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Wilms' Tumour
Optimal Treatment Strategies

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Contents

Abstract

Wilms' tumour (WT) is the most common renal tumour in children. Much progress has been made in the management of patients with this malignancy over the last 3 decades. The improved outcome has mainly resulted from the availability of cooperative national and international trials involving the National Wilms' Tumour Study Group (NWTS) and the International Society of Paediatric Oncology (SIOP). These groups have focused on optimising postoperative (NWTS) and preoperative (SIOP) therapy, respectively.

The early studies by the NWTS (1 and 2) identified the following separate subgroups of patients (based on age and stage) that benefited either from the addition of irradiation to postoperative chemotherapy or from combination chemotherapy as opposed to single agents, and those patients who did not benefit from prolonged chemotherapy administration. Additionally, these studies identified histologic features associated with a poor outcome.

The more recent studies by NWTS (3 and 4) concentrated on reducing treatment for low risk patients to avoid long term sequelae while intensifying therapy for patients with high risk features, such as those with unfavourable histology and/or metastatic disease.

The early SIOP trials (1, 2 and 5) concluded that patients treated with preoperative therapy (chemotherapy alone or combined with irradiation) experienced fewer intraoperative tumour ruptures compared with patients who had immediate surgery. However, preoperative chemotherapy preserved tumour histology at surgical exploration better than preoperative irradiation.

The more recent SIOP trials (6, 9 and 93-01) have compared the use of different preoperative treatment regimens as well as the intensity and duration of postoperative therapy based on prognostic features (stage and histology). These studies have also identified groups benefiting from the addition of irradiation and/or the use of a third chemotherapeutic agent.

Bilateral WT occurs in a small percentage of patients and treatment strategies, although efficacious, are limited by the need to maximise residual renal parenchyma. Recurrent WT occurs in 10 to 15% of cases and although a proportion of patients are curable, the overall outcome is poor with 3-year survival being in the range of 30%. There are several ongoing studies utilising new drug combinations (carboplatin, cyclophosphamide and etoposide) attempting to improve the outcome for these patients.

Overall, the majority of patients with WT will be cured and become long term survivors. Cooperative group studies continue to address the issue of minimising long term morbidity for low risk patients while maximising outcome for high risk patients.

1. Background

Although first described in 1814, Wilms' tumour (WT) bears the name of the German surgeon Carl Max Wilhelm Wilms who described a patient with bilateral renal tumours, or nephroblastomas, in 1899.[1] Since that time, much has been learned about renal tumours in terms of histology, natural history, prognosis and treatment.

WT represents the most common renal tumour in children, accounting for about 6 to 7% of childhood malignancies.[2] The median age at diagnosis is 3 to 5 years and although it can occur in adults, it is rare in patients older than 10 years of age. The most common complaint in patients with WT is an asymptomatic abdominal mass, usually found by a parent or caregiver. However, a smaller proportion of patients can present with hypertension or haematuria.[3]

As with most other childhood malignancies, the prognosis for patients with WT was poor with the use of surgery and/or radiotherapy.[4] With the advent of multiagent chemotherapy, the outcome for these patients dramatically improved. This improved outcome has only occurred through the development of randomised national and international trials, most commonly in the cooperative group setting. These types of studies accrue large numbers of patients and are not feasible in single institutions because of the small number of patients available for study. The management of WT patients has mainly occurred by enrolment in 2 large cooperative groups: The National Wilms' Tumour Study (NWTS) group started in 1969 and is based in the US, while the International Society of Paediatric Oncology (SIOP) started in 1971 and is based in Europe. Although both these groups have different philosophies and approaches to therapy, the current 2-year survival for patients treated by either group are very similar and in the range of 90%.[5,6]

2. Staging

As with most childhood malignancies, staging is an essential part of the management of WT patients. Staging defines the extent of disease at the time of diagnosis through the use of diagnostic imaging studies and surgical exploration. It is also used to direct therapy, since patients with more extensive disease and presumably a higher risk of recurrence receive more aggressive therapy, whereas patients with localised disease receive less therapy. The staging system most commonly used for WT is a surgicopathological system which takes into account the imaging studies along with the surgical findings.[7] It remains the most important predictor of outcome and is defined by the

Table I. Staging system for Wilms' tumour[7]

Stage I	Tumour limited to the kidney and completely excised
Stage II	Tumour extends beyond the kidney but is completely excised. There is regional extension of the tumour, i.e. penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substances are infiltrated or contain tumour thrombus. The tumour may have been biopsied or there has been local spillage of tumour confined to the flank. There is no residual tumour apparent at or beyond the margins of excision
Stage III	Residual nonhaematogenous tumour confined to abdomen
	Any one or more of the following can occur:
	lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond
	there has been diffuse peritoneal contamination by tumour such as spillage of tumour beyond the flank before or during surgery; or by tumour growth that has penetrated through the peritoneal surface
	implants are found on the peritoneal surfaces
	the tumour extends beyond the surgical margins either microscopically or grossly
	the tumour is not completely excisable because of local infiltration into vital structures
Stage IV	Haematogenous metastases
	Deposits beyond stage III; e.g. lung, liver, bone and brain
Stage V	Bilateral renal involvement at diagnosis
	An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy

extent of disease within and beyond the kidney (table I). In earlier trials by the cooperative groups, the term 'group' was used to indicate what is now known as 'stage'. For the purposes of this article they can be considered equivalent, e.g. group I can be considered the same as stage I.

Throughout this article we discuss the management of patients with WT by both the NWTS and the SIOP. We also discuss the management of patients with WT by other, smaller, cooperative groups and compare the outcome to that of patients treated by both the NWTS and SIOP. We end by describing the optimal management for patients with WT and discussing the treatment alternatives for patients with bilateral WT and those with recurrent disease.

3. Management

3.1 National Wilms' Tumour Study Group

The staging for patients with WT managed by the NWTS group is a surgicopathological staging requiring prechemotherapy tissue diagnosis. The first NWTS was conducted between 1969 and 1974. The main objectives were to determine whether routine postoperative radiotherapy was necessary in children with completely resected tumours; to establish whether dactinomycin (actinomycin D, DAM), vincristine (VCR), or the combination was better in the management of children with locally advanced stages; and to study the efficacy of preoperative vincristine in patients with metastatic disease at diagnosis.[8]

This study, which included 606 patients, revealed that the addition of radiotherapy to surgery and dactinomycin produced no significant survival advantage for group I patients aged <2 years. However, group I patients aged >2 years treated with that combination (dactinomycin and radiotherapy) had an improved 2-year relapse-free survival (RFS) [$p = 0.04$]. Additionally, group II/III patients treated with the combination DAM/VCR had a better 2-year RFS than patients treated with either agent alone ($p = 0.002$). Lastly, group IV patients treated with preoperative vincristine had a statistically significant survival advantage over those undergoing immediate surgery. That is, there were 9 deaths (in 13 patients) treated with preoperative vincristine compared with 13 deaths (in 13 patients) in patients having immediate surgery ($p = 0.02$). In addition, histological review of this study identified cytological findings correlating with an unfavourable outcome, most frequently the presence of anaplasia.[9] Two other histological

characteristics associated with worse prognoses were the sarcomatous patterns, which are now recognised as distinct entities, i.e. clear cell sarcoma and rhabdoid tumour of the kidney.[9] Since these 2 tumours are not considered WT, we do not discuss them further here.

NWTS 2 enrolled patients from 1974 to 1978.[10] In this study, group I patients were randomised to receive DAM/VCR postoperatively without radiotherapy for either 6 or 15 months. Patients with group II, III and IV disease all received DAM/VCR and radiotherapy until the sixth postoperative week, and then received 15 months of either DAM/VCR, or DAM/VCR and doxorubicin (DOX). The results of this study showed no significant difference in survival for group I patients receiving 6 months of DAM/VCR compared with those receiving 15 months' therapy with this combination ($p = 0.47$). Group II-III patients receiving doxorubicin had a 2-year RFS of 77% compared with 62% for those receiving DAM/VCR ($p = 0.0004$). Additionally, patients with unfavourable histology (UH), regardless of group, had a significantly worse outcome than those with favourable histology (FH).

The third NWTS was conducted from 1979 to 1985 with the objectives of reducing treatment for low risk patients and improving the outcome for patients likely to relapse.[5] In this study, stage I patients were randomly assigned to receive either 10 weeks or 6 months of postoperative chemotherapy with DAM/VCR. Stage II patients were randomised to receive either no radiotherapy or 2000 cGy to the flank, along with either standard dose dactinomycin, vincristine and doxorubicin or intensive DAM/VCR for 15 months, resulting in 4 different arms. Stage III patients were randomised to receive either 1000 cGy or 2000 cGy to the flank, and to the same chemotherapy randomisation as stage II patients. 'High risk' patients, which included all children with metastases at presentation (regardless of histology) and those with UH (regardless of stage), received 2000 cGy to the flank along with radiotherapy to any other sites of disease, followed by 15 months of DAM/VCR/DOX with or without cyclophosphamide (CPM).

The results of this study revealed that patients with stage II, III and IV FH had a 4-year RFS of 90, 88 and 68%, respectively, and 4-year survivals of 96, 92 and 73%, respectively. There was no significant difference between any of the treatment arms, and specifically the addition of cyclophosphamide did not improve the outcome for high risk patients. However, when UH patients were analysed separately, the addition of cyclophosphamide appeared to improve the outcome for patients with stage II-IV anaplastic tumours.

The goals of NWTS 4, conducted between 1986 and 1994, were to reduce the toxicity and cost of therapy for children with WT without sacrificing their excellent outcomes.[11,12] All stage I patients were randomly assigned to receive DAM/VCR administered at either standard doses for 25 weeks, or in a pulse-intensive regimen for 18 weeks. Stage II FH patients received DAM/VCR administered either at standard doses for 23 or 65 weeks, or in a pulse-intensive regimen for 20 or 60 weeks. Stage III and IV FH patients received DAM/VCR/DOX administered at either standard doses for 28 or 65 weeks, or with a pulse-intensive regimen for 26 or 54 weeks. Additionally, all stage III-IV FH patients received 1080 cGy abdominal radiotherapy.

Results of this study revealed that the 2-year RFS in low risk patients (stage I-II FH and stage I UH) were equivalent in both the pulse-intensive and standard arms at 91% ($p = 0.988$). Additionally, the 2-year RFS in high risk patients (stage III-IV FH) was 87.3% for patients receiving pulse-intensive therapy and 90.0% for those receiving standard therapy ($p = 0.865$). Since there was no significant difference in 2-year RFS in either group, NWTS recommended the use of the pulse-intensive regimen as the new standard since it had less haematological toxicity and appeared to be more cost effective than the standard regimen.[10,11]

The current NWTS study (NWTS 5) is attempting to find biological features predictive of outcome while utilising the pulse-intensive regimen as the standard therapy. This trial is ongoing and there are as yet no published reports.

3.2 International Society of Paediatric Oncology

The approach to the treatment of WT by SIOP differs from that of NWTS in that SIOP has concentrated on the use of preoperative adjuvant or neoadjuvant therapy. The purpose of this approach has been to increase the number of patients identified with stage I disease at surgical exploration while reducing the number of intraoperative tumour ruptures. This approach differs from that of NWTS in that tissue diagnosis is not required for patients receiving preoperative treatment. The first SIOP trial (SIOP 1) was conducted from 1971 to 1974 with the objectives of investigating the use of preoperative versus postoperative radiotherapy and single versus multiple course dactinomycin.[13] In that study, patients treated with preoperative radiotherapy had fewer intraoperative tumour ruptures than those undergoing immediate surgery ($p = 0.001$), but there was no significant difference in actuarial survival between patients receiving preoperative radiotherapy and those who had not. Additionally, there was no difference in outcome whether patients received dactinomycin as a single course or in multiple courses.

SIOP 2 was a nonrandomised trial and entered patients from 1974 to 1976.[6,14] In this study, patients with very small tumours were treated with immediate surgery while all other patients received 2000 cGy preoperative radiotherapy as well as preoperative dactinomycin. The results were similar to SIOP 1 in that there was a higher number of tumour ruptures in patients treated with immediate surgery without any difference in overall survival.

The next study, SIOP 5, accrued patients from 1976 to 1980 and included a randomisation between 4 weeks of preoperative DAM/VCR, and 2 weeks' preoperative radiotherapy (2000 cGy) with 5 days of dactinomycin.[14] Maintenance therapy was the same for both arms and consisted of DAM/VCR for 43 to 45 weeks. The results showed no difference in tumour rupture at the time of surgery or in actuarial survival between the 2 treatment groups. Additionally, patients receiving preoperative chemotherapy did very well in terms of abdominal relapse, suggesting that postoperative radiotherapy may not be necessary in patients receiving preoperative chemotherapy. There was also a statistically significant preservation of histology in patients treated with chemotherapy compared with those receiving radiotherapy ($p < 0.001$).

SIOP 6, conducted from 1980 to 1987, assigned patients with stage I-III FH to receive 4 weeks of preoperative DAM/VCR with postoperative treatment determined by stage, histology and extent of lymph node involvement at postchemotherapy surgical exploration.[6] Postoperative therapy consisted of either 17 or 38 weeks of DAM/VCR for stage I patients. Stage II lymph node negative (LN–) patients received the same postoperative therapy as stage I patients with or without radiotherapy. Stage II lymph node positive (LN+) and stage III patients were randomised to intensive DAM/VCR for 40 weeks or standard DAM/VCR/DOX for 38 weeks. The results of this study showed there was no significant difference in 2-year RFS between the use of 17 or 38 weeks of chemotherapy for stage I patients. The trial, however, was stopped prematurely for stage II LN– patients because all abdominal recurrences occurred in patients who had not received radiotherapy. Subsequently, all stage II LN– patients received postoperative radiotherapy. However, the 2-year RFS and 5-year survival were the same for both groups of patients.

The trial for stage II LN+ and stage III patients was also stopped prematurely because of an improved RFS in patients receiving doxorubicin. Further follow-up of this trial showed that the RFS advantage was maintained with doxorubicin but the 5-year survival was no different for patients who received intensive DAM/VCR than for those who received doxorubicin.

SIOP 9, which began in 1987, was the last completed SIOP trial and patients were randomised to receive either 4 or 8 weeks of preoperative chemotherapy consisting of DAM/VCR in an attempt to increase the number of stage I patients. Postoperative treatment consisted of 17 weeks of DAM/VCR for stage I patients while stage II and III patients

received 26 weeks of DAM/VCR/Epirubicin (DAM/VCR/EPI) and radiotherapy (stage II LN+ and stage III only). The study showed no significant benefit for 8 weeks of preoperative chemotherapy compared with 4 weeks.[15]

The current SIOP trial (93-01) opened in 1993. Patients with localised tumour receive 4 weeks of preoperative DAM/VCR, while those with stage IV disease receive 6 weeks of preoperative DAM/VCR/DOX or DAM/VCR/EPI.[16] Postoperatively, patients receive 4 weeks of chemotherapy using dactinomycin (5 days) and vincristine (4 weekly injections), then either 28 weeks of maintenance therapy, or no further therapy. This trial is still ongoing and the results are not published.

3.3 Other Cooperative Trials

There have been other cooperative trials for patients with WT. The Brazilian Wilms Tumour Study group (GCBTTW) has investigated the benefit of single dose dactinomycin over the standard fractionated regimen delivered over 5 days in a randomised trial. The remainder of the therapy was based on stage and histology as recommended by NWTS 3, and included 6 months of therapy for stage I patients while all others received 15 months. As with the findings on NWTS 4,[11,12] this study revealed no difference in survival between the 2 regimens, but patients treated with single dose dactinomycin had significantly fewer hospital days.[17,18] It should be noted that the dose of dactinomycin for the single dose regimen is not uniform in all cooperative groups. The NWTS found increased hepatotoxicity with 60 μg/kg, and currently uses 45 μg/kg,[19] while GCBTTW found no significant hepatotoxicity in patients receiving 60 μg/kg.[18,20] One reason for these discrepant findings may be that the dosage regimen for the single dose dactinomycin was every 3 weeks in NWTS and every 6 weeks in GCBTTW.[20]

The United Kingdom Children's Cancer Study Group's (UKCCSG) first Wilms' tumour study was published in 1995.[21] This was a nonrandomised trial and its results were compared with those of other cooperative studies. Treatment consisted of vincristine for 26 weeks for stage I patients and DAM/VCR for 26 weeks for stage II patients, while stage III patients received DAM/VCR/DOX for 1 year and stage IV patients and those with UH (regardless of stage) received DAM/VCR/DOX/CPM for 1 year. The results of the study showed that vincristine was as effective as the 2-agent regimen of DAM/VCR (used in NWTS and SIOP) for stage I FH patients. Stage II-III FH patients had similar 5-year RFS to patients treated on NWTS 2 and 3 utilising similar chemotherapy regimens. However, stage IV patients and those with UH had a 6-year survival rate which was inferior to that of patients treated by NWTS and SIOP. Part of this difference could be due to the omission of lung radiotherapy for stage IV patients treated on the UKCCSG regimen.

3.4 Current Management

Since cancer in children is rare and staging is essential for appropriate management, children with WT are better managed using cooperative group studies. Additionally, these patients are best referred to centres where paediatric oncologists, surgeons, radiologists and pathologists with expertise in the management of paediatric cancer patients are available. The current recommended treatment for WT will depend on the cooperative group to which the treating institution belongs, but with currently available therapy in either of the major cooperative groups, WT patients have a 2-year survival of approximately 90%.

The current NWTS (NWTS 5) is concentrating on reducing the secondary effects of treatment in all patients while maintaining the excellent outcomes and identifying biological factors predictive of outcome (fig. 1). In order to minimise the untoward effects of therapy, initial therapy is limited and more intensive retrieval therapy is used for patients who relapse.

The current SIOP trial (93-01) is investigating the use of 4 weeks of preoperative chemotherapy for patients with localised disease and 6 weeks for those with advanced disease, as well as the effect of different lengths of maintenance therapy on out-

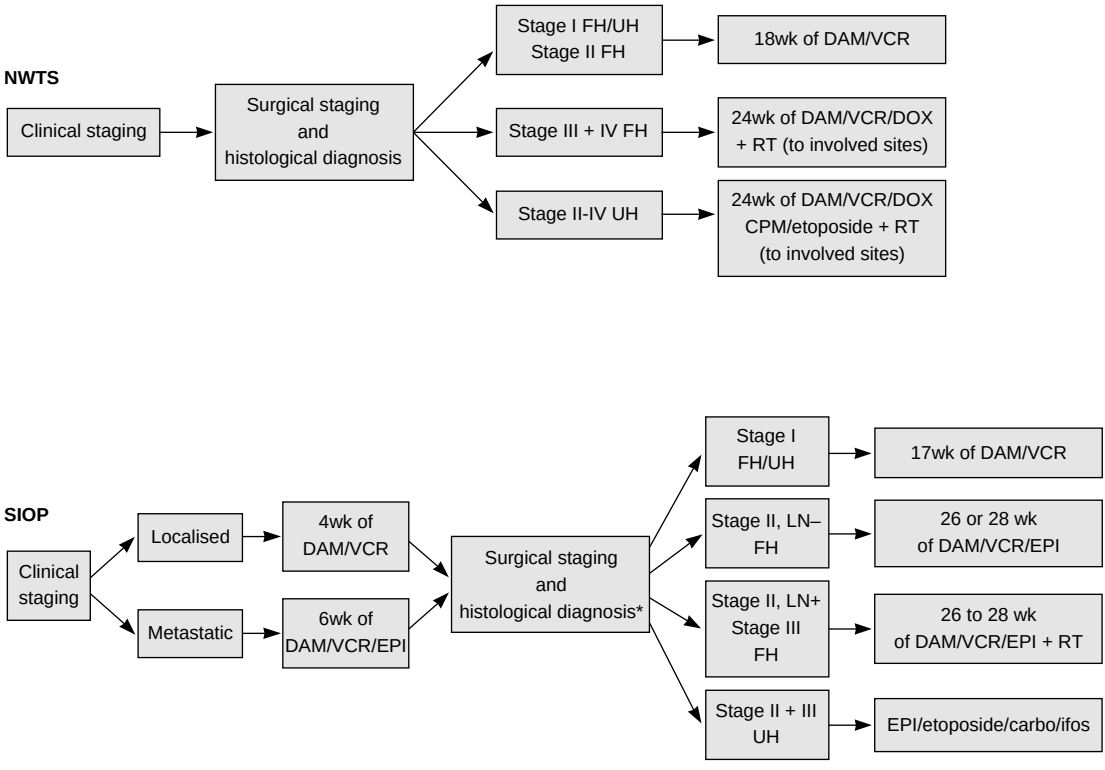

Fig. 1. Algorithm for current management of Wilms' tumour by the National Wilms' Tumour Study (NWTS) group and the International Society of Paediatric Oncology (SIOP). NWTS: clinical staging with diagnostic imaging followed by exploratory laparotomy and surgicopathological staging (see table I). SIOP (algorithm based on SIOP 9 except for that of stage II-IV FH patients which is based on SIOP 93-01): Clinical staging with diagnostic imaging. Preoperative chemotherapy is based on the extent of the disease at diagnosis. ***** = Preoperative therapy is dependent on the intra-abdominal stage at the time of surgery. If metastatic diseas is present at diagnosis, RT is given to the involved sites. **carbo** = carboplatin; **CPM** = cyclophosphamide; **DAM** = dactinomycin (actinomycin D); **DOX** = doxorubicin; **EPI** = epirubicin; **FH** = favourable histology; **ifos** = ifosfamide; **LN+(–)** = lymph node positive (negative); **RT** = radiotherapy; **UH** = unfavourable histology; **VCR** = vincristine; **wk** = week.

come (fig. 1).[15] Additionally, maintenance therapy for stage IV patients consists of 2 or 3 drugs depending on intra-abdominal staging at the time of nephrectomy. Because the staging occurs after chemotherapy administration, and stage IV patients receive maintenance chemotherapy based only on intra-abdominal staging, the amount of anthracycline that these patients receive can vary depending on the response of the primary tumour to the preoperative chemotherapy.

Thus, using SIOP guidelines, a larger proportion of patients with lower stage WT will receive radiotherapy and anthracyclines such as doxorubicin or EPI, which can cause cardiotoxicity. Conversely, using NWTS guidelines, patients with metastatic disease potentially receive more total anthracycline than patients treated in SIOP.

Another point worth mentioning is that since patients in SIOP are treated with chemotherapy without a histological diagnosis, a very small number of patients may receive chemotherapy for what ultimately is diagnosed as malignancy other than WT, or potentially even a nonmalignant condition. In SIOP 6, 1.5% of a total of 1095 registered patients received preoperative chemotherapy for nonmalignant tumours.[6]

Since patients with stage II-IV UH have a dismal outcome with traditional therapy, both NWTS

and SIOP utilise combinations of chemotherapy not traditionally used in WT (fig. 1).

4. Other Topics

4.1 Bilateral Wilms' Tumour

Bilateral WT occurs in roughly 5 to 10% of all WT patients.[22-24] It can occur as synchronous disease (tumour diagnosed in both kidneys simultaneously) or metachronous disease (tumour diagnosed in one kidney followed by development of tumour in the contralateral kidney at a later time) with synchronous disease occurring 4 times more frequently than metachronous disease.[22] Most patients with metachronous disease are diagnosed with tumour in the second kidney within 3.5 years of initial presentation.[23] The incidence of congenital anomalies (e.g. stigmata of Beckwith-Wiedmann syndrome) is slightly higher in patients with bilateral WT than in those with unilateral WT.[23]

The surgical treatment of bilateral WT differs from that of unilateral disease in that primary excision is not recommended. Rather, recommendations include the use of bilateral biopsies to assess histology and stage for each kidney, usually followed by preoperative chemotherapy. Second-look surgery is usually performed at the time of maximal shrinkage to resect the remaining tumour but preserve as much renal parenchyma as possible. Total bilateral nephrectomies are not recommended unless the tumours are unresponsive to chemotherapy and radiotherapy, since the survival for patients with bilateral WT undergoing multimodality therapy has been reported to be between 54 and 71%.[22-24]

4.2 Recurrent Wilms' Tumour

The incidence of recurrence in WT depends on the initial stage of disease and the treatment administered, but has been reported to be about 13% (367 of 2757 patients).[25] The most common sites of relapse within this group are the lungs (58%) and abdomen (29%). Factors associated with a better prognosis in relapsed patients are FH, remission duration greater than 12 months, original stage I disease and a nonabdominal relapse site. Patients usually receive combined modality therapy with drugs similar to those used at initial diagnosis. Unfortunately, however, the outcome is poor, with a 3-year overall survival of 20 to 29% for FH patients and 3 to 5% for those with UH. Therefore, newer treatment strategies for these patients are warranted in an effort to improve outcome. Following preliminary results suggesting that the use of ifosfamide/etoposide[26] and carboplatin/etoposide[27,28] induce responses in a large number of patients, the NWTS is utilising a regimen consisting of high-dose cyclophosphamide, along with carboplatin and etoposide, in relapsed patients. Preliminary results on a small number of patients treated with this regimen are promising.[27]

5. Conclusion

The treatment of WT has become a prototype in cancer therapy since it is considered the most 'curable' paediatric malignancy. The use of multimodality therapy along with the development of cooperative group trials has improved survival to the current rates of 90%.[5] Since more than 80% of WT patients will be long term survivors, the current goals of therapy are to reduce the late drug toxicities in low risk patients while optimising outcome in patients with high risk of recurrence. Unfortunately, the management of patients with bilateral WT or those with recurrent disease continues to be challenging, and current clinical trials focus on improving treatment strategies for these patients. Continued accrual of WT patients to cooperative group studies is the best way to improve the outcome for patients with WT while attempting to minimise long term drug adverse effects.

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