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Research Article

Efficacy of Ifosfamide, Carboplatin and Etoposide Protocol in the Treatment of Relapsed or Refractory Bone and Soft Tissue Sarcomas

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Abstract

Objectives: To aim to show the survival outcomes of ifosfamide, carboplatin and etoposide (ICE) therapy and the characteristics of treatment-related hematological side effects in patients with relapsed/refractory bone sarcomas (BSs) and soft tissue sarcomas (STSs).

Methods: Patients who were treated at the Department of Medical Oncology, Gulhane School of Medicine between January 2017 and June 2021 were included. Post-ICE progression-free survival (PFS), overall survival (OS) rates and treatment-related hematological side effects were determined.

Results: Fifty-six adult patients were included (thirty-four of them BSs). PFS was determined as 6.7 ± 4.4 months and 7.1±3.6 months for STSs and BSs, respectively. OS was 11.4±5.6 monhts and 12.6±7.1 for STSs and BSs, respectively. PFS and OS were not found to be better between groups (p=0.84 and p=0.517, respectively). The median OS and PFS after ICE protocol in patients with two or less systemic chemotherapy lines were significantly higher than those who received three or more lines (7.85±1.66 vs 3.74 ±2.89, p=0.001 and 13.80±8.45 vs 6.73, p=0.001).

Conclusion: In addition to its contribution for all patients, ICE may contribute to longer survival, especially in patients receiving ≤2 lines of systemic chemotherapy.

Keywords: Bone sarcoma, carboplatin, etoposide, ifosfamide, soft tissue sarcoma

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Sarcomas are a group of heterogeneous and rarely observed malignancies with mesenchymal origin. Sarcomas constitute less than one percent of all adult cancers.[1-3] It is accepted that approximately eighty percent of all sarcoma patients have soft tissue sarcomas.[3] Bone sarcomas (BSs) are bone tumors of malignant mesenchymal origin with many different subtypes. Ewing sarcoma (ES) and osteosarcoma are the most common primary bone tumors in young adults. Soft tissue sarcomas (STSs) are a heterogeneous group of tumors that can arise from mesenchymal cells in any area of the body. These tumors most commonly originate from the extremities.[4,5]

There is a poor prognosis for relapsed/refractory BSs and STSs. The desired survival advantage could not be achieved with the second and subsequent chemotherapy lines. Successful treatment regimens in this regard are very limited.

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The ifosfamide, carboplatin and etoposide (ICE) protocol is a systemic conventional chemotherapy protocol that has been shown to provide significant survival and disease control in many relapsed/refractory malignancies.[6,7] But prospective studies showing the efficacy of the ICE protocol in relapsed/refractory BSs and STSs are lacking. There are reports on this subject with a small number of patients.

We aimed to show the effectiveness of the ICE protocol on survival and disease control endpoints in relapsed/refractory BSs and STSs.

Methods

This retrospective, single center study was performed using the medical records of outpatients and inpatients with relapsed/refractory BSs and STSs at Department of Medical Oncology, Gulhane School of Medicine from January 2017 through June 2021. The inclusion criteria were age ≥18 years, those with histologically confirmed advanced stage BSs and STSs, imaging-proven metastases at diagnosis or at recurrence. The exclusion criteria were age <18 years and insufficient clinical data. The local ethics committee approved the study protocol (ethics committee approval number 2021/60).

Gender, age, localization, histology of the primary malignancy and stage at the time of diagnosis were recorded. Lung, liver, bone, soft tissue, lymph node and brain metastasis status before the ICE protocol were evaluated within the scope of the study. Number of previous treatment lines, number of ICE protocol implementation, response to treatment and observed side effects were recorded after the ICE protocol. Survival after the ICE protocol and survival status (alive/exitus status) were evaluated.

Before the ICE protocol, the patients were divided into two groups as BSs and STSs. Progression-free survival (PFS) defined as the time from ICE onset to the first documented disease progression or death due to any cause. Overall survival (OS) after ICE protocol was calculated as the time from the start of the ICE protocol to the last seen date or the patient's exitus date. Objective response rate (ORR), defined as the proportion of participants with a complete response or partial response. The ICE protocol was as follows: Ifosfamide 1667 mg/m^2/day for 3 days, mesna 1667 mg/m^2/day for 3 days, carboplatin AUC 5 for a single day, etoposide 100 mg/m^2/day for 3 days. G-CSF administration is recommended routinely after the ICE protocol.

Statistical analyzes were performed using SPSS 22.0 software (SPSS Inc., Chicago, Illinois). Descriptive data are presented as a percentage of the total. Normality of continuous variables was examined using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and non-normally distributed were expressed as median [interquartile range (IQR)]. Between-group differences were tested using the Chi-Square test, Student's t-test or Mann-Whitney U test, as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

The final sample included 56 patients (males: 64.3%). The median age was 25 (IQR:16). In fifty percent of the sample, the primary tumor site was the extremities. Fifty-nine percent of the sample had Stage III or IV disease at the time of initial diagnosis. In the BSs sample, ES was seen as sixty-two percent. The malignant mesenchymal tumor was found to be thirty-five percent, constituting the largest proportion in the STSs sample. Adjuvant chemotherapy history is present in fourty-one percent of patients. Ninety-one percent of patients have lung metastases. The characteristics of the patients are presented in Table 1.

The ORR to the ICE was 48.2% for whole patients. There was no significant difference in PFS between BSs and STSs groups [median months (IQR) 6.7 (4.4) vs 7.1 (3.6), p=0.840]. Likewise, there was no significant difference in OS between the BSs and STSs groups [mean months (SD), 11.4 (5.6) vs 12.6 (7.1), p=0.517]. The patients were divided into two groups according to the order in which they received the ICE protocol (two or less lines vs. three or more lines). The median PFS (IQR) after the ICE protocol in patients with two or less lines was significantly higher than those who received three or more lines [7.85 (1.66) vs 3.74 (2.89)), p=0.001]. Similarly, the median OS (IQR) after the ICE protocol in patients with two or less lines was significantly higher than those who received three or more lines [13.80 (8.45) vs 6.73 (6.31), p=0.001]. Forty-one percent of patients had a history of more than two systemic chemotherapy prior to the ICE protocol. The frequency of febrile neutropenia during ICE was found to be twenty-five percent. Treatment side effects and responses to treatment are presented in Table 2, Table 3 and Figure 1.

Discussion

Treatment of relapsed/refractory sarcoma, whether BSs or STSs, is a challenging process for both patients and medical oncologists. There are currently no satisfactory survival-prolonging treatments available. We evaluated the use of the ICE in patients with relapsed/refractory BSs and STSs, and determined that it contributed significantly to survival and disease control. In addition, significant PFS and OS contribution was achieved after ICE, especially in those receiving <2 lines of systemic therapy.

Table 1. The demographic and disease and treatment related characteristics of the patients

Features	Soft Tissue Sarcomas (n=22)	Bone Sarcomas (n=34)	Whole Group (n=56)
Gender, male,n(%)	17 (77.3)	19 (55.9)	36 (64.3)
Age at diagnosis, median (IQR), years	32.5 (32.75)	22.5 (6.25)	25 (16)
Age at diagnosis,n(%)			
≥30	12 (54)	7 (20)	19 (34)
<30	10 (46)	27 (80)	37 (66)
Primary location,n(%)			
Head and neck	2 (9)	3 (9)	5 (9)
Extremities	9 (41)	19 (56)	28 (50)
Body	1 (4)	3 (9)	4 (7)
Intrabdominal	4 (18)	1 (3)	5 (9)
Pelvis	6 (27)	8 (23)	14 (25)
Stage,n(%)			
1 or 2	5 (23)	18 (53)	23 (41)
3 or 4	17 (77)	16 (47)	33 (59)
Pathological Subtype,n(%)			
Ewing Sarcoma	- (0)	21 (62)	21 (38)
Osteosarcoma	- (0)	12 (35)	12 (21)
Condrosarcoma	- (0)	1 (3)	1 (2)
Malign Mesenchymal Tumor	8 (35)	- (0)	8 (14)
Rhabdomyosarcoma	6 (27)	- (0)	6 (10)
Leiomyosarcoma	3 (14)	- (0)	3 (5)
Synovial Sarcoma	3 (14)	- (0)	3 (5)
Liposarcoma	1 (5)	- (0)	1 (2)
Angiosarcoma	1 (5)	- (0)	1 (2)
Adjuvant Chemotherapy,n(%)	5 (23)	18 (53)	23 (41)
Adjuvant Radiotherapy,n(%)	- (0)	18 (53)	18 (53)
Visceral Metastases,n(%)			
Lung	21 (95)	30 (88)	51 (91)
Liver	6 (27)	6 (18)	12 (21)
Bone	7 (32)	24 (71)	31 (55)
Soft Tissue	10 (45)	4 (12)	14 (25)
Brain	1 (5)	4 (12)	5 (9)
Lines of Systemic Treatments Before ICE,n(%)			
≤ 2 lines	14 (64)	19 (56)	33 (59)
> 2 lines	8 (36)	15 (44)	23 (41)
Hematological Adverse Events after ICE,n(%)			
Febrile Neutropenia	5 (23)	9 (26)	14 (25)
Grade 3 Neutropenia	5 (23)	9 (26)	14 (25)
Grade 3 Anemia	5 (23)	0 (-)	5 (9)
Grade 3 Thrombocytopenia	4 (18)	4 (12)	8 (14)

IQR: Interquartile range; ICE: Ifosfamide,carboplatin and etoposide.

Fiegl and colleagues evaluated the efficacy of the combined regional hyperthermia approach with the ICE in advanced STSs. They found an ORR of 20% and median OS of 14.6 months for all patients.[8] Aydin et al. conducted a study to evaluate the demographic characteristics, response to treatment, and outcomes of children with relapsing/resistant BSs and STSs treated with the ICE. OS rates were determined as 83% and 62% at 1 and 2 years. The ORR for ICE has been reported as 43%.[9] In these studies, it was reported that the combination of ICE improves the outcome of relapsed or refractory sarcomas and can be used as second-line therapy. Both Fiegl and colleagues and Aydin colleagues used the ICE protocol as second-line systemic therapy.[8,9] More than forty percent of our patients

Table 2. Treatment-related characteristics of the BSs and STSs patients

Features	Soft Tissue Sarcomas (n=22)	Bone Sarcomas (n=34)	p
Best Objective Response, n(%)			
Complete Response	- (0)	- (0)	
Partial Response	10 (46)	17 (50)	
Stable Disease	6 (27)	9 (26)	
Progressive Disease	6 (27)	8 (25)	
PFS, median (IQR), months	6.7 (4.4)	7.1 (3.6)	0.840
OS, mean (SD), months	11.4 (5.6)	12.6 (7.1)	0.517

PFS: Progressin free survival; OS: Overall Survival; IQR: Interquartile range; SD: Standart deviation.

Table 3. Survival and response-related features by treatment lines

Features	≤2 lines systemic therapy before ICE (n=33)	>2 lines systemic therapy before ICE (n=23)	p
Best Objective Response, n(%)			
Complete Response	- (0)	- (0)	
Partial Response	22 (66.7)	5 (21.7)	
Stable Disease	11 (33.3)	4 (17.4)	
Progressive Disease	-(0)	14 (60.9)	
PFS, median (IQR), months	7.85 (1.66)	3.74 (2.89)	0.001
OS, median (IQR), months	13.80 (8.45)	6.73 (6.31)	0.001

PFS: Progressin free survival; OS: Overall Survival; IQR: Interquartile range; SD: Standart deviation.

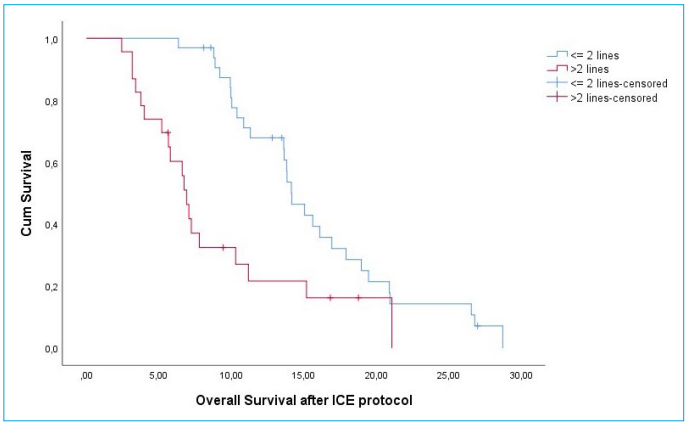

Figure 1. Survival plot by treatment lines.

received more than two systemic treatments before the ICE protocol. In our study sample, OS and ORR are shown similar to the studies mentioned. This can be considered as a sign that the ICE protocol is making a significant contribution to OS and disease control at the second line and beyond. When we evaluated both our BSs and STSs patients according to the order of their systemic treatment regimen, we found a longer PFS and OS contribution especially in patients who received two or less systemic treatments compared to those who received more than two systemic treatments. On explanation of such a difference may be that patients receiving more chemotherapy are generally more fragile and have lower performance.

Van Winkle and colleagues reported that the ORR of the combination of ifosfamide, etoposide, and carboplatin used in three phase I/II studies of the Pediatric Cancer Group was 36% in resistant osteosarcoma patients. They stated that stable disease was obtained in 38% of osteosarcoma patients and the one-year survival rate reached 41%.[10] Brunetto and colleagues, on the other hand, stated that the ICE protocol added to the VDC protocol contributed significantly to local disease control in ES patients.[11]

Our patients were mostly found under the age of thirty. It is known that sarcomas observed at young ages generally go with a relapsed/refractory clinic and have a poor prognosis.[12] Approximately half of our cases have advanced disease at the time of initial diagnosis. Survival is short for metastatic disease at initial diagnosis or at relapse.[13] The most common histopathological subtypes in BSs patients are ES and osteosarcoma.[14,15] Ninety-seven percent of our BSs patients had these two malignancies.

Lung metastases represent a poor prognostic feature for patients and cause interruptions in treatment and poor performance.[16] Most of our patients have lung metastases before the ICE protocol. However, a significant contribution

of PFS and OS may indicate the suitability of the ICE protocol for this patient population.

Bücklein and colleagues reported that Grade 3/4 hematological toxicity was observed in more than 60% of all their patients, despite dose reduction in more than 50% of sarcoma patients who were treated with the ICE protocol and regional hypertemia.[17]

We observed grade 3 neutropenia and febrile neutropenia at a rate of twenty-five percent. But with close follow-up and appropriate G-CSF prophylaxis, the hematological side effects profile can be managed.

This paper has several limitations. First, the number of patients was low, limiting the generalizability of the findings to different populations. Second, retrospective design of the study raises the possibility of errors in data quality. Third, since the analysis was cross-sectional, the results cannot be assumed to be causal. Finally, follow-up times and interval cannot be controlled in retrospective analyzes.

In conclusion, the ICE protocol can contribute to a successful PFS and OS in patients with BSs and STSs who are resistant to chemotherapy and have a poor prognosis and survival in the advanced stage. The timing of the treatment is important for success. The ICE protocol implemented in the early period provides a longer OS contribution. The ICE protocol has a tolerable and manageable hematological side-effect profile.

Disclosures

Ethics Committee Approval: This study was approved by the Gülhane Training and Research Hospital Ethics Committee (Decision No: 2021/60- Date: 29.09.2021).

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References

1. Miller RW, Young JL Jr, Novakovic B. Childhood cancer. Cancer 1995;75:395–405. [CrossRef]
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7–33.
3. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. 5th ed vol 3. Lyon: International Agency for Research on Cancer; 2020.
4. Billingsley KG, Burt ME, Jara E, Ginsberg RJ, Woodruff JM, Leung DH, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602–10. [CrossRef]
5. Potter DA, Glenn J, Kinsella T, Glatstein E, Lack EE, Restrepo C, et al. Patterns of recurrence in patients with high-grade soft-tissue sarcomas. J Clin Oncol 1985;3:353–66. [CrossRef]
6. Lotz JP, André T, Bouleuc C, Péne F, Gattegno B, Bazelly B, et al. The ICE regimen (ifosfamide, carboplatin, etoposide) for the treatment of germ-cell tumors and metastatic trophoblastic disease. Bone Marrow Transplant 1996;18:S55–9.
7. López-Aguilar E, Sepúlveda-Vildósola AC, Rivera-Márquez H, Cerecedo-Díaz F, Valdés-Sánchez M, Delgado-Huerta S, et al. Preirradiation ifosfamide, carboplatin and etoposide (ICE) for the treatment of high-grade astrocytomas in children. Childs Nerv Syst 2003;19:818–23. [CrossRef]
8. Fiegl M, Schlemmer M, Wendtner CM, Abdel-Rahman S, Fahn W, Issels RD. Ifosfamide, carboplatin and etoposide (ICE) as second-line regimen alone and in combination with regional hyperthermia is active in chemo-pre-treated advanced soft tissue sarcoma of adults. Int J Hyperthermia 2004;20:661–70.
9. Aydin B, Akyuz C, Varan A, Yalcin B, Kurucu N, Kutluk T. ICE regimen for relapsed/refractory bone and soft tissue sarcomas in children. Rev Recent Clin Trials 2018;13:126–31. [CrossRef]
10. Van Winkle P, Angiolillo A, Krailo M, Cheung YK, Anderson B, Davenport V, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer 2005;44:338–47. [CrossRef]
11. Brunetto AL, Castillo LA, Petrilli AS, Macedo CD, Boldrini E, Costa C, et al; Brazilian Collaborative On behalf of the Brazilian Collaborative Study Group of Ewing Family of Tumors EWING1 and the Brazilian Society of Pediatric Oncology SOBOPE. Carboplatin in the treatment of Ewing sarcoma: Results of the first Brazilian collaborative study group for Ewing sarcoma family tumors-EWING1. Pediatr Blood Cancer 2015;62:1747–53.
12. Vlenterie M, Ho VK, Kaal SE, Vlenterie R, Haas R, van der Graaf WT. Age as an independent prognostic factor for survival of localised synovial sarcoma patients. Br J Cancer 2015;113:1602–6.
13. Zhan H, Mo F, Zhu M, Xu X, Zhang B, Liu H, et al. A SEER-based nomogram accurately predicts prognosis in Ewing's sarcoma. Sci Rep 2021;11:22723. [CrossRef]
14. Obata H, Ueda T, Kawai A, Ishii T, Ozaki T, Abe S, et al; Japanese Musculoskeletal Oncology Group. Clinical outcome of patients with Ewing sarcoma family of tumors of bone in Japan: the Japanese Musculoskeletal Oncology Group cooperative study. Cancer 2007;109:767–75. [CrossRef]
15. Lee JW, Kim H, Kang HJ, Kim HS, Park SH, Kim IO, et al. Clinical characteristics and treatment results of pediatric osteosarcoma: the role of high dose chemotherapy with autologous stem cell transplantation. Cancer Res Treat 2008;40:172–7.
16. Digesu CS, Wiesel O, Vaporciyan AA, Colson YL. Management of sarcoma metastases to the lung. Surg Oncol Clin N Am 2016;25:721–33. [CrossRef]
17. Bücklein V, Limmroth C, Kampmann E, Schuebbe G, Issels R, Roeder F, et al. Ifosfamide, carboplatin, and etoposide (ICE) in combination with regional hyperthermia as salvage therapy in patients with locally advanced nonmetastatic and metastatic soft-tissue sarcoma. Sarcoma. 2020 Feb 27;2020:6901678.