Ewing sarcoma (ES) is the second most common primary bone tumour in children and young adults. Included among the paediatric "small round blue cell tumours", classical ES of bone, extra-skeletal ES, Askin tumour of the thoracic wall and peripheral primitive neuroectodermal tumour are highly aggressive, poorly differentiated neoplasms with unknown histiogenesis. For this group the unifying terms EFT (Ewing sarcoma family of tumours)/Ewing tumour has been coined after molecular evidence was obtained for shared immunologic (expression of CD99) and genetic traits. Most consistently a reciprocal chromosomal translocation t (11; 22) (q24; q12) is present in about 85% of these tumours, and is considered pathognomonic for the disease. The frequency of ES in the population younger than 20 years is approximately 2.9 per million. It is much more common in white populations, and has a slight male predominance (55% males: 45% females). About a quarter of ES arise in soft tissues rather than bone and about a quarter of patients have detectable metastases at diagnosis. The lungs are the most common site for metastases, followed by bone and bone marrow.¹

Large tumour volume, axial/pelvic location, poor response to neoadjuvant chemotherapy, metastatic disease (extra pulmonary metastasis worse than pulmonary metastasis), and older age at diagnosis adversely affect survival in patients with ES. In contrast to retrospective studies, a prospective evaluation did not confirm a prognostic benefit for type 1 EWS-FLI1 fusions.³⁶

Chemotherapy for newly diagnosed Ewing sarcoma

Before the era of chemotherapy, fewer than 10% of patients with ES survived, despite the well known radio sensitivity of this tumour. Patients commonly died of metastases within two years, indicating the need for systemic treatment. With use of modern multimodal therapeutic regimens, including combination chemotherapy, surgery and radiotherapy, cure

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Abstract

As the second most common bone malignancy in children and young adults, Ewing sarcoma represents almost 3% of paediatric cancers. Multi-disciplinary care incorporating advances in diagnosis, surgery, chemotherapy, supportive care and radiation has substantially improved the survival rate of patients with localised Ewing sarcoma from 10%, four decades ago, to more than 70% in recent times. Unfortunately, these advances have not significantly changed the long-term outcome for patients with metastatic or recurrent disease; five-year survival for this group remains less than 25%. Over the last four decades the chemotherapy for Ewing sarcoma has advanced from use of single agents to multiagent chemotherapy including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide, more recently in dose intense fashion with cytokine support. Multi-institutional co-operative group trials across North America and Europe have been invaluable in this effort. New agents like topotecan, irinotecan, temozolomide, gemcitabine and docetaxel, have been evaluated in phase I and II trials for recurrent disease. The role of high dose chemotherapy and autologous stem cell rescue for metastatic and recurrent tumours remains inconclusive. Enhanced understanding of the biology of Ewing sarcoma has identified new targets like IGF-1R and mTOR amenable to biological therapy. Future clinical trials will focus on how and when to integrate such therapies into clinical practice.
rates up to 75% and more can be achieved in localised tumors.

Conceptually, treatment for those with localised disease includes three distinct phases: cytoreduction (to eradicate micrometastatic disease and facilitate effective local control measures); definitive local control to eradicate all known disease (surgery or radiotherapy or both); and adjuvant chemotherapy to minimise tumour recurrence.

The first reports of drug treatment of ES stem from the 1960s. In 1962, Sutow and Sullivan and Pinkel independently published reports on the use of cyclophosphamide for ES. With Hustu et al’s publication on the combination of cyclophosphamide, vincristine and radiotherapy that resulted in sustained responses in five patients, the era of modern multimodality treatment of ES began. In 1974, Rosen et al from the Memorial Sloan-Kettering Cancer Center, published the first results of a trial of radiotherapy given with a four-drug regimen consisting of vincristine, actinomycin D, cyclophosphamide and doxorubicin used in combination rather than sequentially (the VACD scheme), leading to long-term survival in 12 patients with ES. The VACD scheme then became a standard therapy in numerous clinical trials.

The first North American randomised study, Intergroup Ewing Sarcoma Study, IESS-I 1973-1978, showed the superiority of the VACD scheme, leading to long-term survival in 12 patients with ES. The VACD scheme then became a standard therapy in numerous clinical trials.

In IESS-II 1978-1982, two schedules of the four-drug combination VACD were compared. The authors of the original report claim a “high-dose intermittent” regimen with three-weekly, higher doses of cyclophosphamide was superior to a “low-dose continuous” schedule, in which lower doses were administered weekly, but with identical cumulative drug doses in both arms.

The importance of doxorubicin, and especially of a high initial treatment intensity, was subsequently highlighted by a systematic meta-analysis of clinical trials in ES by Smith et al, concluding that all drugs administered in ES, doxorubicin was probably the most active, followed by alkylating agents. In view of these findings, results of the IESS-II study may have to be reconsidered. There was another significant difference between the two IESS-II treatment schedules, with patients randomised to the high-dose intermittent regimen receiving higher initial doxorubicin dose intensity, than those on the low-dose continuous schedule. Smith et al speculated that at least part of the superior outcome of patients on the high-dose intermittent schedule may have been due to the higher initial doxorubicin dose intensity. Total drug doses of every drug for the whole regimen were comparable between regimens, however those in the high-dose intermittent arm had received all 450 mg per m2 of doxorubicin by week 36, whereas those on the low-dose continuous schedule had received only 150 mg per m2 of doxorubicin by the same time point.

Because the total dose of doxorubicin is restricted owing to the risk of cardiomyopathy, cumulative dose intensification of alkylating agents was studied, both using cyclophosphamide as the main alkylator and using ifosfamide as an alternative alkylating agent, replacing or supplementing cyclophosphamide. In the early 1980s, treatment with ifosfamide, or with without etoposide, produced remarkable responses in patients who had had a relapse after standard therapies for ES. Of 72 patients treated with ifosfamide plus etoposide, 30 had complete or partial responses (combined data from two separate trials). Ifosfamide and etoposide was also introduced into several studies for newly diagnosed patients (EW 92, St.Jude, UKCCSG ET2, CESS 86, INT 0991).

The promising results of ifosfamide and etoposide in relapsed patients led the Children’s Cancer Group and the Pediatric Oncology Group to initiate a randomised control trial, INT 0991, in which they investigated whether the combination of ifosfamide and etoposide, when alternated with standard drugs, would improve the outcome in ES. The patients were assigned randomly at study entry to receive standard chemotherapy (arm A) with doxorubicin, vincristine, cyclophosphamide and actinomycin, or experimental therapy (arm B) consisting of these four drugs alternated with courses of ifosfamide and etoposide. The patients were stratified into groups according to the presence or absence of metastases. A total of 518 patients met the eligibility requirements. Of 120 patients with metastatic disease, 62 were randomly assigned to the standard therapy group and 58 to the experimental therapy group. There was no significant difference in five year EFS (22%) between the treatment groups (P=0.81). Among the 398 patients with non-metastatic disease, the mean (± SE) five year EFS among the 198 patients in the experimental therapy group was 69 ± three per cent, as compared with 54 ± four per cent among the 200 patients in the standard therapy group (P=0.005). Overall survival was also significantly better among patients in the experimental therapy group (72 ± 3.4 per cent v 61 ± 3.6 per cent in the standard-therapy group, P=0.01). The study concluded that the addition of ifosfamide and etoposide to a standard regimen did not affect the outcome for patients with metastatic disease, but it significantly improved the outcome for patients with non-metastatic ES.

After accrual of non-metastatic patients was completed according to protocol design, the study was amended to enrol only patients with detectable metastases at diagnosis to a single arm trial, arm C 1992-1994, with higher doses of chemotherapy.

### Table 1: Chemotherapy regimen with cumulative dose (mg/m²) for each agent by regimen INT 0991.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>40</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>375</td>
<td>375</td>
<td>450</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>21600</td>
<td>9600</td>
<td>17600</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0</td>
<td>90000</td>
<td>140000</td>
</tr>
<tr>
<td>Etoposide</td>
<td>0</td>
<td>5000</td>
<td>5000</td>
</tr>
</tbody>
</table>

Of the 60 patients with metastatic ES of bone enrolled on to this single arm trial, there were three toxic deaths. Six patients (six-year cumulative incidence: 9%) developed second malignant neoplasms and died. The six year EFS
was 28% and overall survival was 29%. The study concluded that an intensified treatment regimen using higher doses of cyclophosphamide, ifosfamide and doxorubicin increased toxicity and risk of second malignancy without improving EFS and overall survival.

In the absence of new active agents, a strategy to improve outlook was to increase dose intensity. Dose intensity is defined as the amount of drug delivered over unit time. Therapy can be dose intensified either by keeping the interval stable while escalating the dose(s) of the chemotherapeutic agents, or by shortening the interval between cycles.

Since the dose limiting toxicity of the alkylating agents is myelosuppression, they are ideal agents for dose escalation with cytokine support. The dose limiting toxicities of doxorubicin include myelosuppression and mucositis, which are ameliorated by cytokine support, and cumulative cardiac toxicity which may be decreased when doxorubicin is delivered by continuous infusion, rather than bolus administration.

Dose intensification was evaluated within two US paediatric co-operative trials.

INT 0154 (dose escalation) and AEWS 0031 (interval compression) both accrued patients with localised disease. In INT 0154 (1995-98) the investigational regimen used dose-intensified alkylating agents, yet kept the cumulative doses of the drugs similar between the two arms. Patients were randomly assigned to standard or intensified therapy by continuous infusion, rather than bolus administration.

The total doses of all agents were similar. The intent was to deliver similar cumulative doses of the agents to determine the effect of early dose intensification without a change in the total chemotherapeutic drug exposure.

**Figure 2: Chemotherapy regimen INT 0154.**

<table>
<thead>
<tr>
<th>Standard</th>
<th>Week</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
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<th>I</th>
<th>V</th>
<th>I</th>
<th>V</th>
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<tbody>
<tr>
<td>0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48</td>
<td>D</td>
<td>E</td>
<td>D</td>
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<td>C</td>
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<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

**Local control**

<table>
<thead>
<tr>
<th>Intensified</th>
<th>Week</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
<th>V</th>
<th>I</th>
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<tr>
<td>0 3 6 9 12 15 18 21 24 27 30</td>
<td>W</td>
<td>W</td>
<td>V</td>
<td>I</td>
<td>V</td>
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The only randomised control trial in this series, EICESS-92, found no difference between VACA and VAIA for standard risk patients with ES, and a slight advantage (although statistically insignificant) for EVAIA over VAIA in patients with high risk localised or metastatic tumours.

The current study Euro-EWING-99 (combined European and American study for localised and metastatic Ewing Sarcoma) uses VIDE (vincristine, ifosfamide, doxorubicin, etoposide) as initial chemotherapy for all patients. In a complex scheme, as shown in figure 3, it compares VAC (vincristine-actinomycin-cyclophosphamide) plus VAI (vincristine-actinomycin-ifosfamide) with VAIA (vincristine-actinomycin-cyclophosphamide), or VAI (vincristine-actinomycin-ifosfamide) as continuing chemotherapy for patients with good histological responses to VIDE, or small (<200 mL) tumours treated with radiation. For patients with poor histological responses, or large tumours treated with radiation, or lung metastases, it compares VAI and lung radiotherapy with busulfan-melphalan high dose chemotherapy/autoologous stem cell rescue (HDCT/ASCR). Patients with extra pulmonary metastases are non-randomly assigned to HDCT/ASCR arm.
The prognosis for patients with metastatic disease remains poor, with patients having extrapulmonary metastasis seldom surviving. Reports on outcomes in patients with metastatic disease are confounded by the varying number of patients included with lung metastases as the sole metastatic site. The addition of ifosfamide-epotodose to vincristine-doxorubicin-cyclophosphamide in the INT-0091 study did not improve the outcome for patients with metastases. Increasing the doses of doxorubicin, cyclophosphamide and ifosfamide by 20%, 83% and 56% respectively, in regimen C of the same protocol, of doxorubicin, cyclophosphamide and ifosfamide by 20%, also produced no improvement, and greatly increased acute toxicity and the incidence of secondary leukaemia and myelodysplasia. Patients with metastases outside the lungs at diagnosis seldom survive, and this has led to several studies using HDCT +/- TBI /ASCR. In a prospective Children’s Cancer Group study of 56 patients with bone or marrow metastases at diagnosis, high dose melphalan, etoposide and total body irradiation did not improve outcomes over those obtained with conventional chemotherapy. A prospective French study of HDCT/ASCR with busulfan, melphalan, ifosfamide and whole lung radiotherapy for pelvic tumours are at high risk for gastrointestinal (GI) toxicity, due to irradiation of bowel; three patients in this study died due to GI toxicity. Local radiotherapy is recommended, 8-10 weeks after busulfan based chemotherapy in these patients.

The Children’s Oncology Group recently completed a study in patients with metastatic ES, adding metronomic anti-angiogenic therapy with vinblastine and celecoxib to the VDC IE backbone; results are pending. An analysis of the European Group for Blood and Marrow Transplantation registry data showed a better outcome for patients with ES who received a busulfan containing regimen as compared with other HDT regimens.

The ongoing EuroEWING-99 trial provides the first randomised evaluation of HDCT/ASCR in patients with ES. Patients with localised tumours and a poor response to initial VIDE chemotherapy, or with lung metastases at diagnosis, are randomly assigned to either further chemotherapy (vincristine, actinomycin and ifosfamide, and whole lung radiotherapy if pulmonary metastases) or busulfan–melphalan with autologous stem cells. EuroEWING 99 recently reported outcome results of 281 patients with extra pulmonary metastases of ES. Following six cycles of VIDE and local treatment, 169/281 patients received HDCT/ASCR, 112 patients did not receive HDCT because of early progression, physician and patient choice, and collection failure in four patients. The three year EFS rate in the 281 patients was 27% and the overall survival rate 34%, with a median follow-up of 3.9 years after diagnosis. Patients who receive busulfan-melphalan HDCT and local radiotherapy for pelvic tumours are at high risk for gastrointestinal (GI) toxicity, due to irradiation of bowel; three patients in this study died due to GI toxicity. Local radiotherapy is recommended, 8-10 weeks after busulfan based chemotherapy in these patients.

**Chemotherapy for recurrent ES in children and young adults**

Thirty to forty per cent of patients with ES experience recurrent disease, despite multimodal therapy, and have a dismal prognosis. Patients with primary metastatic disease have a higher risk for relapse than those with localised disease. Survival after relapse of ES is poor, with only about 10% of patients event free at five years. To evaluate prognostic factors in patients with recurrent disease, the Children’s Oncology Group examined data from the phase III, multi-institutional study INT0091, which accrued patients with ES between 1988 and 1994. The most important prognostic factor in this study was time to first recurrence. There is no established treatment regimen for patients with recurrent disease. Chemotherapy options are limited...
dependent on the patient’s prior treatment and possible impaired function of vital organs (e.g., heart and kidneys). Agents that are considered for combination therapy are chosen to potentiate each other’s activity and circumvent the emergence of drug resistance. These have included combinations of topoisomerase I or topoisomerase II inhibitors with alkylating agents and, in addition, several myeloablative high dose consolidation therapy regimens with and without total body irradiation.

Ifosfamide and etoposide have been shown to be active agents for recurrent ES, but most patients these days receive these in upfront therapy. High dose ifosfamide (15 gm/m2, two courses) has been used with some success in patients with recurrent disease who had received ifosfamide as part of upfront therapy.41

The combination of topotecan and cyclophosphamide has proved to be synergistic; with proven efficacy in paediatric solid malignancies.30 A German group published results of cyclophosphamide and topotecan in 54 patients with relapsed/refractory ES.31 At median follow up of 23 months, 25.9% patients were in complete/partial remission, with overall survival at one year being 61%. A recent Children’s Oncology Group study has established the feasibility of combining bevacizumab, an antiangiogenic agent, with topotecan, cyclophosphamide and vincristine for treatment of recurrent ES.47

Wagner et al reported effectiveness of the combination of temozolomide and irinotecan for ES.35,36 This regimen can be delivered in the outpatient setting with limited cytopenias.

Investigators from MSKCC published results on 20 patients with recurrent/progressive ES treated with temozolomide and irinotecan. Of 19 evaluable patients, there were five complete and seven partial responses (a 63% overall objective response); median time to progression for the subset of 14 patients with recurrent ES, was 16.2 months. Median time to progression was better for patients who sustained a two year first remission than for those who relapsed <24 months from diagnosis and for patients with primary localised v metastatic disease.43

At present, either of these two combinations is considered for use as second-line or salvage therapy for recurrent ES.

Gemcitabine and docetaxel have demonstrated activity in the treatment of soft tissue sarcomas.32,42 The Sarcoma Alliance for Research through Collaboration (SARC) is currently accruing paediatric and adult patients for a phase II study of gemcitabine and docetaxel in relapsed ES.

The role of HDCT/ASCR in relapsed ES remains controversial and is even more difficult to evaluate because there are few patients available for evaluation in contrast to newly diagnosed patients. The European Bone Marrow Transplant Registry reported similar outcomes for patients with ES receiving HDCT/ASCR in first or subsequent remission, suggesting that HDT might be beneficial for a small number of patients with recurrent EFT.33 However, because the use of this modality is limited to patients with responsive disease, evaluating its impact on outcome is difficult, and most reported series are biased by including only patients with responsive disease. They reported that response to salvage therapy was the single most important factor correlating with outcome after HDT. Barker et al reported on intensive chemotherapy followed by HDCT/ASCR as consolidation therapy for patients with ES in second remission.34 They found that patients with a prolonged relapse free interval and responsive disease and those patients receiving HDCT/ASCR have an improved EFS and overall survival.

**Biologically based approaches to treatment**

Conventional cytotoxic chemotherapy is ineffective in some patients with localised tumours, and the majority of patients with metastases or recurrent ES. The growing understanding of ES biology has identified several therapeutic targets. The unique fusion gene, its transcript and protein product, and the pathways it activates all provide opportunities for therapy. Various targeted approaches have been investigated in pre-clinical and clinical phase I and phase II trials. These include inhibition of fusion product, a small molecule targeting the RHA-binding site on the EWS-FLI1 protein, IGF-1R mAbs (insulin like growth factor I receptor monoclonal antibody), Imatinib (C kit inhibitor), Rapamycin and its analogues, antiangiogenic therapy.

ES is associated with enhanced IGF-1R activity, via an autocrine/paracrine mechanism, through the inhibitory binding of the EWS/FLI-1 fusion protein to the IGFBP-3 promoter, consequently reducing IGBP-3 levels and increasing the level of free IGF-1R ligands. The strategies for blocking or disrupting IGF-1R activity in patients include the reduction of ligand levels or bioactivity or the inhibition of the receptor function using receptor-specific antibodies or small-molecule TKIs (tyrosine kinase inhibitors).

Monoclonal antibodies against IGF-1R represent the most evaluated option in sarcoma, with initial promising results in early clinical studies and several ongoing phase II studies. At present, eight different mAbs have been tested in clinical trials - Figitumumab (Pfizer), AMG479 (Amgen), R1507 (Roche), cetuximab/IMC-A12, (ImClone Systems), SCH-717454 (Schering-Plough), MK0646 (Merck), AVE-1642 (Sanofi-Aventis) and BLIB-022 (Biogen Idec). A phase II SARC study reported a CR/PR rate of 14.4% using R1507 for recurrent/refractory ES.35 Ongoing studies are evaluating IGF 1R mAbs alone, and in combination with chemotherapy or mTOR inhibitors. Despite robust pre-clinical evidence supporting the role of IGF-1R targeted agents in ES, clinical results show that only a proportion of patients derive significant benefit, with many progressing or developing resistance to IGF-1R mAbs quickly.

Although initial reports suggested an association between the EWS/FLI-1 type 1 translocation and response in ES, the predictive value of translocation type has not been observed consistently. Further evaluation of predictive biomarkers for IGF-1R targeting mAbs in ES, clinical results show that only a proportion of patients derive significant benefit, with many progressing or developing resistance to IGF-1R mAbs quickly.

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Late effects of chemotherapy

In addition to long-term orthopedic outcome which is dependent on location of the primary tumour and local treatment modality used, chemotherapy agents lead to late effects affecting many organ systems, mandating a need for ongoing medical care for years after the primary treatment is completed.

These late effects include therapy related myelodysplasia and acute myeloid leukemia (t-MDS/AML), cardio-toxicity, infertility and renal impairment.

Bhatia et al described the magnitude of risk of t-MDS/AML in...
578 individuals with ES enrolled on INT0091. Eleven patients developed t-MDS/AML, resulting in cumulative incidence of 2% at five years. While patients treated on regimens A and B were at low risk (0.4% and 0.9% respectively) patients on regimen C were at 16 fold increased risk of developing t-MDS/AML (cumulative incidence 11% at five years), when compared to regimen A. Increased exposure to cyclophosphamide, ifosfamide and doxorubicin increased the risk of t-MDS/AML in regimen C. Several biological factors have been studied to identify patients who are at increased risk of t-MDS/AML. These include polymorphisms in GSTT1 and GSTM1, CYP1A1, and NAT-2 genes. Development of a “mutator phenotype” as demonstrated by developing microsatellite instability is a possible early marker of individuals likely to progress to t-MDS/AML.

Doxorubicin induces a dose related cardiomyopathy. Protocol doses are therefore usually limited to less than a cumulative total of 450 mg/m2. In addition, administration is often prolonged over a 48 hour period. Thoracic irradiation that includes the heart can augment the cardiotoxicity of anthracyclines. A Children's Oncology Group study examined the role of functional polymorphisms in CBP3 (carbonyl reductase enzyme catalyses reduction of anthraquinines to cardiotonic alcohol metabolites) and CBP1 on risk of cardiomyopathy. It showed a clear dose response relation between anthracyclines and cardiomyopathy, and selectively greater impact of CBP3 on risk of cardiomyopathy after low dose anthracycline exposure. Patients with CBP3 may benefit from cardio protection, surveillance or pharmacologic interventions.

The alkylating agents cyclophosphamide and ifosfamide are associated with infertility, especially male infertility, so that sperm cryopreservation is offered to female patients. Ifosfamide can cause a persistent renal tubular electrolyte loss and, less commonly, a decrease in glomerular function, again in a dose-dependent fashion. Despite these concerns, the overall functioning of survivors of ES is reasonably good. Survivors of lower extremity bone tumours had high employment (97%), graduation (high school, 93%; college, 50%) and marriage (67%) rates.

Conclusions

- With modern multimodality treatment survival rates up to 75% are achieved in localised ES, whereas survival in primary metastatic and recurrent tumours remains poor.
- The role of HDCT/ASCR remains inconclusive for patients with high risk and recurrent tumours.
- EuroEwing 99 is the first randomised study to determine the role of HDCT/ASCR in patients with high risk tumours.
- Improved understanding of biology of ES has identified many targets amenable to targeted therapy.
- Current clinical trials aim to incorporate targeted therapeutic agents with conventional chemotherapy.
- Since the number of patients with ES is limited, such integration will require new statistical and study design strategies and further international collaboration.

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