

Rhabdomyosarcoma - A review

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Abstract: Majority of soft-tissue sarcomas diagnosed in children are rhabdomyosarcomas. Despite the clinical advances, subsets of these patients continue to suffer high levels of morbidity and mortality associated with their disease. This review summarizes recent advances in the understanding of the genetic and molecular basis of RMS and highlights how investigators and clinicians are using this information in an effort to improve outcomes for patients with RMS.

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I. Introduction

Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood.¹ After neuroblastoma and Wilms' tumor, it is the third most common extracranial childhood solid tumor.² Majority of the cases are diagnosed in children below six years of age with remaining cases noted between 10 to 18 year old age group. There is a slight predilection for disease in males.³ The majority of soft-tissue sarcomas diagnosed in children are rhabdomyosarcoma (RMS). Initially there were two major histologic subtypes in the form of an embryonal and an alveolar form which appear to be biologically distinct. Patients with embryonal RMS (ERMS) differ from those with alveolar RMS (ARMS) in terms of age of onset, primary tumor sites, propensity for metastases, and long-term outcome.⁴ Rhabdomyosarcomas are currently categorized by histopathology into distinct subtypes, including embryonal, alveolar, pleomorphic, and sclerosing/spindle cell pathology, which have distinct molecular and clinical correlates.⁵ Important epidemiologic, biologic, and therapeutic differences have been elucidated within the RMS family. Common sites of primary disease include the head and neck region, genitourinary tract, and extremities. In head and neck region, RMS are more common in younger children, with orbital tumors being characterized by embryonal histology in most cases. On the other hand, extremity tumors are more commonly found in adolescents and are more likely to have an alveolar histologic subtype. Nearly 80% of genitourinary tract RMS is embryonal in nature. The botryoid variant of RMS, characterized by a protuberant mass arising from the bladder or vagina, is found almost exclusively in infants.⁶

Genetic makeup

Most cases of RMS appear to be sporadic in nature, but the disease has been associated with familial syndromes such as neurofibromatosis and the Li-Fraumeni syndrome (LFS).⁶

Diller *et al.* found evidence of germline mutations of *p53* in children less than three years of age diagnosed with RMS.⁷ The two histologic subtypes of RMS, embryonal and alveolar, have been found to have distinct genetic alterations that may play a role in the pathogenesis of these tumors. Alveolar RMS has been demonstrated to have a characteristic translocation between the long arm of chromosome 2 and the long arm of chromosome 13.⁸ Embryonal RMS is known to have loss of heterozygosity (LOH) at the 11p15 locus with loss

of maternal genetic information and duplication of paternal genetic information.⁹ Both alveolar and embryonal RMS appear to overproduce IGF II, a growth factor that has been shown to stimulate RMS tumor cell growth.¹⁰ In addition, monoclonal antibody blockade of the receptor for IGF II has been demonstrated to inhibit growth of RMS. It therefore appears likely that IGF II plays a role in the unregulated growth of these tumors.⁶

Clinical Presentation

Soft tissue sarcomas constitute less than 1% of all adult malignancies, and RMS accounts for 3% of all soft tissue sarcomas.¹¹ The presenting signs and symptoms of RMS are variable and are influenced by the site of origin of the primary tumor, the age of the patient, and the presence or absence of metastatic disease. Common sites of primary disease include the head and neck region, the GU tract, and extremities. Head and neck RMS arises in the orbit, parameningeal sites (middle ear, nasal cavity, paranasal sinuses, nasopharynx, and infratemporal fossa), and other sites (scalp, parotid gland, oral cavity, pharynx, thyroid and parathyroid glands, and neck). These tumors are most commonly of the embryonal subtype and rarely spread to regional lymph nodes.¹² Orbital tumors produce proptosis, and, occasionally, ophthalmoplegia. Those arising from parameningeal sites often produce nasal, aural, or sinus obstruction with or without a mucopurulent or sanguinous discharge. Head and neck RMS arising from sites other than the orbit or parameningeal sites often presents as a painless, enlarging mass which tends to remain localized.¹³ GU tract RMS often arises from the bladder or prostate. Bladder tumors produce hematuria and urinary obstruction. Prostate tumors can produce large pelvic masses resulting in urinary frequency or constipation if significant compression of the bladder or intestinal tract occurs.¹⁴ The extremities represent the third most common site of origin of RMS. These tumors typically arise in adolescents who present with a painful mass or swelling with or without erythema of the overlying skin. Nearly 50% of extremity RMS are of the alveolar subtype and are more likely than head and neck RMS to spread to regional lymph nodes and along fascial planes.¹⁵ RMS has high propensity of recurrence even after complete response. Less than 25% of patients have metastatic disease at diagnosis. The lung is the most frequent site of metastasis followed by bone, bone marrow, and lymph nodes. Visceral organ metastases are rare in newly diagnosed patients. Distant failure at these same sites can occur in patients who relapse after receiving systemic therapy.^{6,11}

Investigations

Key components of the evaluation of a suspected RMS include the determination of the extent of primary disease and the presence or absence of metastatic spread.⁶ Laboratory studies should include a complete blood count with differential, serum electrolytes, blood urea nitrogen, and liver function tests, as well as serum creatinine, phosphorus, magnesium, uric acid, and calcium. Bilateral bone marrow aspiration and biopsy of the iliac crests should be obtained even in the absence of abnormal peripheral blood counts or obvious bone metastases. Baseline coagulation studies should be performed, although disseminated intravascular coagulation is uncommon.¹⁶ Radiologic evaluation should include plain radiographs of the primary site as well as a computed tomography (CT) scan of the primary and surrounding structures. Radiologic evaluation for possible metastatic disease should include a chest CT and a technetium-99m diphosphonate bone scan. Adequate tissue for routine pathology as well as cytogenetic and molecular genetic studies should be obtained at the time of biopsy or initial resection.⁶

Prognostic factors

Favorable prognostic factors in RMS are: undetectable distant metastases at diagnosis; favorable anatomic sites (orbit, nonparameningeal head/neck, and genitourinary nonbladder/prostate regions); grossly complete surgical removal of the localized tumor at the time of diagnosis; ERMS/botryoid histology; tumor size ≤ 5 cm; and age older than 1 but younger than 10 years at diagnosis.¹⁷ The presence of regional lymph node disease alters the prognosis for patients with ARMS with outcomes similar to distant metastatic disease, thus suggesting the need for more aggressive therapy for patients with ARMS and regional lymph node disease.¹⁸ The outcome of adolescents and adults with RMS appears to be worse than that of children.¹⁹ Other studies evaluating various clinical parameters, such as tumor diameter versus tumor volume at diagnosis, response to initial chemotherapy, and weight loss during therapy, were not of significant prognostic value.²⁰

Management

Management of RMS involves surgery, radiation therapy, and chemotherapy. Radiation therapy is used to control local microscopic or gross residual disease, whereas systemic chemotherapy plays a role in primary cytoreduction as well as eradication of gross and micrometastatic disease. Complete surgical resection is indicated in clinical scenarios where it will not be mutilating or cosmetically damaging. In cases where complete resection is not feasible, initial biopsy followed by neoadjuvant chemotherapy and definitive local control measures are appropriate. In sites such as the head and neck or pelvis, tumors often cannot be completely

removed with surgery. Radiation therapy can eradicate residual tumor cells in such instances. The dose, duration and timing of radiotherapy depends on the clinical group and the site of disease.¹¹ Early guidelines recommended doses as high as 5,500 to 6,000 cGy for control of the primary tumor site. General radiation therapy guidelines have evolved with sequential intergroup studies. For residual microscopic disease, 4,000-4,500 cGy appears sufficient to achieve local control.⁶ In children with small, critically located tumors (such as head and neck, bladder, prostate, vagina), implants may be considered in an attempt to deliver radiation to a restricted volume of tissue with less scatter to adjacent structures.²¹ Agents with known activity in the treatment of RMS include Vincristine, Actinomycin D, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide. Vincristine, Actinomycin D and Cyclophosphamide has been the gold standard for combination chemotherapy in the treatment of most cases of RMS. Autologous bone marrow transplantation (ABMT) has been utilized in a variety of childhood solid tumors. Till date, the use of ABMT has failed to improve outcome in patients with metastatic RMS.²² The biological behaviour and prognosis of adult RMS is still poorly understood. Localized RMS should therefore be treated aggressively with multidisciplinary approach comprising of surgery, radiation, and chemotherapy with primary aim of cure and maintaining quality of life with emphasis on preservation of function and cosmesis. Radiation therapy definitely improves local control. IRS grouping and complete response after primary therapy were predictors of a better survival. Distant metastasis have dismal prognosis.

Late effects

The type of late effect encountered is largely dependent upon a variety of factors, including anatomic site of tumor involvement, types of chemotherapy received, exposure to RT, and extent of surgical resection.¹⁹ Alkylating agents like cyclophosphamide and ifosfamide have been linked to secondary malignancies and have shown a dose-dependent effect on testicular function and fertility.²³ Other chemotherapy-related toxicities include increased peripheral nervous system toxicity in adolescent patients and increased risk of cardiomyopathy or other cardiac dysfunction in patients treated with anthracycline chemotherapy.²⁴ For adolescents and young adults, these effects may lead to increased risk of physical inactivity or decreased exercise tolerance. Following radiotherapy in the head and neck region, facial growth retardation, xerostomia, dental abnormalities, visual and hearing deficits, and neuroendocrine dysfunction can occur. Jaw dysfunction, due to radiation-induced fibrosis of the temporomandibular joint, has also been reported. For the adolescent and young adult patient, facial asymmetry, growth deficiency, and jaw dysfunction can cause significant cosmetic morbidity and can dramatically impact quality of life. Early intervention with an experienced occupational therapy and speech pathology team can help ameliorate some of the risks for trismus and jaw dysfunction.^{25,26}

II. Conclusion

Clear progress has been made in the understanding of the molecular and genetic causes that are the basis of RMS oncogenesis. As current studies for RMS proceed, strategies for future clinical trials require discussion and planning. Ongoing research using human tumor specimens and animal models will guide development of additional novel agents for RMS.

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