Abstract

Background The purpose of this study is to assess the outcome of patients with Ewing sarcoma (EWS) of the bone and to identify prognostic factors.

Materials and methods Seventy-seven patients younger than 18 years old, diagnosed with EWS of the bone between 1979 and 2009, were analysed retrospectively. Four different protocols of chemotherapy were used successively. Local treatment consisted of surgery (N=32), radiotherapy (N=20) and a combination of both (N=19).

Results The median age at diagnosis was 10 years old (range, 2–17) and the median follow-up for survivors 8.6 years (range, 1–18.8). Thirty-two relapses occurred (21 distant, 5 local and 6 both). The 2- and 5-year overall survival rates were 70% and 51%, respectively. Multivariate analysis showed four significant independent predictors for death: age ≥14 years old (HR: 5.06; p=0.019), lack of complete response (HR: 8.04; p<0.001), tumour volume ≥150 ml (HR: 2.21; p=0.045) and distant recurrences (HR: 1.45; p=0.001).

Conclusions Outcome of EWS of bone is influenced by many clinical and treatment-correlated variables. Criteria to stratify patients should include all the variables that have shown prognostic significance. The development of novel therapies should target these high-risk groups.

Keywords Prognostic factors · Ewing sarcoma · Paediatric oncology

Introduction

Ewing sarcoma (EWS) refers histologically to a collection of small, round cell tumours and clinically manifests with a variety of presentations [1, 2]. EWS is the second most common primary malignant bone tumour following osteosarcoma in children worldwide [3] and the most common in Spain, according to the 2008 nationwide paediatric cancer registry. Most cases are between the ages of 10 and 14 years and there is male predominance (male:female, 3:1) [4].

In the last three decades there has been a major improvement in the outcome of patients with EWS. Multi-disciplinary therapy, comprising local control (LC) with surgery, radiation or a combination of both, as well as the use of systemic chemotherapy, has improved the event-free survival and overall survival (OS) for patients with localised disease [5–7]. These advances in the treatment of EWS have derived largely from cooperative trials and the progress made in the multidisciplinary approach. New agents have been incorporated progressively into the treatment armamentarium and improvements in support mea-
sures have allowed for treatment intensification. These advances, however, are also the result of improvements in LC, with better radiation therapy (RT) planning and more aggressive surgical approaches [7]. Nevertheless, despite aggressive treatment, 30–40% of patients with localised disease and 80% of patients with metastatic disease die due to disease progression [8, 9].

Chemotherapy dose intensification and the use of megatherapy with autologous haematopoietic stem cell transplant are valid alternatives for high-risk patients, such as those with high-risk features at presentation and those with recurrent disease, and a number of centres (including our institution) routinely use these treatment modalities. A critical review of the advances and of the current understanding of the nature of the disease must be performed before we engage in the design of newer, more intensive treatments.

We have carried out a comprehensive analysis to assess the clinical outcome of patients with EWS of the bone treated in a single institution during the last three decades and to identify prognostic factors for OS.

Material and methods

Patient population

The institutional review board approved a retrospective chart review, which was conducted for individuals with EWS of bone diagnosed during childhood or adolescence. We identified 77 patients younger than 18 years old from 1979 to 2009. We used the TNM classification according to the American Joint Committee on Cancer 2002 for bone sarcoma for disease staging [10]. Patients in the analyses of survival were included according to the intention-to-treat principle. In all cases, the pathology was reviewed at our institution and diagnoses were confirmed by immunohistochemistry, electron microscopy and cytogenetic analysis (when available). The standard patient evaluation included history and physical examination, complete blood count and serum chemistries (serum lactate dehydrogenase [LDH] levels available in 25 cases), computed tomography (CT) and/or magnetic resonance scan of the primary site, chest CT scan, bone scan and bone marrow biopsy. Before the treatment of any patient, informed consent was obtained. Patients were followed up every 3 months post-therapy for 3 years and then every six months for 2 years and at least once yearly thereafter. The follow-up evaluations consisted of a history and physical examination. CT scans were obtained at intervals of 3–6 months or more frequently if clinically indicated.

Treatment

Our practice has largely reflected the evolving cooperative group standards for treatment. All patients were treated in several institutional or national prospective studies of EWS that included different protocol guidelines (Fig. 1). Four different protocols of chemotherapy were used successively.

The first protocol (T-9; period, 1979–1990; N=19) used at our institution consisted of five cycles of chemotherapy, administered over a 45-week period with the use of analogous doses of all agents [11]. Since 1991, patients were treated according to the Memorial Sloan-Kettering Cancer Center P6 [12] protocol (N=10). In this period (1991–1994) patients were also treated according to the Pediatric Oncology Group (POG) 8346 [13] protocol (N=6), which called for either surgery or definitive RT to be delivered in week 12 after initiation of chemotherapy.

The most recent (period, 1995–2009; N=42) and common scheme used was according to the Spanish Society of Pediatric Oncology (SEOP) protocol. Since 1995, end-intensification with megatherapy using high-dose chemotherapy and stem cell rescue was delivered in 19 patients (25%) after consolidation chemotherapy according to our bone marrow transplant protocol. Local therapy was individually planned for each patient after discussions between the surgeon, paediatric oncologist and radiation oncologist. Tumour site, tumour size and resectability, the patient’s age, and individual preference were considered. Fifty-one patients (66%) were treated with surgery. Tumour location of those patients who received surgery included ribs (N=5), scapula (N=4), extremities (N=26), foot (N=5), pelvis (N=2), spine (N=5) and head (N=4) bones. Limb-salvage surgery was preferred over amputation. Thirty-nine patients received RT. 20 were treated with definitive RT, 18 with postoperative RT and 1 preoperatively. Specific characteristics of RT treatment, including dose, fractionation and technique, were determined by reviewing radiation treatment charts and films. Patients treated before 2000 (53% of cases) received two-dimensional non-conformal techniques in which the initial fields encompassed the primary tumour plus a 2 cm margin. Patients treated in 2000 or later were treated with three-dimensional conformal techniques targeting the primary lesion at diagnosis plus a 2 cm cranio-caudal margin and 2 cm in the other axis, except in cases in which this would result in overdosing of an adjacent critical structure (such as epiphysis, spinal cord or ovary). Definitive RT was delivered in the following cases: unresectable location or insufficient tumour regression to allow for complete resection. Postoperative RT was delivered in those cases with poor histological tumour response (≥10% viable tumour cells) or positive margins after surgery. According to the SEOP protocol, postoperative RT was initiated as soon as possible if there was residual tumour after surgery or concurrent with the second cycle of adjuvant chemotherapy (approximately three weeks after surgery) if there was complete resection. Preoperative RT was indicated in emergency cases (such as medullar compression) or tumour progression after induction chemotherapy. Definitive RT was initiated after eight weeks of the bone marrow transplant.