

Chemotherapy for Rhabdomyosarcoma: Beyond the Standard

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Abstract

Chemotherapy plays an important part in the treatment of rhabdomyosarcoma. Multicenter protocols have helped the intensity of chemotherapy to be tailored to prognostic factors. The VAC and IVA regimens have been confirmed as the standard multidrug solutions by Cooperative Groups in North America and Europe, respectively. Several fruitless attempts have been made to find new drug combinations capable of improving the survival of high-risk patients, but novel agents and experimental strategies have recently become available. This review covers some of the options being tested in the search for better RMS treatment, beyond the accepted standard approach.

Chemotherapy has a major role in the multidisciplinary treatment of soft tissue sarcoma. This is especially true for patients with RMS as chemotherapy is highly effective in reducing the primary tumor and controlling occult and evident metastases.

Experience since the 1970's has established the activity of a number of chemotherapeutic agents, the value of multi-agent chemotherapeutic combinations and the importance of adjuvant therapy in patients without macroscopic residual disease after initial surgery. It has also long been recognized that, in the case of large, unresectable tumors, chemotherapy can reduce the extent of subsequent surgery or radiation therapy. Intensified chemotherapy "alone", i.e. without further local treatments, may even cure some patients. This approach has been consistently investigated by the SIOP MMT Group in an attempt to contain long-term sequelae (especially those related to radiotherapy), but it remains controversial because it coincides with a higher relapse rate [1].

As rhabdomyosarcoma often occurs in young children, the treatment strategy has to balance

the best chance of cure against the lightest possible burden of therapy in order to contain the side effects and the future health risk. Modern protocols base treatment strategies on extent of disease (localized vs. metastatic), histology, post-surgical status, tumor site and size, and the patient's age.

Broadly speaking, the following groups can be identified:

1. *Low risk group*: 90% survival. This includes patients with embryonal RMS completely resected at diagnosis and occurring in favorable sites. Most of them have paratesticular RMS.
2. *Intermediate risk group*: 60-80% survival. This includes patients with a favorable histology and site (i.e. embryonal RMS localized in the orbit, head and neck).
3. *High risk group*: survival below 60%. This includes patients with RMS in unfavorable sites (trunk, pelvis, extremities, ...) and/or an alveolar histology.
4. *Very high risk group*: 20-30% survival. This mainly includes patients with metastatic RMS.

Standard chemotherapy for RMS

A number of antineoplastic agents have been tested in the last decades and the most effective have been incorporated in multidrug regimens, the most widely used of which are presented in (Table 1).

Vincristine, actinomycin D, cyclophosphamide and doxorubicin (adriamycin) have been the most frequently used agents in the treatment of RMS, in various combinations (VA, VAC, VACAdr), in IRSG and European studies.

The American COG (Children Oncology Group) investigators generally use VA for children in the most favorable groups and VAC for intermediate and high-risk patients.

Table 1: Rhabdomyosarcoma – most common multidrug regimens

<p>VA Vincristine 1.5 mg/m² for 1 day (usually repeated weekly for 7-12 weeks) Actinomycin 1.5 mg/m² for 1 day</p> <p>VAC Vincristine 1.5 mg/m² for 1 day Actinomycin 1.5 mg/m² for 1 day Cyclophosphamide 250 mg/m² for 5 days or 2.2 mg/m² for 1 day or 1.2 g/m² for 1 day</p> <p>VACA Vincristine 1.5 mg/m² day 1, wks 1 to 4 Actinomycin 1.5 mg/m² day 1, wk 4 Cyclophosphamide 1200 mg/m² wks 1,4,7 Adriamycin 30 mg/m² for 2 days, wks 1,7</p> <p>VTC Vincristine 1.5 mg/m² for 1 day Topotecan 0.75 mg/m² for 5 days Cyclophosphamide 250 mg/m² for 5 days</p>	<p>IVA Ifosfamide 3 mg/m² for 2 days Vincristine 1.5 mg/m² for 1 day Actinomycin 1.5 mg/m² for 1 day</p> <p>VAIA Vincristine 1.5 mg/m² day 1, wks 1 to 7 Actinomycin 1.5 mg/m² day 1, wks 1&7 Ifosfamide 2 mg/m² for 3 or 5 days, wks 1,4,7 Adriamycin 40 mg/m² for 2 days, wk 4</p> <p>CEVAIE Carboplatin 500 mg/m² for 1 days, wk 1 Epirubicin 150 mg/m² for 1 days, wk 1 Vincristine 1.5 mg/m² for 1 days, wks 1 to 7 Actinomycin 1.5 mg/m² for 1 days, wk 4 Ifosfamide 3 mg/m² for 3 days, wk 4,7 Etoposide 200 mg/m² for 3 days, wk 7</p> <p>IVADo As per IVA with Doxorubicin 30 mg/m² for 3 days, wks 1,3,7</p>
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The dosage of cyclophosphamide has varied in different IRS protocols, rising to 2.2 g/m² in the IRS IV study [2]. It has been claimed that this increasing dosage is one of the reasons for the progressive improvement in the results obtained in successive IRS studies. This claim was recently questioned, however, when further analyses showed no significant improvement in intermediate-risk patients and a higher risk of veno-occlusive disease [3]. The suggested cyclophosphamide dose in the ongoing protocol is 1.2 g/m².

Since replacing cyclophosphamide with ifosfamide seemed to improve the response rate [4], IVA or VAIA regimens were adopted in several European studies, but the results of the IRS-IV study in which patients were randomized to receive chemotherapy with VAC or IVA or VIE (vincristine, ifosfamide, etoposide) at similar myelotoxic doses have cast doubts on the supposed superiority of such a treatment. No significant difference in outcome was apparent and VAC was elected as the gold standard by the American investigators due to its lower cost and to the ifosfamide-related risk of nephrotoxicity [2].

European cooperative groups have recently intensified their joint efforts, founding the European pediatric Soft tissue sarcoma Study Group (EpSSG), which has decided to retain IVA as the standard combination in its ongoing

protocol because data suggest that the risk of significant renal toxicity is minimal at cumulative ifosfamide doses < 60 g/m², while the risk of gonadal toxicity with cyclophosphamide is higher. The ifosfamide dose has been set at 3 g/m² on days 1 and 2 (total dose/course = 6 g/m²) because using higher doses (3 g/m²/day for 3 days or 2 g/m²/day for 5 days) was not associated with any significant improvement in survival.

Moving beyond the standard

Despite the effectiveness of what can now be considered as a standard chemotherapy, some groups of patients still have an unsatisfactory prognosis. The most striking example concerns patients with metastatic RMS, whose prognosis has improved very little over the years. Investigators are moving in several directions in their attempt to improve the results in these patients, i.e.

1. a better use of “standard” drugs;
2. testing the value of new drugs;
3. exploring new strategies;
4. looking for experimental approaches.

Better use of standard drugs

Many multiagent combinations that include active drugs have shown no substantial improvement in outcome when compared with VAC or IVA. The case of doxorubicin is emblematic: though very effective against RMS and other STS as a

single drug, doxorubicin is not part of any standard combinations. This is the consequence of various randomized trials and historical comparisons performed by the IRS Group: results were no different when patients were given VAC with or without doxorubicin. Only a marginal improvement was noted in some subgroups, i.e. IRS groups I/II with an alveolar histology and pelvic sites^[5]. Since the role of anthracyclines in a multi-drug regimen remains to be established, the EpSSG is testing a novel intensive doxorubicin-based combination (IVADo) in the initial part of the recently-opened RMS2005 protocol.

Testing the value of new drugs

A variety of drugs proved active in phase I-II studies, but their utility was not confirmed when they were compared with the standard approach.

The camptothecin derivatives, topotecan and irinotecan, are now under evaluation in phase III studies. A COG study for intermediate-risk patients comparing topotecan in combination with vincristine and cyclophosphamide (VTC regimen) against VAC has recently completed the patient enrollment stage.

Using a prolonged administration (daily x5 x2), irinotecan induced an interesting response rate in patients with recurrent or metastatic RMS. The low hematological toxicity profile of irinotecan makes it attractive for use in association with other myelotoxic agents^[6]. Several studies reported a rapid progression after an initial response, however, suggesting an early onset of drug resistance^[7] - but this was not the case when irinotecan was combined with vincristine. This association is now being considered in phase III trials^[5].

Vinorelbine has shown an interesting activity in heavily-pretreated patients, either alone or in combination with cyclophosphamide^[8]: this combination has been included in an arm of the randomized trial recently opened by the EpSSG.

Apart from these drugs, which are being investigated in phase III trials, a number of new agents or new combinations are also under evaluation in phase I and II studies (**Table 2**)^[9,10].

New strategies

Different dose intensification strategies have been tested in an attempt to overcome tumor cell chemoresistance. In particular, high-dose chemotherapy (HDCT) followed by hematopoietic stem cell rescue (HSCR) has been explored in several trials.

In the European MMT4 protocol, the use of high-dose melphalan as consolidation therapy in children with metastatic disease in first complete remission resulted in an unsatisfactory 3-year EFS of 29%. Similarly poor results were obtained with other myeloablative regimens, such as combinations of melphalan, etoposide and carboplatin (MEC regimen), or thiothepa, cyclophosphamide and carboplatin, or melphalan and etoposide. The 2- and 3-year EFS in these studies ranged from 19% to 44%.^[11]

A trial using repeated courses of HDCT with HSCR earlier in the treatment was recently evaluated by the SIOP and the Italian Groups, revealing no advantage of this approach^[12].

On the other hand, the German Cooperative Group (CWS) recently identified a survival advantage for metastatic patients when low-dose "maintenance" chemotherapy (oral treatment with trofosfamide + idarubicin) was administered instead of high-dose chemotherapy (thiothepa + cyclophosphamide and melphalan + etoposide). The results in 62 patients are very promising, with a 3-year EFS above 50% for patients taking oral treatment (as opposed to an EFS of 20% after high-dose treatment). Since the comparison was not randomized, this result needs to be confirmed, but this different approach warrants further investigation.^[13]

In fact, low-dose continuous chemotherapy has been used with some degree of success and new hypotheses on antitumor mechanisms, including an anti-angiogenic action, have been put forward^[14]. This approach is also attractive in terms of its more limited toxicity and the EpSSG studies have adopted low-dose continuous cyclophosphamide administered in combination with weekly vinorelbine.

Finally, an alternative way to increase the dose intensity while reducing the interval between cycles was recently explored in Ewing sarcoma and RMS patients. The chemotherapy consisted

Table 2 : Ongoing Phase I-II trials including patients with rhabdomyosarcoma

Agent	Action	Study Phase	Patients	Study status
ABT-751	Tubulin binding	I	Young patients with refractory solid tumors	Recruiting
Iressa (ZD1839) (with Irinotecan)	EGFR inhibitor	I	Glioblastoma Rhabdomyosarcomas Neuroblastoma Osteosarcoma	Recruiting
Oxliplatin and etoposide	Antineoplastic drugs	I	Young patients with recurrent or refractory solid tumors	Recruiting
Lexatumumab	Trail-agonist monoclonal antibodies	I	Young patients with relapsed or not responding solid tumors or lymphoma	Recruiting
Everolimus (RAD001)	m-TOR inhibitor	I-II	Recurrent or refractory rhabdomyosarcomas and those with recurrent or refractory non-rhabdomyosarcomatous soft tissue sarcomas	Recruiting
Temsirolimus (CCI-779)	m-TOR inhibitor	I-II	Children with neuroblastoma, rhabdomyosarcoma, and high-grade gliomas	Recruiting
Dasatinib (BMS-354825)	Src kinase activity inhibitor	II	Patients > 13 years with advanced sarcoma	No yet recruiting
Ecteinascidin (ET 743)	Interferes with DNA binding factors and transcription	II	Children with recurrent rhabdomyosarcoma, Ewing sarcoma, or non-rhabdomyosarcomatous soft tissue sarcoma	Not active yet
Gemcitabine and oxaliplatin	Antineoplastic drugs	II	Young patients with recurrent refractory solid tumors	Recruiting
Ixabepilone (BMS-	Microtubule stabilization	II	Young patients with refractory solid tumors	Not active yet
Pemetrexed	Antifolate	II	Young patients with solid tumors	Not yet recruiting

of alternate courses of vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide, followed by G-CSF administration during a 14-day interval between courses. The median chemotherapy interval was 16 days in the induction phase and 21 in the continuation phase, which included radiotherapy. This preliminary experience demonstrated that it was feasible to deliver chemotherapy more frequently than every 3 weeks and the idea of a dose-compressed treatment will be tested in the next COG trial on high-risk metastatic patients^[15].

Experimental approaches

A number of potential novel approaches are being investigated in preclinical studies, including the use of immunotherapy, antiangiogenic drugs, and molecules directed against specific targets.

The demonstration of a graft effect against some solid tumor cells has led to allogeneic bone marrow transplant being considered in pediatric soft tissue sarcoma^[16]. Data from BMT registries and small series are controversial, but have provided the basis for ongoing prospective trials in very high-risk patients (mainly with recurrent

disease) using related or unrelated donors as the source of stem cells, with or without post-transplant immunomodulation.

The use of antiangiogenic drugs is being assessed in adult patients, but studies on pediatric patients are lacking. The observation that RMS cell lines express VEGF^[17] and that blocking VEGFR1 antibody inhibits VEGF signaling and delays RMS proliferation has made antiangiogenic treatment an attractive option. Studies on the use of bevacizumab, a humanized monoclonal antibody that blocks the binding of human VEGF to its receptors are in the planning stages. The safety of this agent in combination with the standard drugs needs to be confirmed, however.

Both epidermal growth factor receptor (EGFR) and ErbB-2 play an important part in cancer biology and are promising molecular targets for treatment. EGFR and ErbB-2 expression has been observed in pediatric STS cell lines, including synovial sarcoma and RMS^[18]. This provides the rationale for testing agents such as gefitinib, a small molecule that competes with ATP for the intracellular catalytic site of EGFR.

Initial experience with targeted therapy has hardly been impressive - as in the case of bortezomib, for instance, which is a reversible proteasome inhibitor: the limited activity of this molecule against STS (including a few patients with RMS) when administered as a single agent suggests that target agents may have a role in future but it will be in association with antineoplastic drugs^[19].

In conclusion, several novel agents may have a part to play in the future treatment of RMS, probably in association with the standard VAC or IVA regimens.

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