EWING SARCOMA

Executive Summary

Ewing sarcoma family of tumors (ESFT) form a group of highly malignant diseases that peak in incidence in adolescence and early adult life. These tumors arise in either bone or soft tissue and the term ESFT includes the ASKIN tumor of the chest wall and peripheral primitive neuroectodermal tumors (pPNET) that are related closely to medulloblastoma and intracranial PNET, reflecting the neural differentiating potential of these tumors. The ESFT are much more common in Caucasians than in Africans and Asians, for which a genetic explanation has been proposed. The hallmark of ESFT is a translocation between chromosomes 11 and 22 resulting in a fusion protein referred to commonly as EWS-FLI1.

Prior to the introduction of chemotherapy more than 90% of patients died from tumor spread. Now at least 70% of those presenting with apparently localized disease are cured by multi-modal treatment, though the outlook for those who have evident metastases at diagnosis remains poor with five year survival rates of 25-30%. Other adverse prognostic features include the location (especially in the pelvis) and size (>8cm) of the tumor. The outcomes may be better for patients with extra-osseous primary tumors.

Pre-treatment evaluation should include plain radiographs of the primary tumor, CT scans of that site and of the chest (to screen for metastases), MRI of the primary site (especially to clarify surgical options), radioisotopic bone scan and possibly PET scan (both to detect metastatic disease). Bone marrow biopsies appear to be unnecessary in patients who have seemingly localized disease after comprehensive radiological assessment.

At the core of chemotherapeutic strategies is the combination of vincristine, doxorubicin and cyclophosphamide (VDC); both in North America and Western Europe. The addition of ifosfamide and etoposide (IE) was pioneered by the Rizzoli Orthopedic Institute in Bologna, Italy. The combination of VDC-IE is now standard of care in the United States and forms the basis of various protocols in Europe. Studies by the Children’s Oncology Group demonstrated no advantage to dose intensification that came with a predictably greater burden of toxicity, but survival benefit with interval compression, gained without adding to toxicity, in patients with localized disease. For patients with relapsed disease the combination of irinotecan and temozolomide may be useful.

Public Health Relevance

Primary bone tumors account for 5% of all cancers in childhood and Ewing sarcoma is the second most common bone tumor in this age group. The incidence of ESFT in the US between 1973 and 2004 was estimated to be approximately 3 per 1,000,000.
EWING SARCOMA
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

Requirements for diagnosis, treatment, and monitoring

**Diagnostics:**
A definitive diagnosis is made almost always on biopsied material. This should be obtained incisionally rather than by needle core in order to provide sufficient material for pathologic interpretation and for biologic studies. Frozen sections may be used to determine whether the biopsy has provided lesional tissue but should not be the basis for a final diagnosis. It is strongly preferred that the biopsy be obtained by the orthopedic surgeon who will perform the operation to achieve local tumor control, adhering to the principles of surgical oncology. At the time of tumor resection a histological response to neo-adjuvant chemotherapy has prognostic implications.

**Testing:**
Determination of the extent of disease is critical to selection of appropriate therapy and initial assessment of prognosis. Plain radiographs of the primary site are complemented by CT scans (including the chest to look for pulmonary metastases), MRI (particularly of the primary site) to provide anatomical detail of value to both the radiation and surgical oncologists, radio-isotopic bone scan to detect osseous metastases and PET scan to confirm these findings and identify other sites of occult disease. PET scans are also of value in assessing response to therapy.

Institutions caring for patients with ESFT should be able to detect the EWS-FLI1 related translocation by one of various techniques or CD 99 by immunohistochemistry. However, although CD 99 expression is a highly sensitive marker for ESFT it has low specificity, being found in other “small round blue cell” tumors of childhood. Standard blood tests to assess organ function and a baseline echocardiogram are required. For those with very large tumor volumes biochemical monitoring for tumor lysis syndrome is valuable. Serum lactate dehydrogenase is a surrogate marker of tumor volume.

**Administration and Care of Patients:**
Chemotherapy for ESFT is given by the IV route and consists of multiple agents. This requires careful management of fluid and electrolyte balance as well as prophylactic anti-emetic therapy and other supportive care measures e.g. mesna to offset bladder toxicity from cyclophosphamide and ifosfamide. All of this is accomplished usually through a central venous catheter and so should be undertaken only in a specialized cancer centre.

Likewise, control of local disease demands careful consideration of and planning for radiotherapy and surgery, which may involve limb conservation procedures; all requiring attention to health-related quality of life.

Management of the side effects of chemotherapy in the short term include nausea, vomiting, anorexia, mucositis, pancytopenia, electrolyte imbalance, peripheral neuropathy and hematuria. In the long-term, survivors are at risk for infertility (notably from cyclophosphamide), cardiomyopathy (especially from doxorubicin) and second cancers (particularly leukemia from etoposide and solid tumors in the radiation fields).
Overview of Regimens

The following tables include basic information on administration and dosing for AEWS 1031 and EURO-W.W.I.N.G. 99, and exclude ancillary medications pertaining to the management of side effects. For the therapeutic regimens considered AEWS 1031: 11 cycles and EURO-W.W.I.N.G. 99: 6 cycles of therapy is recommended, respectively.

Standard Regimens (of equivalent efficacy)

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<tr>
<th>AEWS 1031: 11 cycles</th>
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<tr>
<td><strong>Vincristine</strong></td>
<td>IV push</td>
<td>1.5 mg/m^2 (max 2mg/m^2)</td>
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<td></td>
<td>Approximately weekly intervals x 18 doses</td>
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<tr>
<td><strong>Doxorubicin</strong></td>
<td>IV infusion</td>
<td>37.5 mg/m^2</td>
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<td>Approximately monthly intervals x 5 doses</td>
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<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>IV infusion</td>
<td>1200 mg/m^2</td>
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<td></td>
<td>Approximately monthly intervals x 9 doses</td>
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<tr>
<td><strong>Ifosfamide</strong>*</td>
<td>IV infusion</td>
<td>1800 mg/m^2</td>
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<td>Approximately monthly intervals x 8 doses</td>
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<tr>
<td><strong>Etoposide</strong></td>
<td>IV infusion</td>
<td>100 mg/m^2</td>
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<td>Approximately monthly intervals x 8 doses</td>
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<tr>
<th>EURO-E.W.I.N.G. 99 : 6 cycles**</th>
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<tr>
<td><strong>Vincristine</strong></td>
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*Administration of ifosfamide requires the accompanying drug, mesna.

**Patients with localized disease are then randomized to Vincristine, Actinomycin, Ifosfamide (VAI) for one cycle then 7 cycles of Vincristine, Actinomycin, Cyclophosphamide OR VAI for 8 cycles.

Advanced Regimen

There are no protocols of notable efficacy in patients with metastatic disease. The Children’s Oncology Group has joined with EURO-E.W.I.N.G. in the treatment of these patients. Myelo-ablative therapy with autologous hematopoietic stem cell rescue has not been shown consistently to be of benefit.
Review of Benefits and Harms

Survival Benefits

For patients with localized disease the strategy of neo-adjuvant multi-agent chemotherapy followed by local control (surgery/radiotherapy) then further chemotherapy has achieved 5 year survival rates of approximately 70%. Treatment of relapsed and metastatic disease achieves survival rates that seldom exceed 20%.

Harms and Toxicity Considerations

**Vincristine** commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible, though recovery may be gradual. Vincristine also causes constipation which can be severe and patients should receive prophylaxis.\(^{18}\)

Anthracyclines including **doxorubicin** are associated with a risk of cardiotoxicity. Development of severe heart failure is uncommon, however myocardial dysfunction may appear in long-term follow up. In pediatric patients, the risk of heart failure and pericardial disease increases with cumulative doses \( \geq \)250mg/m\(^2\).\(^{19}\)

Patients treated with **cyclophosphamide** have a high risk of bladder toxicity and potentially hemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients need to be supraphydrated (at least 2L/m\(^2\)/day), need to void frequently and/or receive mesna prophylaxis to reduce the incidence of hemorrhagic cystitis.\(^{20}\) The drug also commonly causes alopecia, mucositis, stomatitis, and may result in infertility.\(^{21}\)

**Ifosfamide** can also cause bladder toxicity and administration should be managed as with **cyclophosphamide**. Ifosfamide also causes alopecia and myelosuppression in most patients.

The most frequent dose-limiting toxicity for **etoposide** is myelosuppression, primarily leukopenia which can be grade 3-4 in \( >10\% \) of patients. A small percentage (up to 2%) of patients receiving intravenous etoposide experience hypersensitivity reactions, which may include angioedema, bronchospasm, and/or chest discomfort.\(^{22}\) Etoposide also causes reversible alopecia in up to 60% of patients.\(^{23}\) The use of etoposide has been associated with an increased risk of a second cancer.

Patients treated for ESFT have a risk of developing a second malignancy. In one long term follow up study this risk was as high as 9% and appears to be highest among patients receiving radiation.\(^{24}\)

Systematic Reviews

**Key Points:** The improvement in outcome for patients with localized and metastatic Ewing sarcoma since the development of cytotoxic chemotherapy remains one of the most profound advances in oncology. Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) remains the chemotherapeutic backbone of Ewing sarcoma therapy, and the addition of other cytotoxic agents to this regimen is unlikely to produce significant benefits. Identification of molecular targets for new treatments has become an intense area within Ewing sarcoma research. The development of improved preclinical Ewing sarcoma models and advanced molecular techniques, including high-throughput sequencing, will build on knowledge of EWS/FLI1 function, EWS/FLI1 transcription targets, and the other critical driver events in these tumors.


**Abstract:** Ewing's sarcoma of bone is a primary bone sarcoma found predominantly in patients during their second decade of life. It is a high-grade aggressive small round blue cell tumor that is part of the Ewing's family of tumors. Its exact etiology is unknown but it commonly demonstrates reproducible staining of CD99 and translocations of the EWS gene. Historically, this diagnosis was associated with near certain metastasis and subsequent mortality. However, current management consists of extensive chemotherapy in addition to local control with surgical resection and/or radiation. As a result, survival has improved to the 55–75% range in those patients who present without known metastases. Current research aims to continue this improvement by looking further into the associated gene abnormalities and possibly targeted therapies.


**Recommendations**

The reviewers recommend the incorporation of ESFT cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that ifosfamide and etoposide be added for pediatric indications in the core Essential Medicines List.

**Medicines proposed for Section 8.2 of the Child EML**

Ifosfamide (already on adult EML)
Etoposide (already on adult EML)
References


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22. Infusion reactions to systemic chemotherapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.


24. Harmon DC, Gebhardt MC. Treatment of the Ewing sarcoma family of tumors. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.