

Review of phase I and II trials for Wilms' tumour

- *Can we optimise the search for novel agents?*

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ABSTRACT

Survival rates for patients with Wilms' tumour (WT) approximate 90% with refined use of currently available interventions. However, a subgroup of patients with initial high-risk histopathology or relapsing disease have a poor prognosis and it is a challenge to identify and prioritise the development of new innovative approaches for these subgroups. We conducted a systematic literature search for published phase I and II clinical trials that registered patients with WTs, and characterised the early-phase trial activity, quantified response rates and highlighted avenues for further development. We identified 63 trials (48 phase I, three phase I/II, and 12 phase II trials) enrolling 214 patients with WTs, alongside other malignancies. The number of annually recruited WTs did not change significantly and was less than 20% of the potential candidates. The vast majority of the trials were conducted in North America and 56 different interventions were investigated, including conventional chemotherapy and biologically-targeted therapies. Overall, 33 WTs revealed some degree of tumour control. Of these, five patients demonstrated complete remission (2%), 15 patients partial response (7%) and 13 patients stable disease (6%). None of the included novel biologically-targeted therapies emerged as promising interventions and only conventional chemotherapy was able to induce a complete and partial response. We conclude that early phase trial recruitment of WTs is below expected and the clinical outcome of the included patients is dismal. Improvement of the availability and recruitment to early-phase trials for WT, especially in Europe, is needed.

Keywords Wilms' tumour, phase I/II trials, relapse, refractory, targeted therapy, chemotherapy.

1. Introduction

Wilms' tumour (WT) is the most common paediatric renal tumour, affecting approximately 1 in 10,000 children, with a peak incidence at three years of age [1]. Nearly 1,000 new cases are diagnosed in Europe every year, and 600 in the United States. Disease-free survival rates approximating 90% can be achieved with optimised use of currently-available interventions [2-4]. However, a subset of patients still have a poor prognosis, which is linked to high-risk histopathology, especially with advanced-stage disease and/or when disease relapse occur. In addition, one in four survivors experience severe chronic health conditions related to the antitumour therapies that they have received [5].

One standard treatment for localised low- and intermediate-risk histology WT is a two drug regimen, vincristine and actinomycin D according to the European Société Internationale d'Oncologie Pédiatrique (SIOP) protocol [6]. A third drug, doxorubicin is further added in metastatic cases. Radiotherapy is administered for most patients with residual tumour after nephrectomy and for persistent (drug resistant) metastases predominantly occurring in the lungs [7,8]. Interestingly, it is known that WT was the first metastatic solid tumour to demonstrate response to chemotherapy in the mid 1950's and that radiotherapy and actinomycin D were remarkably synergistic [9]. Accordingly, at least two thirds of children with WT are currently treated successfully with refinement of drug regimens and radiotherapy that were introduced in clinical practice more than 50 years ago.

For approximately 10% of patients diagnosed with high-risk histology WT (blastemal type remaining after pre-operative chemotherapy or diffuse anaplasia), standard treatment

additionally includes carboplatin, etoposide, and cyclophosphamide [7,8]. Despite intensification of therapy, such patients, maintain unsatisfactory overall survival rates with one third succumbing to their disease if presenting with metastases (table 1).

'Second-line' chemotherapy for relapsed or refractory WT depends on which drugs have been previously used upfront but is usually based on ifosfamide or cyclophosphamide, carboplatin and etoposide combined with irradiation and attempt of surgical resection [10]. The introduction of these drugs subsequently to phase II trials [11-14] led to improved post-recurrence disease-free survival rates ranging between 30% and 70% depending on the initial treatment and primary tumour histology [15,16]. Unlike 'first-line' treatment, 'second-line' chemotherapy is not based on evidence from randomised trials, but solely on prospective single arm studies and case series. Alternative chemotherapy (e.g., irinotecan, topotecan and temozolamide) or a further increase in dose intensity, like those reached in myeloid-ablative regimens, have demonstrated limited evidence for improvement in survival rates [17-20].

Of all the 1,600 WTs expected to occur annually across countries who apply the clinical protocols of the SIOP-RTSG and COG, approximately 15% will recur or have refractory disease to initial chemotherapy regimens, of whom about 50% eventually fail to second line conventional chemotherapy. Hence, we would expect that more than 100 relapsed patients yearly are ultimately potential candidates for entering early-phase clinical trials on new or alternative drugs. Therefore, the aim of this review is to establish the level of phase I and II trial activity and outcomes reported for patients with WT over the last 10 years and discuss potential areas for improvement and related actions for optimising development of new therapeutic strategies.

2. Methods

2.1. Inclusion criteria

We searched for any phase I or II early phase clinical trial published in 2005 onwards that have enrolled relapsed or refractory WT to any previous treatment regimen. We excluded studies not registered as phase I/II studies. Likewise, we did not include phase I/II trials focusing on supportive care.

2.2. Search strategy

We identified phase I and II trials in Medline (Pubmed) and hand-searched relevant conference abstract books (SIOP, ASCO (American Society of Clinical Oncology) and ASPHO (American Society of Pediatric Hematology/Oncology) meetings) for additional trials. We searched for registered clinical trials and registered trials on <http://clinicaltrials.gov>, <http://who.int/trialsearch/> and the European ITCC (Innovative Therapies for Children with Cancer) and North American Children's Oncology Group (COG) homepages. The last search was carried out in July 2016. We used the key search terms: 'Wilms' or 'nephroblastoma', 'solid tumour', 'paediatric' or 'children' and phase I/II trial. There were no language restrictions. Two authors (JB and FS) screened the titles and abstracts for relevant trials identified by the search strategy. Disagreements were resolved by discussion. Authors of the included trials were contacted by e-mail if additional information was needed.

2.3. Data extraction

We identified the first author's name, responsible group/country, reported funding/support (non-profit, for-profit, or both), publication year and journal or conference, phase of trial (I or II) and design, inclusion criteria, number of patients with WT and with other solid tumour enrolled, drug/treatment regimen tested, and evaluation of target lesions (complete remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) for patients with WT.

2.4. Response criteria

We defined a 'response' to treatment depending on whether the patients obtained CR (disappearance of lesion(s)), PR (at least 30% decrease in the sum of diameters of target lesions) or SD (insufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) [21]. Tumour response was assessed and reported according to the RECIST criteria by the individual trials. Whether SD is a specific response related to treatment is debatable. However, as WT is a rapidly growing tumour and many patients entered the early phase trials with progressive disease, we considered SD a clinical response for purpose of this study.

3. Results

We identified 63 trials enrolling at least one patient with a WT (Table 2) (references in Appendix A). Of these, 48 were phase I trials, three embedded phase I/II, and 12 phase II on relapse or refractory paediatric solid tumours. All studies were non-randomised and 56 different interventions were investigated. Two studies included solely patients diagnosed with WT [22,23]. The remaining studies enrolled WT cases alongside various paediatric solid and/or haematological cancers. Overall, the identified trials enrolled 214 patients with WT

(range 1-25). We previously estimated that each year at least 100 relapsed patients in North America/Europe were potential candidates for early-phase clinical trials. Hence, 19% (214 out of 1,100 WTs from 2005-2016) of the candidates were enrolled in published trials in the study period. Through the years of reporting the number of published trials and number of recruited WTs per year did not indicate a significant trend towards increased or reduced activity (fig 1 and 2).

Fifty-four studies (86%) were conducted in North America, predominantly as multi-institutional cooperative trials through the COG and National Cancer Institute (NCI) collaboration. One trial was conducted in South America, one in Japan, and six trials (10%) were conducted in Europe, with two by the ITCC. A single trans-Atlantic trial has recently been published (table 2). Forty-one trials (65%) were supported by both for-profit and non-profit organisation, 15 trials were supported only by non-profit, three trials by for-profit and four trials had unclear funding status.

In 17 trials, solely licensed cytotoxic chemotherapeutic agent(s) rarely incorporated in front-line standard protocols was administered. Novel agents or alternative non-chemotherapeutic compounds were assessed in 54 trials, either as monotherapy (83%) or combined with chemotherapy (17%). The most frequently used cytotoxic agents were irinotecan (ten trials), oxaliplatin (five trials) and cyclophosphamide (five trials). The novel agent trials encompassed a heterogeneous group of immunotherapy, receptor inhibitors, and differentiating agents. These agents mainly belonged to the biologically-targeted therapies of tyrosine kinase inhibitors or VEGF/IGF antibodies, most frequently sorafenib (four trials), bevacizumab (four trials) and cixutumumab (three trials) (table 2). The overall trend was that relatively more

novel agents were being investigated over the years of reporting compared to conventional chemotherapy (Fig 1).

The majority of trials (92%) reported on the anti-tumour effects for the WTs according to the RECIST criteria. For the trials where chemotherapy predominated, a response was observed in 25 out of 115 patients; irinotecan (1 PR), topotecan (12 PR), actinomycin D/rTNF α (3 CR, 5 SD), vincristine/irinotecan/temozolomide/bevacizumab (2 CR, 1 PR), and carboplatin/irinotecan (1 SD) (Table 3). For monotherapy with novel agent a response was observed in eight out of 99 patients; gefitinib (2 SD), ixabepilone (1 SD), adenovirus (OCIVIR-7) (1 PR), Seneca Valley Virus (2 SD), and sorafenib (2 SD) (table 3). Accordingly, overall 33 WTs revealed some degree of tumour control in early phase trials i.e., five CR, 15 PR, and 13 SD. Only conventional chemotherapy induced CR and PR (table 3) (appendix B and C).

Through an *ad hoc* search at clinicaltrials.gov using the search terms 'solid tumour' or 'nephroblastoma/Wilms' and the criteria 'ongoing study', '0-17 years' also identified 44 ongoing early phase I/II studies with the potential to recruit WT patients (July 2016).

4. Discussion

In this study, we found that approximately 200 patients with relapsed or refractory WT have been enrolled in published early phase studies over the last 10 years. As expected, according to standard evaluation criteria, only a small proportion of patients demonstrated response to treatment. This included a heterogeneous group of traditional chemotherapy to novel targeted therapy or a combination of both.

Through this review of published early phase trials for WT, we found it clinically important to provide the oncologists and researchers with an overview of the activity on new drug development, the outcomes on advanced WT, and to identify areas that could potentially be improved. We know that our report has limitations. Although we adhered to an exhaustive and reproducible search strategy, we may not have identified all relevant studies, for example those published in other databases or meeting books that were not included in our search. Some potential eligible studies only reported on overall toxicity and did not report about inclusion and outcomes of WT. Finally, publication bias will always influence a review as some relevant trials remain unpublished. Hence, our review may slightly underestimate the activity but we considered it less likely that a significant number of WT recruited for early phase trials have been missed.

Standard treatment recommendations with chemotherapy for relapse/refractory WT have been available for many years [10,24]. Accordingly, the patients recruited for the early phase trials were mainly either 2nd relapse or advanced refractory disease. Overall, the enrolled WTs include a variety of subgroups with prognostically different histological features, like the SIOP high-risk (diffuse anaplasia and blastemal-type histology) or intermediate-risk histology WT, and the COG unfavourable (histology with anaplasia) or favourable histology. Furthermore, acknowledging the additional and substantial intra-tumour genetic heterogeneity highlights the complexity of WT treatment and the challenge of gathering a group of WT in trials with comparable risk features [5].

The considerable improvement in the survival rates for children with WT during the last few decades is based on more optimised chemotherapy dosing, timing and intensity rather than adoption of novel compounds or strategies. Despite this refinement, children with high-risk prognostic features and metastatic disease still have a poor prognosis and the intensified treatment for these children comes with significant acute and late toxicities [5,26].

Identification of novel therapies is therefore essential [27,28]. Hence, one concern emerging from our study is the paucity of patients with recurrent WT tested for new drugs in comparison to the number of potential candidates. The number of trials and WT recruitment seems consistent throughout our search period, and is in the range of about 20 patients per year. Hence, the recruitment rate could be strengthened knowing that up to 100 cases could be eligible each year. This rough estimate illustrates that a considerable number of relapsed patients are treated outside controlled clinical trials, and likely with regimens with unregistered clinical efficacy. This contrasts the high proportion of children with WT enrolled in frontline treatment protocols [6].

There may be multiple explanations for the low accrual rate of children with WT in trials on new drugs. The rapid growth of relapsing WT and unavailability of new drug trials locally may narrow the window for clinicians and parents to decide on additional trial enrolment and to bridge to early phase trials. In addition, marrow and other prolonged toxicities subsequent to high-dose chemotherapy (frequently used at first WT relapse) and radiotherapy cause some patients to be ineligible for early phase trials due to the strict inclusion criteria. The genetic heterogeneity of WT and the low prevalence of known druggable somatic mutations, also makes it challenging to design a WT biologically driven new drug trial [26,27]. More 'subjective' reasons may be that WT has a high remission rate achieved frontline and a good

response rate in relapsing tumours, which may explain why research on new strategies/compounds for WT has attracted less attention and fewer resources than other paediatric cancers. In this vein the local responsible clinician may also consider that patients with recurrent/refractory WT are still curable, often after multiple lines of chemotherapy (outside protocols) and underestimate the poor prognosis for such cases.

Although the acceptable post-relapse outcome for standard-risk patients may justify the use of conventional drugs at first relapse, the prognosis is dismal for patients with subsequent relapses or with unfavourable features at first relapse [15,29,30]. The latest generation of active agents for relapse WT, such as etoposide, carboplatin, ifosfamide, and cyclophosphamide have demonstrated objective responses in 50-75% in phase II trials [11-14]. Intensified use of these drugs is included as backbone treatment for relapsed WT across SIOP and COG recommendations. It is noteworthy that convincing evidence for high-dose chemotherapy with autologous stem cell rescue remains inadequate despite thorough Bayesian analysis of the published evidence [17]. More recently, topoisomerase inhibitors (irinotecan and topotecan) have been tested as promising alternatives for subgroups of WT, but further evidence is required [18,19,23,31].

Unfortunately, the recruitment of relapsed WT is scattered throughout many different trials resulting in very few patients in each individual trial. Three trials (on topotecan, rTNF/actinomycin D and vincristine/irinotecan/temozolomide/bevacizumab, respectively) demonstrated some response, but due to such small numbers, it is impossible to make any firm recommendations (table 2) [22,23,32]. Looking at the novel agent trials revealed that numerous biological interventions were assessed and focus was on anti-angiogenic

compounds (inhibitors and antibodies), IGF-1R antibodies and mTOR inhibitors. Compared to conventional chemotherapy very few novel agents, such as monotherapy, demonstrated tumour response and at best, stable disease. Based on these findings, standard chemotherapy currently seems more promising on short-term basis in comparison to the use of novel agents for WT. However, the trend is clearly going towards assessing more novel agents but we are still awaiting a more promising biologic agent (Table 2). We also have to recognise that early phase trials design focuses on toxicity and safety as primary endpoints – especially those conducted in the earliest period of this review -, whereas tumour response, although reported in the vast majority of the trials, represents a secondary outcome endpoint. Therefore some agents may not have shown efficacy because they have been tested using suboptimal drug doses or tested in a limited number of patients.

Our understanding of WT tumorigenesis is evolving, and several signalling pathways, microRNA processing genes and epigenetics are now known to play some roles [33]. A drug development approach focusing on renal tumour biology could adequately direct the resources for new trials. A recent European drug development workshop focused on a comprehensive analysis of WT tumorigenesis and hence proposed a wide range of potential biological targets and relative therapies for WT [26,27]. Targeting the aberrant activation of the WNT/beta-catenin signalling cascade or the insulin-like growth factor (IGF) signalling pathway have been discussed, but not yet transferred into clinical trials. Currently, the most WT-focused ongoing early phase trial is targeting the cell-surface glycoprotein CD56 with an antibody (lorvotuzumab mertansine) [34]. CD56 is mainly expressed in blastemal components. Blastemal predominant histopathologies have a poorer prognosis, therefore

lorvotuzumab may be most beneficial for this subgroup [35]. Over the first year this trial has impressively recruited 16 patients with WT.

We noticed a contrast between the efforts made on each side of the Atlantic. Only six early-phase trials have been published in Europe since 2005, as opposed to 54 in North America. New drug development programs in North America mainly rely on collaborations between the Developmental Therapeutics and the Renal Tumour Committee of the COG and medical research agencies (National Institutes of Health and NCI), along with pharmaceutical agency input. Adjacently, the Paediatric Preclinical Testing Program in USA systematically tests agents' *in vitro* and *in vivo* preclinical models of common childhood cancers. This "collaboration" has led to the initiation of several trials including new frontline drug trials for high-risk renal tumours. For example, a phase II window trial with irinotecan/vincristine in metastatic diffuse anaplastic WT was undertaken as this group of patients traditionally had a less than 30% disease-free survival expectancy [29,31]. In Europe, the two analogous organisations are the SIOP Renal Tumour Study Group (SIOP-RTSG) and the ITCC consortium, and further enhancing a reciprocal collaboration is a priority of The European Network for Cancer Research in Children initiative (ENNCA) [36]. Ideally, a trans-Atlantic collaboration would ensure adequate early phase trials for the relatively few WT cases, though challenged by non-trivial legislative and pharmaceutical logistics. Such collaboration may also facilitate a promising novel agents into a joint phase III randomised clinical trial despite the different treatment approach/regimen between COG and SIOP. An active interaction and discussion between the two disease-specific working groups across the ocean is ongoing.

In conclusion, further initiatives are needed to optimise recruitment of relapsed WT patients, like the successful COG approach of prioritising a single early phase trial or having a WT-stratum. The profound clinical and genetic heterogeneity of WT make designing early phase trials focusing on WT a challenge. In Europe especially, more available early phase trials are required and an organised cooperative effort between the ITCC and the SIOP-RTSG is considered a priority to emulate the COG's fruitful approach to patient recruitment. Efforts to channel patients with WT on a biologically rationale basis into a limited number of studies presents challenges when needed across several different countries e.g. in Europe. Developing such a strategy requires a cooperative approach from the pharmaceutical industry and regulatory bodies, with strong parental and patient involvement.

Conflicts of interest

None declared

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'innovative therapies for children with cancer' European consortium. *Cancer Treat*

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Fig. 1. Number of annual phase I and II trials that have reported on Wilms' tumour patients according to year of publication.

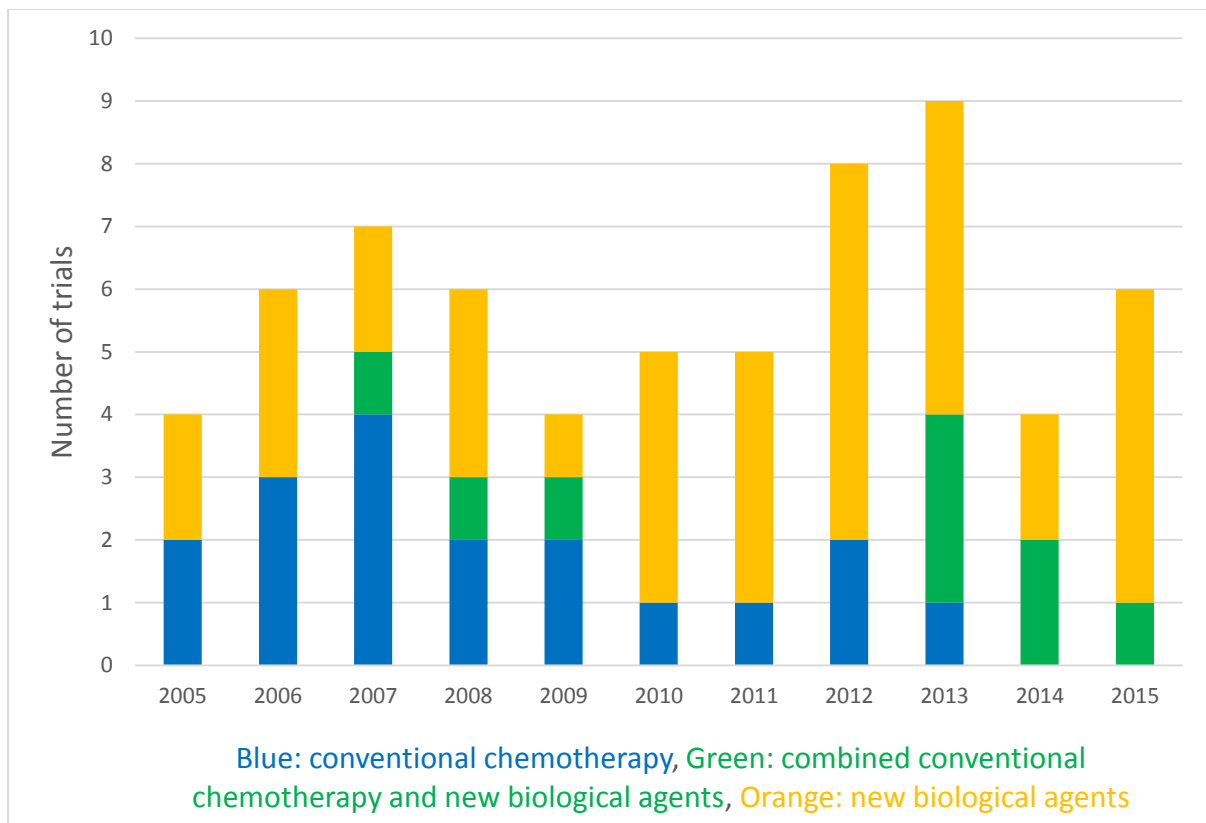


Fig. 2. Number of patients with Wilms' tumour included in phase I and II trials according to year of publication

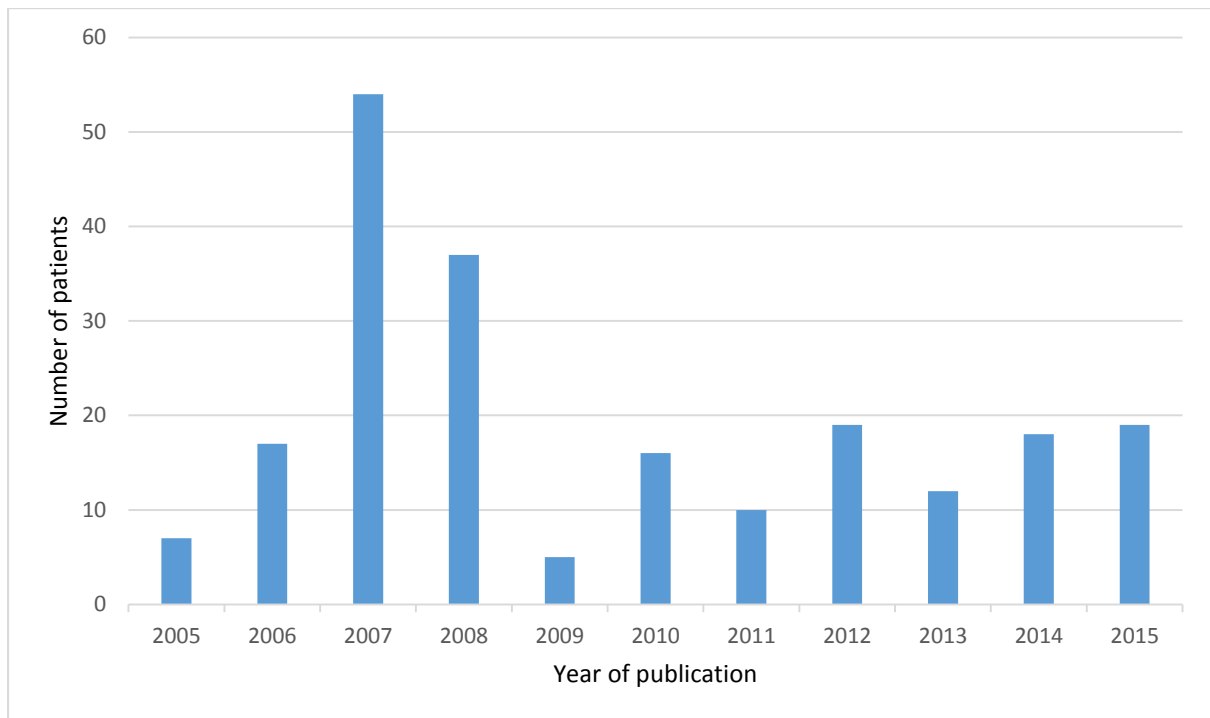


Table 1

2-year event free survival and 5-year overall survival for Wilms' tumour in the SIOP 2001 protocol.

Histopathology Risk Group	Stage I	Stage II	Stage III	Stage IV	All
Low Risk (N)	95	6	23	61	185
2y EFS (%)	97	100	100	91	95
5y OS (%)	99	100	100	94	98
Intermediate Risk (N)	1352	625	514	389	2880
2y EFS (%)	92	89	88	81	89
5y OS (%)	98	97	94	89	96
High Risk (N)	163	115	141	75	494
2y EFS (%)	91	84	68	31	74
5y OS (%)	97	82	70	35	76
All (N)	1610	746	678	525	3559
2y EFS (%)	92	88	84	76	87
5y OS (%)	98	94	90	82	93

N, number of patients; OS, overall survival; EFS, event free survival

Source: SIOP WT 2001 database for all patients with stage I-IV Wilms' tumour treated as per-protocol with pre-op chemotherapy, 5,731 patients were registered from 2001-2015. Analysis provided by Harm van Tinteren, trial statistician ((V Tinteren 2015).

Table 2: Published phase I or II trials including at least one patient with Wilms tumour.

Treatment	Enrolled solid tumours	Enrolled WT (tumour response)	Phase of trial (Origin/Group)	Funding	Author, publication year
Gefitinib	25	2 (2 SD)	I (NA/COG)	Both	Daw, 2005
Cisplatin/Temozolomide	38	2 (none)	I/II (France)	NP	Geoerger, 2005
Trabectedin	12	2 (none)	I (NA/COG)	Both	Lau 2005
Flavopiridol	25	1 (NR) ²	I (NA/COG)	NP	Whitlock, 2005
ABT-751 (tubulin inhibitor)	24	2 (none)	I (NA)	Both	Fox, 2006
Depsipeptide	18	2 (none)	I (NA)	NP	Fouladi, 2006
Irinotecan	16	2 (1 PR)	I (Japan)	NA	Shitara, 2006
Fenretinide	54	1 (none)	I (NA)	NP	Villablanca, 2006
Gemcitabine	8	1 (none)	II (Germany)	Both	Wagner-Bohn 2006
Docetaxel	178	9 (none)	II (NA/COG)	NP	Zwerdling, 2006
All-trans-retinoic acid/IFN- α_{2A}	32	14 (none) ²	II (NA)	NP	Adamson, 2007
Irinotecan	161	11 (none)	II (NA/COG)	NP	Bomgaars, 2007
Pemetrexed	33	1 (none)	I (NA/COG)	Both	Malempati, 2007
Topotecan	37	25 (12 PR)	II (NA)	Both	Metzger, 2007
G3139/Doxorubicin/Cyclophosphamide	37	5 (none)	I (NA/COG)	NP	Rheingold 2007
Oxaliplatin	26	1 (none)	I (NA)	NP	Spunt, 2007
17-allylaminogeldanamycin	17	2 (none)	I (NA/COG)	NP	Weigel, 2007
Oxaliplatin	45	2 (none) ²	I (France)	Both	Geoerger, 2008
Bevacizumab	21	2 (none)	I (NA/COG)	Both	Glade Bender, 2008
Rebeccamycin analogue	133	7 (none)	II (NA/COG)	NP	Langevin, 2008
Carboplatin/Irinotecan	28	2 (1 SD)	I (NA)	NP	Levy, 2008
rTNF α /Actinomycin D	21	19 (3 CR, 5 SD)	II (NA)	NR	Meany, 2008
Paclitaxel/Ifosfamide	15	1 (none)	I (NA/POG)	NP	Geller, 2009
Oxaliplatin/irinotecan	16	1 (none)	I (NA)	NP	McGregor, 2009
Cetuximab/Irinotecan	46	1 (none) ²	I (NA/PC)	FP	Trippett, 2009
Ixabepilone	19	2 (none)	I (NA)	NP	Widemann, 2009
Cediranib	16	1 (none)	I (NA)	Both	Fox, 2010
Ixabepilone	61	10 (1 SD)	II (NA/COG)	NP	Jacobs, 2010
Adenovirus (OCIVIR-7)	21	1 (1 PR)	I (Finland)	NP	Nokisalmi, 2010
Ispinesib	24	2 (none)	I (NA/COG)	NP	Souid, 2010
Vincristine/Irinotecan/Temozolomide	42	2 (none)	I (NA/COG)	NP	Wagner, 2010
Dasatinib	28	1 (none)	I (NA/COG)	NP	Aplenc, 2011
Lenalidomide	46	2 (none)	I (NA/COG)	NP	Berg, 2011
Oxaliplatin/Gemcitabine	93	5 (none)	II (EU/ITCC)	Both	Geoerger 2011
Temsirolimus	13	1 (none) ²	I (NA)	Both	Spunt, 2011
Valproic acid	26	1 (none)	I (NA/COG)	NP	Su 2011
Plitidepsin	38	4 (none)	I (EU/ITCC)	FP	Geoerger, 2012
Aflibercept	21	1 (none)	I (NA/COG)	Both	Glader Bender, 2012
Cyclophosphamide/Topotecan	51	2 (NR)	I/II (NA)	NP	Kasow, 2012

Irinotecan	17	3 (none)	I (NA)	NP	McGregor, 2012
Cixutumumab	47	2 (none)	I/II (NA/COG)	NP	Malempati, 2012
Lexatumumab	17	1 (none)	I (NA)	NP	Merchant, 2012
Alisertib	37	2 (none)	I (NA/COG)	NR	Mossé, 2012
Sorafenib	49	4 (none) ²	I (NA/COG)	NP	Widemann 2012
Pazopanib	53	1 (none)	I (NA/COG)	Both	Glade-Bender 2013
Ridaforolimus	18	1 (none)	I (NA)	NP	Gore, 2013
Oxaliplatin/Doxorubicin	13	1 (none)	I (NA)	NP	Mascarenhas, 2013
Crizotinib	70	1 (none)	I (NA/COG)	Both	Mosse 2013
Vorinostat/Bortezomib	23	1 (none)	I (NA/COG)	NP	Muscal, 2013
Bevacizumab/Sorafenib/Cyclophosphamide	19	1 (none)	I (NA)	NP	Navid 2013
Imetelstat	20	1 (none)	I (NA/COG)	NP	Thompson 2013
Vincristine/Irinotecan/Temozolomide/Bevacizumab	13	3 (2 CR, 1 PR)	I (NA)	NP	Venkatramani, 2013
Bevacizumab/Vincristine/Irinotecan/Temozolamide	13	1 (none)	I (NA)	NP	Wagner 2013
MK2206 AKT inhibitor	50	1 (none)	I (NA/COG)	NP	Fouladi 2014
Sorafenib/Irinotecan (abstract)	12	4 (NR)	I (NA/COG)	NR	Meany 2014
Celecoxib/Thalidomide/Cyclophosphamide/Etoposide	101	3 (NR)	II (NA)	Both	Robison 2014
Cixutumumab	102	10 (none)	II (NA/COG)	NP	Weigel 2014
Seneca Valley Virus (NTX-010)	22	3 (2 SD)	I (NA/COG)	NP	Burke, 2015
Vaccine Racotumomab	14	1 (none)	I (Argentina)	NP	Cacciavillano 2015
Reovirus (reolysin)/cyclophosphamide	29	3 (NR)	I (NA/COG)	NP	Kolb, 2015
Cixutumumab/Temsirolimus	39	2 (none)	I (NA/COG)	NP	Fouladi 2015
Sorafenib	20	10 (2 SD)	II (NA/COG)	NP	Kim, 2015
Dalotuzumab/Ridaforolimus	24	1 (none)	I (EU/NA)	FP	Frappaz 2016
Total	2.571	214 (5 CR; 15 PR; 13 SD)			

Abbreviations: COG, Children's Oncology Group; CR, Complete response; FP, For-profit; EU, Europe; ITCC, Innovative Therapies for Children with Cancer; SD, Stable disease; PR, Partial response; NA, North America; NP, Non-profit; NR, Not reported; PC, Pediatric oncology therapeutic investigators experimental consortium; POG, Pediatric Oncology Group; WT, Wilms' tumour

¹trials designed for Wilms tumour alone. ²it is not explicitly stated whether Wilms tumour stabilization was observed.

Table 3 Tumour response according to intervention with conventional chemotherapy or novel agents in patients with Wilms tumours

Response Intervention	Complete Response (%)	Partial Response (%)	Stable Disease (%)	Progression (%)
Novel agent monotherapy (N = 99)	0 (0%)	1 (1%)	7 (7%)	91 (91%)
Predominantly chemotherapy (N = 115)	5 (4%)	14 (12%)	6 (5%)	90 (78%)

Appendix B: Wilms' tumours on biological/targeted treatment in phase I or II trials. Accumulated number of patients and the number of responders for each novel agent irrespective whether it has been used alone or in combination with other drugs.

Type of biological treatment	Number of trials (WT patients)	Response
Immunotherapy		
<i>Viruses</i> Adenovirus Seneca Valley virus Reovirus	1 (1) 1 (3) 1 (3)	1 PR 2 SD
Racotumomab (tumor antigen NGcGM3 active vaccine)	1 (1)	
<i>Antibodies</i> Bevacizumab (VEGF) Cetuximab (EGFR) Cixutumumab (IGF-1R) Dalotuzumab (IGF-1R) Lexatumumab (TRAIL-R2)	4 (7) 1(1) 3 (11) 1 (1) 1 (1)	2 CR, 1 PR 1 SD 1 SD
rTNF α	1 (19)	3 CR, 5 SD
Interferon- α_{2A}	1 (14)	
Thalidomide Lenalidomide	1(3) 2(5)	
Other targeted therapies		
<i>Angiogenesis inhibitors</i> Aflibercept (Ligand-binding) Cediranib (VEGFR) Pazopanib (VEGFR) Dasatinib (ABL) Sorafenib (VEGFR)	1(1) 1(1) 1 (1) 1(1) 4 (19)	2 SD 2 SD
<i>Mammalian target of rapamycin (mTOR) inhibitors</i> Ridaforolimus Temozolimus	2 (2) 2 (3)	
<i>Histone deacetylase inhibitors</i> Depsipeptide Valproic acid Vorinostat	1 (2) 1 (1) 1 (1)	
Alisertib (aurora A kinase inhibitor)	1 (2)	
Bortezomib (proteasome inhibitor)	1 (1)	
Ispinesib (kinesin spindle protein inhibitor)	1 (2)	
Crizotinib (ALK/c-met inhibitor)	1 (1)	
Gefitinib (EGFR inhibitor)	1 (2)	2 SD
MK2206b (protein kinase B (AKT), inhibitor)	1 (1)	
Flavopiridol (cyclindependent kinase inhibitor)	1 (1)	
Imetelstat (telomerase inhibitor)	1 (1)	
17-allylaminogeldanamycin (heat shock protein inhibitor)	1 (2)	
G3139 (inhibition of bcl-2 expression)	1 (5)	
Celecoxib (selective cyclooxygenase-2 (COX-2) inhibitor)	1 (3)	
<i>Differentiating agents</i> All-trans-retinoic acid (vitamin A analogue) Fenretinide (synthetic retinoid derivative)	1 (14) 1 (1)	
Abbreviations: ALK, anaplastic lymphoma kinase; CR, Complete response; EGFR, <i>epidermal growth factor receptor</i> ; IGF-1R, insulin-like growth factor-1 receptor; SD, Stable disease; PR, Partial response; VEGF, <i>vascular</i>		

endothelial growth facto; VEGFR, vascular endothelial growth factor receptor; WT, Wilms' tumour.

Appendix C: Wilms' tumours on conventional chemotherapy in a phase I or II trials.

Accumulated number of patients and the number of responders for each chemotherapeutic irrespective whether it has been used alone or in combination with other drugs.

Type of chemotherapy	Number of trials (WT patients)	Response
<i>Alkylating agents</i> Carboplatin Cisplatin Cyclophosphamide Ifosfamide Oxaliplatin Temozolomide	1 (2) 1 (2) 5 (14) 1 (1) 5 (10) 4 (8)	1 SD 2 CR, 1 PR
<i>Antimetabolites</i> Gemcitabine Pemetrexed	2 (6) 1 (1)	
<i>Anti-tumor antibiotics</i> Doxorubicin Actinomycin D	2 (6) 1 (19)	3 CR, 5 SD
<i>Topoisomerase inhibitors (I, II)</i> Topotecan Irinotecan Etoposide Rebeccamycin analogue	2 (27) 10 (30) 1 (4) 1 (7)	12 PR 2 CR, 2 PR, 1 SD
<i>Mitotic inhibitors</i> ABT-751 Docetaxel Paclitaxel Ixabepilone Vincristine	1 (2) 1 (9) 1 (1) 2 (12) 3 (8)	1 SD 2 CR, 1 PR
<i>Other</i> Plitidepsin Trabectedin	1 (4) 1 (2)	
Abbreviations: CR, Complete response, SD, Stable disease; PR, Partial response; WT, Wilms' tumour		