Ewing Sarcoma: Focus on Medical Management

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Abstract

The management of Ewing sarcoma has evolved over the last few decades with successive improvement in survival rates. Multidisciplinary management is the key to successful outcomes. Dose intensity of chemotherapy is of vital importance. Local control can be effectively achieved with surgery, radiation therapy or a combination of the two. The choice of appropriate local therapy should be individualized and depends on various factors such as site, size, respectability, expected morbidity, long term effects etc. Metastatic disease remains a significant challenge and optimal therapeutic strategies still need to be defined. Current management and the role of radiation therapy in Ewing sarcoma are reviewed.

Keywords: Ewing sarcoma, radiation therapy, management

Introduction

In 1921, James Ewing reported a group of primary radiosensitive tumors as diffuse endothelioma of bone, believing they arose from the blood vessels of bone tissue [1]. A few years later the noted Boston surgeon, Ernest Codman, referred to this new entity as Ewing sarcoma (EWS) [2]. EWS, a rare malignancy with a strong pediatric predilection, typically presents as a bone tumor [3]. It is the second most common primary malignant bone tumor in children and young adults, following osteosarcoma [3]. It is the second most common malignancy with a strong pediatric predilection, typically presents as a bone tumor [3]. It is the second most common primary malignant bone tumor in children and young adults, following osteosarcoma [3].

Epidemiology

Over the last 30 years, the incidence of EWS has remained unchanged at around 3 cases per million per year [5]. With a median age of 15 years, it most commonly occurs in the second decade of life (Fig 1) [6]. There is a slight male predilection (male: female 1.2:1) and Caucasians are much more frequently affected than Asians and Africans [7,8]. Lower extremities are the most common site of bone disease (43%) while extraosseous primary tumors mostly occur in the trunk (32%) (Fig 2). Metastatic disease is present at diagnosis in about 20-25% of patients and affects the lungs, other bones or multiple systems [5,9].

Biology & Pathology

The World Health Organisation (WHO) classification uses EWS/primitive neuroectodermal tumor (PNET) as an inclusive term which encompasses classic EWS, Askin tumor of the thoracic wall, Ewing tumor, peripheral neuroepithelioma, peripheral neuroblastoma, Ewing family of tumors and Ewing sarcoma family of tumors [10]. EWS is derived from a primordial bone marrow-derived mesenchymal stem cell [11,12]. Histologically, EWS is characterised by a monotonous population of small round blue cells with a low mitotic activity of 15-20%. Cytoplasmic glycogen is abundant which gives periodic acid-Schiff (PAS) positivity [13]. The MIC2 gene product, CD99, a surface membrane glycoprotein is overexpressed [14] but it is not specific for EWS. Neural differentiation is evident in the form of positive vimentin in approximately one third of cases. A reciprocal chromosomal translocation involving the EWSR1 gene on chromosome 22 band q12 combined with any of a number of partner chromosomes is pathognomonic of the diagnosis of EWS. The breakpoint was first cloned in the 1990s [12,15]. Although abnormalities of chromosome 11 are involved in 95% of cases [16], the translocation may involve chromosomes 21, 7 and 17 uncommonly [17,18]. The fusion protein resulting from this chromosomal rearrangement is a potent transcriptional factor which inappropriately activates the target genes, thereby exerting the oncogenic activity. Other numerical and structural alterations seen in EWS are gains of chromosomes 2, 5, 8, 9, 12, and 15; deletions on the short arm of chromosome 6; the nonreciprocal translocation...
Staging
EWS is defined by clinical and imaging techniques as localized when there is no spread beyond the primary site or metastatic when the tumor has disseminated to distant organs. Of all imaging modalities, 18FDG PET-CT has the highest specificity (96%) and sensitivity (92%) [21] and is superior to the traditionally used 99mTc-MDP bone scan for detection of bone metastases except for skull lesions [22]. Current recommendations for staging work-up include CT and/or MRI of the primary tumor, chest CT to detect lung metastases and 18FDG PET-CT for identification of distant metastases [23]. As bone marrow involvement is an independent risk factor [24], marrow biopsy has been an integral part of the initial work-up and is still recommended in ongoing clinical trials [25] [26]. But recent studies have questioned the utility of bone marrow biopsy in localized [22,27] and metastatic disease [23].

Prognosis
The 5 year survival rate for EWS was less than 10% before the advent of modern chemotherapy [28,29]. Currently, the survival rates are 70% for the patients with localized disease [30] and 30% for the patients with metastatic disease [9]. Among patients with refractory or recurrent disease, fewer than 20% of patients can expect to be long term survivors [31,32]. The presence of metastatic disease at diagnosis remains the most important adverse prognostic factor in EWS [33,34,35,36]. In patients with metastatic disease the site(s) of metastases can have an impact on the outcome. Patients with only lung metastases fare better (event free survival, EFS 29% to 52%) than patients with bone and/or bone marrow involvement (EFS 19%) [37,38] or combined bones and lungs involvement (EFS 8%) [39]. Unilateral lung involvement has a better outcome compared with bilateral lung lesions [39]. Younger age (<15 years old) [5,40,41], female gender [42], tumor site (distal extremity better than proximal extremity and pelvis) [9], tumor size (volume less than 200 ml and single dimension less than 8 cm) [43], normal serum lactate dehydrogenase (LDH) levels at diagnosis [44], and decreased metabolic activity on 18FDG PET scan after presurgical chemotherapy [45,46] are associated with a more favourable prognosis. Complex karyotypic abnormalities or chromosome number less than 50 in tumor cells at diagnosis [19], detection of fusion transcripts by polymerase chain reaction (PCR) in morphologically normal bone marrow [47], p53 protein overexpression, Ki67 expression, loss of 16q [48,49], overexpression of microsomal glutathione S-transferase (associated with doxorubicin resistance [50] may be associated with inferior outcome. Patients with secondary Ewing sarcoma [51] or with a poor response to presurgical chemotherapy [52,53] and patients relapsing less than two
years after diagnosis (early) have a poorer prognosis [54].

**Treatment options**

Chemotherapy for a total of 10-12 months before and after local control is common practice [33,55]. Initial chemotherapy aims to shrink the tumor to increase to probability of effective local control. Alkylating agents, mainly ifosfamide and cyclophosphamide and anthracyclines form the chemotherapeutic backbone Etoposide, vincristine and actinomycin-D make up the remainder of the four-to five-drug combination chemotherapy.

**Chemotherapy for newly diagnosed patients:**

Clinical trials in the early years (pre-1990)

Before 1960s, radiation therapy and surgery were used for the treatment of EWS which provided adequate control of the primary disease but patients invariably died of metastatic disease [56]. Chemotherapy was added based on the hypothesis that, in most cases of apparently localized disease, tumor cells were already disseminated without clinical manifestations. Single chemotherapy agents including vincristine, actinomycin-D, cyclophosphamide and doxorubicin was universally accepted for the treatment by the early 1980s [75] with survival rates between 36-60%. Ifosfamide and etoposide were identified as effective single agents [76,77] and subsequent studies established a survival benefit of their addition to VACD [78]. National Cancer Institute protocol INT0091 was a randomized trial conducted by the Children’s Cancer Group (CCG), the Pediatric Oncology Group (POG) and subsequently the Children’s Oncology Group (COG) conducted trials for EWS. Four-drug combination chemotherapy including vincristine, actinomycin-D, cyclophosphamide and doxorubicin was universally accepted for the treatment by the early 1980s [75] with survival rates between 36-60%. Ifosfamide and etoposide were identified as effective single agents [76,77] and subsequent studies established a survival benefit of their addition to VACD [78]. National Cancer Institute protocol INT0091 was a randomized trial conducted by the Children’s Cancer Group (CCG) and Pediatric Oncology Group (POG) from 1988 through 1992. Patients were assigned to receive VACD or VACD plus ifosfamide and etoposide (VACD-IE). In patients without metastatic disease, the five-year EFS for the VACD group was 54% while the same for the VACD-IE group was 69%. These results established VACD-IE as the gold standard for the treatment of localized Ewing sarcoma [30]. Clinical trials for standard risk (SR) and high risk (HR) EWS since 1990

The disease risk stratification into SR and HR has varied depending on the trial but in general SR means localized small tumors (<200 mL), or tumors with a good histological response to preoperative chemotherapy (<10% cells). HR tumors include metastatic tumors, or large localized tumors (>200 mL). The trials for SR EWS have tried to address the important questions like the superiority of one alkylating agent over the other (cyclophosphamide and ifosfamide) and survival advantage by dose intensification or addition newer chemotherapy agents.

**Cyclophosphamide vs Ifosfamide**

Historically, cyclophosphamide was used for the treatment of EWS. Promising results were seen with ifosfamide in relapsed patients who did not respond to cyclophosphamide [83]. It was postulated that 9 g/m2 of ifosfamide was equimyelotoxic to 2.1 g/m2 of cyclophosphamide [84]. With the potential for less myelotoxicity and high-dose administration, cyclophosphamide was replaced with ifosfamide in the 1980s. But the results of these non-randomized, single-arm studies were mixed, with one study showing no benefit [66] while others proving superiority of ifosfamide over cyclophosphamide [71,67,69]. With this uncertainty of greater efficacy and long-term renal tubular damage with the cumulative dose of ifosfamide [85], its role in the consolidation treatment of EWS was debated. Two large randomized trials, EICESS-92 [79] and its successor Euro-Ewing99-R1 [80] investigated if cyclophosphamide can replace ifosfamide in

Table 1. Chemotherapy trials for SR EWS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Randomization</th>
<th>n</th>
<th>Treatment</th>
<th>%EFS</th>
<th>%OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EICESS-92</td>
<td>1992-1999</td>
<td>Yes</td>
<td>155</td>
<td>VAID vs VACD</td>
<td>74%</td>
<td>80%</td>
</tr>
<tr>
<td>EURO-</td>
<td>2000-2010</td>
<td>Yes</td>
<td>856</td>
<td>VAID vs VACD</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>EWING99-R1</td>
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<td></td>
<td></td>
<td>VACD</td>
<td>78.9%</td>
<td>95%</td>
</tr>
<tr>
<td>INT-0154/CCG</td>
<td>2000-2010</td>
<td></td>
<td>478</td>
<td>VCD+IMC</td>
<td>72.1%</td>
<td>80.5%</td>
</tr>
<tr>
<td>7942/POG9354</td>
<td></td>
<td></td>
<td></td>
<td>Standard</td>
<td>70.1%</td>
<td>77.0%</td>
</tr>
<tr>
<td>SGI</td>
<td>2001-2005</td>
<td></td>
<td>568</td>
<td>VCD+IMC</td>
<td>65%</td>
<td>83%</td>
</tr>
<tr>
<td>AEWS0031/CCG</td>
<td></td>
<td></td>
<td></td>
<td>2 weeks</td>
<td>73%</td>
<td>77%</td>
</tr>
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n-number of patients, a-%EFS at 3 years b-%OS at 3 years
the consolidation treatment of standard-risk EWS. The results of these studies confirmed that both the drugs had similar efficacy and though cyclophosphamide was associated with more haematological toxicity, the incidence of renal toxicity was much less as compared to ifosfamide. But the question of superiority of one drug over the other is far from resolved and needs further investigation in light of their efficacy to improve the survival [75].

**Standard dose vs dose intensification**
To improve the outcome, intensification of chemotherapy drug doses was investigated. One way of achieving dose intensification is by escalating the doses of chemotherapy agents while keeping the interval stable. National Cancer Institute protocol INT0154 used VDC+IE chemotherapy and randomized patients to standard (17 cycles over 48 weeks) or intensified (11 cycles over 30 weeks) arms. This study showed no improvement in the outcome of patients with nonmetastatic disease by dose escalation of alkylating agents (81) which was in contrast to an earlier similar study, IESS-II [74]. AEWS0031 trial investigated the feasibility of dose intensification by interval compression (increased dose density) in patients with localized disease [82]. Patients treated every two weeks (intensified arm) had an improved five-year EFS (73%) compared with the standard arm group receiving chemotherapy every 3 weeks (65%) with no increase in toxicity. Due to its superiority, interval compression is used in many ongoing trials.

The Children’s Oncology Group is currently conducting a phase III randomized trial of adding vincristine, topotecan and cyclophosphamide to standard chemotherapy for patients with localized EWS in an attempt to improve the outcome further [25]. The EICESS-92 study recruited 492 high risk patients of which 157 had metastatic disease at diagnosis. These patients were randomized to receive either VAID or etoposide in addition to VAID (EVAID). Although there was evidence that etoposide had a more pronounced effect in localized HR group, there was no benefit for the patients with metastatic disease with a three-year EFS of 30% [79].

The EURO-EWING99-R3 study enrolled 281 patients with primary disseminated multifocal EWS. 169 patients received the high dose therapy (HDT)/stem cell transplant (SCT) post completion of chemotherapy and local therapy. 3-year EFS for whole cohort was 27% and for patients receiving HDT was 37% [24].

**Local therapy**
The goal of local therapy is to maximize the local control with minimal morbidity. Surgery and radiation therapy are the two local control modalities employed for EWS. No randomized trials have compared these and as such their relative roles remain controversial [13]. Surgical resection provides information about the amount of tumor necrosis and may be less morbid in the younger patients. Radiation therapy is also associated with the development of second malignant neoplasms in a dose and time dependent manner [86]. A retrospective analysis of patients treated on three consecutive clinical trials for localized EWS showed that the risk of local failure was greater for patients receiving definitive radiotherapy but the EFS and OS were comparable for both surgery and radiation as local control modalities [87]. Microscopically complete surgical resection of localized disease remains the goal of neoadjuvant (or upfront) chemotherapy. Large bone defects after the surgery may be reconstructed using autogenous or allogenic bone grafts and endoprosthetic replacements [13].

Radiation therapy may be used as the main modality of primary disease control in patients with axial or unresectable primary disease. Careful consideration about the use of radiation, dose and volume is required, particularly in younger patients. In patients with lung metastases, upfront whole-lung radiation may be used irrespective of the radiographic response following chemotherapy [88]. The results of the recently concluded Euro-EWING99 R2 pulmonary (AEWS0331) study which compared the HDT and peripheral blood stem cell (PBSC) rescue with the standard chemotherapy and whole lung irradiation are awaited. A multivariate analysis of the R3 arm of this trial including patients with metastatic disease emphasized the importance of aggressive local control of primary and metastatic sites. The EFS was higher with combined surgery and radiation compared to either modality alone or no local control [89].

**High-dose therapy (HDT) and stem cell transplantation (SCT)**
Despite advances in multimodal therapy of EWS, there remains a group of patients with high risk of treatment failure. These are primarily the patients with metastatic disease or with extensive unresectable localized disease and patients with a poor response to chemotherapy. This group has a poor 20%-30% disease free survival (DFS) [90,91]. Although conventional chemotherapy regimens induce remission, patients with metastatic disease relapse after a median of one to two years after completion of therapy owing to minimal residual or metastatic disease (MRD/MMD). In the 1980s trials investigating the role of SCT to consolidate remission by reduction of MRD/MMD began. The results of the initial National Cancer Institute (NCI) studies investigating total body irradiation (TBI) with autologous bone marrow transplant (ABMT) showed no improvement in survival [92]. Since then multiple reports have been published of consolidation using HDT followed by SCT but its role in the treatment of EWS has yet to be conclusively determined [93].

**Melphalan vs busulfan-based conditioning regimens**
Response to melphalan-based HDT has been variable. Some studies showed no additional benefit with poor survival rates between 5%-27% [34,90,94,95] while others [96,97,98] reported improved survival rates of 45%-50%. As use of high-dose busulfan combined with melphalan or other agents has shown promising results with survival rates between 36%-60% [99,100,101,102,103,104], these regimens have been widely used in high-risk patients.

**Role of total-body irradiation (TBI)**
Use of TBI during the consolidation phase had no survival advantage but increased the incidence of toxicity [92,94]. Two Meta European Intergroup Cooperative Ewing Sarcoma Studies (MetaEICESS) assessed the role of TBI in consolidation treatment.
Patients received systemic consolidation in the form of hyperfractionated TBI with melphalan/etoposide in the first HyperME study or two times the melphalan/etoposide in the second TandemME study. EFS were similar in both studies while TBI containing regimen was associated with a higher incidence of toxicity [105]. In conclusion, although EWS is a radiosensitive tumor, there is limited role of TBI in its treatment because of poor efficacy and increased toxicity.

**Autologous vs allogeneic BMT**

Allogeneic transplant may overcome the concerns with tumor cell contamination of stem cell products during autologous transplant [106] and have a potential of graft-versus-tumor (GVT) effect with improved survival. A retrospective analysis of the MetaEICESS study data showed that the EFS was 25% after autologous and 20% after allogeneic transplant [54]. As there was increased incidence of toxicity and no evidence of GVT effect after allogeneic transplant, there seems to be no advantage of allogeneic over autologous transplant.

**Chemotherapy for recurrent EWS**

Although around 80% of relapses occur within 2 years of initial diagnosis [107], late relapses occurring more than five years from the initial diagnosis are more common in EWS than any other pediatric solid tumors. The Childhood Cancer Survivor Study (108) retrospectively assessed more than 12,700 childhood cancer survivors and concluded that survivors with EWS were at a higher risk of late recurrence, 5-20 years after the diagnosis, than survivors with acute lymphoblastic leukemia. Time to relapse is an important prognostic factor with recurrences occurring within two years of initial diagnosis having worse five-year survival of 7% compared to 30% for patients relapsing after two years [32,107]. Number of recurrences also impacts the outcome with multiple metastatic recurrences having worse prognosis than isolated local or metastatic recurrence [107]. There is no established treatment for these patients and the preferred approach is to combine multiagent chemotherapy with local modality of surgery and/or radiotherapy [109,110]. High dose ifosfamide alone [111] or with carboplatin and etoposide (ICE) has been commonly used with survival rates between 29%-33% [112,113]. Cytosphophamide and topotecan combination achieved response rates of 23%-44% with low toxicity and an added advantage of outpatient administration [114,115] but with a small median duration of response of 8 months [116]. Response rates of 29% to 68% and median time to progression of 3 to 8.5 months were seen with irinotecan and temozolomide [117,118,119,120]. Diarrhea was a troublesome complication which was managed effectively with oral cephalosporins. The combination was otherwise well tolerated. Although gemcitabine and docetaxel showed activity in one study [121], the results were not confirmed by subsequent studies. [122]. In case of recurrent EWS, the addition of HDT to salvage regimens is controversial. Some studies showed a good response in specific groups of patients who responded to relapse therapy and underwent HDT with OS rates of 53 to 66% [123,124], but most of the reports indicate HDT does not improve prognosis [54,125,126].

**Targeted therapy for EWS**

Tyrosine kinase (TK) inhibitors

TKs are important modulators of growth factor signaling and play a critical role in tumor growth. TK inhibitors are used alone or in combination with conventional chemotherapy agents in treatment of various cancers (127). A number of TK inhibitors have been tried in EWS with variable response.

**Insulin-like growth factor 1 receptor (IGF1R) inhibitors**

IGF1R is necessary for growth and development of normal as well as cancer cells [128]. With promising pre-clinical results showing IGF1R inhibition in EWS cell lines and xenografts [129], more than 25 agents inhibiting IGF1R are currently under investigation [130].

IGF1R monoclonal antibodies including R1S07’ (131), figitumumab [132], ganitumab (AMG479) [133], cixutumumab [134,135], and robatumumab (SCH-717454) [136] have shown activity in early phase clinical trials with response rates ranging from 6-14% and a favourable safety profile. But the results of the phase II studies were less impressive compared with the promising preclinical and early clinical data [137]. Small-molecule inhibitors of IGF1R such as GSK1838705A [138], GSK1904529A [139], BMS-754807 [140], and INSM-18 [141] are also in preclinical and clinical development.

**Biologic agents**

**Angiogenesis inhibitors**

Neovascularization plays a critical role in the pathogenesis of EWS [146] and targeting vascular endothelial growth factor (VEGF) may interfere with vasculogenesis, providing a novel therapeutic approach [147]. A phase I study [148] and a randomized phase II trial [149] conducted by the Children’s Oncology Group have shown the feasibility and tolerability of bevacinuzumab in EWS patients. Another phase II study investigated the role of vinblastine and celecoxib as angiogenesis inhibitors in combination with the standard chemotherapy (150). Although the feasibility of this combination was established, there were significant pulmonary and bladder toxicities.

**Histone deacetylase (HDAC) inhibitors**

HDAC inhibition suppresses EWS-FLI1 expression and may represent a novel therapeutic target for EWS (151).

**Mammalian target of rapamycin (mTOR) inhibitors**

MTOR is a serine/threonine kinase with critical role in protein synthesis, cell growth and proliferation regulation. mTOR inhibitors have shown activity in preclinical models. A phase I study of temsirolimus, irinotecan and temozolomide demonstrated efficacy and tolerability [152]. But another phase II study of temsirolimus with cixutumumab did not show any objective response despite the encouraging preclinical data [153]. Ridaforolimus was associated with a statistically significant but clinically small benefit on PFS [154].

**Aurora A kinase inhibitors**

Although alisertib (MLN8237), an Aurora
A kinase inhibitor produced promising results in the Pediatric Preclinical Testing Program [155], a recently concluded Children’s Oncology Group phase II trial failed to establish its efficacy in EWS [156].

Hedgehog pathway modulation
Arsenic trioxide was effective in inhibiting EWS growth in preclinical cell culture models by targeting p38(MAPK) and c-Jun N-terminal kinase [157]. These observations warrant further investigation.

Bisphosphonates
Zoledronic acid acts by inducing apoptosis by upregulating osteoprotegerin which was the basis of activity seen in EWS preclinical models [158,159]. However, confirmatory clinical trials have not been performed.

Immune therapy
Interleukin-15-activated natural killer (NK) cells combined with HDAC inhibitors improve immune recognition of therapy-sensitive and –resistant EWS and sensitize for NK cell cytotoxicity [160]. Allogenic NK cells have shown activity against EWS cells on their own [161].

EWS-FLI1 targeting
Targeting the EWS-FLI1 fusion protein or its key signalling pathway is another attractive approach [162]. YK-4279, a small molecule inhibitor of EWS-FLI1 protein activity [163,164], mithramycin, a chemotherapy drug [165] and midostaurin (PKC412), a multikinase inhibitor [166] have shown activity in preclinical models.

References


Conclusion

Many advances have been made in the management of EWS since its first description almost 100 years ago. Molecular and imaging techniques are progressing at a rapid pace allowing for newer insights into the biology of this disease. From radiation therapy alone, the treatment has evolved to include multiple modalities. The outcome for localized disease has improved dramatically but more needs to be done for patients with metastatic or recurrent EWS. Targeted therapies may offer some hope for the latter group.


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