ORIGINAL ARTICLE   **ÖZGÜN ARAŞTIRMA**

Clinical Features, Prognostic Factors and Outcome of Children with Ewing Sarcoma: A Single-center Experience

Ewing Sarkomlu Çocuk Hastaların Klinik Özellikleri, Prognostik Faktörleri ve Tedavi Sonuçları: Tek Merkez Deneyimi

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Abstract

Introduction: Ewing sarcoma (ES) is a rare, aggressive, malignant tumor. It is the second most common malignant bone tumor in children. A total of 20-25% of patients are metastatic at the time of diagnosis. The survival rate for localized disease (LD) is approximately 70-74%. For metastatic disease (MD), it is about 30%. The most important prognostic factor affecting survival is the presence of MD at diagnosis. In this study, we investigated the clinical characteristics, treatment outcome, and factors affecting the prognosis and survival of patients followed up with the diagnosis of ES.

Materials and Methods: Between 2007 and 2020, a total of 24 ES patients aged 0-18 years were retrospectively analyzed.

Results: The most common complaint was pain and swelling in the lesion area (n=9), followed by pain (n=5), swelling (n=3), abdominal pain (n=2), shortness of breath (n=2), facial paralysis (n=1), spinal compression findings (leg pain and walking difficulty) (n=1) and hematuria (n=1). ES was bone-derived in 19 patients (79%). Of these, 14 had LD and 5 had MD at the time of diagnosis. Extraskeletal Ewing sarcomas (EES), was detected in five patients (21%) and derived from the kidney (n=1), rectus abdominis (n=1), left quadriceps femoris muscle (n=1), left upper thoracic region and lumbar region paraspinal muscles (n=2). The rate of MD was 25% (6/24) in the entire patient group. Disease progression was observed in three patients during treatment. Relapse at follow-up was observed in 6 of 19 patients in complete remission. The median time to relapse was 20 months (minimum 13, maximum 34 months) from diagnosis. The median survival of our patients after relapse was 14.5 months (minimum 6-maximum 27 months). Radiological response and histopathological response to induction therapy, presence of relapse or progression, and relapse site were found to be correlated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001 respectiveley).

Conclusion: ES is a cancer with high mortality and morbidity. Although the most common symptoms are pain and swelling, the symptoms may vary depending on the region from which the tumor originates. Response to induction therapy and the presence of relapse-progression are factors affecting prognosis. Treatment should be personalized to improve survival.

Öz

Giriş: Ewing sarkomu nadir görülen, agresif, malign bir tümördür. Çocuklarda görülen ikinci en sık malign kemik tümörüdür ES tanı sırasında lokal (LH) ve metastatik hastalık (MH) olarak karşımıza çıkabilir. %20-25 hasta tanı sırasında metastatiktir. LH'de sağkalım yaklaşık %70-74'tür. MH'de ise %30 civarındadır. Sağkalımı etkileyen en önemli prognostik faktör tanı sırasında MH varlığıdır. Bu çalışmamızda ES tanısı ile takip ettiğimiz hastaların klinik özelliklerini, tedavi yanıtlarını, prognozu etkileyen faktörleri ve sağkalımlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hastanemizde 2007-2020 yılları arasında ES tanısı ile tedavi gören 0-18 yaş 24 hasta retrospektif olarak değerlendirildi.

Bulgular: Başvuru şikayetleri en sık lezyon bölgesinde ağrı ve şişlik (n=9) iken, ağrı (n=5), şişlik (n=3), karın ağrısı (n=2), nefes darlığı (n=2), yüz felci (n=1), bacaklarda ağrı-yürümede zorluk yakınması ile gelen olgumuzda spinal bası bulguları (n=1) ve hematüri (n=1) hastaneye başvuru nedenleri idi. ES 19 hastada (79%) kemik kaynaklıydı. Bunların 14'ünde tanı sırasında lokal, 5'inde metastatik hastalık mevcuttu. Beş hastada (21%) ise ekstraskeletal saptanmış olup, böbrek (n=1), rektus abdominis (n=1), sol kuadriseps femoris kası (n=1), sol üst torakal bölge ve lomber bölge paraspinal kasları (n=2) kaynaklıydı. Tüm hasta grubunda MH oranı 25% (6/24) idi. Üç hastada tedavi altında progresyon görüldü. Tam remisyona giren 19 hastanın 6'sında (6/19) izlemde relaps gözlendi. Relaps zamanı tanıdan itibaren ise ortanca 20 ay (minimum 13, maksimum 34) idi. Hastalarımızın relaps sonrası yaşam süresi ortanca 14.5 ay (minimum 6-maksimum 27 ay) idi. İndüksiyon tedavisine radyolojik yanıt, indüksiyon tedavisine histopatolojik yanıt, relaps ya da progresyon varlığı ve relaps yeri sağkalım ile ilişkili olarak bulundu (Fisher's exact test p=0,02, 0,0047, <0,001, 0,001).

Sonuç: ES mortalite ve morbiditesi yüksek olan bir kanser türüdür. En sık semptom ağrı ve şişlik olmakla birlikte tümörün kaynaklandığı bölgeye göre semptomlar farklılık gösterebilir. İndüksiyon tedavisine yanıt, relaps-progresyon varlığı prognozu etkileyen faktörlerdir. Sağkalımı artırmak için tedavi kişiselleştirilmelidir.

Introduction

Ewing sarcoma family tumors (ESFTs) are used to identify tumors composed of small, round tumor cells that share common neural histology and genetic mechanisms. The most common of these tumors are bone Ewing sarcomas (ES), extraskeletal Ewing sarcomas (EES), pPNET, and Askin tumors with chest wall-derived pPNET. ES is a rare, aggressive, malignant tumor (1). It was first described by Ewing in 1921. It is the second most common malignant bone tumor in children, adolescents, and young adults accounting for less than 5% of the cancers in this age group (2-5). It is more prevalent in males, and its annual incidence ranges from one to three cases per million (5). Clinically, it often presents as a painful, mass lesion (6). Localization in the long bones is the most common (5). The axial skeletal system is the second most common site. ESFTs can originate from anywhere in the body, and approximately 20% of them are EES cases (2,7). EES is 10 times less common than bone ES, and the incidence is 0.4 per million. Most cases occur at ages younger than 5 years and older than 35 years. Contrary to bone ES, there is no gender relationship in ESS. It most commonly occurs in the upper femoral region, hip, shoulders, and upper arm (7).

ES may present as a local (LD) or metastatic disease (MD) at the time of diagnosis. A total of 20-25% of patients are metastatic at the time of diagnosis. Forty percent of them have isolated lung metastases, and metastases may also occur in bone and bone marrow (BM) (2). The diagnosis is based on histopathologic examination (2). Treatment requires a multidisciplinary approach (8). Treatment modalities include neoadjuvant chemotherapy, surgery, radiotherapy (RT), and autologous stem cell transplantation (ASCT). The survival rate for LD is approximately 70-74% (2,4). For MD, it is about 30% (2). In patients with pulmonary metastases, the 3-year survival rate is 52% (1). The most important prognostic factor affecting survival is the presence of MD at diagnosis (2). For LD, histopathological response to induction treatment and tumor volume and diameter are the most important factors. Other prognostic factors include patient age, tumor location, and lactat dehydrogenase (LDH) level (1).

In this study, we investigated the clinical characteristics, treatments, treatment outcome, and factors affecting the prognosis and survival of patients followed up with the diagnosis of ES.

Materials and Methods

Study Design and Data Collection

Twenty-four patients aged 0-18 years who were treated at our hospital with a diagnosis of ES between 2007 and 2020 were retrospectively evaluated. The patients were divided into 3 groups: 0-10 years, 11-14 years, and 15-18 years. Patient information was retrieved from patient files and electronic recording systems. Demographic and clinical characteristics of the patients, treatments applied and treatment outcomes were recorded.

Diagnosis and Staging

The diagnosis was made according to standard histopathological criteria. Molecular analysis was not performed. Patients were divided into two groups: osseous and extraosseous. Tumor regions were classified as the axial skeleton, extremities, pelvis, and extraosseous. Contrast-enhanced magnetic resonance imaging (MRI) was performed at the tumor site in each patient as an imaging modality. Tumor diameter was classified as <8 cm and ≥ 8 cm considering the largest diameter on MRI examination. Thoracic computed tomography (CT) and whole-body bone scintigraphy were performed on each patient for metastasis screening. Bilateral BM biopsy was performed to detect BM involvement. The patients were divided into those with LD, those with pulmonary and pleural metastases, and those with disseminated disease (pulmonary, bone, bone marrow).

Evaluation of Treatment, Prognosis, and Treatment Outcomes

EICESS 92 and Euro-Ewing 99 were used as chemotherapy protocols. Accordingly, neoadjuvant chemotherapy was administered after the diagnosis and followed by surgery and/or RT in local treatment, while the treatment was completed with adjuvant chemotherapy. While <50% reduction in tumor soft tissue mass was considered a poor response, and >50% reduction was considered a good response, in the post-surgical histopathological evaluation, viable tumor tissue was considered poor if ≥10% and as good response if <10%. Complete disappearance of the tumor was considered a complete response, ≥50% reduction in size was considered a partial response,

while <50% reduction or <25% increase in size was considered a stable disease, and ≥25% increase in size was considered progression. Relapse and progression were detected using imaging methods and a histopathological examination was not performed.

Statistical Analysis

Demographic data and descriptive statistics were used. Descriptive statistics were expressed as the number of units (n), percentage (%), mean ± standard deviation (x ≤ ± SD), median values, and minimum-maximum values. Whether the categorical variables were dependent was compared using chi-square, Yates correction (continuity correction), and Fisher's Exact test. $P<0.05$ was considered statistically significant. All statistical analyzes were conducted using SPSS software for Windows version 25.0 (IBM Corp. Released 2017. Armonk, NY, USA).

Ethics approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital Ethics Committee (approvel number: 2022/04-02, date: 24.02.2022).

Results

Baseline Characteristics

Twenty-four patients (F/M: 14/10) were included in the study. The median age of patients at diagnosis was 12.8 years (min 4.7, max 16.8 years), and the median duration of follow-up was 33 months (min 5, max 151 months). The most common complaint was pain and swelling in the lesion area (n=9), followed by pain (n=5), swelling (n=3), abdominal pain (n=2), shortness of breath (n=2), facial paralysis (n=1), spinal compression findings (leg pain and walking difficulty) (n=1) and hematuria (n=1). The mean time between the onset of the symptoms and admission to the hospital was 8.5±17 months (min 15 days, max 69 months). As the first imaging method, the patients were underwent direct radiography (n=2), CT (n=4), and MRI (n=18). ES was bone-derived in 19 patients (79%). Of these, 14 had LD and 5 had MD at the time of diagnosis (Table 1). EES was detected in five patients (21%) and derived from the kidney (n=1), rectus abdominis (n=1), left quadriceps femoris muscle (n=1), left upper thoracic region and lumbar region paraspinal muscles (n=2). The patient with

renal origin had isolated BM metastasis, and the other 4 patients were staged as LD. The rate of MD was 25% (6/24) in the entire patient group. Of the patients with MD, 3 had lung and pleural metastases, 1 had BM, and 2 had the disseminated disease (bone, BM, and lung). Histopathologic diagnosis was made by tru-cut needle biopsy in 16 patients, open mass biopsy in 6 patients,

Table 1. Clinical characteristics of the patients		
	All patients (n=24)	
Characteristics	No.	%
Age groups (years)		
0-10	3	12.5
11-14	15	62.5
15-18	6	25
Sex		
Female	14	58
Male	10	42
Primary tumor site		
Extremity	9	37.5
Pelvis	4	16.7
Axial	6	25
Extraosseous	5	20.8
Primary tumor source		
Bone	19	79
Soft tissue	5	21
Primary tumor diameter		
<8 cm	12	50
≥8 cm	12	50
Disease spread		
Local	18	75
Lung and pleura metastatic	3	12.5
Isolated bone marrow	1	4.2
Disseminated disease	2	8.3
Chemotherapy protocol		
EICESS 92	21	87.5
Euro-Ewing 99	3	12.5
Local treatment		
Surgery	7	29.2
Radiotherapy	9	37.5
Surgery and radiotherapy	6	25
No treatment	2	8.3
Treatment results		
Complete response	19	79
Disease progression	3	12.5
Sepsis and cardiac toxicity	2	8.3
Relapse		
Yes	6	25
None	18	75
Last event		
Alive	14	58
Deceased	10	42

and total mass excision in 2 patients (rectus abdominis muscle, kidney).

Treatment

EICESS 92 protocol was initiated in 21 patients, and the Euro-Ewing 99 protocol was initiated in 3 patients. Local treatment to the primary tumor region was applied to 7 patients (29.2%) with surgery, 9 (37.5%) with RT, and 6 (25%) with surgery and RT. One of the 2 patients (8.3%) who could not be treated locally had sacrum, vertebrae, and cranial bone involvement at the time of diagnosis, and the primary tumor region was not clear, and the other died due to sepsis before completion of induction treatment. None of our patients underwent ASCT.

Treatment Results

Radiologic response to induction therapy was poor in 10 patients (41.7%), good in 9 (37.5%), and unclear in 5 (20.8%) because of the quality of radiologic imaging. The postoperative histopathologic response was good in 4 patients (16.7%) and poor in 8 patients (33.3%), and could not be studied in 12 patients (50%). Total excision was performed in 3 of the patients in whom tissue response to treatment could not be assessed. In the remaining 9 patients, only RT was used as a local treatment, while in 2 patients no local treatment could be performed. In one patient with poor response to treatment, treatment with ifosfamide, carboplatin, and etoposide (ICE) was started. Nineteen patients (19/24) achieved a complete response.

Events

Disease progression was observed in three patients during treatment. Progression occurred during neoadjuvant chemotherapy in one and adjuvant chemotherapy period in other two patients. Relapse at follow-up was observed in 6 of 19 patients in complete remission (Table 2). The median time to relapse was 8 months (min 1, max 23 months) from treatment discontinuation and 20 months (min 13, max 34 months) from diagnosis. The median survival of our patients after relapse was 14.5 months (min 6-max 27 months). Rescue treatments applied due to disease progression and relapse are shown in Table 3. Sorafenib (29.2%) was started in seven patients with conventional chemotherapy due to progression and relapse.

Table 2. Clinical characteristics of patients with disease progression and relapse

No	Diagnosis age (years)	Primary region/Stage	Tm size (cm)	Primary treatment	Induction radiological response	Local treatment in primary diagnosis	*Relapse duration (months)	Relapse/progression site	Applied treatment	Last event	Time of death (month)
1	13.6	Left hemithorax/local	<8	EICESS 92	Poor	Surgery + RT	21	Local and lung	ICE 6 courses	Deceased (progression)	33
2	15	Right tibia/local	≥8	EICESS 92	Poor	Surgery + RT	22	Local	VIT + amputation	Deceased (Progression)	39
3	14.4	Left quadriceps femoris muscle/local	≥8	EICESS 92	Poor	Surgery + RT	34	Osseous, (tibia)	VIT 6 courses + sorafenib	Alive	43
4	11	Pelvis/metastatic (bone + lung)	≥8	EICESS 92	Good	RT	13	Lung	VIT 6 courses + sorafebib	Deceased (progression)	19
5	10.1	Right femur distal/local	≥8	EICESS 92	Poor	Surgery	14	Lung	Metastasectomy/VIT 4 courses/ICE 1 course/Sorafenib/lung RT	Deceased (progression)	11
6	11.2	Pelvis/local	≥8	EICESS 92	Poor	Surgery + RT	19	Lung and bone	Metastasectomy/VIT 6 courses/Sorafenib	Deceased (Progression)	19
7	1.9	Right humerus/local	<8	EICESS 92	Could not be determined	RT	-	Disseminated bone	Topotecan/cyclo-Ice 2 courses-RT/metronomic	Deceased (progression)	10
8	11.7	Left kidney/metastatic	≥8	EICESS 92	Could not be determined	RT	-	Disseminated bone	ICE 4 courses	Deceased (progression)	11
9	16.7	Left humerus/metastatic	≥8	EICESS 92	Poor	Surgery + RT	-	Lung	Treatment rejection	Deceased (progression)	7

*Time since diagnosis
ICE: ifosphamide + carboplatin + etoposide, q3w, every 3 weeks; VIT: vinkristin, irinotecan, temozolimide, ; q3w, every 3 weeks; metronomic treatment: cyclophosphamide, etoposide, celebrex

Table 3. Clinical characteristics of patients with relapsed or primary disease progression		
	All patients (n=9)	
Characteristics	No.	%
Relapse-free interval <24 months 24 months	 2 4	 33.3 66.6
Type of relapse or progression Local Lung Diffuse bone Local and lung Bone and lung	 2 3 2 1 1	 22.2 33.3 22.2 11.1 11.1
Primary tumor diameter <8 cm ≥8 cm	 2 7	 22.2 77.8
Salvage chemotherapy protocol ICE VIT ICE-VIT* Topotecan/cyclo-Ice-metronomic therapy** Sorafenib No	 2 4 1 1 5 1	 22.2 44.4 11.1 11.1 55.5 11.1
Last event Alive Deceased	 1 8	 11 89

*2 cycles of VIT unresponsive followed by 1 cure of ICE

**cyclophosphamide, etoposide, celebrex

ICE: Ifosfamide + carboplatin + etoposide, q3w, every 3 weeks; VIT: Vincristine, irinotecan, temozolimide; q3w, every 3 weeks

During the follow-up period, 10 patients (41.7%) died. The cause of death was progression in 8 patients (80%), sepsis in one patient (10%), and cardiac toxicity in one patient (10%). One patient developed a secondary tumor of soft tissue origin on the right knee 8 years after discontinuation of treatment. He was diagnosed with round cell sarcoma with rhabdoid differentiation. After mass excision, local RT was applied with 4 cycles of vincristine, irinotecan, and temozolomide (VIT) treatment. The patient is in complete remission.

Factors Associated with Survival

Factors affecting survival were evaluated. Radiological response and histopathological response to induction therapy, presence of relapse or progression, and relapse site were found to be correlated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001 respectiveley). On the other hand, there was no correlation between age, sex, tumor region, tumor size, LDH level, local treatment, disease status (local-metastatic), and survival (p=0.847, 0.678, 0.218, 0.214, 0.321, 1, 0.192 respectiveley).

Discussion

The aim of this study was to analyze the clinical admission findings, treatments administered, and treatment responses of our patients and to evaluate the factors affecting the treatment outcomes. ES is a tumor that is more common in children after the age of 10 years (2,3) and tends to be 1.5 times more common in males than in females (5). While 15 of our patients (62.5%) were in the 11-14 age group and were consistent with the literature, our number of female patients was higher, with a female/male ratio of 1.4. The fact that most of our cases were of bone origin was also consistent with the literature. Although the symptoms vary according to the region, size, and stage of the tumor (6), pain and swelling were the most common symptoms in our patient group, in parallel

with other studies. One patient with temporal bone origin presented with facial paralysis, and one patient with kidney origin presented with complaints not suggestive of ES, such as hematuria. Because of the nonspecific presenting symptoms, the establishment of the diagnosis is delayed which affects survival results (6). Therefore, early diagnosis of patients is extremely important (8). In our patient group, the mean time to diagnosis after the onset of symptoms was 8.5±17 months (min 15 days, max 69 months).

The periosteum reaction in ES looks like an onion membrane on direct radiography. It refers to the new bone tissue surrounding the cortical destruction caused by the tumor. Therefore, direct radiography and MRI, thoracic CT, and whole bone scintigraphy should be performed for staging. Today, although not routinely, PET-CT is used in some centers, and because PET-CT is not available in our hospital, it could not be taken.

In diagnosis, tru-cut biopsy is sufficient at >90% to determine the tumor grade and specific subtype (8). A large part of ESFT is positive in the CD 99 membranous pattern. Cytoplasmic pattern positivity can also be seen. ETS-family gene translocations with EWSR1 are characteristic of the ESFT family. Approximately 85% of them are composed of t (11;22), encoding the EWSR1-FLI1 oncoprotein (2). Our patients were diagnosed according to histopathological criteria, and no molecular genetic analysis could be performed on any of them. Although TNM staging (tumor, lymph node, metastasis) is performed as in all bone tumors in staging, two classifications as MD and LD are used, because they are not significant in terms of prognosis (2). In our study, the rate of MD was 25% (6/24).

Treatment of the disease requires a multidisciplinary team (8). The standard initial treatment is systemic chemotherapy. Treatment is based on vincristine, ifosfamide, doxorubicin, actinomycin D, and etoposide. It has not been established that adding topotecan, cyclophosphamide, carboplatin, and cisplatin to the treatment of localized ES is beneficial. The effectiveness of ASCT with high-dose busulfan and melphalan (BuMel) as consolidation therapy in patients with high-risk localized tumors has been studied, and event-free survival was found to be better than that of standard treatment (60.7 vs 47.1%) (9). However, we did not have the opportunity to use the ASCT procedure in our patient group.

The prognosis is poor in relapsed patients. Relapse time is the most important factor affecting prognosis. The survival rate was <10% in patients with relapse within the first 2 years after diagnosis, while it was 30% in patients with relapse after 2 years. Another important factor is the localization of the relapse. The coexistence of local and distant metastases indicates a worse prognosis (4). Some of the treatment options for relapse are topotecan-cyclophosphamide and irinotecan-temozolomide-vincristine. There are publications emphasizing that 30% and 28% of responses are achieved with these treatments, respectively (4). There was a 14% response to gemcitabine at low doses and a 66% response at high doses with the docetaxel combination. In patients who respond to salvage therapy, high-dose chemotherapy with BuMel can be administered (9).

The optimal local treatment after neoadjuvant chemotherapy remains controversial (1). Surgery, RT, or both are applied together. There are no randomized controlled trials comparing local therapies. Controversial and conflicting results have been reported in trials comparing surgery and RT in local treatment. In trials comparing patients treated with surgery and RT together with patients treated with surgery alone, there was no significant difference in event-free survival (EFS) and overall survival (OS) (5). In a study that provided results on overall survival (OS), it was found that there was no significant difference in either group (10). As a result, surgery or RT alone may be the treatment option for local treatment in ES. Tumor location, size, radiologic and histopathologic response to chemotherapy, and patient comorbidity should be considered when deciding on local treatment (11).

In our patient group, RT could not be applied on a patient because she was mentally disabled and RT required daily anesthesia. In this patient an expanded tumor bed excision was performed. When the treatment-related complications were examined; fractures, functional losses, and skin lesions were reported in the bone region in patients RT applied, and functional mechanical disorders were reported most frequently in relation to S (5).

In our patient group, 5 patients had EES. Chemotherapy and local treatment were given to all of them. The efficacy of systemic chemotherapy in EES has been proven and is essential for treatment.

The definitive treatment is neoadjuvant chemotherapy and surgery. Although EES is radiosensitive, RT alone is not sufficient for local control. The definitive indication of RT is tumors that cannot be surgically removed and cases with positive surgical margins and should be applied at 54-55 Gy (7). A negative surgical margin is the most important factor in the local control of tumors. Although the prognosis of EES is better than that of bone tumors, the prognostic factors are the same. Despite the publications stating that BM biopsy is not required for the staging, especially in patients without metastases (12), the presence of BM metastases in our ES patient of kidney origin in the primary diagnosis was notable, although there were no lung or bone metastases, and it was thought that BM biopsy may be important in the diagnosis, particularly for the extraosseous group.

Disease relapse occurs in 30-40% of ES patients. Relapse disease is associated with a poor prognosis. <20% of patients who develop relapse survive in the 5-year follow-up. However, the prognosis may be better in patients with limited local or relapse 2 years after diagnosis (2). In our study, disease recurrence was observed in 6 patients, 5 patients died, and one patient was followed up for 27 months after relapse. While the primary tumor of this patient was of quadriceps femoris origin and EES, relaps was seen in tibia 34 months after the first diagnosis. The median survival of our patients after relapse was 14.5 months (min 6-max 27 months).

There has been an increase in treatment related secondary cancer incidence, especially among children, as a result of improvements in treatment modalities and increased survival rates. ES is one of the disease with the highest risk of secondary cancer. Alkylating agents and anthracyclines used in treatment pose an increased risk for tumor development, such as hematologic malignancies, breast cancer and osteosarcoma (13). The cumulative incidence of treatment-related secondary tumors in surviving patients was 9-10% over 30 years. The incidence has been shown to be lower in patients diagnosed after 1990 compared with previous years, which is related to lower RT doses (14). In our patient group, one patient diagnosed with localized ES from the pelvis developed round cell sarcoma from the soft tissue 8 years after the diagnosis, and this patient continues to live in complete remission with chemotherapy (VIT scheme) and RT.

Over the years, with the changes in treatment protocols and the development of supportive treatments, survival in ES has increased to 70-74% for LD and 30% for MD (2,4). With the addition of ifosfamide and etoposide to the treatment consisting of vincristine, doxorubicin, and cyclophosphamide, improvement in OS and EFS was achieved in LD (61% vs. 72%, 54% vs. 69%, respectively) (15). The most important prognostic factor affecting survival is the presence of MD at diagnosis (2). The prognosis is poor in patients with pelvic tumors, patients without local control, large tumors and poor histologic response. Histologic response to induction therapy is significantly predictive of survival. The disease-free 5-year survival was significantly better in patients with <5% viable tumors than in patients with >30% viable tumors (75% vs 20%, p<0.001) (16). The 5-year EFS has been reported to be 50% in pelvic and sacral tumors. Tumor size and age are other prognostic factors. Tumors ≥8 cm have a poor prognosis. Young patients have a better prognosis (2). In patients with relapse or progression, the prognosis is very poor and the survival rate is around 10-30%. Response to salvage therapy is also a prognostic indicator in this patient group (3). When the factors affecting survival were evaluated in our study, radiological response and histopathologic response to induction therapy, presence of relapse or progression, and relapse site were found to be associated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001). On the other hand, there was no relationship between age, sex, tumor region, tumor size, LDH levels, local treatment, local or metastatic disease, and survival (p=0.847, 0.678, 0.218, 0.214, 0.321, 1, 0.192). This can be explained by the low number of patients and especially the lower rate of metastatic patients (6/24 patients).

ASCT can be used in the metastatic patient group when there is a good response to chemotherapy or to eliminate chemotherapy resistance in relapsed-refractory patients. However, the clinical significance is controversial in many studies (3). In our patient group, relapse and/or progression were observed in 9 patients (37.5%) (9/24), 6 of whom had primary LD, and 8 (8/9) died to follow-up (Table 3). None of them underwent ASCT. Studies to improve the prognosis

in relapsed and progressed patients are ongoing. In a phase 2 trial conducted by the pediatric oncology group, 7 different single drugs were tested in relapsed/progressed disease, and the 6-month EFS rate was 12.7%. In this study, the radiological response was evaluated, and it was obtained with docetaxel, but its effect on EFS was not shown (4).

Our study has limitations due to its retrospective design and the small number of patients enrolled.

Conclusion

ES is a cancer with high mortality and morbidity. Although the most common symptoms are pain and swelling, the symptoms may vary depending on the region from which the tumor originates. Response to induction therapy and the presence of relapse-progression are factors affecting prognosis. Treatment should be personalized to improve survival.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital Ethics Committee (approvel number: 2022/04-02, date: 24.02.2022).
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