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What's New in the Biology and Treatment of Pediatric Rhabdomyosarcoma?

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Abstract

Purpose of review—The purpose of this review is to highlight some of the advances in the way we think about rhabdomyosarcoma (RMS). Recent outcome and biological analyses have shifted the risk stratification and treatment paradigms for pediatric RMS.

Recent Findings—The presence or absence of the *FOXO1* translocation is one of the most important prognostic factors in rhabdomyosarcoma. Future clinical studies will incorporate *FOXO1* translocation status within risk stratification criteria. Molecular analyses have identified RAS/NF1, hedgehog, IL-4R, and ALK pathway abnormalities as potential therapeutic targets in RMS. Reductions in systemic therapy are possible, although radiation therapy remains essential to prevent local failures in most patients.

Summary—Although survival for RMS has not improved in the recent years, refinement in risk stratification, further understanding of the biological drivers of the disease, and modifications in treatment intensity have set the stage for the next generation of studies in RMS.

Keywords

rhabdomyosarcoma; FOXO1 translocations; toxicity; radiotherapy

Introduction

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcomas in children, comprising 2.9% of all pediatric cancers with an annual incidence in the United States of 4.3 per million children less than 20 years. There are two broad RMS histologic subtypes: embryonal (ERMS) and alveolar (ARMS). Treatment has evolved significantly over the past 50 years to include intensive, multiagent chemotherapy (mostly commonly vincristine,

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dactinomycin, and cyclophosphamide (VAC) in North America) for all patients, radiation therapy (RT) for most, and surgical resection for some. Although survival rates improved dramatically from 1960-1996, there has been little change in more recent years. To adjust the intensity of therapy to the probability of recurrence, treatment is guided by a risk stratification based on pre-treatment histology, site of primary tumor, the extent of residual tumor after surgery, and presence of distant metastases to define three distinct RMS risk group: low-, intermediate-, and high-risk (Table I). Recent Children's Oncology Group (COG) clinical trials have attempted to reduce the short- and long-term toxicity of therapy for low-risk RMS and improve the survival for intermediate- and high-risk RMS.

In this review, we describe novel aspects of biology, diagnosis, risk stratification, staging and therapy of pediatric RMS. The identification of the prognostic value of the *FOXO1* (previously referred to as *FKHR)* translocation status in RMS is one of the most important shifts in the risk stratification of this disease which will be incorporated in all future studies. Genomic analyses have identified several recurring somatic alterations, including some that are potential therapeutic targets. Although recent large clinical trials show no overall improvement in outcome of patients with RMS, important lessons have been confirmed regarding the value of radiotherapy and the specific situations in which reduction of treatment intensity would be safe.(1, 2)

Prognostic subgroups of alveolar rhabdomyosarcoma

Fusion of the *PAX3* or *PAX7* genes on chromosome 2 or 1, respectively, with the *FOXO1* gene on chromosome 13 is seen in the vast majority of ARMS. However, approximately 20% of ARMS lack evidence of a gene fusion.(3) Using gene expression profiling and metagene analysis, Davicioni et al showed that fusion negative ARMS (ARMSn) are molecularly indistinguishable from ERMS.(4, 5) Williamson et al confirmed these findings and suggested that ARMSn are clinically similar to ERMS.(6) While these studies demonstrated intriguing biologic similarities between ERMS and ARMSn, the clinical utility was limited by the use of convenience cohorts. (3, 7) The limitations of convenience cohorts were illustrated by the conflicting results seen in subsequent studies. The Cooperative Soft Tissue Sarcoma Study Group (CWS) found no prognostic significance of fusion status,(8) while the Innovative Therapies for Children/Carte d'Identité de Tumeurs (ITCC/CIT) showed fusion gene status was the key prognostic marker in RMS(9).

Shifts in the histologic criteria for ARMS confounded some of these studies, as well. Rudzinski et al showed that a uniform definition of ARMS requiring predominant alveolar histology, recognition of new histologic variants of RMS, and increased emphasis on a strong diffuse pattern of myogenin expression in ARMS resulted in the re-classification of one third of ARMS to ERMS, noting that re-classified tumors were uniformly *FOXO1* fusion negative.(10) Using this current histologic definition of ARMS and looking at data obtained from a single prospective trial, COG confirmed that *FOXO1* fusion status drives outcome in children with intermediate risk RMS.(11) This new emphasis on fusion status rather than histologic subtype for risk-stratification will be reflected in future COG studies. ARMS have amplification of the 13q31 chromosomal region and increased expression of the MIR17HG gene encoding the polycistronic microRNA cluster, miR-17-92.(12) This

chromosomal amplification showed a marked preference for *PAX7-FOXO1* cases and was associated with a significantly worse outcome than non-amplified cases.

Basic Science Advances

The cell of origin for RMS remains unknown. It is thought that ERMS develops from muscle progenitor cells given the similar expression of skeletal muscle markers in both cell types. The development of ERMS at sites that lack striated muscle, such as the bladder, prostate and biliary tree, remains unexplained. Several studies have provided new insights into the genetic origin of RMS. Hatley et al developed a mouse model of ERMS originating from an adipocyte lineage through adipocyte restricted activation of the hedgehog (Hh) pathway by an oncogenic *Smoothened* allele. This model may account for ERMS at sites that normally lack skeletal muscle, and suggests that ERMS may arise through transdifferentiation of mesenchymal, non-skeletal muscle, precursors.(13)

In contrast, Rubin et al developed mouse models of RMS using p53 and Ptch1 mutations in muscle stem cells and proliferating and mature myoblasts.(14) RMS developed from all subpopulations of muscle cells, although the mutational profile and cell of origin were important in determining the proportion of tumors with an RMS versus undifferentiated pleomorphic/spindle cell sarcoma (UPS) phenotype. Maturing myoblasts gave rise to more ERMS, while UPS were more likely to evolve from PAX7 expressing satellite cells (muscle stem cells). Additionally, Rb1 expression modified the tumor phenotype to mimic UPS. These results suggest that a continuum exists between ERMS and UPS, and that at least a subset of ERMS and UPS share a common myogenic cell(s) of origin.

MacQuarrie et al have examined the role of epigenetic modifications in the development of RMS, (15, 16) proposing that RMS cells represent an arrested state of development of normal skeletal muscle, with regional and local silencing of differentiation factors contributing to the maturation defect in RMS. Additionally, they showed that genome-wide DNA methylation patterns can distinguish RMS subtypes, suggesting aberrant DNA methylation silences genes important for the pathogenesis of RMS.

Other groups have also examined the mechanism of failure of myogenic differentiation in RMS. Jothi et al demonstrated that AKT regulation of the PAX3-FOXO1 fusion protein suppresses myogenic gene expression in ARMS cells, causing a failure in differentiation. (17) Hosoyama et al examined the role of interleukin-4 receptor (IL-4R), which is important for the maturation of myotubes. (18) Stimulation of IL-4R signaling in RMS enhanced tumor cell proliferation, while inhibition of this pathway decreased cell proliferation but not apoptosis. IL-4R blockade may therefore be used therapeutically to modulate the expression of myogenic transcription factors (MyoD or myogenin).

Translational Research

Aberrant activation of cell signaling pathways resulting in therapeutically relevant mutations allows for novel treatment options in many tumors, including RMS (Table II). Pressey et al showed that a substantial subset of ERMS and undifferentiated sarcomas show activation of the Hh pathway.(19) This was confirmed by array comparative genomic hybridization

(aCGH) studies which showed that over 50% of ERMS tumors had activation of the Hh-pathway transcription factor *GLI1*. (20) CGH data also showed inactivation of p53 and Rb pathways, *CDKN2A/B*, and activation of *FGFR4* and Ras in varying subsets of ERMS tumors. Intragenic deletions of *NF1*, a tumor suppressor and inhibitor of Ras, were mutually exclusive from activating Ras mutations, suggesting that *NF1* loss may be an alternative mechanism of Ras activation in ERMS.(20) Using targeted sequencing for common cancer-associated mutations, Shukla et al also confirmed previously identified *Ras* and *FGFR4* mutations but also identified *PIK3CA* and *CTNNB1* (β-catenin) mutations in a minority of ERMS.(21)

In contrast to the variety of mutations seen in ERMS, *FOXO1* fusion positive ARMS are genetically simpler. Although over expressed in both ARMS and ERMS, ALK aberrations are more commonly seen in ARMS.(22) Described ALK abnormalities include increased protein expression by immunohistochemistry as well as *ALK* gene copy number gain in a majority of ARMS (88%). Sequencing of the tyrosine kinase domain revealed rare point mutations (2%) and several whole exon deletions (16%). It is unclear whether increased protein expression without an activating mutation or translocation will confirm pharmacologic sensitivity to an ALK inhibitor, such as crizotinib.

Re-staging RMS

FDG-PET imaging in patients with RMS offers an alternate imaging modality to predict outcome based on response to initial chemotherapy. Standard cross-sectional imaging (CT or MRI) performed either early (23) or late in the treatment plan (24) fail to predict disease recurrence. A single institutional review demonstrated that patients who had a negative PET following induction chemotherapy and radiotherapy had a superior local-relapse free survival than patients with a positive PET (94% vs. 75%, 0=0.02) (25) In the future, FDG-PET might replace conventional staging imaging studies, particularly for lymph node disease.(26, 27) Routine staging evaluation, including bone marrow aspiration/biopsy and bone scans, are unnecessary in one third of ERMS, and CT chest could be omitted in patients with node-negative, non-invasive disease.(28)

Toxicity of Chemotherapy – Individualized Care

VAC has been the North American standard treatment for RMS for more than four decades. (1, 2) However, increasing attention is being devoted to the understanding of age-related dosing and chemotherapy toxicities and outcome. Patients < 1 or >10 years fare worse than those ages 1-10 years.(29-31) Patients < 1 year of age had increased rates of hepatopathy on COG D9803, which led to dose reductions in VAC for infants.(32) Despite dose reductions, the significantly increased rates of toxicity to VA in children < 1 year of age were confirmed in a multi-study analysis performed on 4567 patients.(33) Furthermore, risk of toxicity with dactinomycin does not correlate with increasing cumulative exposure to the drug (dose or time) suggesting that toxicity may be related to specific susceptibility. Adolescents experience significantly less hematologic toxicity compared with younger children despite receiving comparable cumulative chemotherapy doses in one study of intermediate risk RMS.(34) Therefore, dose modifications in response to toxicity do not explain the age-

related difference in outcome. Rather, the lower degree of hematologic toxicity observed in adolescents may reflect relatively lower systemic exposure to chemotherapy.

The impact of body mass index (BMI) on toxicity and outcome in RMS has also been explored.(35) Patients with low BMI (<5%ile), or those who lose significant weight experience greater toxicity than other children. Patients with low BMI may also have inferior survival. Whether this effect is influenced by patient age remains unknown. Future studies may consider early and more aggressive nutritional interventions to minimize toxicity.

Recent Trials in RMS – Reduction in Dose Intensity

COG D9803 randomized patients with intermediate risk RMS to VAC versus VAC alternating with vincristine, topotecan and cyclophosphamide (VTC). A total of 617 eligible patients were entered onto the study and at a median follow-up of 4.3 years, 4-year FFS was 73% with VAC and 68% with VAC/VTC (p=0.3).(36) The outcome between the two arms was similar despite a 20% decrease in the total dose of cyclophosphamide in the VAC/VTC arm (30.8 g/m^2 compared with 25.1 g/m^2). Concurrent with COG D9803, COG D9602 tested reductions in treatment in low-risk RMS.(37) In this study, subgroup A patients (lowest risk, with ERMS, stage 1 group I/IIA, stage 1 group III orbit, stage 2 group I) received VA, and subgroup B patients (ERMS, stage 1 group IIB/C, stage I group III non-orbit, stage 2 group II, stage 3 group I/II) received VAC (13 cycles of VAC, total dose of cyclophosphamide = 28.6 g/m^2).(37) The complete elimination of cyclophosphamide in subgroup A resulted in an inferior 5-year failure-free survival (FFS) of 81% compared with 85% on IRS-IV. Patients in subgroup B had a 5-yr FFS of 85%.

Vaginal primary site ERMS illustrate the challenge of balancing effective local treatment with long-term morbidity. On the most recent COG low-risk RMS study, ARST0331, vaginal primary ERMS was treated a low cumulative dose of cyclophosphamide (4.8 g/m^2) and used a local control strategy designed to minimize radiation and extensive surgery. The 5-year cumulative incidence of local recurrence was 43% on ARST0331, compared to 26% on COG D9602 with higher dose cyclophosphamide.(38) The omission of RT was the most likely cause for the high rate of local failures, although lower cyclophosphamide dose may have contributed.

The International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor (MMT) group compared standard versus intensive chemotherapy in patients with high-risk nonmetastatic RMS (MMT 95).(39) After one course of ifosfamide, vincristine, and dactinomycin (IVA), 385 patients with RMS were randomly assigned to IVA or IVA alternating with carboplatin, etoposide, and vincristine (CEV) and ifosfamide, vincristine, and etoposide (IVE). Intensifying chemotherapy did not improve survival or reduce the intensity of local therapy, but was associated with increased toxicity.

Optimizing Dose and Delivery of Radiotherapy

Several factors drive the desire to reduce or omit RT in the treatment of RMS: 1) low risk RMS has a favorable outcome; 2) there is increasing awareness of late effects of RT; 3) RMS is very radiosensitive. Reduction in the dose of radiation from 41.4 Gy to 36 Gy for

marginally resected ERMS and from 50.4 to 45 Gy for orbital ERMS did not compromise outcome on COG D9602.(40) Very young children or patients with pelvic primary sites are particular candidates for omission of RT due to the profound impact on growth. However, omission of RT results in a higher recurrence rate, necessitating more aggressive second-line therapy and potentially compromising overall survival. SIOP MMT, CWS, and the Italian Cooperative Group (ICG) have incorporated response to chemotherapy and conservative surgery to omit RT whenever possible. An international analysis of bladder/prostate ERMS showed this strategy resulted in a slightly higher relapse risk but similar overall survival compared to the COG strategy.(41)

COG recently analyzed non-compliance with RT among nearly 700 RMS patients who had post-operative microscopic residual disease (Group II).(42) The majority of operative bed recurrences were associated with omission of RT. This analysis differs from prior SIOP MMT and CWS reports in that half the patients were non-ERMS and included all sites of disease. Infants with RMS have a higher rate of disease recurrence than older children, in part due to the compromise in RT delivery and consequent local failures.(31) Thus, the late toxicity from RT needs to be balanced with the risk of failure; although these decisions continue to be difficult for physicians and families, data continue to support the need for RT to optimize cure in most patients with RMS.

There have also been evolutions in the modality of RT used to treat patients with pediatric RMS. Intensity-modulated RT (IMRT) offers the potential to provide improved target coverage and a lower radiation dose to the surrounding critical organs compared with 3-dimensional conformal RT (3D-CRT). In COG D9803, the technique of RT varied by treating institution; sufficient dosimetric data on 179 patients was available for analysis.(43) There was no difference in 5-year FFS; however in patients with primary parameningeal tumors, toxicity (dermatitis, thrombocytopenia) was less in those who received IMRT compared to those who received 3D-CRT.

Re-thinking Lymph Node Disease

Patients with RMS are at high risk for presenting with regional lymph node disease (N1), and subsequent nodal failure if not adequately treated. Nodal disease is an independent prognostic marker, especially in ARMS and extremity primary sites. On IRS-IV, 23% of patients were N1 at presentation, which was an independent prognostic factor in ARMS.(44) N1 status was more common in older patients, those with ARMS, large tumors and tumors at certain anatomic sites (including perineum, retroperitoneum, extremity, bladder/prostate, parameningeal, and paratesticular). Two primary sites deserve surgical lymph node staging: extremity and paratesticular in > 10 years olds. A recent analysis of the Surveillance, Epidemiology, and End Results database demonstrated that 40% of patients > 10 years of age with paratesticular RMS had N1 disease. Among these older patients, the 5 year survival was better for those patients who underwent lymph node dissection than those did not (92% vs. 76%, p=0.028).(45) Furthermore, the addition of RT improved the 5year survival in N1 patients (90% vs. 36%; p<0.0001), but made no difference to those with N0 disease. These data support routine retroperitoneal lymph node sampling in patients > age 10 years and regional lymph node radiation in N1 patients.

Conclusion

FOXO1 fusion status will replace histologic classification for risk stratification in future RMS clinical trials. Comprehensive genomic analysis and mouse models of RMS provide novel insights into the etiology of RMS and potential therapeutic targets. Recent randomized chemotherapy trials have failed to improve outcome despite the introduction of newer or more intensive therapy. Future clinical trials will refine the use of RT, particularly in the youngest children.

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Key Points

- *FOXO1* fusion status is more closely associated with outcome than histologic classification and will be used in future clinical trials for risk stratification
- In *FOXO1* fusion positive RMS, abnormalities of ALK are common, while RAS, Hh, p53, NF1, PIK3CA, and β-catenin are more common in *FOXO1* fusion negative RMS.
- FDG PET may be more sensitive to detect metastatic disease (particularly in lymph nodes) and may be useful to evaluate response to therapy.
- Recent chemotherapy clinical trials have failed to show improved outcome despite the incorporation of additional agents.
- RT remains essential to optimize the probability of cure, although balancing effective cancer therapy with the late effects of local treatment is a challenge.

Table I

Current Children's Oncology Group rhabdomyosarcoma risk stratification

Risk Group	Histology	Primary site	Initial resection	Distant metastases	Proportion of patients	EFS
Low	ERMS	Favorable	Any	None	32%	70-95%%
		Unfavorable	Yes	None		
Intermediate	ERMS	Unfavorable	No	None	27%	73%
	ARMS	Any	Any	None	25%	65%
High	ERMS	Any	Any	Present	8%	35%
	ARMS			Present	8%	15%

ERMS, embryonal rhabdomyosarcoma; ARMS, alveolar rhabdomyosarcoma; EFS, event-free survival

Table II

Potentially therapeutically relevant mutations in rhabdomyosarcoma

Histology	Mutations	Frequency
Alveolar		
	Anaplastic lymphoma kinase (ALK) protein expression	50-80%
Embryonal		
	CDKN2A/B ($p16^{INK4\alpha}$/$p14^{ARF}$)	20-25%
	Anaplastic lymphoma kinase (ALK) protein expression	15-30%
	GLI1/Sonic hedgehog pathway (high expression only)	15-20%
	H, K or NRAS	10-40%
	Fibroblast growth factor receptor 4 (FGFR4)	10-20%
	PIK3CA (phosphatidylinositol 3-kinase)	5%
	CTNNB1 (α-catenin)	0-3%