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Current treatment for Wilms tumor: COG and SIOP standards

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ABSTRACT

Background Wilms tumor (WT) is the most common renal malignant tumor in children. It occurs primarily at preschool age. The purpose of this review is to present current standards of diagnosis and treatment of WT around the world.

Data sources All the recent literature on diagnosis and treatment of WT were searched and reviewed.

Results Most cases with WT are sporadic. The current survival in patients with WT is high (90%). Involvement of mutidisciplinary collaborative groups in the diagnosis and treatment of WT. National Wilms Tumor Study Group (NWTSG)/Children's Oncology Group (COG) and The International Society of Paediatric Oncology (SIOP) are two major guidelines used for the current management of WT worldwide. The major difference exists in the two guidelines is the timing of surgery: SIOP recommends using preoperative chemotherapy, and NWTSG/COG prefers using primary surgery before any adjuvant treatments.

Conclusions Most patients with WT have good overall survival outcomes. Further studies should be highlighted on how to use chemotherapy and radiotherapy under more accurate risk-stratified strategies. Surgeons must be more focusing on how to maximize preoperative and postoperative treatment possibilities for achieving optimal results of patients with WT.

INTRODUCTION

Wilms tumor (WT; nephroblastoma) is the most common malignant renal tumor in children, accounting for about 85% of pediatric renal tumors.[1 2] The incidence of WT is about 1 per 10 000 children in Europe and North America. The incidence is much lower (3–4 per 10 000 children) in Asian countries.[3]

US National Wilms Tumor Study revealed that the median onset age is 38 months, and girls had diseased onset 6 months older than boys. In most populations, no gender difference has been found in cases with WT; however, females are more likely to have WT than males (combined M:F=1:4) in some Asian countries.[3]

Although WT can be inherited at autosomal dominant mode, most patients are sporadic.[4] Children with WAGR syndrome, Beckwith-Wiedemann syndrome, Denys-Drash syndrome, and Edwards or Perlman syndromes, may be more likely to have WT.[5] Studies on the etiology of these syndromes have shown a link between the occurrence of WT and disorders of chromosome 11 genes, such as *WT1* and *WT2*.[6]

The current survival in patients with WT is high (90%). Mutidisciplinary collaborative groups are involved in the diagnosis and treatment of WT. The NWTSG/COG[7] and SIOP[8] guidelines are the two major guidelines used for the current management of WT worldwide. The major difference exists in the two guidelines is the timing of surgery: SIOP recommends using preoperative chemotherapy and NWTSG/COG prefers using primary surgery before any adjuvant treatments. Large-scale clinical trials have found that the two treatment strategies have their own advantages and disadvantages.[9]

The purpose of this review is to present the similarities and differences of diagnosis and treatment strategies of WT used worldwide mainly based on COG and SIOP guidelines.

TREATMENT OPTIONS FOR WT

Surgery, chemotherapy, and radiotherapy comprise the treatment modalities for WT. NWTSG/COG and SIOP guidelines provide two different strategies for the initial treatment of WT in children. NWTSG/COG recommends patients undergo surgery before chemotherapy. North America commonly adopts NWTSG/COG guideline. However, most children in European countries are treated with preoperative chemotherapy based on the SIOP guideline. Different treatment strategies are based on different staging systems. The COG staging system relies on pathology analysis from a primary nephrectomy in most cases. The SIOP staging is based on the results after preoperative chemotherapy.[10] Though with so remarkable differences, the overall survival rate for the patients treated by the two guidelines is similar over 90%.[11]

DIFFERENCES BETWEEN THE COG AND SIOP TREATMENT PROTOCOLS FOR WT

Surgery

1. The COG recommends primary surgery before chemotherapy. For resectable tumors, preoperative biopsy or intraoperative biopsy is also not performed.[7] Radical nephrectomy and lymph node sampling are done through a transabdominal incision.[7] En bloc resection can be done to avoid tumor spill.[12] Resection of the primary renal tumor should be considered even if in a stage IV disease (usually pulmonary metastases); renal-sparing surgery is not recommended by COG guideline, except when children having a solitary kidney, with predisposition to bilateral tumors, horseshoe kidney or in infants with Denys-Drash or Frasier syndrome (to delay the need for dialysis).[13–15]
2. The SIOP recommends radical tumor nephrectomy performed after preoperative chemotherapy. Lymph node sampling is important for staging, and sampling seven locoregional lymph nodes is necessary for accurate staging.[8] Nephron-sparing surgery is used for non-syndromic unilateral WTs under following conditions such as with small tumor volume (<300 mL) and the expectation of a substantial remnant kidney function in patients who never had lymph node involvement.[8]

Chemotherapy

Preoperative chemotherapy

1. The COG guideline recommends surgery as the initial therapy before chemotherapy. Preoperative chemotherapy is only indicated under the following conditions[1 16]: with inoperable WT; with a solitary kidney; with synchronous bilateral WT; tumor thrombus in the inferior vena cava extending above the level of the hepatic veins; tumor involving contiguous structures whereby removing the kidney tumor requiring removal of the other organs, such as spleen, pancreas, or colon and with extensive pulmonary metastases. Preoperative chemotherapy by the COG has four regimes (table 1). The agents for chemotherapy commonly are doxorubicin plus dactinomycin and vincristine; if with anaplastic histology, chemotherapy then includes regimen I (table 1).
2. The SIOP guideline recommends preoperative chemotherapy for all patients after diagnosis.[8] For patients with unilateral localized tumor, 4-week pretreatment with vincristine (weekly) and dactinomycin (biweekly) is given; for patients with bilateral tumors, vincristine–dactinomycin for no longer than 9–12 weeks is recommended (doxorubicin is added for reinforcement in some patients); for patients with metastasis, a regimen including 6 weeks of vincristine–dactinomycin (like above) and doxorubicine on weeks 1 and 5 is given.[8]

Table 1 The Children's Oncology Group standard chemotherapy regimens for Wilms tumor[8]

Regimen name	Regimen description
Regimen EE-4A	Vincristine, dactinomycin ×18 weeks postnephrectomy
Regimen DD-4A	Vincristine, dactinomycin, doxorubicin ×24 weeks; baseline nephrectomy or biopsy with subsequent nephrectomy
Regimen I	Vincristine, doxorubicin, cyclophosphamide, etoposide ×24 weeks postnephrectomy
Regimen M	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide with subsequent radiation therapy

Postoperative chemotherapy

1. The COG recommends postoperative chemotherapy routinely used in all patients with WT except those at a very low risk: younger than 2 years at diagnosis with stage I favorable histology tumor weighing <550 g was sampled and confirmed negative lymph nodes.[7]
2. The SIOP recommends postoperative chemotherapy in all patients with WT except those with stage I low-risk tumor.[8]

Postoperative radiation

1. The COG recommends postoperative radiation used to the tumor bed for all patients with tumor stage III.[7]
2. The SIOP recommends whole-abdominal radiotherapy for patients with intermediate-risk or high-risk histology tumors with major preoperative or intraoperative tumor rupture, or macroscopic peritoneal deposits; pulmonary radiotherapy is indicated for lung metastases lacking complete response until postoperative week 10.[8] Patients with a complete response after induction chemotherapy with or without surgery do not need pulmonary radiotherapy. Patients with viable metastases at surgery or high-risk histology require pulmonary radiotherapy. Whole-lung irradiation is recommended for patients who did not receive lung irradiation during the first-line treatment, irrespective of histology.[8]

Treatment under the following conditions

Stage V WT

Both the COG and SIOP recommends preoperative chemotherapy and resection for bilateral WT. Bilateral renal-sparing surgery can be done in patients with synchronous bilateral WT. Renal parenchyma sparing may help preserve the renal function in these children. Renal transplantation is recommended and is usually delayed until 1–2 years without evidence of relapse.[17] The SIOP also suggests that preoperative chemotherapy should be limited to not longer than 12 weeks, with time intervals for evaluation fixed to 6 weeks.[8]

Infants with WT

The SIOP recommends primary nephrectomy for infants younger than 6 months (182 days) unless tumors are

judged not suitable to immediate nephrectomy.[8] Postoperative chemotherapy is similar for infants to that in older patients undergoing direct nephrectomy, with drug doses adjusting according to age and body weight.[18]

Recurrent WT

The recurrence rate in patients with familial hypercholesterolemia WT is about 15% and patients with anaplastic histology is about 50%.[19] The leading locations of relapse are the lung, abdomen/flank and liver. Historically, the mortality rate of patients with recurrent favorable histology, WT ranges from 25% to 40%. Outcome has recently improved to 60% in patients with relapse.[20]

1. The COG guideline has categorized the patients with recurrent WT into three risk groups: standard risk, high risk and very high risk.[1] For standard-risk relapsed WTs, surgery is given when feasible; radiation therapy and chemotherapy (alternating courses of vincristine/doxorubicin/cyclophosphamide and etoposide/cyclophosphamide) are given. For patients with high risk and very high risk relapsed WTs, chemotherapy (alternating courses of cyclophosphamide/etoposide and carboplatin/etoposide), surgery, and/or radiation therapy and hematopoietic stem cell transplantation are recommended.[7]
2. The SIOP classifies the patients with recurrent WT into group AA, group BB and group CC.[8] For patients in group AA, only vincristine and/or dactinomycin (no radiotherapy) is adopted as the first-line treatment, containing four drugs in the regime (combinations of doxorubicin and/or cyclophosphamide and carboplatin and/or etoposide); for group BB, an intensive reinduction regimen is given (including the combination of etoposide and carboplatin with either ifosfamide or cyclophosphamide), followed by either high-dose melphalan and autologous stem cell rescue or two further reinduction courses;[21] for group CC, camptothecins (irinotecan or topotecan) or novel compounds are recommended.

Our center's experience

Currently, the standards for treatment of WT in China are not consistent. The treatment strategies adopted by most units are similar to the COG guidelines. In our center, we adopted both COG and SIOP guidelines. The diagnosis and treatment procedure of our center is to first evaluate the tumor, then conduct surgery for the patients with safe first-stage operation and develop further treatment plan according to the postoperative histology analysis and staging. Staging, evaluation and treatment strategy were undertaken according to the COG guideline. For cases with high stages, those with huge tumors, had liquefied necrotic area and those at risk of intraoperative spill, preoperative chemotherapy is given after biopsy. For the patients not responsive to preoperative chemotherapy, transarterial chemoembolization is given before surgery. Postoperative chemotherapy and radiation therapy are based on the SIOP guideline. The difference from SIOP guideline is that in our center, all children must have histological examination results before chemotherapy, that is to say, for children who cannot receive one-stage surgery, histological examination results must be obtained through biopsy before chemotherapy, regardless of the age of the children.

CONCLUSIONS

Most patients with WT have good overall survival outcomes. Further studies should be highlighted on how to use chemotherapy and radiotherapy under more accurate risk-stratified strategies and decrease the late effects of surgery. Surgeons must be more focusing on how to maximize preoperative and postoperative treatment possibilities for achieving optimal results of patients with WT.

Contributors MJL proposed the study, wrote the first draft and is responsible for the overall content as guarantor. WJ contributed to the planning of the work described in the article. DXT, WZG, JQM and QS contributed to the design and interpretation of the study and further drafts.

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