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Tumour Review

Fifty years of rhabdomyosarcoma studies on both sides of the pond and lessons learned

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ABSTRACT

We review and summarize the highlights of almost five decades of cooperative group trials in rhabdomyosarcoma on both sides of the Atlantic, concentrating on chemotherapy regimens, what has been learned, and where remaining challenges are. The most important achievements have been to decrease or omit the dose of alkylator therapy for many patients, to clarify after much controversy that doxorubicin does not improve the outcome of patients even in the highest risk groups, and to show that high dose chemotherapy and stem cell rescue do not improve the outcome of the highest risk patients. In North America, vincristine/actinomycin/cyclophosphamide (VAC) remains an important part of therapy, whereas in Europe the alkylating agent of choice is ifosfamide. The highest risk patients, namely those with the poorest prognostic score, have had no improvement in outcome since the first cooperative group trial in 1972 and remain the greatest challenge. Philosophical differences between European and North American strategies still revolve somewhat around the total burden of therapy received, that is should certain groups of patients be spared aggressive local control in order to reduce late effects, recognizing that it is not possible to identify priori the children that can be cured with this approach exposing the whole population to a higher risk of relapse. Collaboration and joining resources may help answer some difficult questions.

Introduction

Soft tissue sarcomas comprise approximately 7.4% of all pediatric malignancies, with rhabdomyosarcoma being the most common soft tissue sarcoma in children. Two thirds of cases arise in children under 10 years of age, and it can arise virtually in any part of the body with two main histological subtypes (alveolar and embryonal).

Risk stratification for treatment assignment has been a moving target over the past 50 years. In the initial Intergroup Rhabdomyosarcoma Studies (IRSG) I, II and III, the staging system incorporated that initially described by Maurer, based on clinical factors such as primary site, degree of surgical resection prior to initiation of chemotherapy, and nodal involvement, and was subsequently refined by Rodary [1–4]. The difficulty with the original staging system was that it was a system in some cases based on the aggressiveness of a surgeon in resecting tumor at initial diagnosis, and did not take into account the unresectability in certain sites (such as skull base). Tables 1 and 2 describe group and stage respectively. Subsequently Meza et al further refined prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on IRS III and IV, which led to slightly different risk group assignment on subsequent studies [5]. Oberlin and colleagues have evaluated prognostic factors in patients with metastatic disease in a pooled analysis of patients from the United States and Europe and developed a scoring system for prognosis based on age, primary site, number of metastatic sites, histology, and bone or marrow involvement [6]. Risk group assignment has also differed between the United States and Europe, thus making exact comparison of therapy difficult between international studies [7].

More recently, the importance of including molecular classification based on presence or absence of the t(2;13)(q35;q14) or variant t(1;13)(p36, q14) chromosomal translocation in most cases of alveolar RMS has been recognized. Almost all embryonal RMS lacks this fusion [8]. However, studies on the prognostic importance of this have been conflicting. Two retrospective studies on patients treated on multiple different clinical trials spanning two decades have shown conflicting results on the prognostic significance of FOXO1 fusion status. Missiaglia et al. found that fusion positive patients have an inferior outcome compared to fusion negative patients, whereas Stegmaier et al showed

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Table 1
IRSG grouping system [3].

Group	Description
I	Localized disease, completely resected A. Confined to organ or muscle of origin B. Infiltration outside organ or muscle of origin; regional nodes not involved
II	Compromised or regional resection of three types including: A. Grossly resected tumors with microscopic residual B. Regional disease, completely resected, in which nodes may be involved, and/or extension of tumor into an adjacent organ present C. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual
III	Incomplete resection of biopsy with gross residual disease
IV	Distant metastases, present at onset

Table 2
Rhabdomyosarcoma staging system (adapted from [3]).

Stage	Sites	T	Size	N	M
1	Favorable	T1 or T2	any	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	≤5 cm	N0 or Nx	M0
3	Unfavorable	T1 or T2	≤5 cm	N1	M0
			> 5 cm	No or N1 or Nx	
4	Unfavorable	T1 or T2	any	N0 or N1	M1

T1 confined to anatomic site of origin; T2 extension and/or fixed to surrounding tissue.
N0 regional nodes not clinically involved.
N1 regional nodes clinically involved by neoplasm.
Nx clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation.

no association between outcome and fusion status in patients with ARMS [9,10]. Analyses of patients with low- (n = 16) and intermediate-risk (n = 434) RMS treated on a series of recent Children's Oncology Group (COG) trials confirmed the prognostic significance of FOXO1 fusion status [11,12]. The rationale for the current Children's Oncology Group studies and risk stratification system was recently summarized by Malempati and colleagues [13].

The first cooperative group trial for rhabdomyosarcoma, Intergroup Rhabdomyosarcoma Study (IRS)-I opened in 1972, beginning a series of cooperative group studies in the US and subsequently in Europe to improve and refine the treatment and cure rate. This review concentrates on summarizing the design and findings in regards to chemotherapy regimens, discussing differences and similarities of North American and European studies and underlining the increasing collaboration among the investigators on both sides of the Atlantic. Detailed discussion of local control issues and questions with surgery and/or radiotherapy (XRT) is beyond the scope of this review. An overview of the treatment strategies in provided in Table 3.

North American IRSG and Children's Oncology Group (COG) studies

Early North American Studies had a prolonged duration of therapy, up to two years, which has decreased to 22–40 weeks, depending on risk group, in the current era. Overall philosophy of local control has changed from aggressive local surgical control which often resulted in loss of function to more conservative surgery and use of radiation (XRT) to avoid mutilating surgery [14]. None of the North American randomized studies for newly diagnosed patients have shown a difference by regimen, however overall outcome has improved for all but the highest risk patients. IRS-IV and the "D" series of studies utilized a series of "phase II windows" to identify agents to bring forward [15–19]. Although vincristine/actinomycin/cyclophosphamide are referred to as "VAC" chemotherapy, the doses, route, schedule of administration as

Table 3
Basic concepts in evolution of treatment strategies in rhabdomyosarcoma.

North American studies
IRS I/II
Established VAC as standard of care for RMS in North America. IRS II movement towards more organ/limb sparing surgical approaches
IRS III
Recognition of more "special" sites, such as pelvic sites. Continued attempt at conservative surgical approaches and organ/limb sparing. Complex chemotherapy regimens
IRS IV
Comparison of cyclophosphamide and ifosfamide as alklyator of choice in upfront therapy for rhabdomyosarcoma. Initiated concept of "up front windows" to identify active agents in high risk patients
IRS V "D" series
Risk groups determined by outcomes from IRS III and IV, with significant de-escaltion of alkylator therapy in low risk patients, continued "window" therapy with topoisomerase inhibitors for highest risk groups
ARST series
Overall dose reduction of cyclophosphamide in all risk groups. Intensive multiagent chemotherapy regimen in highest risk group which did not improve outcome. Use of temsirolimus in relapsed patients showed improved time to progression compared to bevacizumab, prompting use of m-tor inhibition in the current intermediate risk upfront study

European studies
CWS-81
Reduction of therapy duration in patients with primary resected tumors to 35 weeks compared with 57 weeks in the IRS-I by giving an intensified four drug regimen (VACA: vincristine, VCR, actinomycin D ACT-D, cyclophosphamide CYC, and doxorubicin DOX). Assessment of the response to neoadjuvant chemotherapy in patients with gross residual tumor as a possible prognostic factor
CWS-86
Substitution of CYC with ifosfamide (IFO) in the four-drug cycle VAIA. Further reduction of the duration of therapy (IRS Group I to 16 weeks and IRS Group II to 26 weeks (compared with 35 weeks in the CWS-81 Study). Introduction of an innovative accelerated hyperfractionated radiotherapy concept (2 × 1,6 Gy/day). Stratification of RT indication and dose according to the response to CHT after 7–9 weeks, site, size and surgery options
CWS-91
Novel stratification system for primary and secondary treatment additionally including primary site, TNM classification and, for secondary local therapy response to CHT. Reintroducing CYC instead of IFO for low risk group, intensification of chemotherapy by adding etoposide to VAIA for high risk patients. Reduction of therapy duration and cumulative doses of cytostatics by 25–60% in comparison to CWS-86
CWS-96 /ICG-96
Deletion of alkylators in the low risk and anthracylines in the standard risk group
High risk group- randomization of the 6-drug regimen CEVAIE against the 4-drug regimen VAIA (CWS-96 /ICG-96) and three drug IVA (MMT-95)
CWS- 2002P
Addition of maintenance therapy with CYC and vinblastine (6 months) in the high risk group

SIOP studies
Progressive reduction of aggressiveness of treatment without impairing patients outcome:
RMS75:
reduction of treatment duration to 8 months
No difference between early vs late local control treatment
MMTS84:
Further reduction of treatment duration: 3 months for low risk patients, 6–7 months for the other patients
MMT89
reduction of ifosfamide cumulative dose
introduction of carboplatin and etoposide did not improve outcome in patients poor responding to standard chemotherapy
Caution in reducing further the duration of chemotherapy in low risk patients
Reduction of radiotherapy field or avoidance of radiotherapy in certain groups of patients, i.e. orbital RMS (MMT84), but not in young children with parameningeal RMS
MMT96
The use of a multifdrug intensive regimen including epirubin, carboplatin, etoposide, does not improve outcomes

AIEOP STSC studies
RMS79:
No difference in term of tumor response and toxicity comparing high, single doses vs five-day, divided doses actinomycin

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