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Review

Biology and treatment of renal tumours in childhood

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Abstract In Europe, almost 1000 children are diagnosed with a malignant renal tumour each year. The vast majority of cases are nephroblastoma, also known as Wilms' tumour (WT). Most children are treated according to *Société Internationale d'Oncologie Pédiatrique* Renal Tumour Study Group (SIOP-RTSG) protocols with pre-operative chemotherapy, surgery, and post-operative treatment dependent on stage and histology. Overall survival approaches 90%, but a subgroup of WT, with high-risk histology and/or relapsed disease, still have a much poorer prognosis. Outcome is similarly poor for the rare non-WT, particularly for malignant rhabdoid tumour of the kidney, metastatic clear cell sarcoma of the kidney (CCSK), and metastatic renal cell carcinoma (RCC).

Improving outcome and long-term quality of life requires more accurate risk stratification through biological insights. Biomarkers are also needed to signpost potential targeted therapies for high-risk subgroups. Our understanding of Wilms' tumourigenesis is evolving and several signalling pathways, microRNA processing and epigenetics are now known to play pivotal roles. Most rhabdoid tumours display somatic and/or germline mutations in the *SMARCB1* gene, whereas CCSK and paediatric RCC reveal a more varied genetic basis, including characteristic translocations. Conducting early-phase trials of targeted therapies is challenging due to the scarcity of patients with refractory or relapsed disease, the rapid progression of relapse and the genetic heterogeneity of the tumours with a low prevalence of individual somatic mutations. A further consideration in improving population survival rates is the geographical variation in outcomes across Europe.

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This review provides a comprehensive overview of the current biological knowledge of childhood renal tumours alongside the progress achieved through international collaboration. Ongoing collaboration is needed to ensure consistency of outcomes through standardised diagnostics and treatment and incorporation of biomarker research. Together, these objectives constitute the rationale for the forthcoming SIOP-RTSG 'UMBRELLA' study.

1. Introduction

Childhood renal tumours account for around 7% of all childhood cancers. The majority of cases (90%) are Wilms' tumour (WT or nephroblastoma), with an annual incidence of approximately 1 in 100,000 children [1]. Thus, a large European country, such as Germany, will experience around 100 new cases a year, whereas a small country like Denmark diagnose less than 10 cases annually.

The median age at diagnosis of WT is 3 years but bilateral cases and those associated with congenital syndromes occur earlier. The most common presentation is that of an abdominal mass or swelling, and children are usually otherwise clinically well [2]. Other symptoms include abdominal pain, haematuria, fever, and symptoms related to hypertension. About 10% of WT have haematogenous spread, most commonly to the lungs (85%), liver (10%) and only very rarely to the bones and brain [1].

WT may occur as a part of a genetic predisposition syndrome in 5–10% of cases. The more common phenotypes include WAGR (WT, aniridia, genitourinary anomalies, and mental retardation), Denys–Drash syndrome, Beckwith–Wiedemann syndrome, asymmetric overgrowth, or family history of WT [3]. If predisposition is suspected prior to the diagnosis of WT, the tumour may be detected through a screening programme.

The most frequently occurring non-Wilms' renal tumours (non-WT) include clear cell sarcoma of the kidney (CCSK) with an identical age distribution to WT, malignant rhabdoid tumour of the kidney (MRTK) with a peak incidence between the age of 10–18 months and renal cell carcinoma (RCC), which usually occurs in adolescence. Altogether, CCSK and MRTK comprise about 3–5% of all primary renal tumours in children, whereas RCC accounts for around 1% (Fig. 1) [4]. Other types of malignant renal tumours, such as anaplastic sarcoma and primitive neuroectodermal tumour of the kidney, are extremely rare. Overall non-WT have a poorer outcome than WT. Relatively benign renal tumours, such as congenital mesoblastic nephroma, are mainly diagnosed in newborns or during foetal anomaly scanning, and cure can usually be achieved with surgery alone.

There are two different approaches to the initial management of renal tumours in childhood. Most children in Europe are treated with pre-operative chemotherapy, according to the *Société Internationale d'Oncologie Pédiatrique* Renal Tumour Study Group (SIOP-RTSG) protocols. In North America, patients are treated with upfront surgery prior to administration of chemotherapy, as per the National Wilms' Tumour Study/Children's Oncology Group (COG) protocols. Although the SIOP and COG strategies differ in their upfront treatment approach, they have a similar overall survival (OS) of nearly 90% [5,6].

Despite the excellent prognosis for most children with WT, just under 15% of patients will relapse, usually within 2 years of diagnosis [5]. Furthermore, a proportion of patients will experience severe early and late treatment-related adverse events, e.g. cardiotoxicity secondary to doxorubicin (DOX) or radiotherapy-induced organ dysfunction, musculoskeletal abnormalities, infertility and secondary malignancies [7,8]. The current aims of treatment optimisation are to standardise diagnosis, to improve risk stratification, to minimise side-effects of treatment and to improve relapse monitoring according to clinical, molecular, histopathological and imaging data.

The aim of this review is to provide the clinician with an overview of tumour biology, current treatment and research into more effective therapies for subgroups of paediatric renal tumours. Focus will be on WT, due to its relatively higher incidence, but other renal tumours will be discussed within the context of the SIOP-RTSG strategy.

2. Biology of sporadic WT and predisposition syndromes

2.1. Genetics

Despite our incomplete understanding of the pathogenesis of WT, there is increasing evidence that several signalling pathways, microRNA processing, and epigenetics all play pivotal roles (Table 1). In general, WT represent a genetically heterogeneous group, displaying a low prevalence of known somatic alterations and a high degree of intra-tumoural heterogeneity [9].

The first WT-related gene to be characterised was *WT1*, a zinc finger DNA-binding transcription factor,