Ewing sarcoma – EMLc

The application sought the inclusion of medicines used in the treatment of Ewing sarcoma – vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide – on the core list of the Model List of Essential Medicines for Children

The Committee noted that all of these medicines are currently included in the complementary list of the Model List for adults, and that vincristine, doxorubicin and cyclophosphamide are currently included on the complementary list of the EMLc for other specific indications.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Ewing sarcoma family of tumours (ESFT) is a group of highly malignant diseases with peak incidence in adolescence and early adult life. These tumours arise in either bone or soft tissue and the term ESFT includes the Askin tumour of the chest wall and peripheral primitive neuroectodermal tumours (pPNET). pPNET are related closely to medulloblastoma and intracranial PNET, reflecting the neural differentiating potential of these tumours *(1)*. The hallmark of ESFT is a translocation between chromosomes 11 and 22, resulting in a fusion protein referred to commonly as EWS-FLI1 *(2)*. The incidence of ESFT is higher among Caucasians than among Africans and Asians, for which a genetic explanation has been proposed *(3)*.

Before the introduction of chemotherapy, more than 90% of patients died from tumour spread *(4)*. Now, at least 70% of those presenting with apparently localized disease are cured by multimodal treatment *(5, 6)*; however, the outlook for those with evident metastases at diagnosis remains poor, with five-year survival rates of 25–30% *(7)*. Other adverse prognostic features include the location (especially in the pelvis) and size (>8 cm) of the tumour *(8)*. Outcomes may be better for patients with extra-osseous primary tumours *(9)*.

Since the early 1970s, the core of chemotherapeutic strategies in both North America and western Europe, has been the combination of vincristine, doxorubicin and cyclophosphamide (VDC). The addition of ifosfamide and etoposide (IE) was pioneered by the U.S. National Cancer Institute *(10)*. The VDC-IE combination is now the standard of care in the United States and forms the basis of various protocols in Europe *(8)*. Studies by the Children's Oncology Group demonstrated that dose intensification offered no advantage and gave rise to a predictably greater burden of toxicity *(6)*, but that chemotherapy intensification through interval compression offered benefit in terms of survival, without increasing toxicity, in patients with localized extradural disease *(11)*.

Public health relevance

Primary bone tumours account for 5% of all cancers in childhood, and Ewing sarcoma is the second most common bone tumour in this age group. The incidence of ESFT in the USA between 1973 and 2004 was estimated to be approximately 3 per 1 000 000 *(5)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

A definitive diagnosis is almost always made on biopsied material. Incisional rather than needle core biopsy is necessary to provide sufficient material for pathological interpretation and for biological 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 recommended that the biopsy be obtained by the orthopaedic surgeon who will perform the operation to achieve local tumour control, adhering to the principles of surgical oncology *(12)*. At the time of tumour resection, a histological response to neoadjuvant chemotherapy has prognostic implications *(13)*. Bone marrow biopsies appear to be unnecessary in patients who have seemingly localized disease after comprehensive radiological assessment *(14)*.

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: computerized tomography (CT) scans, including scans of the chest to look for pulmonary metastases; magnetic resonance imaging (MRI), particularly of the primary site, to provide anatomical detail of value to both radiation and surgical oncologists; radioisotopic bone scan to detect osseous metastases; and positron emission tomography (PET) scan to confirm findings and identify other sites of occult disease *(15)*. PET scans are also of value in assessing response to therapy *(12)*.

Institutions caring for patients with ESFT should be able to detect the EWS-FLI1 related translocation by one of various techniques or expression of CD99 by immunohistochemical methods. However, CD99 expression, while a highly sensitive marker for ESFT, has low specificity, being found in other "small round blue cell" tumours of childhood. Standard blood tests to assess organ function and a baseline echocardiogram are required. For very large tumour volumes, biochemical monitoring for tumour lysis syndrome is valuable. Serum lactate dehydrogenase is a surrogate marker of tumour volume *(12)*.

Administration and care of patients

Chemotherapy for ESFT consists of multiple agents given intravenously. This requires careful management of fluid and electrolyte balance, as well as prophylactic antiemetic therapy and other supportive care measures, e.g. mesna to offset bladder toxicity from cyclophosphamide and ifosfamide. Since all of this is usually accomplished through a central venous catheter, it should be undertaken only in a specialized cancer centre.

Local control of ESFT demands careful consideration of and planning for radiotherapy and surgery, which may involve limb conservation procedures.

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

Overview of regimens

The following sections include basic information on administration and dosing of standard regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens (of equivalent efficacy)

- **AEWS 1031 (11 cycles)**
  - vincristine 1.5 mg/m^2 (max. 2 mg/m^2) IV push, approx. weekly intervals x 18 doses
  - doxorubicin 37.5 mg/m^2 IV infusion, approx. monthly intervals x 5 doses
  - cyclophosphamide 1200 mg/m^2 IV infusion, approx. monthly intervals x 9 doses
  - ifosfamide[1] 1800 mg/m^2 IV infusion, approx. monthly intervals x 8 doses
  - etoposide 100 mg/m^2 IV infusion, approx. monthly intervals x 8 doses

- **Euro-EWING 99 (6 cycles)**
  - vincristine 1.5 mg/m^2 (max. 2 mg/m^2) IV push, every 1 week x 6 doses
  - ifosfamide 3000 mg/m^2 IV infusion, daily x 3 days per cycle = 18 doses
  - doxorubicin 20 mg/m^2 IV infusions, daily x 3 days per cycle = 18 doses
  - etoposide 150 mg/m^2 IV infusion, daily x 3 days per cycle = 18 doses

[1] Administration of ifosfamide requires the accompanying drug, mesna.

Review of benefits and harms

Benefits

For patients with localized disease, several studies have shown that the strategy of neoadjuvant multi-agent chemotherapy with vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide and etoposide, followed by local control (surgery/radiotherapy) then further chemotherapy is associated with 5-year survival rates of around 70% *(5, 6, 10, 16)*.

A randomized controlled trial conducted by the Children's Cancer Group and the Pediatric Oncology Group investigated the effect of the combination of ifosfamide and etoposide, alternated with standard chemotherapy with doxorubicin, vincristine, cyclophosphamide and dactinomycin (used in combination) in 518 patients with Ewing sarcoma, PNET of bone or primitive sarcoma of bone *(10)*. In patients without metastatic disease (n = 398), 5-year event-free survival was higher in the group receiving alternating therapy with ifosfamide/etoposide than in the standard chemotherapy group (69% vs 54%); 5-year overall survival rate was also greater in the ifosfamide/etoposide group (72% vs 61%).

A randomized controlled trial of 568 patients with Ewing sarcoma tested whether intensification through interval compression improved outcomes of chemotherapy with alternating vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide cycles *(11)*. The results for the primary end-point of event-free survival at 5 years were 65% in the standard treatment arm (21-day interval) and 73% in the intensified treatment arm (15-day interval). Toxicity of the two regimens was similar.

A second treatment intensification strategy is high-dose chemotherapy with autologous haematopoietic stem cell rescue *(17-19)*. Because of the considerable toxicity of this approach, most studies investigate high-dose chemotherapy for very high-risk patients, most commonly those with primary disseminated multifocal diagnosis, or following recurrence. In the European Ewing Tumour Initiative of National Groups (Euro-EWING 99), treatment consisted of six cycles of vincristine, ifosfamide, doxorubicin and etoposide, one cycle of vincristine, dactinomycin and ifosfamide, local treatment (surgery and/or radiotherapy), and high-dose busulfan–melphalan followed by autologous stem-cell transplantation. After a median follow-up of 3.8 years, event-free survival (EFS) and overall survival (OS) at 3 years for all 281 patients were 27% and 34%, respectively *(20)*. High-dose regimens caused profound grade 4 aplasia in 93% of patients, but with acceptable grade 3 and 4 infection rates. The protocol was associated with six transplant-associated deaths.

Treatment with conventional chemotherapy regimens using cyclophosphamide, doxorubicin, vincristine and dactinomycin with radiation and/or surgery among patients with metastatic disease at diagnosis has been associated with high rates of complete response at metastatic sites and local control *(21)*. However, OS remains poor, with about one quarter of patients surviving: relapse-free survival has increased from less than 15% to 20–30% using more recent regimens, including increased doses of alkylating agents and anthracyclines. Age is a prognostic factor, with outcomes being age-dependent: in two

intergroup Ewing's sarcoma studies, 5-year OS for patients aged 10 years or less was 40%, compared with 20% for patients aged over 10 years *(22)*. Prognosis is also worse for patients with pelvic primary, marrow diseases or multiple sites of disease. Studies incorporating intensive therapy followed by stem-cell infusion have not shown clear benefit *(23)*.

Harms and toxicity considerations

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. The neurotoxicity is usually reversible, although recovery may be gradual. Vincristine also causes constipation, which can be severe, and patients should receive appropriate prophylaxis *(24)*.

Anthracyclines including doxorubicin are associated with a risk of cardiotoxicity. Development of severe heart failure is uncommon but myocardial dysfunction may appear during long-term follow-up. In paediatric patients, the risk of heart failure and pericardial disease increases with cumulative doses ≥250 mg/m^2 *(25)*.

Patients treated with cyclophosphamide have a high risk of bladder toxicity and possibly haemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients should be suprahydrated (at least 2 L/m^2 per day), need to void frequently and/or should receive mesna prophylaxis to reduce the incidence of haemorrhagic cystitis *(26)*. Cyclophosphamide also commonly causes alopecia, mucositis and stomatitis and may result in infertility *(27)*.

Ifosfamide can also cause bladder toxicity, and administration should be managed as for 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 more than 10% of patients. A small percentage (up to 2%) of patients experience hypersensitivity reactions to intravenous etoposide, which may include angioedema, bronchospasm and/or chest discomfort *(28)*. Etoposide also causes reversible alopecia in up to 60% of patients *(29)*. The use of etoposide has been associated with an increased risk of a second cancer.

One long-term follow-up study found that the risk of developing a second malignancy in patients treated for ESFT was as high as 9% – and apparently highest among patients receiving radiation *(30)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide be included on the complementary list of the EMLc for the treatment of Ewing sarcoma. The Committee also recommended the inclusion of mesna for this indication, to counter the bladder toxicity associated with cyclophosphamide and ifosfamide.

The Committee noted the availability of a 500-mg vial of ifosfamide powder for injection, which it considered would represent a less expensive option than the 2-g vial currently listed on the EML for treatment of paediatric patients. The Committee recommended this formulation be included on the EMLc.

The Committee also considered it appropriate to include these medicines in the complementary list of the EML for treatment of Ewing sarcoma, noting that the peak incidence of this disease is in the second decade of life.

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