ICE regimen for advanced or relapsed STS, respectively (p=0.19). This study provided a significant difference in median OS in patients who received 1–2 lines of therapy before ICE regimen for advanced or relapsed disease compared to those who had undergone more than 2 lines of therapy [median OS;1–2nd line: 22.8 months (4.2–41.4) and >2nd line: 5 months (2.8–7.2) p=0.006] (Fig. 1).

Of the total, five patients (17.9%) responded to treatment with PR and five (17.9%) had SD, CR was 7.1% (2/28) and 16 patients (57.1%) were diagnosed with disease progression. The ORR (CR, PR) and disease control rate (CR, PR, SD) were 25% and 42.9%, respectively. The response rates did not differ between patients that had previously received 1–2 lines of chemotherapy and those who received >2 previous lines of treatment for advanced or relapsed STS (p: 0.41). That said, the disease control rates were 52.9% and 27.3% in patients treated with 1–2 lines and with >2 previous therapeutic regimens (p: 0.66). Overall survival was significantly longer in patients with disease control than in

Table 1. Tumor characteristics and clinical features of patients who received ifosfamide,carboplatin and etoposide

Characteristics (total 28 patients)	n (%)	Characteristics (total 28 patients)	n (%)
Age at diagnosis (median, range)	40 (15-65)	Site of metastasis*	
>50	5 (17.9)	Lung	17
≤50	23 (82.1)	Osseous	12
Gender		Liver	2
Female	8 (28.6)	Others	3
Male	20 (71.4)	Site of relapse (n: 18)	
Tumor histologic subtypes		Local	6 (33.3)
Leiomyosarcoma	7 (25)	Distant	12 (66.7)
Liposarcoma	3 (10.7)	Previous therapies	
Fibrosarcoma	3 (10.7)	Ifosfamide+doxorubicin (IMA)	15 (53.5)
Pleomorphic sarcoma	9 (32.1)	Gemcitabine+docetaxel	18 (64.2)
Synovial sarcoma	3 (10.7)	Pazopanib	15 (53.5)
Others	3 (10.7)	Cyclophosphamide+etoposide	1 (3.5)
Tumor size		ICE treatment line	
<10 cm	17 (60.7)	1nd line	8 (28.6)
≥10 cm	11 (39.3)	2nd line	9 (32.1)
Tumor grade		>2nd line	11 (39.3)
Grade 1	1 (3.6)	Responses to ICE regimen	
Grade 2	7 (25)	Partial response	5 (17.9)
Grade 3	20 (71.4)	Complete response	2 (7.1)
Tumor localization		Stable disease	5 (17.9)
Extremity	10 (35.7)	Progressive disease	16 (57.1)
Trunk	14 (50)	Adjuvant chemotherapy (n: 18)	
Head and neck	2 (7.1)	Yes	13 (72.2)
Other	2 (7.1)	No	5 (27.8)
Stage at initial diagnosis		Radiotherapy prior to ICE regimen (n: 18)	
I	1 (3.6)	Adjuvant	13 (72.2)
II	8 (28.6)	Palliative	5 (27.8)
III	9 (32.1)	Surgery prior to ICE regimen (n: 21)	
IV	10 (35.7)	Curative	17 (60.7)
		Palliative	4 (14.3)

*: It can be more than one.

those whose disease control could not be achieved [median OS; 23.4 months (17.7–29) and 5.4 months (4.0–6.9), respectively (p: 0.001)] (Fig. 2).

The prognostic factors, defined as patient age (>50/≤50), gender (male/female), histologic subtype (non-adipose/adipose), tumor size (>10 cm/≤10 cm), tumor grade (1–2/3), tumor site (extremity/non-extremity), stage at diagnosis (stage 1–2/3–4), ICE treatment line (1–2nd line/>2nd line), response to ICE regimen, region of relapse (locally/distant), surgical history, and presence of adjuvant chemotherapy and radiotherapy, were analyzed with univariate and multivariate analyses, the results of which are summarized in Table 2. The Multivariate analysis for PFS showed that only adjuvant chemotherapy among the variables [HR: 0.05, (95% CI 0.004–0.7), p: 0.02] was associated with improved PFS. The multivariate analysis for OS showed that the ICE treatment line [HR: 4.8, (95% CI 1.7–12.8), p: 0.002], tumor site [HR: 0.12, (95% CI 0.03–0.4), p: 0.001] and response to ICE regimen [HR: 0.09, (95% CI 0.01–0.49), p: 0.005] were independent prognostic factors for OS. The other variables in the multivariate analysis did not reach prognostic significance for OS (Table 2).

Toxicity

The most common toxicity was myelosuppression. Hematological toxicities of grade 3–4 occurred despite GCSF support for primary prophylaxis. Some 32% of patients experienced grade 3–4 neutropenia and 17.8% experienced grade 3–4 thrombocytopenia. Febrile neutropenia and infections were observed. The reported toxic effects are shown in Table 3. The most common non-hematological

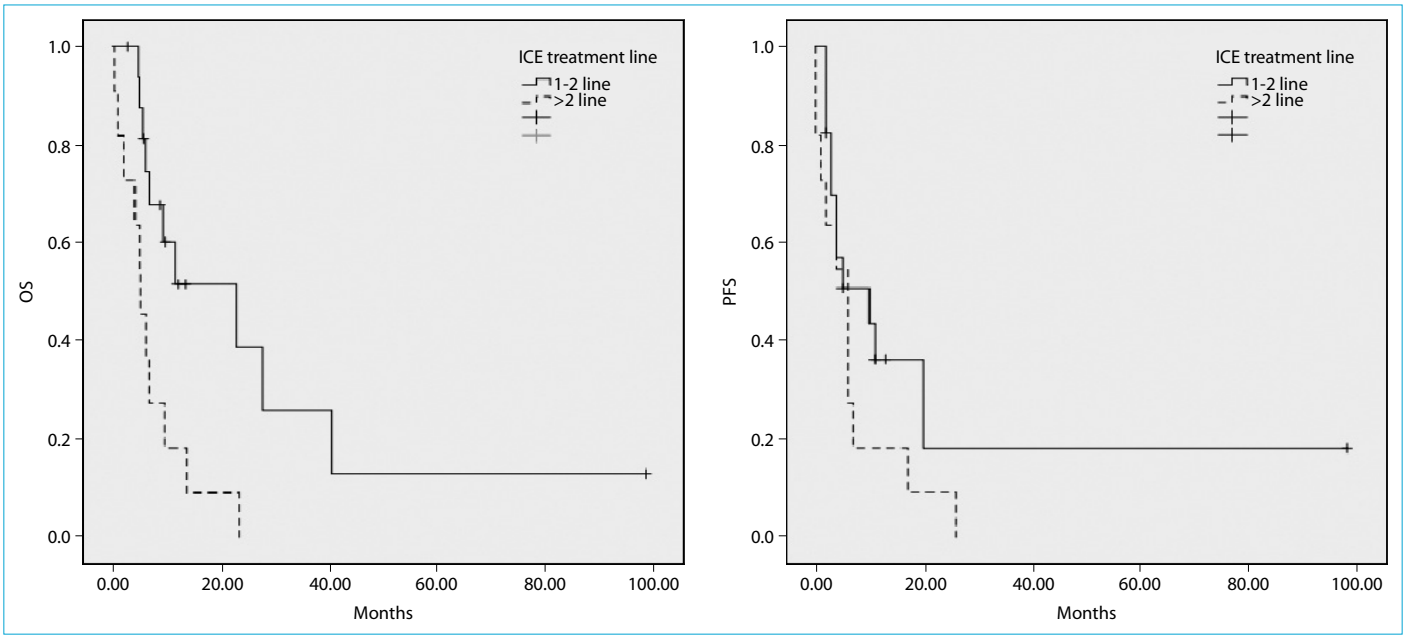

Figure 1. Kaplan-Meier curves of overall survival (OS) and progression-free survival (PFS) in 28 patients with advanced/relapsed soft tissue sarcoma who received 1-2 lines of therapy versus >2 lines of therapy before ICE regimen.

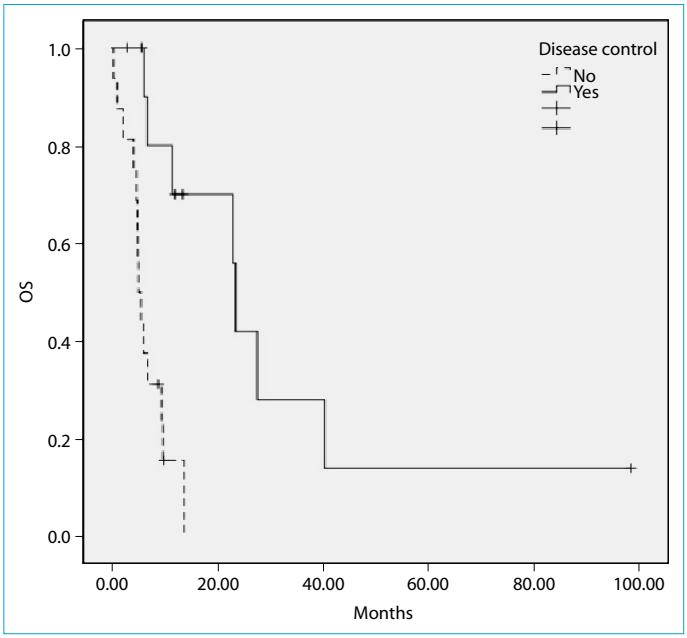

Figure 2. Kaplan-Meier curves for overall survival according to disease control rates.

toxicities were alopecia and nausea/vomiting. The non-hematological toxicities were relatively tolerable, with increased creatinine in 17.8% of grade 1 or 2 cases (Table 3). No grade 3 or 4 neurologic or hepatic toxicities were observed. Dose reductions were applied if severe thrombocytopenia or neutropenic fever occurred, or in the event of repeated treatment delays. Dose reduction was necessary for 40% (11/28) of the patients due to grade 3–4 toxicity, and a postponement of chemotherapy was necessary for 30% (8/28) of the patients. No chemotherapy-related toxic deaths occurred.

Discussion

Despite the significant progress made in understanding the pathophysiology of sarcoma, as well as the addition of new agents to the treatment algorithm in recent years, survival outcomes are still poor in patients with advanced soft tissue sarcomas, with a median overall survival rate of 14–17 months.[4,8,9,18] The standard therapeutic approach to first-line treatment for patients with advanced soft tissue sarcoma has been doxorubicin and ifosfamide, either alone or in combination, while no standard treatment exists for patients with soft tissue sarcomas after first-line treatment, and there are few treatment options for second-line treatment.[4,18] The efficacy of treatment options such as gemcitabine/docetaxel, pazopanib and trabectedine developed over the last decade are also limited.[8,9] In patients who progressed after doxorubicin and ifosfamide-based treatment, the objective response rate using gemcitabine plus docetaxel used in the second line is 27–50%, and the median OS is 14.7 months.[19-21] That said, the gemcitabine and docetaxel combination is widely used in all sarcoma types, and with moderate treatment outcomes. Pazopanib – a multitargeted tyrosine kinase inhibitor – was shown to improve PFS in patients with previous treatment compared to a placebo (4.6 months vs 1.6 months, p<0.001) in a PALETTE trial involving non-adipocytic soft tissue sarcomas, although no significant difference was observed in OS (12.5 months vs 10.7 months; p: 0.25).[22] With pazopanib, the ORR

Table 2. Univariate and multivariate analysis of prognostic factors for progression free survival and overall survival

Variables	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (>50/≤50)	0.24 (0.56-1.1)	0.06			0.5 (0.17-2)	0.39		
Gender (male/female)	0.9 (0.34-2.3)	0.08			1 (0.4-2.7)	0.92		
Tumor size (>10 cm/≤10 cm)	1.6 (0.6-3.8)	0.27			0.8 (0.3-2)	0.69		
Tumor grade (1-2/3)	1.9 (0.7-5.3)	0.19			1.8 (0.6-5.1)	0.2		
Tumor site (extremity/non-extremity)	0.35 (0.13-0.93)	**0.03**	2.8 (0.39-20.3)	0.29	0.3 (0.12-0.82)	**0.01**	0.12 (0.03-0.4)	**0.001**
Histologic subtype (non-adipose/adipose)	0.7 (0.16-3.1)	0.65			0.5 (0.13-2.7)	0.5		
Stage at initial diagnosis (stage 1-2/3-4)	0.68 (0.26-1.7)	0.43			0.69 (0.24-1.9)	0.48		
ICE treatment line (1-2nd line/>2nd line)	1.7 (0.7-3.9)	0.2			3.3 (1.3-8.4)	**0.009**	4.8 (1.7-12.8)	**0.002**
Response to ICE regimen (Yes/No)	0.3 (0.1-0.9)	**0.04**			0.17 (0.03-0.8)	**0.02**	0.09 (0.01-0.49)	**0.005**
Relaps (locally/distant)	1.8 (0.5-6.3)	0.3			1.7 (0.51-6.1)	0.35		
Surgery at diagnosis (Yes/No)	0.4 (0.18-1)	**0.05**	0.33 (0.31-3.6)	0.37	0.45 (0.18-1)	0.07		
Adjuvant radiotherapy (Yes/No)	1.6 (0.4-6)	0.46			0.94 (0.28-3.1)	0.92		
Adjuvant chemotherapy (Yes/No)	0.25 (0.08-0.8)	**0.02**	0.05 (0.004-0.7)	**0.02**	0.39 (0.12-1.2)	0.1		

PFS: Progression free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ICE: ifosfamide,carboplatin and etoposide.

was reported to be 6%, while the stable disease rate was 67%. Trabectedine provided greater improvement to PFS when compared to dacarbazine in a phase 3 study (median PFS 4.2 vs 1.5 months, [HR 0.55, (95% CI, 0.44–0.70), p<0.001], but with no difference in overall survival (12.4 vs 12.9 months, p: 0.37). The ORR with trabectedine was 9.9% and the clinical benefit rate was 34%. Trabectedine was found to be much more effective in liposarcoma with a myxoid/round histology.[23]

Ifosfamide is an effective agent against metastatic soft tissue sarcoma.[24] High-dose ifosfamide has been shown to be effective after the use of ifosfamide as a first-line treatment in advanced STS.[25-28] Ifosfamide, etoposide and carboplatin are effective chemotherapeutic agents that have been reported to demonstrate a synergistic effect when administered together in different doses in patients with relapsed or refractory sarcoma.[29-31] The present study assessed the activity of the ICE regimen in advanced stage soft tissue sarcomas in a sample in which all patients had previously undergone doxorubicin and ifosfamide treatments. The ICE regimen provided 25% objective response and 42.9% disease control. The median PFS was 6 months (95% CI: 3.6–8.3), and the median OS was 9.3 months (95% CI: 4.7–13.9). In the present study, overall survival was significantly longer in patients with disease control than in those without disease control [23.4 months (17.7–29) and 5.4 months (4.0–6.9), respectively, (p: 0.001)] (Fig. 2). When the ICE regimen was used in early lines of treatment, it showed no superiority over PFS when compared to late lines of treatment, but provided a significant difference in median OS [(22.8 months (4.2–41.4) for 1-2 lines of therapy vs 5 months (2.8–7.2) for >2 lines of therapy, (p: 0.006)] (Fig. 1). Furthermore, a multivariate analysis identified the ICE treatment line [HR: 4.8 (95% CI 1.7–12.8), p: 0.002], tumor site [HR: 0.12, (95% CI, 0.03–0.4), p: 0.001] and response to ICE regimen [HR: 0.09, (95% CI, 0.01–0.49), p: 0.005] as independent prognostic factors that are predictive of OS. The ICE regimen is a treatment option that can be recommended in early lines of treatment after standard doxorubicin and ifosfamide therapy (IMA) in young patients with good performance due to its greater efficacy when used in the early lines of treatment, and reflections of disease control on overall survival.

Few studies to date have demonstrated the activity of the ICE regimen in soft tissue sarcomas. The study by Fields et al,[32] which included a wide variety of cancer types, identified a partial response (95% CI confidence 0–50%) with the ICE regimen in 2 of 10 patients with sarcomas. Again, few studies have investigated the efficacy of reduced dose ICE combined with hyperthermia in patients with locally advanced, non-resectable or metastatic STS, refractory to

Table 3. Most common adverse events

Type of toxicity (n/%)	Grade ½	Grade ¾
Hematologic toxicity		
Neutropenia	7 (25)	9 (32)
Febrile Neutropenia	6 (21)	7 (25)
Thrombocytopenia	7 (25)	5(17.8)
Anemia	9 (32)	8 (28.5)
Non-hematologic toxicity		
Nause/vomitting	13 (46.4)	10 (35.7)
Stomatitis	3 (10.7)	6 (21)
Fatigue	14 (50)	9 (32)
Appetite loss	11 (39)	5 (17.8)
Alopesia	14 (50)	10 (35.7)
Allergic reaction	8 (28.5)	0
Neuropathy	8 (28.5)	2 (7.1)
Encephalopathy	0	0
Renal toxicity	5 (17.8)	2 (7.1)
Constipation	11 (39)	4 (14.2)
Diarrhea	3 (10.7)	1 (3.5)
Hepatotoxicity	0	0

standard IMA treatment.[29,30,33,34] The administration of concurrent hyperthermia and chemotherapy is based on experimental studies, while it has also been shown that heat exposure combined with chemotherapy can increase cell death in tumor cells by increasing the sensitivity to chemotherapy.[29,30] Another study by Fiegl et al.[33] evaluated the efficacy of the addition of regional hyperthermia to a reduced dose of the ICE regimen (ifosfamide 1.5 mg/m^2, carboplatin 100 mg/m^2, etoposide 150 mg/m^2 (1-4) every 28 days). With the combination of ICE regimen and hyperthermia, the objective response rate was 20%, median overall survival was 14.6 months (95% CI 10.6–16.1) and progression-free survival was 6 months (95% CI 4.9–12.1), although no statistically significant difference was found in the median overall survival between those who responded to treatment and those who did not (p: 0.62). The study by Wideman et al.,[34] in turn, reported a response rate with ICE and whole body hyperthermia treatment of 58% (28–85).

The study by Bücklein et al.[30] evaluated the efficacy of ICE regimen combined with regional hyperthermia in both metastatic and locally advanced non-metastatic patients. Disease control was reported as 59% and 47% in the locally advanced disease group and in the metastatic disease group, respectively. The objective response rate was 20.5% in locally advanced disease and 10.9% in metastatic disease. The PFS and OS were much better in the locally advanced disease group than in the metastatic group (median PFS 10–4 months (p<0.0001), median OS 26–12 months, p: 0.002). In the study, disease control was identified as the only prognostic factor in a multivariate analysis. In the present study, in turn, the ORR with only the ICE regimen was 25%, and the disease control rate was 42.9%. The multivariate analysis identified response to the ICE regimen as an independent prognostic factor that is predictive of overall survival. Considering the findings of the present study and all ICE±hyperthermia studies, it can be said that the ICE regimen alone is effective, while the additional contribution of hyperthermia is limited.

There have been studies investigating the efficacy of the VIP regimen, in which cisplatin is used instead of carboplatin, alongside ifosfamide and etoposide, unlike in the ICE regimen, for patients with advanced and metastatic soft tissue sarcoma.[35,36] A phase 2 study by Papai et al.[35] assessed the efficacy of the VIP regimen in patients with previously untreated inoperable/metastatic soft tissue sarcomas. The study reported an overall response rate with a manageable side effect profile of 46% (complete response 10%, partial response 36%), and the median OS was 8 months. In a study by Moon et al.,[36] in turn, the ORR with the VIP regimen was 37.5%, and the disease control rate was 50% in patients with sarcoma, but with no previously received treatment. The median PFS was 3.7 months (95% CI, 1.3–6.1) and the median OS was 10.0 months (95% CI, 6.6–13.5). The response rates and survival outcomes achieved with the VIP regimen were similar to those recorded in the present study, and in previous studies evaluating ICE±hyperthermia.[30,33,34] Considering toxicity (nephrotoxicity, myelotoxicity, etc.), carboplatin or cisplatin may be preferred in patients scheduled for therapy, in combination with ifosfamide.

High doses of chemotherapy can be expected to increase response and survival than standard chemotherapy doses in general, although it increases toxicity and treatment-related mortality. In the present study, myelosuppression was the most common toxicity, despite prophylactic GCSF support. Despite the high myelosuppression profile, the ICE combination was otherwise well tolerated, and had modest nonhematologic side effects. There were no toxic deaths recorded in the present study. The toxicity results were similar to those of previous studies.[33,34]

There are several limitations to the present study, the main ones being its retrospective design, the limited number of patients and the heterogeneous patient group, due to the different histological subtypes and the heterogeneity of the treatment regimens before and after the ICE regimen application. Another limitation of the study is that the patients who received ICE regimen and those who did not receive ICE regimen were not evaluated comparatively.The heterogeneity of the treatments administered may have influenced the treatment outcomes. Despite the limited

number of patients and the retrospective design of the study, the ICE regimen has been shown to be efficient for the treatment of patients previously treated for STS.

In conclusion, patients with advanced/relapsed soft tissue sarcomas have access to limited treatment options and treatment management can be difficult. In patients with advanced/relapsed STS, treatment with the ICE regimen seems promising after the failure of first-line systemic chemotherapy. The present study found that the ICE regimen may be much more effective when used in early lines of treatment. Despite the high myelosuppressive side effect profile, the side effects can be tolerable and manageable when the appropriate supportive treatments are administered for the side effects. There is a need for randomized controlled studies to be conducted in larger populations regarding using ICE regimen as an alternative treatment regimen in soft tissue sarcoma cases.

Disclosures

Ethics Committee Approval: The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations (permit no:126/2021).

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