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Pharmacotherapeutic management of Wilms tumour: an update

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Abstract

Although differences exist in treatment and risk stratification strategies for children with Wilms tumour (WT) between the European (SIOP) and American (COG) study groups, outcomes are very similar with an overall survival of >85%. Future strategies aim to de-intensify treatment and reduce toxicity for children with low risk of relapse and intensify treatment for children with high risk disease. For metastatic WT response of lung nodules to chemotherapy is used as a marker to modify treatment intensity. For recurrent WT a unified approach based on the use of agents that were not used for primary therapy is being introduced. Irinotecan is being explored as a new strategy in both metastatic and relapsed WT. Introduction of biology-driven approaches to risk stratification and new drug treatments has been slower in WT compared to some other childhood cancers. Whilst several new biological pathways have been identified recently in WT, their individual rarity has hampered their translation into clinical utility. Identification of robust prognostic factors requires extensive international collaborative studies due to the low proportion who relapse or die. Molecular profiling studies are in progress that should ultimately improve both risk classification and sign-posting to more targeted therapies for the small group who fail current therapies. Accrual of patients with WT to early phase trials has been low and efficacy of these new agents has so far been very disappointing. There is a need for better in vitro model systems to test mechanistic dependence so that available new agents can be more rationally prioritised for recruitment of children with WT to early-phase trials.

Key points

- Collaboration in international clinical trials, improvement of multimodal therapy and risk stratification strategies have led to improved outcome for children with Wilms tumour (WT).
- In children with WT where cure rates are high it is critical that the balance of risk and benefit of treatment continues to be optimised through further fine tuning of risk stratification strategies that determine which children need more intensive therapy and those that can do with less.
- Work in the field of genetics and epigenetics is pointing towards common signalling pathways, dysregulation of the epigenome and the identification of gene expression profile subsets in children with WT that will direct future research into targeted therapies and enable better predictions of tumour sensitivity to therapy and recurrence.

1 Introduction

Primary renal tumours account for 4-7% of all childhood cancers. In the Western world about 90% of these cases are Wilms tumours (WT) or nephroblastoma. Renal tumours are common in children aged 0-4, accounting for 8.9% of all cancers but their relative frequency decreases in older age groups (1). Incidence rates for renal tumours vary between ethnic groups with an age standardized incidence rate (ASR) of 3.1 per million in Japan versus 9.0 in England (2). Typically, WT comprises three histological components; blastemal, epithelial and stromal. The proportion and the degree of maturation of these components varies significantly, forming the basis for histological sub-classification, which may correlate with tumour genetics and outcome. A wide range of syndromes, congenital anomalies and constitutional chromosomal abnormalities have been reported to be associated with an increased risk of WT development (3). Several new genes and pathways of WT tumorigenesis have been extensively reviewed elsewhere (4-7). These discoveries have strengthened the evidence for WT origin in early renal maldevelopment describing genes which are specifically involved in early nephrogenesis (e.g. SIX1/2, WT1, CREBBP and MYCN) as well as genes that have wide-ranging functions in cellular control pathways including epigenetic regulation (e.g. MLLT1, BCOR, HDAC4) and miRNA processor genes (miRNAPGs) (4, 5).

2 Management of localised Wilms tumour

WT treatment consists of surgery, chemotherapy and for some patients, radiotherapy. With the introduction of multimodal treatment, long-term cure rates have improved to greater than 90% (4). Further improvements have been made through increasingly sophisticated approaches to risk stratification and refining the multimodal treatment approach, rather than adoption of novel compounds.

Much of this success has to be attributed to two multi-disciplinary cooperative groups: SIOP (International Society of Paediatric Oncology) and COG (Children's Oncology Group), previously the National Wilms Tumor Study Group (NWTSG) who have conducted large international multi-centre trials. For all WT patients, surgery is mainstay of treatment but the timing of surgery differs between SIOP and COG protocols. Each strategy has its pros and cons, but with similar survival rates (8-10). Due to differences in upfront treatment approaches, slight differences in staging and histology also exist (11). Treatment type and intensity are influenced by several clinical and biological prognostic factors for both groups (table 1)(12, 13).

In table 2 a summary of events and deaths is given for the SIOP WT 2001 study and the NWTS-5 study (4, 14, 15). Whilst we make no attempt to directly compare these, the data emphasise how children whose tumours are initially predicted to have a good prognosis actually contribute 37-39% of all events. They would potentially benefit from more accurate risk stratification of those receiving reduced therapy. Those initially identified as 'high risk' contribute 42-49% of all deaths. This group would benefit from earlier treatment intensification or new drugs to optimise survival rates.

In this review, we discuss different strategies to further optimise total burden of therapy to maximise overall survival (OS) and predicted quality of survival. This includes increasing the success of first line therapy through improved accuracy of initial risk stratification to reduce the numbers of patients who relapse and earlier introduction of new therapeutic approaches for those who do. For this purpose we consider three main categories of patients whose current risk-adapted first line treatment regimen consists of either 2, 3 or more than 3 drugs (table 3)(16).

The first category includes patients with good risk disease who will receive either no chemotherapy or a 2-drug regimen with vincristine and actinomycin-D (VA) and no radiotherapy. These are mainly patients with stage I or II unilateral tumours and favourable histology – in this paper we will use 'favourable histology' for both low (LR)/intermediate (IR) risk histology according to SIOP and favourable histology WT (FHWT) according to COG. In spite of an excellent prognosis, due to the large numbers of patients, they account for nearly 40% of all relapses, of which approximately half can be salvaged (table 2).

Progressive therapy reduction has been successfully achieved over time, first by omitting radiotherapy and then by reducing duration and intensity of chemotherapy. To further minimise toxicity in this very young group of children, several early studies have explored the possibility of nephrectomy only (17, 18). Two studies from the Dana-Farber Cancer Institute in Boston suggested that a subgroup of children with verified WT, had an excellent prognosis with nephrectomy only (19, 20). Furthermore, a review of all patients treated on NWTS 1-3 revealed that changes in treatment regimens did not significantly improve the already excellent prognosis which poses the question of the added benefit of chemotherapy to these patients (21). These results led to the NWTS-5 study including a trial arm with no adjuvant chemotherapy for children under 2 years of age, with small (≤ 550g) stage I FHWT. The study was closed prematurely due to the relapse rate exceeding the predefined stringent limit, but the observed salvage rate was much higher (91%) than expected, leading to an excellent overall survival (OS) (22-24). COG have re-assessed the nephrectomy only approach but with mandatory multidisciplinary scrutiny of tumour staging and mandatory lymph node biopsy for any patient to be treated by surgery alone (25). In 116 patients 4-year event free survival (EFS) was 89.7% and OS was 100%. The study confirmed earlier findings that loss of imprinting (LOI) and loss of heterozygosity (LOH) of 11p15 was associated with higher risk of relapse (26). Only 1/116 patients developed a metachronous tumour.

For most children with stage I favourable histology tumours, VA chemotherapy remains the standard of care. However, this treatment can cause severe myelosuppression and hepatic toxicity (27-29), which can be life-threatening in children under 2 years of age (30). Moreover, the only evidence for any synergy of this combination is based on results of the NWTS-1 study, small by today's standards, which randomised 63 patients to actinomycin-D monotherapy, 44 to vincristine monotherapy and 59 to the combination, with all patients receiving abdominal radiotherapy. This showed 2 year disease free survival of 57%, 55%, 81%, respectively for these patients who all had group II/III tumours (31). The chemotherapy randomisation was not tested in children with group I tumours (now considered equivalent to stage I). There has been no other randomised trial of the combination versus monotherapy of either drug, therefore it is legitimate to pose the question whether today's standard of VA chemotherapy could be further optimised for stage I favourable histology tumours.

Vincristine monotherapy has been used in the UK for the treatment of stage I FHWT after immediate nephrectomy since the 1970's (32, 33). In 242 children on UKW2 and UKW3 4-year EFS was 86.5% and 4-year OS was 94.7% with age >4 years being an adverse prognostic factor (34). This may be due to more adverse tumour biology in older children such as anaplasia, 1q gain and LOH 1p and 16q (15, 35, 36). A decision tree analysis comparing VA, vincristine alone, or observation alone in younger patients with upfront nephrectomy and stage I favourable histology WT calculated expected survival rates of >98% for each approach and concluded that nephrectomy-only is an acceptable strategy although it may carry a small increased risk of long-term side effects due to the increased proportion exposed to relapse therapy (37). However, for the many children that do not fit the strict criteria for nephrectomy only and do not have access to expert multidisciplinary review of their case, vincristine monotherapy might be considered a perfectly reasonable option for favourable histology stage I WT (38).

Further strategies to reduce side effects in children receiving VA chemotherapy come from the field of pharmacogenomics and pharmacokinetics. Several polymorphisms of the vincristine pathway have been identified in children with childhood acute lymphoblastic leukaemia and may provide a new predictive marker for efficacy and toxicity of vincristine treatment (39-41). Additionally, better characterisation of the pharmacokinetics of actinomycin-D might help to better predict its exposure in younger patients and guide further dosing (42, 43).

Efforts to better characterise the biological features of children who relapse in this group is hindered by low numbers. In their current approach the COG group give extra treatment to stage I-II FHWT with LOH at 1p and 16q except in the Very Low Risk (VLR) category of patients (table 3b). Gene expression profiling and allele loss analyses suggest that there are at least three distinct biological subgroups among the VLR patients that may more precisely predict relapse risk (44). It is quite possible that in the setting of no adjuvant chemotherapy, these underlying genetic alterations may become significant prognostic risk factors.

The second group consists of patients with higher risk disease who receive 3-drug treatment with actinomycin-D, vincristine and doxorubicin (AVD) and sometimes radiotherapy. This is a very heterogeneous group of patients. For stage II and III LR and IR histology patients the SIOP group has omitted doxorubicin based on the results of the WT SIOP 2001 trial (45). In the forthcoming UMBRELLA trial they will use tumour volume >500ml found at histology after pre-operative chemotherapy and nephrectomy to stratify patients with stage II and III tumours with non-stromal and non-epithelial histology to re-introduce doxorubicin in post-operative chemotherapy (46). This trial will also evaluate gain of 1q and blastemal volume prospectively as possible markers for poor prognosis (12, 47, 48). The COG consortium will continue to use LOH at 1p and 16q but will also explore gain of chromosome 1q as a risk factor for stratification. Their previous studies have found that 1q gain is observed in 25% of WT samples and is associated with a relative risk of recurrence of approximately 2.5 to 3 (36, 49). If 1q gain is validated as a prognostic factor, this may lead to elimination of doxorubicin for patients with stage III FHWT without 1q gain (and without LOH at 1p and 16q) but to augmentation of therapy for patients with stage I-IV FHWT with 1q gain. The challenge to introducing any novel, more targeted therapies to this group is that the underlying biological mechanisms of the adverse molecular biomarkers is not yet understood.

Patients with features of high risk disease, either unfavourable histology or metastases that do not resolve with chemotherapy will all receive more than 3 drugs. In this third group outcome is still not optimal, toxicity is high and there is need for better understanding of mechanisms of metastases and relapse as well as the requirement for better treatment strategies or new drugs. Our understanding of the genetic landscape of WT is rapidly evolving, describing tumour heterogeneity (50) and identifying common processes and pathways that could further be explored as possible therapeutic targets (5) or used to better predict relapse, such as the suggestion that the combination of *SIX* and miRNAPG mutations in the same tumor is associated with evidence of RAS activation and a higher rate of relapse and death (51). Also, the characterisation of biologically unique subsets of WT by gene expression analysis may allow for both subset-specific and targeted therapeutic strategies in the future (52). The development of innovative preclinical models such as organoids provide a novel platform to efficiently test new drugs in different subtypes of WT prior to clinical trials and the development of patient-derived tumoroids would allow for patient-specific drug testing and the development of individualised treatment regimens (53, 54).

3 Metastatic Wilms Tumour

Overall, 17% of patients present with stage IV WT, defined by the presence of haematogenous metastases to lung, liver, bone, brain, extra-abdominal lymph nodes or other site. The lung is by far the most common site of metastasis (46). Traditionally, chest X-ray (CXR) was used to detect pulmonary metastasis, but the introduction of computed tomography (CT) has made it possible to detect lesions less than 1 cm which are too small to be seen on CXR. However, not all of these lesions necessarily represent metastases and CT comes with a much higher inter-observer variability (55, 56). Several retrospective studies have suggested benefit for using more intensive chemotherapy for patients with CT-only nodules. The UKW2 study found that stage I patients, who were treated with vincristine alone, had a higher relapse rate when CT-only lesions were present (57). A NWTSG study suggested that patients with CT-only lung nodules may have improved EFS but not OS from the inclusion of doxorubicin (56). More recently analysis of the SIOP 2001 study showed that EFS and OS of patients with CT-only lung lesions were (significantly) inferior to that of true localised-disease patients and (non-significantly) superior to that of true metastatic patients. Though the difference between CT-only patients treated for localised or metastatic disease did not reach statistical significance, clinicians showed a clear preference to treat CT-only lung nodules as metastatic disease (55).

All study groups currently treat patients with metastases with 3 or more drugs (table 3). In the current COG strategy, for complete response of lung nodules to 6 weeks of AVD chemotherapy, lung radiotherapy is omitted in patients with FHWT. With this strategy, 40% of patients avoid lung radiotherapy and receive a total cumulative doxorubicin dose of 150 mg/m2 to achieve excellent 4-year OS of 96.1%. (10, 58). However tumour biology may allow further sub-stratification of patients who can safely avoid radiotherapy - EFS was only 57% in 21 patients whose primary tumour showed chromosome 1q gain compared to 86% in 75 patients whose tumours lacked 1q gain (58). Patients with incomplete response and/or patients with LOH at 1p and 16q switch to a 5-drug regimen (table 3b). All patients with anaplasia are treated with a different 5-drug regimen. In patients with diffuse anaplasia and measurable disease introduction of a vincristine and irinotecan window therapy in a phase 2 study resulted in a response rate of 79% and was well tolerated (59), allowing further evaluation for incorporation of this strategy into current treatment regimens.

In the new UMBRELLA protocol, lung nodules with a diameter of at least 3mm will be considered metastatic lesions. Pre-operative treatment with AVD will result in 61-67% of patients having complete metastatic response before surgery (60, 61). Stratification of postoperative chemotherapy will take into account local stage of the primary tumour, histology of the primary tumour and metastatic tumour (if resected), size of metastatic lesions and their response to preoperative treatment and surgery. Based on the preliminary data from the COG strategy, the UMBRELLA protocol aims to lower the cumulative dose of doxorubicin for patients with complete response after pre-operative chemotherapy in order to reduce cardiac toxicity. For patients with high risk histology, prognosis is poor and advice of a national tumour panel is recommended (46).

4 Management of relapse

For patients treated according to SIOP, approximately 10% of IR patients and 25% of anaplastic and blastemal patients have recurrent disease with an OS amongst relapsed patients of around 50% (4). Both surgery and radiotherapy play an important role in treating relapsed WT, but studies and clear guidelines are lacking.

A number of potential prognostic features have been analysed, but anaplastic or SIOP high-risk histology and initial chemotherapy including doxorubicin are the two features that have been consistently associated with worse outcome after relapse (16).

The latest generation of active agents for relapsed WT, such as etoposide, carboplatin, ifosfamide and cyclophosphamide have demonstrated objective responses in 50-75% in phase II trials (62-65). Intensified use of these drugs is included as backbone treatment for relapsed WT across SIOP and COG recommendations. Despite thorough Bayesian analysis of published literature there is insufficient evidence for efficacy of high-dose chemotherapy with autologous stem cell rescue (ASCR) (66). Topoisomerase inhibitors have shown promising results, especially in WT patients with diffuse anaplasia, but further evidence is required (59, 67-69).

Treatment regimens for recurrent WT have generally been designed to include drugs that are not used during primary chemotherapy, using a risk-stratified approach which takes into account the nature of initial treatment and histology of the primary tumour. Due to small number of patients, advancing knowledge for second line chemo through randomised clinical trials is difficult and is mainly based on 3 prospective single-arm studies and case series (70-72). UMBRELLA aims to standardise relapse treatment for SIOP patients with recurrent WT. Treatment is given according to three risk categories (16, 46). The standard risk group includes patients with favourable histology WT who relapse after VA chemotherapy. They will receive a 4-drug regimen and survival rates are expected to be between 70-80% (70). The high risk group includes patients with favourable histology WT who relapse after therapy with three or more agents. For these patients survival rates are expected to be between 40-50%. They will receive alternating cycles of Ifosfamide, Carboplatin, Etoposide and Cyclophosphamide, Carboplatin, Etoposide (ICE/CyCE). Due to lack of conclusive evidence of efficacy, consolidation with high-dose melphalan and ASCR is left to the choice of the treating physician. The very high risk group includes patients with recurrent anaplastic or blastemal-type WT. These patients have a dismal long-term survival in the 10% range, with very poor responses to any drug or combination, which is likely due to intrinsic drug resistance (69). Inclusion into novel agent trials is therefore justified for these patients.

In the future, it may be that the small number of patients relapsing after only short course VA or no chemotherapy in the context of stage I favourable or low and intermediate risk histology could be considered for reduced intensity relapse therapy if their long term survival proves to be excellent.

The COG group is planning to conduct a randomised phase II study to evaluate contribution of a biological agent to a chemotherapy backbone of topotecan in addition to other active agents including ifosfamide, carboplatin, etoposide and cyclophosphamide. Selection of the biological agent will depend on results of ongoing COG phase 1 and 2 studies of agents targeting IGF1R, aurora A kinase, c-MET, JAK2 and receptor kinase inhibitors (49).

5 Novel approaches

Despite the improvement in survival rates for children with WT, those with high risk prognostic features and metastatic disease or patients who relapse or progress after first line treatment still have a poor prognosis. The intensified treatment for these children comes with significant acute and late toxicities. Therefore identification of novel therapies is essential for this group.

Our understanding of WT tumorigenesis is evolving and several signalling pathways, microRNA processing genes and epigenetics are now known to play a role in WT (4). The European Network for Cancer Research in Children and Adolescents consortium (ENCCA) organised a workshop to explore the therapeutic potential of the three main pathways linked to the development of WT identified at that time, that might also explain the clinical heterogeneity observed in WT (73, 74). These pathways include aberrant activation of the WNT/beta-catenin signalling cascade, activation of the IGF2 pathway often with evidence of epigenetic aberrations and pathways involving TP53, which seem to be involved in anaplastic WT predominantly. MYCN might be another therapeutic target, as amplification of the oncogene is associated with anaplasia, but also predicts poor outcome regardless of anaplastic histology (75).

A recent review paper summarises the phase I and II trial activity and outcomes for patients with WT over the last 10 years and discusses potential areas for improvement (76). Compared to conventional chemotherapy, very few novel agents demonstrated tumour response and at best, stable disease. Table 4 summarises the results for novel agents that specifically targeted the pathways identified by ENCCA to be significant in WT (73, 74, 76). The lack of promising results can partly be explained by the small numbers of patients with tumours that had not undergone genetic characterisation. Also, due to complex interactions between signalling pathways and resistance mechanisms, rational combination therapies are probably needed (4).

Other promising treatment strategies come from the field of immune-oncology. Lorvotuzumab mertansine, a conjugate between a cytotoxic drug and a monoclonal Antibody to CD56, was tested as a very promising agent against primitive blastemal component of WT, based on high levels of CD56 expression in these cells. Results of a recent phase II study show good tolerability in children, assessment of efficacy is ongoing (77).

Brok et al. reported a very low overall accrual of WT patients to early-phase trials and a relative lack of European studies compared to North America (76). Conducting early-phase trials of targeted therapies in WT patients is challenging due to lack of patients with refractory or relapsed disease, rapid progression of relapse and the profound clinical and genetic heterogeneity of the tumours with a low prevalence of individual somatic druggable mutations. However the proactive strategic decision made by COG to prioritise one promising single agent for WT and enrolling patients from across study groups has proven to be successful in acquiring sufficient numbers of patients and generating results in a reasonable time frame.

6 Conclusions

Multi-modality treatment and risk-stratified approaches have been very successful in the treatment of children with WT. To further improve outcomes improved risk stratification markers are needed to better direct therapy beyond the limitations of current stratification based on age, histology and staging of tumour. The SIOP and COG renal tumour study groups meet regularly to discuss the place of established and emerging molecular biomarkers and clinical (imaging and histological) response to treatment in this endeavour (10, 46, 49). Due to small numbers in many sub-groups, validation of a proposed biomarker is accelerated by parallel assessment in the two populations exposed to different treatment approaches (36, 47). Jointly planned studies may be required to investigate the clinical relevance of the less common genetic abnormalities found in WT and to translate these results into early phase trials that can recruit adequate numbers of appropriate patients internationally.

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Compliance with Ethical Standards

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Conflict of Interest:

Radna Minou Oostveen and Kathy Pritchard-Jones declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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Figures and Tables

Table 1

Factors used in risk stratification by SIOP (UMBRELLA) and COG (12, 13)

	SIOP	COG
Tumour staging **I**	a) Tumour is limited to the kidney. b) Tumour is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule might be infiltrated by viable tumour, which does not reach the outer surface. c) Tumour might show protruding (botryoid) growth into the renal pelvis or the ureter but does not infiltrate their walls. d) The vessels or the soft tissues of the renal sinus are not involved by tumour. Intrarenal vessel involvement might be present.	Tumor is limited to the kidney and has been completely resected. The tumor was not ruptured or biopsied before removal. No penetration of the renal capsule or involvement of renal sinus vessels.
II	a) Viable tumour is present in the perirenal fat and is not covered by a (pseudo)capsule, but it is completely resected (resection margins clear). b) Viable tumour infiltrates the soft tissues of the renal sinus c) Viable tumour infiltrates blood and/or lymphatic vessels of the renal sinus or of the perirenal tissue, but it is completely resected. d) Viable tumour infiltrates the wall of the renal pelvis or of the ureter. e) Viable tumour infiltrates the venal cava or adjacent organs (except the adrenal gland) but is completely resected.	Tumor extends beyond the capsule of the kidney but was completely resected with no evidence of tumor at or beyond the margins of resection. There is penetration of the renal capsule or invasion of the renal sinus vessels.
III	a) Viable tumour is present at a resection margin. Nonviable tumour or chemotherapy-induced changes present at a resection margin are not regarded as stage III unless there is viable tumour present within 5mm of the inked margin. b) Abdominal lymph node involvement is present by either viable or nonviable tumour. c) Preoperative or intraoperative tumour rupture, if confirmed by microscopic examination (viable tumour at the surface of the specimen at the area of the rupture). d) Viable or nonviable tumour thrombus is present at resection margins of ureter, renal vein, or vena cava inferior (always discuss resection margins with the surgeon). e) Viable or nonviable tumour thrombus, which is attached to the IVC wall, is removed piecemeal by surgeon f) Wedge or open tumour biopsy before preoperative chemotherapy or surgery. g) Tumour implants (viable or nonviable) are found anywhere in the abdomen. h) Tumour (viable or nonviable) has penetrated through the peritoneal surface.	Gross or microscopic residual tumor remains post-operatively including inoperable tumor, positive surgical margins, tumor spillage surfaces, regional lymph node metastases, positive peritoneal cytology, or transected tumor thrombus. The tumor was ruptured or biopsied before removal.
IV	Haematogenous metastases (for example lung, liver, bone, brain.) or lymph node metastases outside the abdominopelvic region.	Hematogenous metastases or lymph node metastases outside the abdomen (e.g. lung, liver, bone, and brain)
V	Bilateral renal tumours at diagnosis. Each side should be substaged according to the above criteria.	Bilateral renal involvement is present at diagnosis.

Tumour histology	***Low Risk:*** WT completely necrotic ***Intermediate risk:*** WT mixed type, regressive type, epithelial type, stromal type, focal anaplasia ***High risk:*** WT blastemal type (after pre-operative chemo), diffuse anaplasia	***Favourable histology:*** WT mixed, blastemal predominant, epithelial predominant, stromal predominant ***Unfavourable histology:*** focal and diffuse anaplasia
Age of the patient	<6 months and >16 years	<2 years
Tumour weight/size	Tumour volume > 500ml (after pre-op chemotherapy) for non-epithelial and non-stromal stage II/III tumours of low or intermediate risk histology	Tumour weight <550gr for FHWT
Molecular markers	-	LOH for 1p and 16q in stage I-IV FHWT
Metastatic disease	Imaging and histological lung nodule response after pre-operative week 6 and imaging again if needed at week 10 post-operative	Lung nodule response at week 6

Table 2

Comparison of SIOP WT 2001 study (4) and COG NWTS-5 study (14, 15) events, percentage of total events, deaths and percentage of total deaths by stage and histology

	SIOP WT 2001 study						**COG NWTS-5 study**					
Stage	**Patients LR + IR**	**Events (2y)**	**Deaths (5y)**	**Patients HR**	**Events (2y)**	**Deaths (5y)**	**Patients FH**	**Events (4y)**	**Deaths (4y)**	**Patients FA + DA**	**Events (4y)**	**Deaths (4y)**
I	1447	97 24%	21 11%	163	12 3%	4 2%	415	21 8%	9 7%	29	8 3%	5 4%
II	631	63 15%	16 8%	115	17 4%	17 9%	555	80 29%	16 12%	28	5 2%	5 4%
III	537	57 14%	24 12%	141	42 10%	36 18%	488	66 24%	25 19%	74	26 9%	23 18%
IV	450	73 18%	41 21%	75	46 11%	40 20%	198	46 17%	27 21%	40	23 8%	21 16%
I+II	**2078**	**160 39%**	**37 19%**	**278**	**29 7%**	**21 11%**	**970**	**101 37%**	**25 19%**	**103**	**13 5%**	**10 8%**
III+IV	**987**	**130 32%**	**65 33%**	**216**	**88 22%**	**76 38%**	**686**	**112 41%**	**52 40%**	**114**	**49 18%**	**44 34%**

SIOP WT 2001 study ran from 1st November 2001 – 16th December 2009. NWTS-5 ran from Aug 1995 – June 2002. Interim results FH patients followed through August 17 2004 (15).

Abbreviations: LR=low risk, IR=intermediate risk, HR=high risk, FH=favourable histology, FA=focal anaplasia, DA=diffuse anaplasia

Table 3a

Treatment in the WT SIOP 2001 protocol

Post-op regimen and duration	**Histology, localised/metastatic, local stage, metastatic complete remission after surgery**	**Cumulative treatment (including pre-op)**
	Treatment with 2 drugs or less	
Intensive vincristine	Only for patients after primary nephrectomy with intermediate risk tumours (only non-anaplastic nephroblastoma and its variants)	VCR 15 mg/m2
No post-op chemo	Low risk, localised, stage I	ACT 0.09 mg/kg VCR 6 mg/m2
AV1 4wk	Intermediate risk, localised, stage I	ACT 0.135 mg/kg VCR 12 mg/m2
AV2 27wk	Low risk + Intermediate risk, localised, stage II-III	ACT 0.495 mg/kg VCR 36 mg/m2
	Treatment with 3 drugs	
AVD localised 27wk	High risk, localised, stage I	ACT 0.495 mg/kg VCR 36 mg/m2 DOX 250 mg/m2
AVD metastatic 27wk	Low risk + Intermediate risk, metastatic, local stage I-III, metastatic complete remission after surgery	ACT 0.540 mg/kg VCR 39 mg/m2 DOX 300 mg/m2
	Treatment with more than 3 drugs	
High risk localised 34wk	High risk, localised, stage II-III	ACT 0.09 mg/kg VCR 6 mg/m2 VP16 2700 mg/m2 CARBO 3600 mg/m2 CYCLO 8100 mg/m2 DOX 300 mg/m2
High risk metastatic 24wk	Low risk +Intermediate risk, metastatic, local stage I-III, no metastatic complete remission after surgery High risk, metastatic, local stage I-III, regardless of metastatic complete after surgery	ACT 0.135 mg/kg VCR 9 mg/m2 VP16 3600 mg/m2 CARBO 4800 mg/m2 CYCLO 5400 mg/m2 DOX 300 mg/m2

Abbreviations: Post-op=post-operative, Pre-op=pre-operative, VCR=vincristine, ACT=actinomycin-D, DOX=doxorubicin, VP16=etoposide, CARBO=carboplatin, CYCLO=cyclophosphamide

Table 3b

Treatment according to COG AREN03B2, AREN0321, AREN0532 and AREN0533 protocols

Post-op regimen	Histology, risk category, stage, extra RF	Cumulative Treatment (including pre-op)
	Treatment with 2 drugs or less	
No Surgery	FH, Very Low Risk, localised, stage I, <2y AND <550gr	-
EE-4A 19wk	FH, Low Risk, localised, stage I-II, no LOH 1p and 16q	ACT 0.315 mg/kg VCR 0.701 mg/kg OR 21 mg/m2
	Treatment with 3 drugs	
DD-4A 25wk	FH, Standard Risk, localised, stage I, LOH 1p and 16q and not <2y+<550gr FH, Standard Risk, localised, stage II, LOH 1p and 16q FH, Standard Risk, localised, stage III, no LOH 1p and 16q FH, Standard Risk, metastatic, RCR and no LOH Focal Anaplastic, High Risk, stage I-III Diffuse Anaplastic, High Risk, stage I	ACT 0.225 mg/kg VCR 0.835 mg/kg OR 25 mg/m2 DOX 150 mg/m2
	Treatment with 4 drugs or more	
DD-4A (6wk) + Regimen M 37wk	FH, Higher Risk, stage III, LOH 1p and 16q FH, Higher Risk, stage IV, SIR and no LOH FH, Higher Risk, stage IV, LOH 1p and 16q	ACT 0.145 mg/kg VCR 0.835 mg/kg OR 25 mg/m2 DOX 195 mg/m2 CYCLO 8800 mg/m2 VP16 2000 mg/m2
Revised UH-1 30wk	Focal Anaplastic, High Risk, stage IV Diffuse Anaplastic, High Risk, II-III and IV (no measurable disease)	VCR 0.75 mg/kg OR 22.5 mg/m2 VP16 2000 mg/m2 CARBO* – 1000-2800 mg/m2 CYCLO 14800 mg/m2 DOX 225 mg/m2
VCR/IRIN window + Revised UH-1 33wk	Diffuse Anaplastic, High Risk, stage IV (measurable disease), PD after 1 course VCR/IRIN	VCR 0.85 mg/kg OR 25.5 mg/m2 VP16 – 2000 mg/m2 CARBO* – 1000-2800 mg/m2 CYCLO 14800 mg/m2 DOX 225 mg/m2 IRIN 200 mg/m2
2x VCR/IRIN window + Revised UH-1 36wk	Diffuse Anaplastic, High Risk, stage IV (measurable disease), SD/PD after 2 courses VCR/IRIN	VCR 0.95 mg/kg OR 28.5 mg/m2 VP16 2000 mg/m2 CARBO* 1000-2800 mg/m2 CYCLO 14800 mg/m2 DOX 225 mg/m2 IRIN 400 mg/m2
2x VCR/IRIN window Revised UH-2 42wk	Diffuse Anaplastic, High Risk, stage IV (measurable disease), PR/CR after 2 courses VCR/IRIN	VCR 1.15 mg/kg OR 34.5 mg/m2 VP16 2000 mg/m2 CARBO* 1000-2800 mg/m2 CYCLO 14800 mg/m2 DOX 225 mg/m2 IRIN 480 mg/m2

***) dose dependent on GFR results**

Abbreviations: Post-op=post-operative, Pre-op=pre-operative, LOH=loss of heterozygosity, RCR=rapid complete responders, SIR=slow intermediate responders, SD=stable disease, PD=progressive disease, CR=complete remission, FH=favourable histology, PR=partial remission, ACT=actinomycin-D, VCR=

vincristine, DOX=doxorubicin, VP16=etoposide, CARBO=carboplatin, CYCLO=cyclophosphamide, IRIN=irinotecan

Table 4

Published agents tested in phase I or II trials including at least 1 patient with WT with description of pathway involved and mechanism of action (73, 74, 76)

Treatment	**Pathway**	**Mechanism of action**	**Phase of trial, Author, publication year**	**Enrolled WT (response)**
Cixutumumab	IGF pathway	Human IgGI moAB against IGF-1 receptor	I/II, Malempati 2012 (78)	2 (none)
Cixutumumab	IGF pathway	Human IgGI moAB against IGF-1 receptor	II, Weigel 2014 (79)	10 (none)
Cixutumumab + Temsirolimus	IGF pathway	Human IgGI moAB against IGF-1 receptor	I, Fouladi 2015 (80)	2 (none)
Dalotuzumab + Ridaforolimus	IGF pathway	IGF-1 receptor antagonist	I, Frappaz 2016 (81)	1 (none)
Gemcitabine	Dysregulation of epigenome	Nucleoside analog	II, Wagner-Bohn 2006 (82)	1 (none)
Oxaliplatin **+ Gemcitabine**	Dysregulation of epigenome	Nucleoside analog	II, Geoerger 2011 (83)	5 (none)
Valproic acid	Dysregulation of epigenome	HDAC inhibitor	I, Su 2011 (84)	1 (none)
Vorinostat + Bortezomib	Dysregulation of epigenome	HDAC inhibitor	I, Muscal 2013 (85)	1 (none)
Depsipeptide	Dysregulation of epigenome	HDAC inhibitor	I, Fouladi 2006 (86)	2 (none)
Celecoxib + Thalidomide + Cyclophosphamide + Etoposide	WNT/beta-catenin pathway	Selective COX-2 inhibitor	II, Robison 2014 (87)	3 (NR)
Fenretinide	WNT/beta catenin pathway	Semisynthetic retinoid	I, Villablanca 2006 (88)	1 (none)
All-*trans*-retinoic acid + Interferon-α2a	WNT/beta catenin pathway	Retinoid	II, Adamson 2007 (89)	14 (none)
Alisertib	MYCN	Aurora A kinase inhibitor	I, Mossé 2012 (90)	2 (none)

Abbreviations: IGF=insuline-like growth factor, IgG=immunoglobulin G, moAB=monoclonal antibody, HDAC=histone deacetylase, COX-2=cyclooxygenase-2, NR=not reported