Rhabdomyosarcoma – EMLc

The application sought the addition of ifosfamide to the core list of Essential Medicines for Children for the treatment of rhabdomyosarcoma. The application also sought endorsement for use of vincristine, dactinomycin and cyclophosphamide, already on the complementary list of the EMLc for other indications, for rhabdomyosarcoma.

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

Introduction

Rhabdomyosarcoma (RMS) is an aggressive and highly malignant soft tissue sarcoma that typically affects children and adolescents and can develop in virtually any part of the body where mesenchymal tissue is present. The two largest histological subgroups are embryonal (ERMS) and alveolar (ARMS). Historically, up to the 1960s, less than 15% of children survived *(1)*. Survival rates for RMS have increased dramatically over recent decades. For RMS and ERMS in 1976–1980, the 5-year survival was about 53% and 61%, respectively. Between 1996 and 2000 the 5-year survival reached 62% and 73%, respectively. Improvements for ARMS were more limited, being 40% and 48% at the end of the 1980s and 1990s, respectively *(2)*. In the 1970s, large cooperative national and international study groups started to adopt a systematic multidisciplinary approach including multidrug chemotherapy coordinated with surgery and radiotherapy. This led to a progressive increase of survival, now often above 70% *(3)*, and to the identification of a number of prognostic factors (e.g. tumour histotype, tumour size and site, resectability, presence of nodal or distant metastases, patient age) that can be used to tailor the treatment *(4)*.

More recently, clinical protocols have been linked to pathology and biological studies that have added important insight to the nature of RMS and may give new therapeutic opportunities in the near future. In particular, new treatment strategies are needed for those categories at major risk of treatment failure, e.g. patients with alveolar RMS or metastatic disease. RMS is a chemosensitive tumour and various drugs have proved to be effective. However, despite several drugs in addition to the standard chemotherapy having been investigated in randomized clinical trials over the years, the VAC (vincristine, dactinomycin, cyclophosphamide) and IVA (ifosfamide, vincristine, dactinomycin) regimens are still the gold standard in North America and Europe, respectively *(5)*. New chemotherapeutic strategies are intensification with irinotecan-based therapy or with the "dose-compression" (in North American Children's Oncology Group (COG) protocols) *(6)* and the maintenance "metronomic" therapy with low-dose chemotherapy (for example with vinorelbine and low-dose cyclophosphamide) added at the end of conventional treatments (in the European pediatric Soft Tissue Sarcoma Study Group (EpSSG) studies) *(7)*. Various novel target agents are under investigation, e.g. mammalian target of rapamycin (mTOR), (insulin-like growth factor 1 receptor (IGF1R) and vascular endothelial growth factor (VEGF) inhibitors. The

application proposed inclusion on the EMLc only of regimens that are currently considered to be standard care.

Public health relevance

RMS is the soft tissue sarcoma (STS) found most commonly in children and adolescents under 20 years of age. About 7% of all malignancies are STSs, and rhabdomyosarcoma (RMS) accounts for about 40% of paediatric STSs worldwide *(8)*. While global epidemiological data are limited, there are country-specific studies that examine the incidence and prevalence of RMS. For instance, data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to determine incidence of RMS in children in the USA from 1975 to 2005. The study estimated incidence to be 4.5 cases per million children/adolescents per year with more than 50% of cases occurring in children under 10 years of age *(2)*. About 350 new cases of RMS occur each year in the United States.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Generally speaking, most tumours are ERMS and tend to develop in the head and neck area or in the genital and urinary tracts. Pathological assessment is necessary to identify the histological nature of the tumour. The initial biopsy is intended to define the histological diagnosis but also to provide enough material for immunochemistry, cytogenetics, biological studies and eventual central pathology review or tissue banking for patients who could be included in multicentre trials. Biopsy is recommended as the initial surgical procedure in all patients and when primary excision with adequate margins seems possible. Initial biopsy must be carefully planned by experienced surgeons, taking into account the possible subsequent definitive surgery.

Testing

An adequate patient stratification is needed for risk-adapted therapy. Treatment intensity is stratified in order to improve cure rates in patients with less favourable disease by using more intensive therapy, and to avoid over-treatment and limit side-effects – without jeopardizing results – in cases with more favourable features *(5)*.

A definitive diagnosis involves several pretreatment assessments:

- Ultrasonogram is often the first instrumental assessment
- Computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site is essential for the local extension assessment before any treatment. (MRI can be considered superior in defining soft tissue extension.)
- Distant assessments include:
  - chest CT scan
  - technetium bone scan

- abdominal ultrasound
- bone marrow aspiration plus trephine biopsy
- particular evaluations of special sites if required, e.g. cerebrospinal fluid cytology in parameningeal RMS, to assess meningeal dissemination; regional lymph node biopsy in extremity RMS; retroperitoneal lymph node sampling in paratesticular RMS in boys older than 10 years.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to expert clinical care. For example, full blood count, renal and liver function tests should be evaluated periodically. Careful monitoring is required for patients less than 3 years old and particularly for infants less than 12 months old (e.g. careful dosing of chemotherapeutic agents to avoid hepatotoxicity (e.g. hepatic veno-occlusive disease)).

The "cost" of survival in term of late side-effects must be addressed and should guide the definition of treatment strategies, according to patients' risk stratification, in order to minimize functional and cosmetic damage without limiting potential benefit.

Late complications may be related to chemotherapy: infertility can be a consequence of cyclophosphamide, and long-term renal damage may be caused by ifosfamide-based regimens *(9, 10)*. Moreover, the continuing use of high doses of alkylating agents contributes, together with radiotherapy, to the significantly increased risk of second malignancies in long-term survivors *(11)*. Radiotherapy carries a high risk of causing severe late sequelae, particularly when delivered to young children. For example, survivors who have been treated for parameningeal RMS are at high risk of important sequelae such as facial growth retardation (bone and soft tissue hypoplasia, facial asymmetry), dental abnormalities, neuroendocrine dysfunctions (growth hormone deficiency, hypothyroidism), visual problems and hearing loss and delayed intellectual development *(12)*. Long-term follow-up is necessary according to the treatment received: periodic evaluation of renal, cardiac, and endocrine functions are recommended, and particular attention should be given to any signs and symptoms that suggest the development of second malignant neoplasms.

Overview of regimens

The following sections include basic information on administration and dosing for IVA (ifosfamide, vincristine and dactinomycin) and VAC (vincristine, dactinomycin and cyclophosphamide,) regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens (of equivalent efficacy)

- **IVA (9 cycles)**
  - ifosfamide[1] 3 g/m^2 IV infusion for two days
  - vincristine 1.5 mg/m^2 (max. 2 mg) IV infusion for one day
  - dactinomycin 1.5 mg/m^2 (max. 2 mg) IV infusion for one day

- **VAC (9–15 cycles)**
  - vincristine 1.5 mg/m^2 (max. 2 mg) IV infusion for one day
  - dactinomycin 1.5 mg/m^2 (max. 2 mg) IV infusion for one day
  - cyclophosphamide 1200 mg/m^2 IV infusion for one day

Review of benefits and harms

Survival benefits

RMS is always characterized as a high-grade malignancy, with local invasiveness and a marked propensity to metastasize, to the point that all RMS patients should be assumed to have micrometastatic disease at diagnosis. All patients with RMS should therefore be treated with chemotherapy, even in the case of small tumours completely resected after diagnosis. The disease is generally characterized by a good response to chemotherapy (more than 80% of newly-diagnosed cases respond to chemotherapy) and chemotherapy is thus considered the keystone of treatment for RMS *(13, 14)*.

Since the 1970s, the cure rate for RMS has improved dramatically from 25–30% using local treatments with or without single-agent chemotherapy to approximately 70%. This improvement is largely due to the development of treatment approaches that involve cooperative multi-institutional trials, using multidisciplinary treatment (surgery, radiotherapy and multi-agent chemotherapy) and risk-adapted to take account of known prognostic factors and enable appropriate stratification of treatment intensity *(13)*. However, survival is strongly dependent on the type of RMS and risk group. The prognosis depends on how much of the tumour can be removed surgically.

The IVA and VAC regimens are considered the standard treatments in North America and Europe respectively, and can be considered essentially the same in terms of efficacy. The VAC regimen was launched by the Intergroup Rhabdomyosarcoma Study Group in the 1970s and achieved a 5-year overall survival of approximately 55% across all risk groups – a result welcomed as a large success *(15, 16)*. Overall percentages of patients surviving varied from 20% in the high-risk group to 93% in the low-risk group. In Europe the standard regimen differs in the choice of the alkylating agent: ifosfamide, vincristine and dactinomycin. In the Intergroup Rhabdomyosarcoma Study-IV (IRS-IV), 883 patients with non-metastatic rhabdomyosarcoma following surgery were randomized by primary

[1] Administration of ifosfamide requires the accompanying drug mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine.

tumour site, group and stage of disease to one of three chemotherapy regimens: VAC, IVA, or vincristine, ifosfamide and etoposide (VIE). Patients with group 3 tumours were also randomized to receive radiotherapy (conventional or hyperfractionated) *(17)*. The overall 3-year failure-free survival (FFS) rate was 77%, and the survival rate was 86%. In the three chemotherapy groups, FFS rates were 75%, 77% and 77% for VAC, IVA and VIE, respectively. No significant difference was noted between the two radiotherapy arms, leading the authors to conclude that the three chemotherapy regimens with surgery, and with or without radiotherapy, were equally effective for patients with local or regional rhabdomyosarcoma.

Overall, survival of RMS patients with localized disease is around 70% but this is strictly correlated to the risk group. The prognosis for high-risk patients (e.g. patients with alveolar RMS, patients with metastases) is still unsatisfactory and effective therapies must be found *(13)*. For this reason various alternatives to the VAC and IVA regimens have been investigated over the years by various cooperative groups. The role and effectiveness of cisplatin, etoposide, doxorubicin, melphalan, topotecan and irinotecan in various combinations have been explored, but trials have failed to demonstrate substantial improvements in survival over the established VAC or IVA regimens, or demonstrated only limited progress in other outcomes *(18-23)*.

Harms and toxicity considerations

Patients treated with ifosfamide have a high risk of bladder toxicity and of haemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients need to be suprahydrated (at least 2 L/day) and need to void frequently and/or receive mesna prophylaxis to reduce the incidence of haemorrhagic cystitis *(10)*. Ifosfamide also causes alopecia and myelosuppression in most patients.

Cyclophosphamide can also cause bladder toxicity; patients require additional hydration and frequent voiding in order to reduce the risk of haemorrhagic cystitis. It also commonly causes alopecia, mucositis and stomatitis and may result in infertility *(9)*.

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

Dactinomycin is associated with high emetic potential; patients should receive antiemetics as prophylaxis. It is very corrosive to soft tissue and can lead to tissue damage if extravasation occurs. Dactinomycin causes alopecia in most patients *(25)*.

Recommendations

The Expert Committee noted that the use of multidrug chemotherapy using VAC and IVA, in conjunction with local control measures for the primary tumour, has resulted in survival rates of around 70% in multidisciplinary care settings and across different risks of relapse.

On the basis of the evidence presented, the Committee recommended addition of vincristine, ifosfamide, dactinomycin and cyclophosphamide to the Model List of Essential Medicines for Children for the treatment of rhabdomyosarcoma. The Committee noted that vincristine, dactinomycin and cyclophosphamide are currently listed on the EMLc for use in the treatment of other cancers.

Administration of ifosfamide requires the accompanying drug mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine but considered that its use should be specifically endorsed for treatment of rhabdomyosarcoma alongside ifosfamide.

As rhabdomyosarcoma also affects older children and adolescents, the Committee considered it appropriate to also include vincristine, ifosfamide, dactinomycin, cyclophosphamide and mesna on the Model List for adults, specifically for the treatment of rhabdomyosarcoma.

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