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Building the bridge between rhabdomyosarcoma in children, adolescents and young adults: The road ahead

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Abstract

Rhabdomyosarcoma (RMS) is a rare type of soft tissue sarcoma that mainly affects children, but also occurs in adolescents and (young) adults (AYA). Despite dramatic survival improvements reported by international study groups in children over the past decades, the awareness of a dismal outcome for older patients with RMS has grown. In contrast to the world-wide organization of care for children with RMS, standard care in adults lags behind. A step forward in RMS management for patients of all ages is urgently needed. Both paediatric oncologists and medical oncologists are essential players in development of a concept of RMS care, but bringing two worlds together seems not so easy. This review provides an overview which highlights the similarities and differences in children and adults with RMS. Furthermore, it comes up with a novel concept to overcome the virtual gap between the treatment approach of children and AYA with RMS.

Keywords: Rhabdomyosarcoma; RMS; Age; Adults; Adolescents; AYA; Treatment; Care

1. Introduction

Rhabdomyosarcoma (RMS) is an extremely rare type of soft tissue sarcoma (STS) that is thought to derive from mesenchymal stem cells and shows varying degrees of skeletal muscle differentiation [1]. RMS occurs predominantly in children <7 years, has a second age peak in adolescence, and the incidence subsequently declines in older patients [2,3].

The two main distinguishable histological subtypes that affect both adults and children are embryonal RMS (ERMS) and alveolar RMS (ARMS) [2,4,5]. A third subtype, pleomorphic RMS occurs almost exclusively in adults, and there is growing evidence that this tumour type should be biologically considered rather a distinct type of adulthood soft tissue sarcoma than a subtype of RMS [2,6]. Therefore, this subtype is beyond the scope of this review considering age in relation to RMS.

Over the past decades, the awareness of a dismal outcome for RMS patients with increasing age has grown. Improvement of survival rates in children over the past decades resulted in a current 5-year survival rate of approximately 70–80% for children with RMS [7–9], while survival rates in adults are not exceeding 56% (range 21–56%) [2,4,5,10–18]. Moreover, patients <1 year and ≥10 years fare worse than patients 1–9 years in paediatric study populations [19,20]. Whether this effect of age on outcome is attributable to differences in treatment approach or in tumour biology is unknown.

The centralization of cancer care in specialized childhood oncology centres, together with the standardized treatment of RMS within comprehensive trials, is considered the principal factor that is responsible for the gain in RMS survival in children in the western countries [7–9,21–23]. In contrast to this centralization of RMS treatment in children, the relative rarity of RMS in (young) adults in the burden of all adult-type cancers led to dispersion of patients with RMS in adult oncology centres. Also, the relative lack of clinical trial participation in adolescents and (young) adults with sarcoma has been proposed as one of the major reasons of the consequential lack of survival improvement [24].

RMS requires aggressive multimodality treatment which – as many childhood cancers – results in a significant rate of acute toxicities and long-term effects [25]. The "traditional" VAC/VAI-based (vincristine, D-actinomycin and cyclophosphamide or ifosfamide) regimens developed in the early seventies underwent only minor modifications over time, primarily resulting in improvements for patients with low-risk disease. Unfortunately, survival for high-risk patients (e.g. patients with irresectable ARMS at unfavourable sites, distant metastatic disease, and recurrent disease) remains poor, not exceeding 50% [19,26–30]. Along with the increase of survival rates in the young population of RMS patients, prevention of long-term 'costs' as late organ toxicity, infertility and second tumours becomes more important. Although there is an urgent need for new – less harmful – therapeutic options, an important limitation in childhood RMS trials conducted over the past decades is the relative lack of introduction of new (targeted) therapies.

Although experts in paediatric RMS treatment have proposed that treatment of adults should be based on the current paediatric treatment protocols [5], bringing the two worlds together seems not as easy as that. This review provides an overview highlighting the similarities and differences in epidemiology, tumour biology, diagnosis, treatment approach, and accrual to clinical trials with new agents together with a concept to overcome the existing virtual separation line between treatment approach in children, adolescents and (young) adults (AYA) with RMS.