

# Management of Recurrent Wilms' tumor

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## INTRODUCTION

The management of Wilms' tumor (WT) emerging of the outstanding clinical trials undertaken in the developed world in the last four decades has led to excellent long-term outcomes in the range of 90% in localized disease and over 70% for the metastatic disease<sup>1</sup>. It must be appreciated that long-term follow-ups are mandatory, as approximately 15% of patients with favorable-histology WT and 50% of patients with anaplastic WT in National Wilms' tumor Study (NWTs) had recurrences<sup>2</sup>. Most recurrences occur within 2 years of diagnosis<sup>3</sup>, although the recurrences have been known to occur even after 25 years of initial treatment<sup>4</sup>. While the developed world is seeking international collaboration to conduct appropriately constructed clinical trials and is now bracing up to understand the genetic mechanisms of tumor recurrence<sup>5</sup>, the developing world is still struggling to achieve low abandonment rates and decent survival rates for primary WT using simple adjunct therapy regimens. Successful management of recurrent WT (ReWT) is far-fetched dream in such a scenario. A comprehensive search of literature could reveal only an isolated case report of recurrent WT from India<sup>6</sup>.

Before the 1990s, in many ReWT patients, same chemotherapy agents were generally used for the treatment of both primary and recurrent disease. The salvage rate for patients with recurrent favorable-histology WT used to be 25-40%<sup>2</sup>. Outcomes started improving up to 60% in the last 15-20 years when modern treatment combinations were tried<sup>7</sup>. The general principle of management shifted to include drugs that are not used during primary chemotherapy, using a risk-stratified approach. The drugs such as ifosfamide, carboplatin, and etoposide, either as single agents or in combination (ICE regimen) are often used when we treat ReWT nowadays. Spreafico *et al* have published an excellent review of the literature of ReWT in 2009<sup>5</sup> stating clearly that the best combination, dose-intensity and duration of chemotherapy agents still remain poorly explored. There have been hardly any appropriately constructed clinical trials conducted for lack of numbers. But even of whatever has been previously used, no ready references detailing different protocols are available. The purpose of this article to provide such a ready reference with different chemotherapeutic protocols made available in tabulated form. As management of these ReWT has been multimodal, the roles of surgery and radiotherapy are also briefly mentioned. Importantly, most of the chemotherapeutic schedules that are mentioned below are highly toxic and should be practiced only in specialized pediatric oncology unit.

Before embarking upon the management protocols, general profile

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of relapse sites and risk-stratification needs to be understood. The lungs and pleura alone account for 50–60% recurrences; abdominal recurrences make up to 30% of relapses while other sites (brain or bone) are involved alone in 10–15% of cases<sup>5</sup>. In some reports, recurrences involving the mediastinum have been included under the 'lung recurrences' category. Abdominal recurrence generally involves the original tumor bed (kidney area), but can correspond to retroperitoneal lymph nodes, liver, peritoneum or contralateral kidney. Most 'recurrences' in the contralateral kidney probably represent second primary tumors rather than true recurrences.

## RISK STRATIFICATION

Over the years, a number of potential prognostic features influencing post-recurrence outcomes have been analyzed; the same factors have been used to devise risk-stratification that has now become buzzword in pediatric oncology. It is difficult to say whether these prognostic factors are independent of each other. Further, these prognostic factors appear to be changing over time as therapy for primary and ReWT evolves. Features those are clearly associated with a worse outcome after relapses are anaplastic or post-treated blastemal type (SIOP high-risk histology), advanced tumor stage where initial chemotherapy included doxorubicin (stage III and IV primary WT) and recurrence in multiple organs or in previously irradiated field<sup>3,8</sup>. Gender is also a prognostic factor, with males faring worse than females<sup>5</sup>. Early recurrence within 6 months was also considered as an adverse prognostic factor previously<sup>3,8</sup>, but this is no more important with advent of contemporary therapy.

Based on current data, three risk categories for ReWT can be identified. (Table 1) These are described in detail elsewhere<sup>5</sup>.

## CHEMOTHERAPY

### Management of Standard-risk ReWT

There are two important chemotherapy protocols to be mentioned here, namely, stratum B of the NWTs-5 relapse protocol<sup>10</sup> (Table 2) and UKW-R protocol of United Kingdom Children's Cancer and Leukaemia Group (UKCCLG)<sup>11</sup>. NWTs-5 Relapse treatment included surgical excision, when feasible, radiation therapy and alternating courses of vincristine–doxorubicin–cyclophosphamide and etoposide–cyclophosphamide (Table 2). It may be mentioned here that this protocol is same Regimen I used for Stages II–IV/diffuse anaplasia.

The UKW-R protocol had two arms that are detailed in Table 3 and 4. Twelve out of 22 were patients with ReWT were rescued with intensive vincristine, actinomycin D and doxorubicin (Arm A; Table 3). After the first 10 doses, vincristine was administered 3 weekly for 52 weeks. Actinomycin D was administered 3 weekly from week

**Table 1: Risk stratification in Recurrent Wilms Tumor (Adapted from [5, 9])**

Risk group	Reason	Relative Incidence	Expected EFS	Treatment recommendations
Standard	Initially received VCR+ AMD only (regardless of site or timing of relapse)	30%	70-75%	CTX/D - CARBO/ E (VP-16)
High	DOX already given	40-45%	50-55%	I/CARBO/E (VP-16) (ICE regimen)
Very high	Diffuse anaplasia, pre-treated blastemal-type (HR- chemotherapy already given)	10-15%	10-20%	ICE regimen + HD- Melphalan

VCR Vincristine; AMD Actinomycin D; DOX Doxorubicin; CTX Cyclophosphamide, CARBO Carboplatinum; E (VP-16) Etoposide, EFS - Event Free Survival; HD - High Dose  
ICE - Ifosfamide + Carboplatinum + Etoposide

**Table 2: Stratum B of the NWTS-5 relapse protocol**

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
VCR* 0.05 mg/kg or 1.5 mg/m <sup>2b</sup>		↓	↓		↓	↓	↓	↓	↓	↓	↓	↓	↓ <sup>c</sup>	↓ <sup>c</sup>					↓ <sup>c</sup>						↓ <sup>c</sup>
DOX 1.5 mg/kg or 45 mg/m <sup>2b</sup>	↓						↓						↓						↓						↓
CTX 14.7 mg/kg/d or 440 mg/m <sup>2d</sup>				↓			↓			↓			↓			↓			↓				↓		↓
E (VP-16) 3.3 mg/kg/d or 100 mg/m <sup>2d</sup>				↓						↓						↓							↓		

<sup>a</sup> Maximum single dose 2 mg; <sup>b</sup> for all patients who weigh more than 30 kg; <sup>c</sup> 0.067 mg/kg or 2 mg/m<sup>2</sup> for wk 12, 15 and 18  
The dose of DOX at wk 6 should be decreased by 50% if whole lung or whole abdomen RT has been given CTX and E (VP-16) to be as administered in 200 cc/M<sup>2</sup> of D5/ 6 NS as an IV infusion over 60 min daily  
MESNA 3 mg/kg/dose (or 90 mg/m<sup>2</sup> /dose for children >30 kg wt) x 4 doses in 10 mg IV over 15 min Å~ 3 d, given after CTX

**Table 3: Arm A of UKW-R protocol (shown only up to 34 weeks)**

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
VCR 1.5 mg/m <sup>2</sup>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
AMD 1.5 mg/m <sup>2</sup>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 30 mg/m <sup>2a,b</sup>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓

<sup>a</sup> cumulative dose 360mg/m<sup>2</sup>;  
<sup>b</sup> if patient to receive pulmonary RT, then DOX to be administered only from)week 1 - 28 and cumulative dose reduced to 300mg/m<sup>2</sup>

1-52. The doxorubicin administration varied from 28-34 weeks depending upon whether pulmonary radiation was given or not. An additional ten children, initially receiving two-drug chemotherapy, were rescued with 8 alternating courses of cyclophosphamide-doxorubicin and cyclophosphamide-etoposide (Arm B; Table 4). Ifosfamide could also be used in place of cyclophosphamide, but it is more nephrotoxic.

**MANAGEMENT OF HIGH-RISK REWT**

Two approaches have been used in the management of high-risk ReWT namely conventional-dose chemotherapy, or high-dose (HD) chemotherapy plus autologous stem cell rescue (ASCR). Further, there is no consensus about the chemotherapy protocols when it

comes to conventional chemotherapy; various combinations have been used.

**Conventional-dose chemotherapy**

One of the examples is ifosfamide, carboplatin and etoposide (ICE) chemotherapy used by Abu-Ghosh et al<sup>12</sup>. A median of 4 cycles (range 1-12) was administered (Table 5). Patients were evaluated for complete remission/ partial remission (CR/ PR) after 2 cycles and then every one cycle.

Stratum C of the NWTS-5 relapse protocol has been described by Malogolowkin et al<sup>13</sup>; this regimen of alternate courses of the drug-pairs cyclophosphamide-etoposide and carboplatin-etoposide was 90 weeks in duration (Table 6) and many children had discontinuation

**Table 4: Arm B of UKW-R protocol**

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
CTX 500mg/m <sup>2</sup> X 2 d <sup>a</sup>	↓			↓			↓			↓			↓			↓			↓			↓
E (VP-16) 150mg/m <sup>2</sup> X 3 d	↓						↓						↓						↓			
DOX 30mg/ m <sup>2</sup> X 2 d				↓						↓						↓						↓

<sup>a</sup>Maximum cumulative weekly dose 2gm/m<sup>2</sup>

**Table 5: ICE regimen for high-risk Recurrent Wilms Tumor [12].**

Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Ifosfamide 1.8gm/m <sup>2</sup> X 5 d	↓			↓			↓			↓			↓
CARBO 400mg/m <sup>2</sup> X 2 d	↓			↓			↓			↓			↓
E (VP-16) 100mg/m <sup>2</sup> x 5 d	↓			↓			↓			↓			↓

**Table 6: Stratum C of the NWTS-5 relapse protocol (shown for only 2 pairs of alternating cycles) [13]**

Week	0	1	2	3	4	5	6	7	8	9
CTX 440 mg/m <sup>2</sup> X 5 d	↓						↓			
CARBO 500 mg/m <sup>2</sup> X 2 d				↓				↓		
E (VP-16) 100mg/m <sup>2</sup> X 5 d/ 3 d <sup>a</sup>	↓			↓			↓			↓

<sup>a</sup> for 5 days when CTX is used and 3 days when CARBO is used.

of therapy due to prolonged hematological toxicity.

### High-dose chemotherapy & autologous stem cell rescue

Here, HD myeloablative chemotherapy is coupled with ASCR for consolidation. Either HD ICE regimen, or melphalan, etoposide or carboplatin (MEC regimen) is administered as the induction or conditioning chemotherapy.

Spreafico et al<sup>14</sup> reported for the Associazione Italiana Ematologia Oncologia Pediatrica group. Here, ICE consisted of ifosfamide 1500 mg/m<sup>2</sup>/day × 4 days, carboplatin 600 mg/m<sup>2</sup>/day × 1 day and etoposide 100 mg/m<sup>2</sup>/day × 4 days (compare with Table 5).

French Society of Pediatric Oncology replaced ifosfamide with another alkylating agent Melphalan and used MEC regimen for conditioning chemotherapy<sup>15</sup>. The regimen consisted of Melphalan 180 mg/m<sup>2</sup> for 1 day, Etoposide 200 mg/m<sup>2</sup>/d for 5 days, and carboplatinum at a daily targeted area under the concentration-time curve (AUC) of 4 mg × min/mL for 5 days. Autologous stem cells were re-infused 48 hours after Melphalan. A Korean group has used MEC as conditioning chemotherapy in 3 patients; the regimen consisted Melphalan 140 mg/m<sup>2</sup>/day for 1 day and 70 mg/m<sup>2</sup>/day the next day, etoposide

200 mg/m<sup>2</sup>/day for 4 days and carboplatin 400 mg/m<sup>2</sup>/day for 4 days; autologous stem cells were infused after 5 days of administration of MEC<sup>16</sup>. An Austrian group has used double high-dose chemotherapy (HDCT) and ASCR in one

UKCCLG's strategy was to use induction dose-intense regimen and consolidation with high-dose chemotherapy and ASCR (Table 7)<sup>11</sup>.

After six chemotherapy courses, responding patients received high-dose single-agent melphalan (200 mg/m<sup>2</sup>/day) with ASCR.

Children's Cancer Group (CCG) used 5 alternating course pairs of Stratum C of the NWTS-5 relapse protocol for induction (table 6)<sup>17</sup>. Patients who achieved complete tumor remission received maintenance therapy with a further five identical course pairs, while those with partial response or stable disease received ablative chemotherapy followed by ASCR.

Investigators at St. Jude Children's Research Hospital have used topotecan, a camptothecin analogue that interacts with DNA topoisomerase I, for high-risk ReWT in the past few years<sup>18</sup>.

### MANAGEMENT OF VERY-HIGH-RISK ReWT

An Austrian group had used double high-dose chemotherapy (HDCT) and ASCR in one patient with very-high-risk ReWT successfully<sup>19</sup>. But most children with very-high-risk ReWT display dismal outcome post-recurrence regardless of the use of intense-dose chemotherapy, and should be candidates to enter trials for novel agents. Some of these tumors are chemoresistant. Paclitaxel and oxaliplatin either singly or along with conventional chemotherapeutic drugs have been used<sup>5</sup>. High-dose thiotepa has been also used<sup>5</sup>. Bevacizumab, a monoclonal antibody directed against VEGF has been administered to two children with WT on a compassionate basis<sup>20</sup>. COG has also investigated role of all-trans-retinoic acid and IFN- $\alpha$ 2A<sup>21</sup>.

A meta-analysis of Ha et al. in 2013 showed that a very high risk group of patients with relapsed WT might have a benefit from HDCT<sup>22</sup>.

Table 7: UKCCLG induction (conditioning) chemotherapy for high-risk ReWT

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CTX 500 mg/m <sup>2</sup> twice X 2 d	↓						↓						↓			
CARBO 750 mg/m <sup>2</sup>				↓						↓						↓
E (VP-16) 200mg/m <sup>2</sup> X 3 d	↓			↓			↓			↓			↓			↓

### SURGERY

The evidence about a useful role of surgery in ReWT management is not very clear. After reduction of recurrent disease post-chemotherapy, resection could be considered when radical surgery is possible; it is also indicated in the patients with stable disease where tumor histology needs to be evaluated. In a retrospective analysis, patients who underwent a complete surgical resection of recurrent tumor had a higher probability of survival than did patients who had a partial resection or no surgery<sup>7</sup>. Fuchs et al found that complete surgical resection of liver recurrences improves survival<sup>23</sup>. On the other hand, NWTS group suggested that surgical removal of all pulmonary metastases is unlikely to improve post-relapse survival compared with treatment with whole-lung radiation therapy and chemotherapy<sup>24</sup>. However, dealing with a solitary lung metastasis becomes all the more tricky. Surgical excision of the solitary lung nodule could avoid the toxicity of whole lung radiation therapy. It would be fair to conclude that surgery probably plays an important role in treating ReWT, but it is very possible that patients who undergo a complete surgical resection have less aggressive disease to start with.

### RADIATION THERAPY

Similar to surgery, the indications, dose and modality of radiation

therapy in children with recurrent WT are rather unclear. In the NWTS-5 relapse protocol, the researchers electively decided to administer radiotherapy at higher doses compared with the ones used at initial diagnoses, even if primary therapy did not include radiotherapy<sup>25</sup>. Children with abdominal recurrence received 1260–1800 cGy if aged 0–12 months, and 2160 cGy for those 13 months of age or older. The dose for lung irradiation, using 150 cGy daily fractions, generally reaches 1200 cGy. Indications and radiotherapy dose for recurrent liver disease is more difficult to be standardized and, in general, depends on the quality of surgical resection. Patients with non-resectable liver nodules usually received up to 1980 cGy if the entire liver was diffusely involved. Patients who achieved a complete remission following chemotherapy and/or hepatic resection did not receive radiation therapy to the liver.

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## LITERATURE REVIEW

### LIVING DONOR KIDNEY TRANSPLANTATION USING LAPAROSCOPICALLY PROCURED MULTIPLE RENAL ARTERY KIDNEYS

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The use of kidneys with multiple renal arteries (MRA) and right kidneys procured laparoscopically for living donor kidney transplantation (LDKT) remains controversial. We aimed to evaluate the short- and long-term outcomes of recipients of LDKT using laparoscopically procured MRA and right kidneys. Authors reviewed the medical records of all LDKT recipients with laparoscopically procured kidneys from 2000 to 2009. Pediatric recipients and recipients of positive crossmatch and/or ABO-incompatible transplants were excluded. We compared the outcomes of recipients of MRA kidneys with those receiving single renal artery (SRA) kidneys and the outcomes of recipients of right kidneys with those of left kidneys. Renal function was measured by iothalamate clearance and estimated by the abbreviated Modification of Diet in Renal Disease equation. Multiple renal artery kidneys (192 2-artery and 18 3-artery kidneys) were used in 210 (18.5%) of 1,134 transplantations. The most common reconstructive technique used for MRA kidneys was a side-to-side anastomosis (64.3%). There were no significant differences in vascular complications (1.1% vs 2.4%,  $p = 0.17$ ), urologic complications (3.1% vs 2.9%,  $p = 0.47$ ), graft survival at 1 year (94.6% vs 96.1%,  $p = 0.37$ ), and 1-year iothalamate clearance (64 mL/min/1.73 m<sup>2</sup>) vs 66 mL/min/1.73 m<sup>2</sup> ( $p = 0.52$ ) between recipients of SRA and MRA kidneys. Five-year graft survival was similar for recipients of SRA and MRA kidneys (83.6% vs 82.6%,  $p = 0.82$ ) and for recipients of left vs right kidneys (83.7% vs 82.6%,  $p = 0.70$ ). Excellent long-term outcomes can be obtained after LDKT using laparoscopically procured MRA and right-sided donor kidneys. Unavailability of an SRA left kidney should not preclude LDKT.

## DRUG PROFILE

### Garenoxacin

Garenoxacin is a newly developed novel-des-flouro quinolone in Japan. **Mechanism of action:** Garenoxacin acts on DNA gyrase and DNA topoisomerase IV to inhibit the transcription and replication of DNA like conventional fluoroquinolones. Garenoxacin demonstrates lowest MICs against respiratory pathogens with low potential for resistance development. The complimentary presence of bulky side chains of difluoromethoxy and Methylisoindolyl groups increases the spectrum of activity. **Spectrum:** Garenoxacin demonstrates wide spectrum of antibacterial activity against Gm positive, Gm negative, atypical and anaerobic pathogens. Garenoxacin also demonstrates low Mutation Prevention Concentrations preventing development of resistant strains with double-point mutations. Similarly the novel structure resulted incomplete bacteriological eradication rates against Quinolone-resistant (100%), -lactam resistant (97.7%) and Macrolide resistant (98.7%) strains of strep.pneumoniae. **Pharmacokinetics:** Cmax was 7.43 mcg/mL and the AUC was 100.7 mcgh/mL with half-life (t/2) of 12.36h with a single dose of 400mg Garenoxacin. Garenoxacin shows excellent penetration across the tissues. Garenoxacin concentration in sputum was much higher than the MIC90 (<0.06 mcg/mL) seen with mostcausative pathogens, even 24 h after administration. **Clinical Data:** In a large multicentric study involving 6412 patients with Respiratory tract infections with PRSP, Gm negative and Atypical organisms, Garenoxacin administered at dosages of 400mg for 5 days showed clinical efficacy rate of 92 to 100%. **Indications:** Garenoxacin is indicated for the following bacterial infections caused by susceptible microorganisms including Pharyngitis, Sinusitis Laryngitis Tonsillitis, Otitis media, Acute bronchitis, Pneumonia and Secondary infection in chronic respiratory lesion. **Precaution and Contraindication:** Garenoxacin should be administered with caution in High-risk patients who have convulsive disorders such as epilepsy and elderly patients. Garenoxacin is contraindicated in patients who have a history of hypersensitivity to any component of the formulation. Garenoxacin is well tolerated drug with its safety profile well differentiated due to lack of any significant concerns on photosensitivity, abnormal hepatic functioning, seizures, arthropathy and QTc prolongation. The most frequent adverse effects reported in clinical trails were diarrhea, nausea and headache. **Dosage and administration:** The usually recommended dose for adults, 2 tablets (400mg) to be taken once daily at the same time of the day for 5 to 14 days depending on the severity and type of infection.