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REVIEW

Biology and treatment of Wilms' tumours in childhood

Biologie et traitement des tumeurs de Wilms de l'enfant

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Summary Each year, approximately 1/10,000 children worldwide will be diagnosed with a renal tumour, with almost four-fold variation by ethnicity and geography. Wilms' tumour (WT) or nephroblastoma is by far the most common subgroup, accounting for nearly 90% of renal tumours and 6% of all childhood cancers. In Europe, most cases are managed with neoadjuvant chemotherapy prior to surgery, whereas in North America, children usually undergo immediate surgery. Both groups use stage of disease and histology to risk stratify and dictate postoperative treatment. Irrespective of protocol, almost 90% of WT patients survive. For the non-WT, prognosis is more variable and treatment is usually more intensive. Improvements in risk stratification and relapse monitoring are needed, as approximately half of the 15% of children who relapse do not survive. Several molecular biomarkers with prognostic significance have been identified but most await validation prior to clinical use. As many patients experience severe acute or long-term treatment-related toxicity, a further priority is to identify children for whom a reduction in treatment would not compromise survival. Increased understanding of WT biology, and the advent of cell and animal models for drug testing, has guided development of targeted therapies. Translating these preclinical results into a clinical difference for high-risk patients is challenging, due to the small numbers of children suitable for early phase trials, the genetic heterogeneity of WT and the low prevalence of known somatic mutations. A remaining challenge is the geographical variation in survival seen both within Europe and more

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dramatically across other continents, such as Africa. To improve these inequalities, the current priority is to standardise diagnostics, monitoring and treatment through international collaboration in well-designed prospective clinical observational studies and trials.

MOTS CLÉS
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Tumeur de Wilms ;
Génétique ;
Épigénétique ;
Thérapie ciblée

Résumé Chaque année, un néphroblastome ou tumeur de Wilms (WT) va être diagnostiqué chez 1/10 000 enfants dans le monde. WT est la tumeur rénale la plus fréquente de l'enfant et représente 7 % de l'ensemble des cancers pédiatriques. En Europe, la plupart des patients sont traités selon les recommandations de la Société internationale d'oncologie pédiatrique Renal Tumours Study Group (SIOP-RTSG) avec chimiothérapie néo-adjuvante avant chirurgie. En Amérique du Nord, les patients sont opérés d'emblée au diagnostic selon les recommandations du Children's Oncology Group (COG). Le stade de la maladie et le type histologique de la tumeur sont utilisés par les deux sociétés pour stratifier le risque tumoral et déterminer le traitement postopératoire. La survie globale est proche de 90 %, quel que soit le protocole utilisé. Malgré cet excellent pronostic, environ 15 % des patients rechutent, rendant nécessaire l'amélioration de la stratification du risque tumoral et la prise en charge de la rechute. La moitié des patients qui rechutent ne seront pas en rémission secondaire. Récemment, des marqueurs biologiques ont été identifiés mais nécessitent d'être validés avant leur utilisation en pratique clinique. Une partie des patients présente une toxicité sévère post-traitement, rendant prioritaire l'amélioration de la qualité de vie pour les survivants. Les marqueurs biologiques pourraient être une aide dans l'identification des patients pour lesquels une réduction du traitement permettrait de limiter les effets secondaires sans diminuer les chances de survie. L'amélioration de la connaissance biologique des néphroblastomes et l'apparition de modèles cellulaires ou animaux pour tester les nouveaux médicaments ont conduit au développement de thérapies ciblées. Cependant, les résultats encourageants de la recherche biologique n'ont pas encore trouvés leur traduction en clinique pour les patients de haut-risque, ce qui pourrait s'expliquer par l'hétérogénéité génétique du néphroblastome et la faible prévalence des mutations somatiques connues. La survie des patients atteints de néphroblastome est hétérogène en Europe et extrêmement faible dans le continent africain. Pour améliorer ces inégalités, la priorité actuelle est de standardiser le diagnostic, la prise en charge et le traitement grâce aux collaborations internationales au-delà des frontières.

Introduction

Childhood renal tumours account for around 7% of all childhood cancers. The majority of cases (90%) are Wilms' tumour (WT) or nephroblastoma, which will develop in about 1/100,000 children under the age of 15 years [1]. The remaining 10% of cases are collectively known as the non-Wilms' renal tumours and most frequently include clear cell sarcoma of the kidney, malignant rhabdoid tumour of the kidney and renal cell carcinoma (Fig. 1).

WT occurs sporadically in almost 90% of cases and the median age of diagnosis is 3 years (Fig. 2). Bilateral tumours and those associated with congenital syndromes occur earlier. Three main groups of children are predisposed to developing WT, those with isolated urogenital malformations (UGM), those with UGM as part of a syndrome (e.g. Denys-Drash, WAGR) and those with Beckwith-Wiedemann and related asymmetrical overgrowth syndromes [2].

There are also familial WT pedigrees, accounting for 1—2% of cases. Children with a known significant predisposition (> 5% risk) are advised to be enrolled in screening programmes [3].

Children with WT are usually clinically well and the most common presentation is with an abdominal mass or swelling. Other symptoms can include abdominal pain, haematuria, fever, and symptoms related to hypertension. At diagnosis, around 10% of patients will have disseminated disease, with the lungs (~85%) and liver (~10%) as the most common sites for haematogenous spread. Tumour spread to the bones or brain is very rare [1].

There are two different approaches to the initial treatment of WT. Most children in Europe are managed according to Société internationale d'oncologie pédiatrique (SIOP) protocols and receive preoperative chemotherapy (Fig. 3). In most European countries, patients with the suspected imaging findings of WT start preoperative chemotherapy without a confirmatory biopsy. In North America, patients undergo nephrectomy prior to chemotherapy, as per the Children's Oncology Group (COG). Stage of disease and histology are used by both groups to risk stratify and dictate