RHABDOMYOSARCOMA

Executive Summary

Rhabdomyosarcoma (RMS) is an aggressive and highly malignant soft tissue sarcoma that typically affects children and adolescents and can develop virtually in any part of the body where mesenchymal tissue is present. Historically, less than one third of children survived up to the 1960s. In the 1970s, large co-operative national and international study groups started to adopt a systematic multi-disciplinary approach including multi-drug chemotherapy coordinated with surgery and radiotherapy. This led to a progressive increase of survival (now above 70%) and to the identification of a number of prognostic factors (e.g. tumor histotype, tumor size and site, resectability, presence of nodal or distant metastases, patient age) that can be utilised to tailor the treatment. 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 tumor and various drugs have proven to be effective; however, despite several drugs having been investigated in addition to the standard chemotherapy in randomised clinical trials conducted over the years, the VAC (vincristine, actinomycin D, cyclophosphamide) and the IVA (ifosfamide, vincristine, actinomycin D) regimens are still the gold standard in North America and Europe, respectively. New chemotherapeutic strategies are intensification with irinotecan-based or with the “dose-compression” (in North American Children’s Oncology Group (COG) protocols) 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). Various novel target agents are under investigation, e.g. mTOR, IGF1R and VEGF inhibitors. Only regimens that are standard care have been included; drug combinations still being studied (e.g. irinotecan-based) have been excluded from our recommendations for these reasons.

Public Health Relevance

RMS is the soft tissue sarcoma (STS) found most commonly in children and adolescents younger than 20 years old, accounting for approximately 40% of all pediatric STS worldwide (1). While global epidemiological data are limited, there are country-specific studies that examine incidence and prevalence of RMS. For instance, a US study used data from the Surveillance, Epidemiology, and End Results (SEER) Program to determine incidence of RMS in children in the US from 1975 to 2005. The study estimated RMS incidence to be 4.5 cases per million children/adolescents per year with more than 50% of cases occurring in children younger than age 10 years (1).
Requirements for diagnosis, treatment, and monitoring

**Diagnostics:**
Pathological assessment is necessary to identify the histological nature of the tumor. The initial biopsy aims 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 multi-center trials. It is recommended that biopsy is the initial surgical procedure in all patients; also when primary excision with adequate margins seems possible. Initial biopsy must be planned carefully by experienced surgeons, taking into account the possible subsequent definitive surgery.

**Testing:**
An adequate patient stratification is needed for risk-adapted therapy, to stratify treatment intensity in order to improve cure rates in patients with less favorable disease by using more intensive therapy, while avoiding over-treatment and limiting side effects without jeopardizing the results in cases with more favorable features.

Pre-treatment assessment are:

- Ultrasonogram is often the first instrumental assessment.
- Computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the primary site are mandatory for the local extension assessment before any treatment (MRI can be considered superior in defining soft tissue extension).
- Distant assessment requires:
  - chest CT scan
  - Technetium bone scan
  - abdominal ultrasound
  - bone marrow aspiration plus trephine biopsy
  - special sites may require particular evaluations, e.g. cerebrospinal fluid cytology in parameningeal RMS, to assess meningeal dissemination; regional lymph node biopsy in extremity RMS; retroperitoneal lymph node sampling in para-testicular RMS in boys older than 10 years.

**Administration and Care of Patients:**
Administration requires intravenous infusion capacity, and requires that the patient have regular 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 1 or 3 years old (e.g. careful dosing of chemotherapeutic agents to avoid hepatotoxicity (e.g. veno-occlusive disease).

The “cost” of survival in term of late side effects is an essential issue to be addressed, and should guide the definition of treatment strategies, according to patients’ risk stratification, in order to minimize the functional and cosmetic damage without jeopardizing the outcome. Possible complications of the different treatments should always be balanced with their beneficial effects.
Late complications may be related to chemotherapy: infertility can be a consequence of cyclophosphamide, long-term renal damage can be the result of ifosfamide-based regimens, cardiotoxicity is a well-known complication of doxorubicin when given at a high cumulative dose. Moreover, the continuing use of high doses of alkylating agents (and the use of etoposide) contributes, together with radiotherapy, to the significantly increased risk of second malignancies in long-term survivors. Radiotherapy carries a high risk of causing severe late sequelae, particularly when delivered to young children. For example, survivors after parameningeal RMS have a high risk of important sequelae such as facial growth retardation (bone and soft tissue hypoplasia, facial asymmetry), dental abnormalities, neuro-endocrine dysfunctions (growth hormone deficiency, hypothyroidism), visual problems, hearing loss and intellectual delay. Long term follow-up is necessary according to the treatment received: periodic evaluation of renal, cardiac, and endocrine functions are mandatory, and particular attention should be given to any signs and symptoms that suggest the development of second malignant neoplasms.

Overview of Regimens

The following tables include basic information on administration and dosing for IVA, VAC and Irinotecan-Vincristine regimens, and exclude ancillary medications pertaining to the management of side effects. For the therapeutic regimens considered, 9-15 cycles of therapy are recommended.

**Standard Regimens (of equivalent efficacy)**

**IVA regimen: 9 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide*</td>
<td>Intravenous infusion</td>
<td>3 g/m² for two days</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Intravenous infusion</td>
<td>1.5 mg/m² (max 2 mg) for one day</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>Intravenous infusion</td>
<td>1.5 mg/m² (max 2 mg) for one day</td>
</tr>
</tbody>
</table>

**VAC regimen: 9-15 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Intravenous infusion</td>
<td>1.200 mg/m² for one day</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Intravenous infusion</td>
<td>1.5 mg/m² (max 2 mg) for one day</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>Intravenous infusion</td>
<td>1.5 mg/m² (max 2 mg) for one day</td>
</tr>
</tbody>
</table>

*Administration of ifosfamide requires the accompanying drug, mesna.

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. For this reason, all patients with RMS should be treated with
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Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

Chemotherapy, even in the case of small tumors completely resected at diagnosis. RMS is generally characterized by a good response to chemotherapy (more than 80% of newly-diagnosed cases respond to chemotherapy) and chemotherapy is therefore considered the keystone of treatment for RMS.

In the past 30 years the cure rate for RMS has improved dramatically from 25-30% to approximately 70%, largely due to the development of treatment approaches that are: 1) multi-disciplinary (including surgery, radiotherapy and particularly multi-agent chemotherapy), 2) risk-adapted, i.e. different prognostic factors are used to stratify treatment intensity in order to improve cure rates in patients with less favorable disease by using more intensive therapy, while avoiding over-treatment and limiting side effects without jeopardizing the results for patients with more favorable disease, 3) cooperative multi-institutional trials able to enroll a large number of patients. Since RMS is a rare tumor and its treatment is necessarily multi-disciplinary and complex, patients should be referred to selected institutions with adequate experience in treating pediatric tumors, and with multi-disciplinary skills in enrolling patients in clinical trials.

The overall outcome of RMS patients with localized disease is around 70%, but is strictly correlated to the risk group. The prognosis for high-risk patients (e.g alveolar RMS, patients with metastases), is still unsatisfactory and effective drugs must be found for including in new, intensive regimens.

Harms and Toxicity Considerations

Patients treated with ifosfamide have a high risk of bladder toxicity and potentially hemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients need to be suprhydrated (at least 2L/day) and need to void frequently and/or receive mesna prophylaxis to reduce the incidence of hemorrhagic cystitis.[2] 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 hemorrhagic cystitis. It also commonly causes alopecia, mucositis, stomatitis, and may result in infertility.[3]

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible, though recovery may be gradual and may not be complete. Vincristine also causes constipation which can be severe; patients should receive prophylaxis.[4]

Actinomycin-D 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. Actinomycin causes alopecia in most patients.[5]
Systematic Reviews


Abstract: Rhabdomyosarcoma is a typical tumor of childhood and adolescence. Over the years there has been a gradual but important improvement in survival for patients with this tumor, despite its high grade of malignancy. These results are due to multi-disciplinary treatment approaches including surgery, radiotherapy and especially chemotherapy. Rhabdomyosarcoma is a highly chemo-sensitive neoplasm, and the role of this therapeutic approach has also been clearly demonstrated in the adjuvant setting. This review covers current concepts on chemotherapy for rhabdomyosarcoma, with an overview of the results of the main clinical trials conducted over recent years and considerations of possible strategies for the near future. Recommendations for adult patients with rhabdomyosarcoma are also discussed, suggesting that these patients should be treated according to pediatric guidelines.


Abstract: Introduction: Soft-tissue sarcomas are rare, but they represent about 8% of all malignancies in the pediatric age group. Developing a multi-disciplinary approach to treatment based on risk stratification has led to a dramatic improvement in survival, but a plateau has been reached with current treatment options in the last 20 years. Chemotherapy is usually effective for rhabdomyosarcoma and should be seen as the keystone of its treatment, while non-rhabdomyosarcoma soft-tissue sarcomas are still generally considered poorly chemo-sensitive. Areas covered: An overview of current, emerging and possible future medical therapies for pediatric soft-tissue sarcomas is provided. Insight into different chemotherapeutic strategies based on risk stratification for rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcomas in children is given. Expert opinion: Integrating systemic therapy with local treatments (surgery and/or radiotherapy) is complex and requires adequate experience, which can only be assured in tertiary institutions. Future challenges include identifying novel targeted therapies and optimizing treatment protocols for customized patient care.


Abstract: Rhabdomyosarcoma is a typical tumor of childhood, characterized by a high grade of malignancy, local invasiveness and a marked propensity to metastasize, but also a generally good response to chemotherapy and radiotherapy. Multimodal therapy is essential to cure rhabdomyosarcoma patients, but different uses of surgery, radiotherapy and chemotherapy, and their intensity, need to be selected and modulated to different patient risk groups. This article attempts to give an account of the current treatment options, the open and debated issues and the potential novel strategies for the near future.

Walterhouse DO, Pappo AS, Meza JL, et al. Shorter-duration therapy using vincristine, daetinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with

Abstract: Purpose Intergroup Rhabdomyosarcoma Study Group (IRSG) studies III and IV showed improved failure-free survival (FFS) rates with vincristine, dactinomycin, and cyclophosphamide (VAC; total cumulative cyclophosphamide dose, 26.4 g/m²) compared with vincristine and dactinomycin (VA) for patients with subset-one low-risk embryonal rhabdomyosarcoma (ERMS; stage 1/2 group I/II ERMS or stage 1 group III orbit ERMS). The objective of Children's Oncology Group ARST0331 was to reduce the length of therapy without compromising FFS for this subset of low-risk patients by using VA in combination with lower-dose cyclophosphamide (total cumulative dose, 4.8 g/m²) plus radiotherapy (RT).

Patients and Methods This non-inferiority prospective clinical trial enrolled newly diagnosed patients with subset-one clinical features. Therapy included four cycles of VAC followed by four cycles of VA over 22 weeks. Patients with microscopic or gross residual disease at study entry received RT. Results With a median follow-up of 4.3 years, we observed 35 failures among 271 eligible patients versus 48.4 expected failures, calculated using a fixed outcome based on the FFS expected for similar patients treated on the IRSG D9602 protocol. The estimated 3-year FFS rate was 89% (95% CI, 85% to 92%), and the overall survival rate was 98% (95% CI, 95% to 99%). Patients with para-testicular tumors had the most favorable outcome. Three-year cumulative incidence rates for any local, regional, or distant failures were 7.6%, 1.5%, and 3.4%, respectively. Conclusion Shorter-duration therapy that included lower-dose cyclophosphamide and RT did not compromise FFS for patients with subset-one low-risk ERMS.

Recommendations

The reviewers recommend the incorporation of rhabdomyosarcoma treatment options into the WHO Model List of Essential Medicines, and recommend specifically that ifosfamide be added for pediatric indication to the core Essential Medicines List.

Medicines proposed for Section 8.2 of the Child EML

Ifosfamide (already on Adult EML)
References


Additional Citations

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4. Lee EQ, Wen PY. Overview of neurologic complications of non-platinum cancer chemotherapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.