Ewing’s Sarcoma of the Axial System in Patients Older Than 15 Years: Dismal Prognosis Despite Intensive Multiagent Chemotherapy and Aggressive Local Treatment

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Background: Older age and axial location of Ewing’s sarcoma have been reported as unfavorable prognostic factors.

Methods: The records of patients older than 15 years with the Ewing’s family of tumors were reviewed retrospectively. After the induction chemotherapy consisting of alternating vincristine, adriablastin, cyclophosphamide (VAC) and etoposide, ifosfamide with mesna protection (IE), a local treatment modality was chosen based on tumor and patient characteristics.

Results: Twenty-five patients with a median age of 19 years were evaluated. Median follow-up was 26 months (range 4–58). Seventeen patients (68%) had died. In univariate analysis, factors predictive of shorter survival were the patients presenting with metastatic disease, with the primary tumor located at the pelvis, those who never achieved complete response to chemotherapy and those who had chemotherapy for <12 months. Only a negative link with pelvic location was observed in multivariate analysis [risk ratio 7.5; 95% confidence interval (CI) 1.52–37.06; P = 0.0134]. Median progression-free survival (PFS) and overall survival (OS) were 10 months (95% CI 6.2–13.8) and 14 months (95% CI 9.3–18.7), respectively. Cumulative 2-year PFS and OS were 19.0% (95% CI, SD 8.4) and 32.7% (95% CI, SD 9.8), respectively.

Conclusions: The prognosis of patients with axial Ewing’s sarcoma is dismal despite an intensive, multimodality approach including multiagent, alternating chemotherapy, surgery and/or radiotherapy. A more aggressive approach should be considered for this group of Ewing’s sarcoma patients.

Key words: Ewing’s sarcoma – pelvis – vertebra – prognosis – survival

INTRODUCTION

Ewing’s sarcoma of bone is an aggressive tumor whose prognosis is determined by both the adequacy of the local control of the primary lesion and the efficacy of the systemic chemotherapy aimed at the control of micrometastatic disease (1). The peak incidence is in the second decade of life, and median age at diagnosis ranges from 13 to 19 years in studies not restricted to pediatric recruitment; children <10 years old and those over the age of 20 account for 30% of cases each (2,3). The 5-year survival rate for patients with Ewing’s sarcoma was only 10% in the 1970s (4), with the use of multidrug therapy that combines more effective multiagent chemotherapy, contemporary imaging, radiotherapy and surgery techniques, the current 5-year survival rate has increased to 55–75% (1).

Since few studies have been published on adult patients (5–7), little is known about the clinical outcome of adult patients. On the other hand, treatment protocols in adult patients with Ewing’s sarcoma are usually adapted from pediatric treatment protocols. Accordingly, it is difficult to draw a firm conclusion for adult patients with Ewing’s sarcoma. In most studies, older age has been reported as an unfavorable prognostic factor (1,8–10). Several characteristics of adult Ewing’s sarcoma, such as a different pattern of primary tumor sites (e.g. axial location) (11–13), a greater tumor dimension (14–16) and a lower intensity of chemotherapy doses (1,17,18), may explain why the prognosis in adults is seemingly less favorable.

To determine whether older age and axial location of primary tumor influence outcome and to evaluate the relevance of various parameters to the prognosis in adults, we retrospectively reviewed the records of patients with the diagnosis of the Ewing’s sarcoma family of tumors at our institution.
SUBJECTS AND METHODS

PATIENT CHARACTERISTICS

The records of patients older than 15 years with Ewing’s family of tumors were reviewed retrospectively between September 1991 and September 2002. The clinical characteristics of the patients are summarized in Table 1. Diagnosis was based on biopsy specimens, tumor morphology and immunohistochemical analysis. Staging was based on the patient’s history, physical examination, chest radiographs, computed tomography (CT) scans of the primary tumor and the chest, bone scan, blood chemistries and complete blood cell count. An axial tumor site encompassed tumors of the pelvis and spine. Primary tumor bulk was measured as the greatest diameter on CT scan. Performance status was evaluated according to the Eastern Cooperative Oncology Group Scale (ECOG).

TREATMENT PLAN

The treatment protocol included induction chemotherapy with multiagent cytotoxics followed by evaluation of the response to induction chemotherapy after three cycles (Table 2, Fig. 1). Local treatment consisted of surgery alone (preferably), surgery followed by radiation therapy (in the case of a close margin) or radiation therapy alone. The specific surgical procedure was determined by the surgeon based on the tumor location. Radiation therapy was given either alone or combined with other modalities at a dose of 45–60 Gy.

Chemotherapy was continued during the local treatment phase followed by maintenance chemotherapy courses administered every 3 weeks for a total of 1 year. Induction chemotherapy consisted of alternating vincristine 1.4 mg/m², doxorubicin 75 mg/m², cyclophosphamide 1200 mg/m² (VAC) on day 1 and etoposide 100 mg/m², ifosfamide 1800 mg/m² with mesna protection (IE) daily for 5 days. Along with radiotherapy, only the IE regimen was given. Doxorubicin was replaced by actinomycin D 1.25 mg/m² after reaching a cumulative dose of 450 mg/m². The treatment after local therapy with surgery and/or radiotherapy continued with the alternating chemotherapy regimen (VAC–IE). The treatment protocol was continued until progression for metastatic disease.

TOXICITY

A complete blood count was performed every week during treatment. Biochemical analysis and physical examination were done every 3 weeks. Toxicity was graded according to the WHO common toxicity scale. Table 3 shows hematological and non-hematological toxicities.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
</tr>
<tr>
<td>Range</td>
<td>15–40</td>
</tr>
<tr>
<td>Male/female</td>
<td>18/7</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>PNET</td>
<td>8</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>17</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>14</td>
</tr>
<tr>
<td>2–4</td>
<td>11</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm</td>
<td>14</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>11</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>Non-metastatic</td>
<td>20</td>
</tr>
<tr>
<td>Metastatic</td>
<td>5</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>12</td>
</tr>
<tr>
<td>Columnar vertebrates</td>
<td>13</td>
</tr>
<tr>
<td>Chemotherapy duration</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>13</td>
</tr>
<tr>
<td>1 year</td>
<td>12</td>
</tr>
<tr>
<td>Radiotherapy to primary tumor location</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>22</td>
</tr>
<tr>
<td>Not done</td>
<td>3</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>9</td>
</tr>
<tr>
<td>No resection</td>
<td>16</td>
</tr>
</tbody>
</table>

WHO grade | I–II, n (%) | III–IV, n (%)
--- | --- | ---
Non-hematological toxicity
Emesis | 20 (87.0) | 3 (13.0)
Mucositis | 12 (52.2) | 2 (8.7)
Diarrhea | 8 (34.8) | 1 (4.4)
Renal | 8 (34.8) | 0 (0.0)
Hemorrhagic cystitis | 2 (8.7) | 0 (0.0)
Neuropathy | 22 (95.7) | 1 (4.4)
Hematological toxicity
Neutropenia | 8 (34.8) | 15 (65.2)
Thrombopenia | 9 (39.1) | 10 (43.5)
Anemia | 11 (47.8) | 12 (52.2)
Febrile neutropenia | 8 (34.8) |
Follow-up

Complete disappearance of the soft tissue mass and sclerosis of the lytic bone lesions defined complete response (CR) to induction chemotherapy. Partial response (PR) required a $\geq 50\%$ reduction in the sum of the products of the diameters of all measured lesions, no increase in the size of any previous lesion and no new lesion. Progressive disease (PD) was defined as $\geq 25\%$ increase in the sum of the products of the diameters of any measurable lesions or the appearance of a new lesion. After the completion of therapy, patients were followed-up every 3 months with assessment of interval history, physical examination, chest X-ray and complete blood count. CT scans of the primary tumor location and chest were performed every 6 months for 5 years and yearly afterwards.

Statistics

Survival functions of all patients were measured from the time of initial treatment. For disease-free survival (DFS), progression during therapy, local relapse, metastases and death resulting from tumor were classified as events when occurring as first events. Overall survival (OS) was assessed from the date of initial pathological diagnosis to death from any cause or last follow-up visit. OS and DFS function were estimated by the Kaplan–Meier method. The following features were investigated as potential prognostic factors that may influence OS: age (15–20 versus $> 20$), gender (male versus female), performance status (0–1 versus 2–4), tumor size ($< 10$ cm versus $\geq 10$ cm), disease status (metastatic versus non-metastatic), tumor location (pelvic versus vertebral column), chemotherapy duration ($< 1$ year versus $1$ year) and response to chemotherapy (CR versus other than CR). Survival differences for various parameters were analyzed using the log-rank test (19) (univariate analysis). Cox (20) proportional hazards regression was used for multivariate analysis of prognostic impact-relevant variables. In the multivariate analyses, only the factors that proved significant in the univariate analysis were investigated. The significance level used was $P < 0.05$. For statistical analysis, the SPSS statistical software (Version 11, SPSS Inc., Chicago, IL) was used.

Results

Patients

We retrospectively reviewed 55 consecutive adult patients with Ewing’s sarcoma and analyzed the prognosis of 25 patients with axial, i.e. vertebral column and pelvic, primaries. The median age was 19 years (range 15–40). The majority of patients were male (72%). The location of the primary tumor was pelvis in 12, sacrum in eight, thoracic vertebra in three and cervical vertebra in two patients. Six patients were referred following surgery; the procedure was complete resection in three and incomplete in three patients. Five patients were metastatic on presentation; three had multiple lung, one had lung and bone, and another had lung and liver metastases. The tumor size was $> 10$ cm in 11 patients.

Results of Therapy

A median of 11 (range 1–18) cycles of chemotherapy were administered. The overall response rate after three cycles of induction chemotherapy was 68% (17 out of 25), with eight patients (32%) achieving a complete radiological response. Three patients with vertebral primaries who were referred after surgery with a wide margin received upfront radiotherapy along with chemotherapy. The two other vertebral primaries presenting with tumor after intralesional surgical margins also received radiotherapy starting from the first cycle of chemotherapy. All other patients (20 patients) received...
three cycles of induction chemotherapy followed by core biopsy.

Four patients (16%) remained stable and four patients (16%) progressed during the initial phase of treatment. Among the remaining 17 patients, one patient with a CR (4%) was operated on after induction chemotherapy and the other 16 patients (64%) received radiotherapy after induction chemotherapy (median radiotherapy dose 5580 cGy, range 4500–6600) as local therapy. After radiotherapy, eight patients (32%) were operated on with a wide surgical margin and, after induction chemotherapy and surgery or radiotherapy, 11 patients were disease free. As mentioned above, patients with stable (four patients) or progressive disease (four patients) after radiochemotherapy were treated with palliative intent. Six patients dropped out during maintenance therapy. Eleven patients (44%) completed the planned schedule. The overall response rate at the end of the whole treatment protocol was 44%, with seven (28%) CR and four (16%) PR. Partial responders were again evaluated for surgery and deemed inoperable. Only one patient with metastatic disease achieved a CR at the end of the planned treatment schedule and experienced a recurrence at the 18th month of follow-up.

Twenty-three patients (92%) were evaluated for toxicity. Reasons for early drug discontinuation were as follows: there was disease progression during the treatment period in eight patients (32%); and one patient (4%) refused treatment. Dose reduction was done in 12 patients (52.2%) due to treatment intolerance in three patients (13.1%), and hematological toxicity in nine patients (39.1%). Dose delay was seen in almost all patients (91.3%). The median dose delay was 1 week (range 1–2 weeks). Most of the grade III–IV toxicities were hematological. Grade III–IV neutropenia and thrombocytopenia were experienced in 15 (65.2%) and 10 (43.5%) of 23 patients, respectively. There was no treatment-related death (Table 2).

Univariate analysis, summarized in Table 3, revealed the following pre-treatment factors to be prognostic for OS: patients with metastatic disease, primary tumor located at the pelvis, patients who never achieved CR and patients who could not complete the entire treatment protocol of 1 year. Multivariate analysis was conducted on variables which were found to be significant for poor OS in univariate analysis. Only a negative link with pelvic location was observed in multivariate analysis [risk ratio 7.5; 95% confidence interval (CI) 1.52–37.06; \( P = 0.0134 \)].

**FOLLOW-UP AND SURVIVAL**

Median follow-up was 26 months (range 4–58). At the evaluation, 17 patients (68%) were dead, three (12%) patients were alive without evidence of disease, three (12%) patients were alive with progression or recurrence, and two (8%) patients were lost during the follow-up period. Four of seven patients with a CR at the end of treatment recurred; three systemic and one local and systemic.

Median progression-free survival (PFS) and OS were 10 months (95% CI 6.2–13.8) and 14 months (95% CI 9.3–18.7), respectively. The survival curves for Ewing’s sarcoma patients are shown in Figs 2 and 3. Cumulative 2-year PFS and OS were 19.0% (95% CI, SD ±8.4) and 32.7% (95% CI, SD ±9.8), respectively.

**DISCUSSION**

Ewing’s sarcoma originating from the axial system, which comprises about half of all cases, is qualified as with high risk and has a worse prognosis compared with those at the extremities because of the high tumor volume, frequent loco-regional recurrence and distant metastasis, and difficulties in
radical surgical intervention. In the current study, with the multimodal therapy, OS and PFS were 10 and 14 months, respectively, after a median follow-up of 26 months in patients with Ewing’s sarcoma of the axial system. This dismal prognosis seems to be correlated with the limited number of studies in the literature. Five-year OS rates range between 35 and 72% in several small sized studies performed for patients with central axis Ewing’s sarcoma (21–27). As with many other tumors, identification of prognostic factors is mandatory to tailor the treatment more effectively for Ewing’s sarcoma. Undoubtedly, the presence of detectable metastasis at diagnosis is the most important prognostic factor in Ewing’s sarcoma (7). We also found in univariate analysis that metastatic disease at diagnosis is a strong predictor of poor prognosis. Nevertheless, metastatic disease has lost its significance in multivariate analysis probably due to low sample size. In view of the current study, tumor sites (pelvic and non-pelvic primaries) can be considered as another prognostic factor. Direct comparison between pelvic and non-pelvic locations of the tumor does not exist in the literature, but in a subset analysis of Bacci’s study (1), it is noted that there is no difference in survival between pelvic and non-pelvic locations. In the present study, we showed only pelvic location as a factor predicting shorter survival in multivariate analysis.

Our patients had both typical Ewing’s sarcoma and primitive neuroectodermal tumor pathology (PNET). Although several studies have reported PNET to have a much worse prognosis than Ewing’s sarcoma (28–31), the latest studies have refuted this assumption (7,32–34).

Naturally, it is difficult to achieve wide resection margins especially when the sacrum is involved with larger lesions. According to many pediatric and adult studies, tumor bulk is one of the most important prognostic factor in patients with Ewing’s sarcoma regardless of location (1,7,14,16,35,36). In contrast, Sucato et al. have found no significant relationship between tumor bulk and prognosis (37). In our study, there was no significant difference in PFS and OS rates between patients who have bulky and non-bulky tumors. Small sample size may be an explanation for this finding.

In the present study, we showed that gender, age (cut-off point for age was 20 years) and performance status had no influence on the DFS and OS. While several studies support our results (7,18,34), some authors claim that age and gender have an influence on PFS and OS (1,38,39).

The other important finding of this study is that patients who are complete responders to induction chemotherapy have a more favorable prognosis compared with poor responders. This situation is also in agreement with previous studies (7,18,19,37). Moreover, we found that patients who had 1 year chemotherapy have a better survival rate compared with those who had less. A number of studies have also shown that multimodal therapies including more intensive, multiagent chemotherapy prolong PFS and OS rates (1,7,18,21,23,24,29,34,37); therefore, most authors suggest that multimodal therapies should be standard modality in the treatment of patients with Ewing’s sarcoma regardless of location. On the other hand, it has been suggested recently by various authors that some novel therapies such as dose-intensive or high dose chemotherapy with autologous stem cell rescue, fenretinide, a synthetic retinoid and imatinib mesylate seem to be effective in patients with poor prognosis (40–43).

In conclusion, by identifying patients at high risk due to poor prognostic factors, it is now possible to tailor treatment modalities to target such patients with more intensive and novel therapies and to increase survival. This requires multidisciplinary team cooperation.
References


