Treatment and Outcomes of Ewing Sarcoma in Turkish Adults: A Single Centre Experience

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Abstract

Background: Ewing sarcoma is a small round cell tumor arising from soft tissue and bone that predominantly affects children and adolescents. The most unfavorable prognostic factor is the presence of distant metastasis at the time of diagnosis. Materials and Methods: The records of 26 Ewing sarcoma patients (14 male, 12 female) were re-evaluated retrospectively. Results: The median age was 26.5 (19-42) years. Eight patients (31%) showed a primary tumor in their extremities, 8 (31%) in the thorax, 4 (15%) at the vertebra, 4 (15%) in the head and neck, and 2 (8%) in the abdomen. Five patients (19%) had distant metastasis at diagnosis. The median progression-free survival was 72 months and 10 months in localized and metastatic disease, respectively (p=0.005). The overall survival rate was 19 months in metastatic disease, and the 5-year overall survival rate was 64% in localized disease (p=0.006). Patients who had localized disease in the extremities and were under age 30 had a favorable prognosis. Conclusions: Although Ewing sarcoma is a tumor affecting children and adolescents, it may be seen in adults, where the prognosis is generally worse. Although it is a highly malignant tumor, it is possible to achieve improved survival with combined modality treatments.

Keywords: Adult cases - Ewing sarcoma - prognosis - Turkey
recorded (Table 1). Hemoglobin levels <13 g/dl and 12 g/dl in males and females, respectively, were accepted as anemia.

Twenty one patients (81%) had localized disease and 5 patients (19%) had metastatic disease at the time of diagnosis. Patients with non-metastatic disease were treated with primary surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy, local treatment with radiotherapy and/or surgery, and adjuvant chemotherapy, according to the clinical features and patients’ preference. Metastatic patients were treated with systemic chemotherapy (Figure 1).

The National Cancer Institute’s ES chemotherapy protocol was applied to both non-metastatic and metastatic patients (Table 2) (Granowetter et al., 2009). After every 3 cycles of chemotherapy, all patients were assessed with a physical examination of the thorax, abdomen, and extremities, and, if necessary, imaging and echochroangiography were performed due to cardiotoxicity of anthracyclin.

Results

Twenty-six patients (14 male, 12 female) were included in this study. Participants’ median age was 26.5 (19-42), and ECOG PS was 0-1 in 17 patients (65%) and 2-3 in 9 patients (35%). The primary lesion was located at the extremities in 8 patients (31%), in the thorax in 8 patients (31%), in the vertebral column in 4 patients (15%), at the head and neck in 4 patients (15%), and in abdomen in 2 patients (8%). The median tumor size was 60 mm (20-250 mm). The median time between first symptom and diagnosis was 82 days (30-365), and 20 days between diagnosis and initiation of treatment. The median follow-up time was 49 months (5-143).

The median disease free survival (DFS) was 72 months in patients with localized disease, and median progression free survival (PFS) was 10 months with metastatic disease (p=0.005). DFS in patients under 30 with localized disease was 83 months and 22 months in patients over 30 (p=0.005). DFS in patients under 30 with localized disease and ECOG PS 0-1 was 83 months and 4 months with localized disease and ECOG PS 2 (p=0.001).

DFS was 25 months in non-extremity primary tumors, and 10-year DFS was 85% in extremity primary tumors in non-metastatic patients (p=0.005) (Figure 2). DFS was 22 months in vertebral disease, 25 months in thoracal disease, 56 months in the head and neck, and 83 months in abdominal disease. There was no correlation between tumor localization and DFS in metastatic patients. Also, there was no correlation between tumor size and PFS/DFS in localized and metastatic disease.

The DFS was 22 months in patients with localized disease treated with surgery and no systemic therapy, 56 months in patients treated with surgery followed by adjuvant chemotherapy, and 25 months in patients treated with neoadjuvant chemotherapy followed by local treatment and adjuvant chemotherapy (p>0.05).

All of the metastatic patients (n=5) were anemic, whereas only 41% of the non-metastatic patients (n=7) were anemic (p=0.02). The same as high LDH levels were present in 80% of metastatic patients (n=4) and 41% of patients with localized (n=7) diseases (p>0.05), but there was no correlation between PFS and hemoglobin and LDH level in patients in the same stage.

The median overall survival (OS) was 19 months in metastatic patients. Patients with localized disease has a 5-year survival rate of 64% and a 10-year survival rate of 56% (p=0.006). There was no OS difference between male and female patients. The OS in patients age 30 year and older with localized disease was 41 months. The 10-year survival rate of patients younger than 30 years with localized disease was 77% (p=0.019). Patients younger than 30 with metastatic disease had an OS of 19 months, and patients age 30 and older had an OS of 5 months (p>0.05). The OS in patients with localized disease and ECOG PS 2-3 was 9 months, whereas patients with metastatic patients under 30 and those over 30. There was no PFS/DFS difference between genders with the same stages. The ECOG PS of all of the patients with metastatic disease was 2-3, whereas the ECOG PS of 81% of the non-metastatic patient’s was 0-1, and the PS of 19% was 2 (p=0.001). Also, the DFS of the patients with localized disease and ECOG PS 0-1 was 83 months and 4 months with localized disease and ECOG PS 2 (p=0.001).

Table 1. Complete Blood Counts and Biochemical Parameters

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<th>Localised disease</th>
<th>Metastatic disease</th>
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<tr>
<td>Wbc (10³/µL)</td>
<td>7.2±2.67</td>
<td>7.8±2.46</td>
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<td>Hemoglobin (g/dL)</td>
<td>12.8±2.27</td>
<td>11±0.78</td>
<td>&gt;0.05</td>
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<td>Platelet (106/µL)</td>
<td>339±104</td>
<td>304±177</td>
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<td>Creatinine (mg/dL)</td>
<td>0.8±0.14</td>
<td>0.6±0.19</td>
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<td>Albumin (g/L)</td>
<td>45±5.7</td>
<td>44±8.4</td>
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<tr>
<td>LDH (U/L)</td>
<td>200±585</td>
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<td>&gt;0.05</td>
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Wbc: White blood cell - LDH: Lactate dehydrogenase

Table 2. Chemotherapy Schedule

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Local treatment

V: vincristine 2 mg; d1; A: adriamycin 75 mg/m²; d1; C: cyclophosphamide 1200 mg/m²; d1, Ac: actinomycin 1.25 mg/m²; d1; If: ifosfamide 1800 mg/m²; d1-5, M: mesna 1800 mg/m²; d1-5, E: etoposide 100 mg/m²; d1-5.
ES is an aggressive tumor that is most commonly seen under age 20 (Saeter 2007; Jurgens and Dirksen, 2011). The disease is very uncommon in patients over age 40. In our study, the median age was 27. Only 3.8% of patients (n=1) were older than 40 year, and 19% of the patients (n=5) were older than 30 years, which correlated with the center’s other observations (Cotterill et al., 2000; Applebaum et al., 2011; Collier et al., 2011). Thus, many authors recommend that the clinician first eliminate other small round cell tumors such as small cell carcinoma and large cell lymphoma in patients older than 30 years.

Discussion

ES is an aggressive tumor that is most commonly localized disease and ECOG PS 0-1 had a 10-year survival rate of 76% (p=0.001).

The median OS was 49 months in non-extremity primary tumors, and the 10-year OS was 85% in extremity primary tumors in non-metastatic patients (p=0.08) (Figure 2). The OS was 41 months in patients with localized disease and primary tumor in vertebra, 49 months for thoracal disease, and 65 months for primary tumor at the head or neck. The OS in patients with metastatic disease and thoracal primary tumor was 5 months, 39 months in abdominal primary, and 22 months in vertebral primary (p>0.05).

A toxicity evaluation was done in 18 patients (Table 3). There was no correlation between toxicities and PFS and OS values.

Another remarkable result was that non-metastatic patients under age 30 have better disease-free and overall survival than patients age 30 and older. This difference has not been seen in metastatic patients. Baldini et al. reviewed 37 ES patients and concluded that patients younger than 26 years have a worse survival rate than those older than 26 (Baldini et al., 1999). Similarly, in Grier et al.’s study, the survival rate worsened with advanced age (Grier et al., 2003). But some studies have shown that age has no significant influence on survival (Fizazi et al., 1998; Bacci et al., 2000). Consequently, this issue must be identified with randomized prospective trials.

Another cause of the different clinical outcome is that it is more feasible to apply more effective local therapy in extremity primary ES. It is difficult to achieve successful local treatment in both abdominopelvic and thoracal disease, either with surgery or radiation, due serious morbidities and mortalities (Balamuth and Womer, 2010).

ES suggest that they have subtle biological differences. One of the causes of these differences may arise from the tumor’s microenvironment (Applebaum et al., 2011). Another cause of the different clinical outcome is that it is the presence of metastatic disease (Saeter 2007; Jurgens and Dirksen, 2011). The most common localization of the disease is in the extremities. In our patients, the disease was at the extremities in 31% of the patients and at the thorax in 31% of patients. Similar to other studies, 19% of the patients were metastatic. The most common metastasis sites were lungs (40%) and bones (40%) (Obata et al., 2007; Balamuth and Womer, 2010).

Many parameters such as age, gender, tumor size, and localization have been investigated as prognostic factors. But the results are conflicting (Oberlin et al., 2001; Grier et al., 2003; Kolb et al., 2003). Currently, the only evidence-based prognostic factor accepted by all authors is the presence of metastatic disease (Bacci et al., 2000; van Doorninck et al., 2010; Shannon Orr et al., 2012).

In our study, there was no correlation between gender, tumor size, and overall and disease-free survival. But in the extremity primary disease, progression/disease-free survival was significantly better. Although not statistically significant, the overall survival rate was better in extremity primary disease. The differences in tumor characteristics and clinical outcomes between skeletal and extraskeletal ES suggest that they have subtle biological differences.
to the physician’s and patient’s preferences. However, in our study, and in other studies, patients treated with combined modality have much better survival outcomes than patients treated with only surgery or radiotherapy or chemotherapy (Jurgens et al., 1988; Bacci et al., 1989; Barbieri et al., 1990). In particular, the addition of ifosfamide and etoposide to vincristine, doxorubicine, and cyclophosphamide showed significant improvement in both event-free survival and in overall survival (OS) for non-metastatic ES patients. An intergroup study demonstrated that patients in the experimental arm had a 5-year OS rate of 72%, compared with 61% for patients in the standard therapy arm (p=0.01) (Grier et al., 2003).

ES is generally considered a childhood disease, but it can be seen in adults. In particular, patients with localized disease may have longer survival rates. Thus, early diagnosis and effective treatment have great importance. Also, we need more effective agents for metastatic patients. There are ongoing clinical trials investigating monoclonal antibodies, small molecule inhibitors targeting the insulin like growth factor-1 receptor (Jurgens et al., 2011; Tap et al., 2012; Schwartz et al., 2013). But most of them are phase I or II trials. Therefore, we should wait some years for to gain advanced survivals in ES patients in our daily practice.

References


