

New risk classification is necessary in the treatment of Wilms tumor

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Abstract: The National Wilms Tumor Group (NWTG) presented the clinicopathological findings predicting relapse in children with stage III favorable-histology (FH) Wilms tumor (WT) treated in the NWTG-5 study. They reported that lymph node involvement and a microscopic residual tumor were highly predictive of the EFS and OS, and concluded that patients with different stage III criteria may receive different therapies. These data suggest that the current risk classification of WT is not satisfactory. Like other pediatric tumors, such as neuroblastoma and rhabdomyosarcoma, more systemic and detailed risk classification for WT should be established using various clinical and biological markers. In the previous therapeutic protocols for WT, no biological marker was used for risk classification. Therefore, it is important to identify effective biological markers related to the prognosis of WT. The presence of LOH at 1p and 16q was associated with a worse EFS and OS, and was used for risk classification to choose the treatment regimens used in the recent COG clinical trials. There are some candidate prognostic factors that can be used in the future risk classification of WT, such as the methylation status of RASSF1A. A worldwide cooperative study should be conducted in the future to confirm whether these factors are useful in the risk classification. The goal of treatment for WT is to identify approaches that provide excellent outcomes for children with low-risk tumors without the need for chemotherapy or XRT. Conversely, more aggressive therapy may be used for children with high-risk tumors in an effort to improve their survival. To meet these goals, a new effective risk classification for WT should be established via collaborative clinical trials.

Keywords: Wilms tumor (WT); risk classification; treatment

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Wilms tumor (WT), or nephroblastoma, is the most common malignant renal tumor in childhood. The survival of patients with WT has improved dramatically to almost 90% in the modern era (1). The improvements in survival have occurred as a result of advances in multimodality treatments, including surgical management, irradiation and chemotherapy, established in clinical trials and studies conducted by many national and international cooperative groups. In the USA and Canada, the National Wilms Tumor Study (NWTG) group, now part of the Children's Oncology Group (COG), has studied the treatments and outcomes of children with WT since 1969 (2). In Europe, international cooperative studies have been conducted

predominantly by the International Society of Paediatric Oncology (SIOP) since 1971 (3). The goals of these groups are to increase the cure rates while minimizing morbidity.

In the NWTG studies, primary surgical resection of the tumor was the initial treatment of most children, whereas in the SIOP studies, chemotherapy was the initial treatment. Both approaches have distinct advantages and disadvantages. The benefit of the NWTG approach is that it enables accurate assessment of the histology, extent and molecular biological features of the untreated tumor. However, resection of large tumors sometimes results in intraoperative tumor spillage, which increases the risk of local abdominal relapse and a subsequent poor outcome (4).

These tumors are included in Stage III disease.

In a recent issue of the *Journal of Clinical Oncology* (JCO), Ehrlich *et al.* presented the clinicopathological findings of the National Wilms Tumor Group and the COG with regard to predicting relapse in children with stage III favorable-histology (FH) Wilms tumor treated in the NWTS-5 study (5). They reported that lymph node (LN) involvement and a microscopic residual tumor are the stage III criteria highly predictive of the EFS and OS for patients with stage III FHWT, and concluded that in future studies, patients with different stage III criteria may receive different therapies. These data suggest that the current risk classification of WT is not satisfactory to treat advanced WTs, so that a new risk classification system should be created.

The current therapeutic strategy for WT is based only on the post-surgical staging and histological findings. On the other hand, for other major pediatric malignancies, such as neuroblastoma and rhabdomyosarcoma, the therapeutic strategy is based on a more systematic and detailed risk classification using various clinical and biological risk factors (6,7). For example, the risk classification of the International Neuroblastoma Risk Group (INRG) consists of the INRG stage, age, histology, tumor differentiation, MYCN amplification, 11q aberration and ploidy. The patients are divided into four risk groups; very low, low, intermediate and high, and are treated with different intensity protocols (6). The COG-STS Risk Stratification consists of the combination of stage, group, histology and tumor site, and the patients with rhabdomyosarcoma are divided into four risk groups; low risk 1, low risk 2, intermediate risk and high risk (7). Chemotherapy and radiation therapy are performed according to the risk groups. Like these tumors, a more systematic and detailed risk classification for WT should be established using various clinical and biological markers.

In the previous therapeutic protocols for WT, no biological marker was used for risk classification. Therefore, it is important to identify effective biological markers related to the prognosis of WT. To date, some biological markers have been reported that were related to the prognosis of WT. For example, Grundy *et al.* showed that the presence of LOH at 1p and 16q was associated with a worse EFS and OS (8). In the recent COG clinical trials for WT, LOH at 1p and 16q was used for risk classification to choose the treatment regimens. Ohshima *et al.* reported that methylation of the RASSF1A promoter is predictive of a poor outcome among patients with Wilms tumor,

and concluded that the methylation status of RASSF1A might be a novel biomarker to predict the outcome of WT patients (9). Kinoshita *et al.* reported that the patients with blastemal predominant tumors demonstrated a significantly worse prognosis compared with those who had other tumor subtypes. The treatment strategy for the blastemal predominant category should therefore be distinguished from that of the other favorable subtypes (10). The last two studies were performed using Japanese cases of WT. Therefore, the Japanese Wilms Study Group (JWiTS) plans to confirm that these factors are useful to predict the prognosis, and to identify which factors are most critical to establish the risk classification in the next clinical trials for WT.

In the NWTS study for stage III FHWT, Ehrlich *et al.* analyzed 717 patients with local stage III renal tumors enrolled in the NWTS-5 trial. To discover the new prognostic parameter(s) useful to create a risk classification of WT, it is necessary to analyze a large number of cases. Since the incidence of WT is much lower than that of most adult tumors, only about 50 cases have been registered in the JWiTS. Therefore, it is impossible to collect hundreds of patients within a reasonable time frame, even in a nationwide study. Therefore, a worldwide cooperative study should be conducted in the future. For example, in the study of hepatoblastoma, four nation-wide cooperative groups, the COG in the USA, SIOPEL in Europe, GPOH in Germany and JPLT in Japan joined forces to create a world-wide cooperative group, the CHIC (Children's Hepatic Tumor International Collaboration) in 2011 (11). A similar international cooperative study group should be established in the field of WT in the near future by the COG, SIOP, JWiTS and other study groups to create the new risk classification and treatment strategy.

The missions of the cooperative group should be: to develop an international database of patients with WT; to identify prognostic factors at diagnosis, independent of the initial therapeutic approach; to develop risk classification criteria to be used in the development of future therapeutic trials; to determine the treatment parameters impacting the outcomes of children with WT and finally, to perform world-wide cooperative clinical trials to develop a novel treatment for WT.

The major goal of the treatment of WT is to identify approaches that maintain excellent outcomes for children with low-risk tumors without the use of anthracycline chemotherapy or XRT, or in some cases, without chemotherapy at all. Conversely, therapy may be intensified

for children with high-risk tumors in an effort to improve their survival. To achieve these goals, new effective risk classification for WT should be established as soon as possible via collaborative clinical studies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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