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Seminar article

Future directions in risk stratification and therapy for advanced pediatric genitourinary rhabdomyosarcoma

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Abstract

Rhabdomyosarcoma (RMS) represents the most common soft tissue sarcoma in infants and children and the third most common pediatric solid tumor, accounting for 5% to 15% of all childhood solid tumors. Of these, 15% to 20% arise from the genitourinary tract, with the most common sites originating from the prostate, bladder, and paratesticular regions, followed by the vagina and uterus. Although upfront radical surgery was used at the initiation of Intergroup RMS Study-I (1972–1978), the treatment paradigm has shifted to include initial biopsy with the goal of organ preservation, systemic chemotherapy for all patients, and local control involving surgical resection with or without radiation therapy for most patients. Collaborative group clinical trials have led to dramatic improvement in survival rates from 1960 to 1996 among patients with low- or intermediate-risk disease; however, outcomes appear to have plateaued in more recent years, and the prognosis for patients with metastatic or relapsed/refractory disease remains poor.

Current management goals include minimizing toxicity while maintaining the excellent outcomes in low-risk disease, as well as improving outcomes in patients with intermediate- and high-risk disease. Advances in genetic analysis have allowed further refinement in risk stratification of patients. Perhaps the most significant recent development in RMS research was the discovery of an association of alveolar RMS (ARMS) with translocations t(2;13) and t(1;13). Translocation fusion-positive tumors comprise 80% of ARMS and are more aggressive. Fusion-negative ARMS may have a clinical course similar to embryonal RMS. Future Children's Oncology Group sarcoma studies will likely incorporate fusion status into risk stratification and treatment allocation.

Newer radiotherapy modalities hold promise for providing local control of disease while minimizing morbidity. The addition of traditional cytotoxic chemotherapeutic agents does not seem to improve outcomes in high-risk patients. Ultimately, the most substantial progress may arise from further elucidation of genetic and molecular pathways involved in RMS tumor formation in an effort to identify novel, targeted therapeutic approaches.

Keywords: Rhabdomyosarcoma; Genitourinary; Pediatric; Risk stratification; Multimodal therapy

Introduction

Rhabdomyosarcoma (RMS) represents the most common soft tissue sarcoma in infants and children and the third most common pediatric solid tumor, accounting for 5% to 15% of all childhood solid tumors. Approximately 350 new cases of RMS are diagnosed in the United States each year [1]. Of these, 15% to 20% arise from the genitourinary tract, with the most common sites originating from the prostate, bladder, and paratesticular regions, followed by the vagina and uterus [2,3]. A bimodal age distribution exists, with a peak incidence during the first 2 years of life and then again during adolescence. There is a slight predominance in men, with a male to female ratio of 1.5:1 [4]. Although most cases occur sporadically, RMS has been observed in certain genetic syndromes, including Li-Fraumeni syndrome, neurofibromatosis type I, basal cell nevus syndrome, Costello syndrome, Noonan syndrome, and multiple endocrine neoplasia type 2A [4–7].

Collaborative group clinical trials have led to dramatic improvement in survival rates from 1960 to 1996 among

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patients with low- or intermediate-risk disease; however, outcomes appear to have plateaued in more recent years, and the prognosis for patients with metastatic or relapsed/refractory disease remains poor [4,8]. Future treatment strategies will focus on improved risk stratification, refinement of radiation and chemotherapy protocols, and further elucidation of genetic and molecular pathways involved in RMS tumor formation in an effort to identify novel, targeted therapeutic approaches.

Pathology and molecular biology

A total of 3 pathologic subtypes of RMS are currently recognized. Embryonal RMS (ERMS) accounts for approximately 80% of cases and typically has an intermediate prognosis. Sarcoma botryoides, a variant of ERMS, is a polypoid tumor that arises in hollow organs such as the bladder or vagina and often appears as a "cluster of grapes." Spindle cell RMS was initially described in 1992 as another variant of ERMS, commonly found in the paratesticular region. Both the botryoid and spindle cell subtypes are most common in young children and have favorable survival rates of 85% to 90% [9]. Sclerosing RMS, characterized by prominent hyaline sclerosis and a pseudovascular growth pattern, has been found to share morphological similarities with spindle cell RMS, and spindle cell/sclerosing RMS has been proposed as a separate entity in the World Health Organization Classification of Tumours of Soft Tissue and Bone [10]. A mutation of the *MYOD1* gene, which may act as a key factor in skeletal muscle oncogenesis, has been identified in a large proportion of older children and adults with spindle cell/sclerosing RMS and is associated with an increased risk of treatment failure [10].

Alveolar RMS (ARMS) comprises 15% to 20% of cases, with the remainder of cases classified as undifferentiated tumors. Both alveolar and undifferentiated RMS have an unfavorable prognosis. The most significant recent development in RMS research was the discovery of oncogenic fusion proteins produced by chromosomal translocations in ARMS.

Chromosomal translocation involves the physical transfer of chromosomal material from one location to another (unbalanced) or the parallel exchange of 2 chromosomal segments (balanced) to create novel, chimeric gene products that juxtapose portions of the original chromosomes. Most translocations introduce breaks within the body of the gene and result in hybrid or "fusion" proteins containing parts of 2 proteins, often creating molecules with novel functional properties [11]. The fusion of the proteins can result in loss of function, such as an inability to appropriately regulate expression of normal target genes or loss of expression in the appropriate tissue, again changing gene expression. Alternatively, merging the proteins can produce a gain of function by acquiring the ability to bind novel regulatory DNA sites or to interact with new driver proteins to promote or repress expression of novel target genes. Although the underlying mechanisms of translocation are not fully understood, effects of either radiation or chemical damage to chromosomal DNA or errors in normal recombination processes are likely causative. The resulting changes in gene expression may contribute to tumor initiation and progression by modifying cellular pathways involved in cell division, differentiation, survival, and cell death [11].

Recent molecular studies have identified balanced translocations between chromosomes 2;13(q35;q14) or 1;13(p36q14) in approximately 80% of ARMS. These translocations result in fusion of either the *PAX3* or *PAX7* gene from chromosomes 2 and 1, respectively, with the *FOXO1* gene on chromosome 13 [12]. *PAX3* and *PAX7* genes are members of the paired-box family of transcription factors [13,14], and *FOXO1* is a member of the forkhead family of transcription factors [14,15]. The resulting fusion genes *PAX3-FOXO1* and *PAX7-FOXO1* encode transcription factors that are more potent than their native proteins. These fusion proteins induce cell transformation and inhibit apoptosis and myogenic differentiation; thus, they are potent oncogenic proteins that confer a more aggressive phenotype in ARMS [16]. The clinical relevance of these molecular features has been demonstrated in a recent report from the Children's Oncology Group (COG) sarcoma committee [12]. The survival analysis included 434 patients with intermediate-risk disease. Fusion status was determined by either reverse transcriptase polymerase chain reaction for identification of the fusion transcript or fluorescence *in situ* hybridization for the translocation. Patients with ERMS ($n = 305$), *PAX3-FOXO1* ARMS ($n = 85$), *PAX7-FOXO1* ARMS ($n = 23$), and fusion-negative ARMS ($n = 21$) were evaluated for event-free survival (EFS) and overall survival (OS) at 5 years. Patients with fusion-positive ARMS had an inferior EFS compared with those with fusion-negative ARMS or ERMS. Furthermore, OS was worse for patients with *PAX3-FOXO1* ARMS compared with those with *PAX7-FOXO1* ARMS [12]. Fusion-positive ARMS was also associated with a significant increase in the rate of metastatic disease among older patients with RMS [17]. Additionally, the European Pediatric Soft Tissue Sarcoma Study Group demonstrated that fusion-negative ARMS is indistinguishable from ERMS regarding molecular biology and clinical course [18]. Future COG sarcoma studies will likely incorporate fusion status into risk stratification and treatment allocation.

Presentation and evaluation

Most bladder/prostate (B/P) primary lesions are localized at diagnosis and may present with urinary retention, urgency, frequency, incontinence, or gross hematuria. RMS of the female genital tract can present with an introital mass or vaginal bleeding, and paratesticular RMS typically presents as a painless scrotal mass [19,20].