Research Paper

Efficacy of replacing actinomycin-D with carboplatin in Ewing sarcoma consolidation treatment: Single-center experience

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ABSTRACT

Background: Treatment of Ewing sarcoma (ES) requires multidisciplinary approach and deficiencies in treatment adversely affect the results. This study included patients diagnosed with ES and aimed to determine the factors affecting prognosis and investigate the efficacy of replacing actinomycin-D with carboplatin in consolidation treatment.

Methods: Eighty-two pediatric ES patients diagnosed at a single institution between 2005 and 2020 were retrospectively evaluated. Clinical and epidemiological features, treatment modalities, prognostic criteria, and overall survival (OS) rates of patients reviewed. In consolidation treatment, 22 patients were treated with actinomycin-D and 32 patients with carboplatin (500 mg/m^2/dose), 24 patients could not receive consolidation treatment. The 5- and 10-year OS rates of the patients were compared.

Results: The 5- and 10-year OS rates of the 82 patients with ES were 46% and 40%, respectively. The 5-year OS rates in the group with localized disease (n = 55) and metastasis (n = 27) at diagnosis were 54% and 26%, respectively (p = 0.006). When evaluated according to the consolidation treatment administered both the 5- and 10-year OS rates of the patients receiving actinomycin-D were 50%. The 5-year OS rate was 58% in the carboplatin group, and the 5- and 10-year OS rates of patients that did not receive consolidation treatment was 20%.

Conclusions: Survival was significantly worse in the group that did not receive consolidation treatment. Furthermore, our results suggested that carboplatin could be used effectively as an alternative to actinomycin-D in ES consolidation treatment.

1. Introduction

Ewing sarcoma (ES) is the second most prevalent primary bone tumor following osteosarcoma. ES is locally aggressive, has high metastasis risk, and characterized by poor prognosis [1]. More than two-thirds of the patients with localized disease can be treated using multidisciplinary treatment regimens. In contrast, the survival rate of patients with metastatic disease at diagnosis is very low. Over the last decade, the overall survival (OS) rate has remarkably increased owing to advancements in multidisciplinary treatments. In the United States, the 5-year OS rate has increased from 44% in the 1970s to 68% in the early 2000s in patients with localized disease and from 16% to 39% in patients with metastatic disease [2].

The primary tumor, if resectable, is treated via surgery and/or radiotherapy. However, there is a high risk of metastasis even in patients with localized disease; therefore, chemotherapy should also be administered for preventing distant metastases and eliminating microscopic tumors. Treatment strategies intended for ES vary as per institutional preferences [3]. For example, in North America, young patients with localized ES receive intensively timed chemotherapy program every two weeks where vincristine, doxorubicin, and cyclophosphamide (VDC) are combined and alternately used with ifosfamide and etoposide (IE) [4]. Conversely, in Europe, the initial chemotherapy regimen is composed of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) [5].

In our clinic, all the patients diagnosed with ES receive standard induction VIDE chemotherapy, followed by vincristine, actinomycin-D,

A

VIDE X 6

VCR	1.5 mg/m^2/d	d1 (max 2mg)
IFO	3000 mg/m^2/d	d1,d2,d3
DOX	20 mg/m^2/d	d1,d2,d3
ETO	150 mg/m^2/d	d1,d2,d3

VAC X 8

VCR	1.5 mg/m^2/d	d1 (max 2mg)
ACT-D	0.75 mg/m^2/d	d1,d2
CYC	1500 mg/m^2/d d1	

B

VIDE X 6

VCR	1.5 mg/m^2/d	d1 (max 2mg)
IFO	3000 mg/m^2/d	d1,d2,d3
DOX	20 mg/m^2/d	d1,d2,d3
ETO	150 mg/m^2/d	d1,d2,d3

VCC X 8

VCR	1.5 mg/m^2/d	d1 (max 2mg)
CARBO	250 mg/m^2/d	d1,d2
CYC	1500 mg/m^2/d d1	

Fig. 1. Treatment administered to patients diagnosed with ES. **A.** Chemotherapy regimen used before 2013 that included VAC administration during consolidation therapy of patients diagnosed with ES. **B.** Chemotherapy regimen used since 2013 that includes VCC administration during consolidation therapy of patients diagnosed with ES. VCR, vincristine; IFO, ifosfamide; DOX, doxorubicine; ETO, Etoposide; ACT-D, actinomycin-D; CYC, cyclophosphamide; CARBO, carboplatine; d, day.

and cyclophosphamide (VAC) as consolidation therapy. As of 2013, carboplatin has been used as a replacement of actinomycin-D in the ES consolidation therapy performed in our clinic because actinomycin-D is not produced in Turkey and there are delays in its transportation.

Carboplatin is a drug used in the treatment of several solid tumors, including brain tumors, neuroblastoma, sarcomas, and germ cell tumors [6]. The present study aimed to determine the factors affecting prognosis and investigate the efficacy of replacing actinomycin-D with carboplatin in consolidation therapy for patients with ES.

2. Materials and methods

2.1. Study design

The medical files of 82 patients with ES who were observed at the Division of Pediatric Oncology/Stem Cell Transplantation Unit, ukurova University, Balcali Research Hospital between January 2005 and February 2020 were retrospectively reviewed in this study. Patients diagnosed and treated in another center and applied for the continuation of their treatment or those who were diagnosed in our clinic and applied to another center for treatment were excluded from the study. The clinical and epidemiological characteristics and chemotherapy protocols of the patients were recorded. The data were locked on September 30, 2021. All the patients received chemotherapy based on the EURO-EWING 99 protocol [5].

The patients were staged at diagnosis according to the Musculoskeletal Tumor Society and the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control criteria for bone and soft tissue tumors [7]. Progression was defined as an increase in the mass size or metastases development during the treatment period.

2.2. Treatments

Since Balcali Research Hospital is a referral hospital in the region, the number of visiting patients is high. Patients diagnosed with ES received VAC, which can be administered in outpatient settings, instead of inpatient treatment with vincristine, actinomycin-D, and ifosfamide as maintenance therapy (Fig. 1A). Since actinomycin-D is not produced in Turkey and has a low profit margin, there are controversies associated

with its supply. Since 2013, carboplatin has been used instead of actinomycin-D in the consolidation therapy of ES with an aim to avoid delays and deficiencies in treatment (Fig. 1B). An ethics committee approval associated with this treatment alteration was not obtained before treatment administration as a prospective study was not planned. Relevant written informed consents were obtained from the patients' parents or legal guardians before starting the chemotherapy. Certain patients were unable to receive maintenance therapy because of switching to another treatment option due to disease progression, treatment discontinuation, or death. Ethical approval for this research was obtained.

During the treatment process, the patients underwent imaging studies following three cycles of VIDE and were first referred to surgery for local control. Further, if the tumor was considered to be unresectable until the end of the 6th cycle of VIDE or surgery was rejected by the patients or their relatives due to the possible morbidity and mortality associated with it, the patients were referred to radiotherapy. Patients with macroscopic or microscopic residual tumors were also referred to radiotherapy for local control. The Common Terminology Criteria for Adverse Events v4.0 was used to assess the hematological and non-hematological toxicities after each chemotherapy cycle [8].

2.3. Statistical analysis

The Statistical Package for Social Sciences (version 21.0 SPSS, IL, USA) software was used for statistical analyses. The categorical variables were analyzed using chi-square test, and the numerical variables with normal distribution were analyzed using Student's t-test. The OS rates of our patients were calculated according to the Kaplan–Meier method. The log-rank test was used to compare the OS results of the patients. The statistical significance level was considered to be 0.05 for all the tests.

3. Results

Among the 82 patients, 48 (58.5%) were male and 34 (41.5%) were female. The median age at diagnosis was 118.5 months (range 3.0–216.0 months). The mean follow-up period of the patients was 47 ± 42.9 months (4–166 months). Thirteen patients (15.9%) were refugees and 69 (84.1%) were Turkish citizens. Of the refugee patients, 13 were

Table 1
Demographic and clinical characteristics of the patients.

	n (%)	5th year OS	10th year OS	p
Gender				
Boy	48 (58.5%)	37	37	0.094
Girl	34 (41.5%)	56	45	
Age				
0–10	42 (51.2%)	48	40	0.978
11–18	40 (48.8%)	42	42	
Year of diagnosis				
2004–2012	33 (40.2%)	43	39	0.798
2013–2020	49 (59.8%)	48	–	
Nationality				
Turkish citizen	69 (84.1%)	43	39	0.688
Refugee	13 (15.9%)	47	–	
Tumor location				
Extremity	22 (26.8%)	46	46	0.303
Chest wall	12 (14.6%)	66	66	
Spine	14 (17.1%)	70	61	
Pelvis	13 (15.8%)	31	31	
Other	21 (25.7%)	35	35	
Origin of tumor				
Bone	64 (78%)	52	44	0.020
Soft tissue	18 (22%)	22	22	
Metastasis at diagnosis				
Yes	27 (32.9%)	26	26	0.006
No	55 (67.1%)	54	47	
Location of metastasis at admission				
Lung	11 (13.4%)	44	–	0.722
Bone/bone marrow	8 (9.8%)	30	–	
Lung and bone	6 (7.2%)	–	–	
Other	2 (2.4%)	–	–	
Stage				
II	26 (31.7%)	71	71	0.0001
III–IV	56 (68.3%)	32	22	

OS: overall survival.

Table 2
Treatment outcomes of patients.

	n (%)	5th year OS	10th year OS	p
Relapse				
Yes	16 (19.5%)	38	21	0.573
No	66 (80.5%)	48	48	
Relapse status				
Local recurrence only	5 (38.54%)	60	60	0.257
Local and metastatic recurrence	8 (61.5%)	30	–	
Progression				
Yes	31 (37.8%)	18	–	0.001
No	51 (62.2%)	62	62	
RT				
Received	33 (40.2%)	44	40	0.848
Did not receive	49 (59.8%)	50	41	
Type of treatment				
CT alone	9 (11%)	–	–	0.103
CT + S	23 (28%)	59	49	
CT + RT	25 (30.5%)	38	33	
CT + RT + S	25 (30.5%)	50	50	
Consolidation CT				
With actinomycin-D	26 (31.7%)	50	45	0.002
With caboplatin	32 (39%)	58	–	
Did not receive consolidation CT	24 (29.3%)	26	26	

CT: chemotherapy; OS: overall survival; S: surgery; RT: radiotherapy.

Syrians. The demographic and clinical characteristics of the patients included in the study are given in the Tables 1 and 2.

There were 27 patients with metastasis at diagnosis. Of all the patients who were followed up, metastases were detected during induction therapy in five patients, consolidation therapy in five patients, and disease relapse in eight patients. Forty-five patients showed metastasis, whereas no metastasis was observed in 37 patients. The location of metastasis at diagnosis is shown in Table 1. There were 21 (25.6%) Stage IIA, 5 (6.1%) Stage IIB, 18 (22%) Stage III, 4 (4.9%) Stage IVA, and 34 (41.4%) Stage IVB patients.
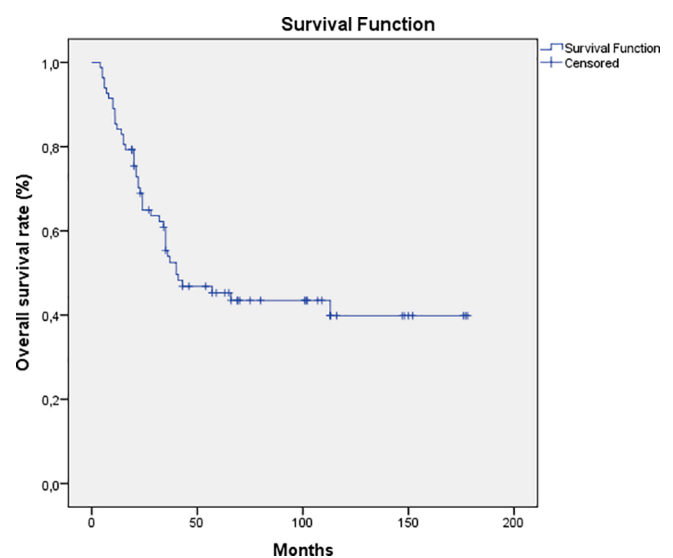
Twenty-two (26.8%) patients were operated at diagnosis. The mass was completely resected in 11 of the 22 patients, and partial resection was achieved in 11 patients. Eight (9.8%) patients were operated during the induction therapy, 16 patients (19.5%) were operated during maintenance therapy, and 2 patients (2.4%) were operated after the end of chemotherapy. A total of 48 (58.5%) patients were operated on, and the tumors of 18 (22%) patients were unresectable. The relatives of 16 (19.5%) patients did not agree to the operation.

The 5- and 10-year OS of the 82 patients diagnosed with ES was 46% and 40%, respectively (Fig. 2). A review of the patients by the year of diagnosis indicated that there was no statistically significant difference between the OS rates of the patients before and after 2013 (p = 0.798) (Table 1). With regard to consolidation therapy, the 5- and 10-year OS

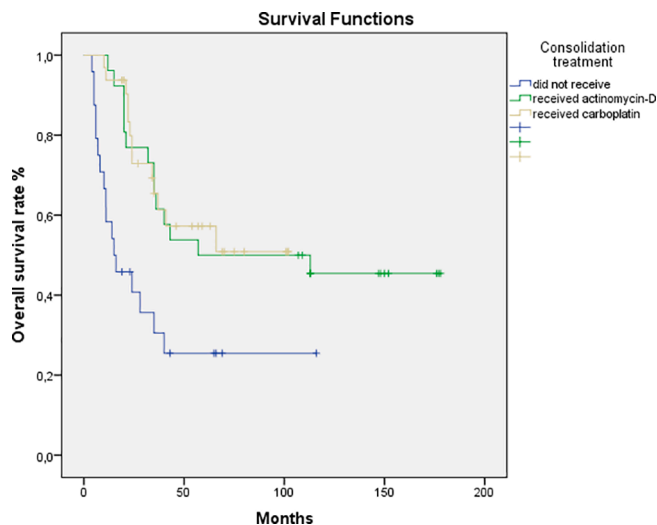**Fig. 2.** Overall survival in 82 patients with Ewing sarcoma.

Fig. 3. Overall survival in patients with Ewing sarcoma according to the consolidation treatment.

Table 3
Outcomes of patients receiving and those not receiving VAC and VCC consolidation therapy.

Variable	VAC (n = 26)	VCC (n = 32)	Did not receive consolidation CT (n = 24)	Total (n = 82)
Progression				
No	19 (73.1%)	18 (56.3%)	14 (58.3%)	51 (62.2%)
Yes	7 (26.9%)	14 (43.8%)	10 (41.7%)	31 (37.8%)
Relapse				
No	17 (65.4%)	26 (81.3%)	23 (95.8%)	66 (80.5%)
Yes	9 (34.6%)	6 (18.8%)	1 (4.2%)	16 (19.5%)
Progression/relapse				
No	11 (42.3%)	17 (53.1%)	14 (58.3%)	42 (51.2%)
Yes	15 (57.7%)	15 (46.9%)	10 (41.7%)	40 (48.8%)
Outcome				
Alive	12 (46.1%)	19 (59.4%)	7 (29.2%)	38 (46.3%)
Dead	14 (53.9%)	13 (40.6%)	17 (70.8%)	44 (53.7%)
Cause of mortality				
Ewing sarcoma	11 (78.6%)	11 (84.6%)	11 (64.7%)	33 (75%)
Infection	2 (14.3%)	2 (15.4%)	5 (29.4%)	9 (20.5%)
Secondary tumor	1 (7.1%)	0 (0%)	1 (5.9%)	2 (4.5%)

VAC: vincristine, actinomycin-D, cyclophosphamide; VCC: vincristine, carboplatin, cyclophosphamide; CT: chemotherapy.

rates of the patients in the actinomycin-D group was 50%, and the 5-year OS rate was 58% in the carboplatin group. Since the patients in this group have been followed up since 2013, their 10-year information is not available. The OS rate of patients who did not receive consolidation therapy was 20% at 5 and 10 years (Fig. 3). Although a higher 5-year OS

rate was seen in the carboplatin group, the difference between the actinomycin-D and carboplatin groups was not statistically significant (p = 0.856). Nevertheless, the OS rate of the patient group that did not receive consolidation therapy was significantly lower (p = 0.002) (Table 2).

The conditions of the patients who did not receive consolidation therapy in both periods were examined. Furthermore, 7 and 17 patients could not receive consolidation therapy before and after 2013, respectively. A review of the reasons as to why the patients did not receive consolidation therapy revealed that before 2013, four of the seven patients died due to infection complications prior to consolidation therapy, two patients experienced disease progression and switched to another treatment option, and one patient rejected the operation and discontinued treatment. During and after the year 2013, 7 of the 17 patients showed disease progression and thus switched to another treatment option prior to consolidation therapy, 3 patients rejected the operation and discontinued treatment, and 6 patients discontinued treatment although they were operated at diagnosis or during induction therapy.

4. Discussion

ES is a rare but malignant sarcoma of the bone and soft tissue observed in children, adolescents, and young adults [1]. There are a number of clinical and biological factors that determine prognosis. The intensity of treatment should be decided in centers experienced in this field based on multidisciplinary approaches by taking these prognostic factors into consideration.

It was reported that advanced age was associated with poor prognosis. For example, in a study, the 5-year relapse-free survival rate was significantly better in children aged < 10 years compared with that in older children (86% vs. 55%, respectively) [8]. Nevertheless, the OS outcomes of children aged < 10 years and those aged ≥ 10 years were similar in our study.

Pelvic tumors present a worse prognosis compared with extremity lesions. In a series study, the 5-year relapse-free survival rates were shown to be 40% versus 61% for extremity lesions and pelvic lesions [9]. The present study also concluded that the outcomes of patients with tumors originating from the pelvis were worse. Nevertheless, no statistically significant results were observed when the 5-year OS rates of patients with tumors originating from the pelvis and those with tumors originating from the spine were compared (31% and 70%, respectively, p = 0.227). In this study, there was no association between tumor location and prognosis, but a significant relationship might have been observed if the number of cases included was higher.

A number of relevant studies in the literature failed to show that the origin tissue of the tumor had a significant prognostic effect on OS and event-free survival (EFS) [5,10,11]. In our study, the 5- and 10-year OS rates of the patients with soft tissue-originated ES were worse compared with those with bone-originated lesions (22%, 22%, and 52%, 44%, respectively, p = 0.02).

The presence of metastasis at diagnosis is considered as the most important prognostic factor in ES [9,12]. While the 5-year OS rate is approximately 70% in patients with localized disease, the same rate drops to 30% in patients with metastasis at diagnosis [2]. Our results were also consistent with other studies [9–11]. The 5-year OS rate was 54% in the group with localized disease at diagnosis and 26% in the group with metastasis (p = 0.006). The rate of metastasis in our patients at diagnosis was 32.9%. Cotterill et al. showed that patients with isolated lung metastases had better OS rates compared with those with bone metastases or a combination of lung and bone metastases [9]. In that respect, our results were consistent with the aforementioned studies in the literature.

We found that the disease stage was a significant prognostic factor that affected the OS rate as previously reported [13]. The 5- and 10-year OS rates of the Stage II patients were better compared with those of the Stage III and IV patients (71%, 71% and 32%, 22%. respectively, p =

Table 4
Treatment regimens using carboplatin in Ewing's sarcoma.

Author, year, reference	Patient characteristics	Patients (n)	The time carboplatin is used	Outcome			p
Castello, 1990, (17)	Solid tumors, 0.5–16 years	23 (3 ESFT)	Induction therapy, second line therapy	Two patients used carboplatin and etoposide during the induction and one during the second-line therapy and partial remission was observed in all 3 patients			
Yildiz, 2014, (18)	Recurrent or refractory ESFT, 16–39 years	54	Recurrent or refractory Treatment		median OS		
				IE/ICE (n = 24)	17.2		0.004
				Other CT (n = 22)	6		
				No CT (n = 4)	3		
Milano, 2006, (19)	ESFT, 1.7–17.8 years	36	Induction therapy		3-year EFS (%)	OS (%)	
				Various regimens (n = 18)	22	27	0.023
				(RMS 88, CECAT, ICE)	67	74	
				ICE/CAV (n = 18)			
Brunetto, 2015, (20)	ESFT, 0.2–28.8 years	175	Induction therapy	VDC/ICE			
					5-year EFS (%)	OS (%)	<0.001
				LR (n = 52)	76.7	80.1	
				HRL (n = 54)	59.4	60.8	
				HRM (n = 68)	25.5	29.1	
Koscielniak, 2021, (21)	Lokalized EES, ≤30 years	243	Induction therapy		5-year EFS (%)	OS (%)	
				CWS-91*(n = 84)	64	72	>0.05
				CWS-96 (n = 115)	57	70	
				CWS-2002P (n = 44)	79	86	
The present study	ESFT, 0.3–18 years	82	Consolidation therapy		5-year OS (%)		
				VAC (n = 26)	50		
				VCC (n = 32)	58		0.002
				No consolidation CT (n = 24)	20		

ESFT: Ewing sarcoma family of tumors; EFS: event-free survival; OS: overall survival; RMS 88: ifosfamide, doxorubicin, actinomycin-D, and vincristine followed by ifosfamide, actinomycinD, and vincristine with or without radiotherapy; CECAT: cyclophosphamide, etoposide, carboplatin, and thiotepa; ICE: ifosfamide, carboplatin, and etoposide; CT: chemotherapy; CAV: cyclophosphamide, doxorubicin, and vincristine; IE: ifosfamide and etoposide; VDC: vincristine, doxorubicin, cyclophosphamide; LR: low risk; HRL: high-risk localized; HRM: high risk metastatic; EES: extraskeletal Ewing sarcoma; *CWS-91 with four- (vincristine, actinomycin-D, doxorubicin, and ifosfamide [VAIA] or cyclophosphamide [VACA II]) or five-drug (+etoposide [EVAIA]) cycles, CWS-96 receive VAIA or CEVAIE (+carboplatin and etoposide), and in CWS-2002P with VAIA III plus optional maintenance therapy (MT) with cyclophosphamide and vinblastine.

0.0001) (Table 1). These results were associated with tumor size and metastases presence, i.e., important indicators of prognosis. Relapse occurs in approximately 25% of patients with localized disease at diagnosis. There is no standard treatment for relapsed and refractory ES, and the survival rate is <30% in patients with isolated lung metastases and <20% in patients with bone and bone marrow involvement [3]. In the present study, the 5- and 10-year OS rates of the patients with relapse were 38% and 21%, respectively. Our results were better compared with the literature data, and no statistically significant difference in the OS rates between relapsed and non-relapsed patients was observed. This may be associated with the intensified treatment administered to the patients. In particular, the outcomes of the patients with solely local recurrence were much better, with 60% at 5 and 10 years.

The outcomes of the patients who progressed during the treatment were worse, which was expected. While the 5-year OS was 62% in patients with no progression, the same rate was 18% in patients with progression (p = 0.001).

Observational studies showed reduced local recurrence and better survival in patients who underwent chemotherapy and surgery compared with patients who received chemotherapy and radiotherapy [5,14]. In our patient group, although the 5- and 10-year OS of the chemotherapy and surgery groups were better compared with the chemotherapy and radiotherapy groups, there was no statistically significant difference (59%, 49% and 38%, 33%, respectively, p = 0.253). The reason may be the fact that patients received radiotherapy in addition to chemotherapy in cases where the patient's tumor was located in a difficult place, such as the pelvis, which was considered unresectable, or the patient rejected the operation due to the morbidity and mortality rates of the operation.

As of 2020, an approximate 3.7 million Syrian refugees are under temporary protection status in Turkey since 2011, when the civil war

started in Syria [15]. Thirteen of the patients included in the study were refugees and these patients were diagnosed, followed up, and treated in our clinic since 2013. A comparison of the OS rates in the refugee and Turkish patients indicated similar results (Table 1). Lower survival rates in the Syrian refugee children compared with Turkish children were reported by another study, which was conducted in a different center in our region, on the OS rate of Syrian and Turkish children with cancer. In this study, it was considered that apart from cancer-specific factors, such as stage and tumor type, non-adherence to treatment due to barriers, including language, accommodation, and transportation problems in accessing cancer treatment may account for the lower OS rates in Syrian children [16].

One of the first studies in the literature on the use of carboplatin in ES was published in 1990 by Castello *et al.* who used high-dose carboplatin and etoposide in childhood solid tumors. Three out of the 23 patients with solid tumors were diagnosed with ES, and 2 of those patients received 500 mg/m^2/day carboplatin for 2 days during the induction treatment and one during second-line therapy, and partial remission was observed in all the three patients [17]. The literature on the use of carboplatin in the treatment of Ewing's sarcoma is shown in Table 4.

Today, chemotherapies with carboplatin, and especially with ICE (ifosfamide, carboplatin, and etoposide), are mostly used in the treatment of relapsed/refractory solid tumors. However, there are only a few studies in the relevant literature on the use of ICE in relapsed/refractory ES [18].

Milano *et al.* showed for the first time in their study that ICE used in induction therapy for high-risk ES family tumors was effective and successful. They administered ICE alternately with VDC and showed that ICE–VDC treatment was well tolerated and the disease was controlled faster in this group of patients [19].

The induction chemotherapy comprised two cycles of ICE followed by two cycles of VDC and local control thereafter in a study by Brunetto

et al. on the use of carboplatin in the treatment of ES. Patients at low risk (with normal LDH and localized resectable disease) received continuation therapy in the form of alternating ten VDC cycles with IE. Patients with high-risk disease (unresectable, pelvic, metastatic, or elevated LDH) received two additional cycles of ICE. In this study, although the use of carboplatin did not improve the treatment outcomes, the intensification of treatment partially narrowed the early gap between the low- and high-risk patients. Nevertheless, despite treatment intensification in the said study, the long-term outcomes for patients with high-risk localized disease were poor (5-year EFS 67.9% and 5-year OS 29.1%) [20].

The results of a recent study regarding patients with extraskeletal ES that examined the use of carboplatin, the randomized comparison of six drugs cycles CEVAIE (carboplatin, etoposid, vincristine, dactinomycin, ifosfamide, epi-doxorubcin) (experimental arm) versus four drugs VAIA III (vincristine, dactinomycin, ifosfamide, doxorubicin) (standard arm) in the CWS-96 study showed better EFS and OS in the VAIA arm, without statistical significance [21].

Since actinomycin-D supply is problematic in Turkey, carboplatin was used as a replacement in our clinic for patients diagnosed with rhabdomyosarcoma and Wilms tumor. Furthermore, Acipayam and Sezgin *et al.* have showed the efficacy of the drug [22,23]. In the light of their results, we decided to use carboplatin to avoid delay and deficiency in the treatment, when actinomycin-D was not available for the maintenance treatment of ES. There was no statistically significant difference between the survival of patients on actinomycin-D and carboplatin. Nevertheless, a review of the patients in this group indicated that the rate of relapsed patients in the actinomycin-D group was higher compared with those in the carboplatin group (34.6% and 18.8%, respectively, p = 0.14), and similarly, the mortality rate was higher in the patients of the actinomycin-D group (53.9% and 40.6%, respectively, p < 0.05). Furthermore, there was no difference between the two groups in terms of hematological and nonhematological toxicities. As expected, the outcomes of patients without maintenance therapy were statistically significantly worse (5 and 10-year OS 26%, p = 0.002) (Table 3).

5. Conclusion

In conclusion, the presence of metastases at diagnosis, tumor originating in the soft tissue, advanced-stage tumor, and disease progression led to a worse prognosis in ES. In cases where treatment was discontinued due to reasons such as disease progression or failure to perform surgery, the survival rates were significantly worse in the group of patients, who did not receive maintenance therapy. The results of the present study showed that carboplatin could be effectively used as an alternative to actinomycin-D in the maintenance treatment of ES.

Furthermore, both maintenance chemotherapy regimens are effective in newly diagnosed patients with localized ES, but this treatments can be improved. In addition, an effective treatment option should be established for cases that include progression and relapse.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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