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Omission of doxorubicin from the treatment of stage II–III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial

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Summary

Background Before this study started, the standard postoperative chemotherapy regimen for stage II–III Wilms' tumour pretreated with chemotherapy was to include doxorubicin. However, avoidance of doxorubicin-related cardiotoxicity effects is important to improve long-term outcomes for childhood cancers that have excellent prognosis. We aimed to assess whether doxorubicin can be omitted safely from chemotherapy for stage II–III, histological intermediate-risk Wilms' tumour when a newly defined high-risk blastemal subtype was excluded from randomisation.

Methods For this international, multicentre, open-label, non-inferiority, phase 3, randomised SIOP WT 2001 trial, we recruited children aged 6 months to 18 years at the time of diagnosis of a primary renal tumour from 251 hospitals in 26 countries who had received 4 weeks of preoperative chemotherapy with vincristine and actinomycin D. Children with stage II–III intermediate-risk Wilms' tumours assessed after delayed nephrectomy were randomly assigned (1:1) by a minimisation technique to receive vincristine 1·5 mg/m² at weeks 1–8, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, and 27, plus actinomycin D 45 μg/kg every 3 weeks from week 2, either with five doses of doxorubicin 50 mg/m² given every 6 weeks from week 2 (standard treatment) or without doxorubicin (experimental treatment). The primary endpoint was non-inferiority of event-free survival at 2 years, analysed by intention to treat and a margin of 10%. Assessment of safety and adverse events included systematic monitoring of hepatic toxicity and cardiotoxicity. This trial is registered with EudraCT, number 2007-004591-39, and is closed to new participants.

Findings Between Nov 1, 2001, and Dec 16, 2009, we recruited 583 patients, 341 with stage II and 242 with stage III tumours, and randomly assigned 291 children to treatment including doxorubicin, and 292 children to treatment excluding doxorubicin. Median follow-up was 60·8 months (IQR 40·8–79·8). 2 year event-free survival was 92·6% (95% CI 89·6–95·7) for treatment including doxorubicin and 88·2% (84·5–92·1) for treatment excluding doxorubicin, a difference of 4·4% (95% CI 0·4–9·3) that did not exceed the predefined 10% margin. 5 year overall survival was 96·5% (94·3–98·8) for treatment including doxorubicin and 95·8% (93·3–98·4) for treatment excluding doxorubicin. Four children died from a treatment-related toxic effect; one (<1%) of 291 receiving treatment including doxorubicin died of sepsis, three (1%) of 292 receiving treatment excluding doxorubicin died of varicella, metabolic seizure, and sepsis during treatment for relapse. 17 patients (3%) had hepatic veno-occlusive disease. Cardiotoxic effects were reported in 15 (5%) of 291 children receiving treatment including doxorubicin. 12 children receiving treatment including doxorubicin, and ten children receiving treatment excluding doxorubicin, died, with the remaining deaths from tumour recurrence.

Interpretation Doxorubicin does not need to be included in treatment of stage II–III intermediate risk Wilms' tumour when the histological response to preoperative chemotherapy is incorporated into the risk stratification.

Funding See Acknowledgments for funders.

Introduction

Wilms' tumour (or nephroblastoma) is an embryonal kidney cancer that affects about 1 in 10 000 children, with 90% of cases occurring before the age of 7 years.[1] Treatment of localised, non-anaplastic Wilms' tumour, which accounts for nearly three-quarters of all cases, is highly successful, with a cure rate of almost 90%.[2–5] Treatment consists of nephrectomy and chemotherapy, together with radiotherapy when the tumour is classified as stage III. Chemotherapy regimens have not changed much since the late 1990s—vincristine and actinomycin D are used for nearly all patients. Doxorubicin is added to postoperative chemotherapy for stage III tumours after immediate nephrectomy (the approach of the North American Children's Oncology Group), and for stage II and III tumours after preoperative chemotherapy (the approach of the International Society of Paediatric Oncology Renal Tumours Study Group [SIOP-RTSG]).

Overall, 33–40% of all patients with unilateral, localised, non-anaplastic Wilms' tumour receive doxorubicin.[3,5,6]

In the setting of such a highly curable childhood cancer, the reduction of potential harm from irreversible side-effects of treatment is of paramount importance to improve overall outcomes.[7–9] Survival from Wilms' tumour has been increasing over the past 40 years, while, paradoxically, the overall duration and intensity of treatment has been decreasing for most patients.[2,4] This finding suggests that further treatment reductions could be possible for many patients.

The potential for doxorubicin to cause clinically significant cardiac disease after treatment for childhood cancers has long been recognised; in some patients this cardiac disease can first manifest itself more than 20 years after treatment.[10,11] Although the risk of cardiotoxicity is related to the total cumulative dose of doxorubicin, there is probably no completely safe dosing schedule for doxorubicin,[11,12] especially in very young patients who are typically affected by Wilms' tumour (median age at diagnosis 3–4 years). In the SIOP WT 2001 trial, we therefore investigated the outcome of complete removal of doxorubicin rather than a dose reduction in the relevant regimens.

The SIOP approach of neoadjuvant treatment of Wilms' tumour provides a unique opportunity to assess the in-vivo histological response of each child's tumour. Tumours are subtyped according to the proportion of necrosis and the cellular composition of the residual viable tumour.[13] Results from a retrospective analysis of the SIOP 9 and 93-01 trials[14,15] showed that patients with blastemal-type Wilms' tumour—of which a high proportion of any surviving viable tumour after preoperative chemotherapy consists of undifferentiated tumour cells—have a significantly worse chance of event-free survival compared with patients with other subtypes of histologically determined intermediate-risk, non-anaplastic Wilms' tumour. Therefore, we classified the blastemal subtype as high-risk histology, and we excluded patients with this subtype, and the diffuse anaplastic subtype, from the randomised trial.[16]

We aimed to assess whether doxorubicin could be safely removed from the treatment of intermediate-risk (as determined by histology), stage II–III Wilms' tumours after preoperative chemotherapy.

Methods

Study design and participants

We did an international, multicentre, unmasked, randomised, non-inferiority trial in 251 hospitals in 26 countries (appendix). A description of the trial protocol is available online. National and local regulatory and ethical approvals were obtained according to national regulations.

We recruited patients aged between 6 months and 18 years at diagnosis of a primary intrarenal tumour for randomisation of their postoperative chemotherapy. Patients had to have received preoperative chemotherapy of 4 weeks of vincristine and actinomycin D as per protocol, and have a stage II–III intermediate-risk (as determined by histology) Wilms' tumour when assessed at delayed nephrectomy by the institutional pathologist.[16] We excluded patients with high-risk blastemal or diffuse anaplastic subtypes, or evidence of metastases, and patients who had been given an immediate nephrectomy or who had not received protocol-defined preoperative chemotherapy, or whose legal guardians did not consent to the randomisation. Rapid central review of tumour stage and histological subtype was encouraged and available in all participating countries but was not mandated before randomisation.

The parents or legal guardians of all patients gave written informed consent at diagnosis for registration in the study, and after nephrectomy for the randomisation, when details about the tumour stage and histological risk group were available from the institutional pathologist.

Randomisation and masking

Patients' eligibility for randomisation after nephrectomy was assessed according to the local institutional pathologist's decision about tumour stage and histological risk group, and this information was submitted on a randomisation request form. We randomly assigned patients (1:1) to receive chemotherapy either with or without doxorubicin via a central computer system over the internet (ALEA, Netherlands Cancer Institute, Amsterdam, Netherlands) by a minimisation technique, stratified by trial office (Brazil, France, Germany, UK, and the SIOP-Amsterdam office for all other countries) and pathological stage (II or III). All patients, treating clinicians, and those assessing outcomes and analysing the data were unmasked to treatment allocation.

Procedures

We used the revised SIOP tumour staging system and histological risk classification (appendix) to classify tumours.[13] A percutaneous cutting needle biopsy (18 gauge) was allowed without affecting tumour stage. This biopsy was done routinely to confirm histological abnormalities before starting chemotherapy only in patients treated in the UK and Ireland, according to national practice.[17] All other countries continued the well established SIOP approach of starting preoperative chemotherapy on the basis of clinical and imaging characteristics consistent with a diagnosis of Wilms' tumour, combined with measuring urinary catecholamines to exclude neuroblastoma, and reserving biopsy for cases with diagnostic dilemma.[2,18,19]

Three-dimensional tumour volume was recorded at diagnosis and after completion of preoperative chemotherapy, according to whichever imaging method had been applied (ultrasonography, CT scan, or MRI scan). The calculated volume showed close correlation between methods (appendix). In Germany, children

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See **Online** for appendix

For **trial profile** see http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-treatment-for-children-and-young-people-with-kidney-cancer-including-wilms-tumour

whose tumour volume after preoperative chemotherapy was larger than 500 mL were classified as high risk and excluded from random assignment unless they had stromal or epithelial-type Wilms' tumours—subtypes that do not shrink but do have a good prognosis.[3,20]

We gave all patients the same preoperative chemotherapy of vincristine 1·5 mg/m² intravenously every week combined with actinomycin D 45 µg/kg intravenously every 2 weeks for 4 weeks, followed by unilateral nephrectomy, for which lymph node sampling was recommended but not mandatory. Randomly assigned patients received postoperative chemotherapy for 27 weeks. The treatment including doxorubicin consisted of vincristine 1·5 mg/m² (maximum dose 2 mg) intravenous bolus each week for weeks 1–8, then at weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, and 27, combined with actinomycin D 45 µg/kg (maximum dose 2 mg) intravenous bolus every 3 weeks from week 2, and five doses of doxorubicin 50 mg/m² in 4–6 h infusions (total dose 250 mg/m²) given once every 6 weeks from week 2. The treatment excluding doxorubicin omitted doxorubicin entirely and consisted of the identical backbone of vincristine and actinomycin D only (with the same doses and timing). We reduced the dose for all drugs in patients who weighed less than 12 kg (two-thirds of the standard dose). We recommended that children with stage III Wilms' tumour receive flank radiotherapy (14·4 Gy) with a 10 Gy boost to locoregional lymph nodes with microscopic tumour involvement or any sites of macroscopic residual tumour, or whole abdominal radiotherapy (21 Gy) if gross tumour rupture had occurred. We modified chemotherapy scheduling accordingly to avoid concurrent radiotherapy with doxorubicin or actinomycin D.

We ascertained patient demographic characteristics, tumour characteristics and response, treatments given, adverse events, and outcomes from standard case report forms completed at registration, the end of preoperative chemotherapy, after nephrectomy, at the end of treatment, and annually thereafter or at the time of any event. These were submitted to one of five national trial offices in Brazil, France, Germany, the Netherlands, and the UK. The Netherlands trial office (SIOP-NL) registered patients from all other participating countries and held the master trial database that received 6 monthly data transfers from the other trial offices. Spain started a national trial office in March, 2007, but was not deemed as a separate office for stratification of randomisation because of the few cases randomised in the time period. We assessed safety and adverse events through specific sections in the case report forms.

Outcomes

The primary endpoint of the trial was to test the non-inferiority of 2 year event-free survival between treatment including doxorubicin versus treatment excluding doxorubicin. Secondary outcomes were 5 year event-free survival and 5 year overall survival.

Both treatment regimens are well tolerated,[15] hence our assessment of safety and adverse events focused on systematic monitoring of hepatic toxicity and cardiotoxicity, which are infrequent but sometimes serious side-effects of actinomycin D (hepatic toxic effects) and doxorubicin (cardiotoxic effects).

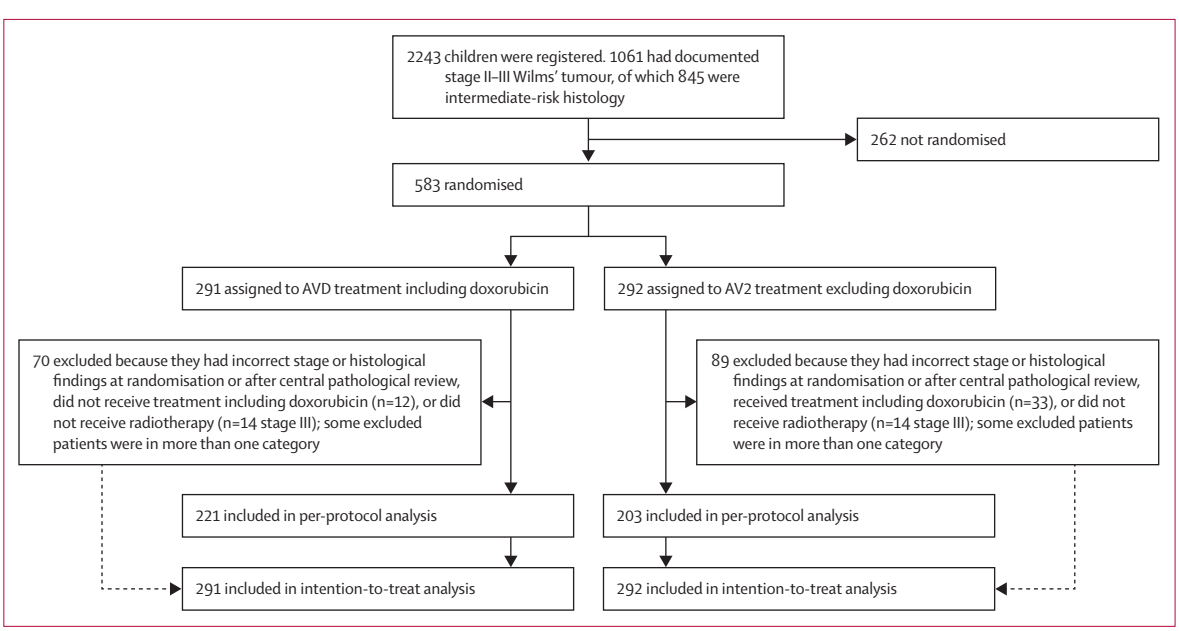

Figure 1: **Trial profile**
AVD=actinomycin plus vincristine plus doxorubicin. AV2=actinomycin plus vincristine only (no doxorubicin).

Statistical analysis

We assumed a 2 year event-free survival of 86%, with a non-inferiority margin of 10%, 5% type I error, and 80% power, and estimated that at least 350 patients would need to be included in our study.[21] Our assumption of 86% event-free survival was based on the data from the SIOP 93-01 study,[3] in which two-thirds of potentially eligible patients had stage II (2 year event-free survival 88%) and a third had stage III (2 year event-free survival 83%) Wilms' tumour, and in which blastemal-type Wilms' tumour would have been included within intermediate-risk histology because its recognition was not required by the local pathologist. However, since this subtype includes less than 9% of all localised Wilms' tumours, its removal would be unlikely to have a major effect on the predicted numbers for the calculation of sample size. We estimated that patient accrual would take 7 years, and another 2 years of follow-up would be needed to analyse the data at full power. The trial reached its target sample size early (Nov 6, 2006). Hence, the trial management group, in conjunction with the Independent Data Monitoring Committee review of the Feb 17, 2007, interim analysis, agreed to increase the sample size to 550 randomly assigned patients to provide about 104 events for an increased power of 90% and a reduction in the type I error to 0·025 (one sided) to improve the reliability of the overall results and to allow separate analysis of stage II and III tumours.

The intention-to-treat analyses included all randomly assigned patients. The primary endpoint of 2 year event-free survival was first analysed when the last randomly assigned patient had a minimum of 2 years of follow-up. Event-free survival was calculated from the date of randomisation to the date of recurrence or death, whichever happened first. Patients alive and without recurrence were censored at their last date of follow-up. We tested non-inferiority at 2 years with the Kaplan-Meier estimator of the survival proportion with an absolute 10% margin, with Greenwood's variance estimator for the difference between two survival proportions.[22,23] Kaplan-Meier survival curves (not restricted to 2 years) are presented with 95% CIs. Cox proportional hazard ratios (HRs) were calculated for the overall groups and for different subgroups (stage and national trial office). The CI of the HR was provided to show the precision of the estimate, not to assess non-inferiority. We assessed the assumption of proportional hazards by use of Schoenfeld residuals and by testing a time-dependent covariate, defined as the interaction between treatment group and log survival time. We did a test for interaction to explore heterogeneity in subgroups, and also calculated the number needed to treat based on survival probabilities and HR estimates. We calculated overall survival from the date

	Treatment including doxorubicin (n=291)	Treatment without doxorubicin (n=292)	Estimated eligible but not randomised (n=262)
Sex			
Male	138 (47%)	138 (47%)	47%
Female	153 (53%)	154 (53%)	53%
Age (months)	38 (25–54)	41 (25–57)	41 (26–57)
Study group			
Grupo Cooperativo Brasileiro para o Tratamento do Tumor de Wilms	62 (21%)	64 (22%)	16%
Gesellschaft für Pädiatrische Onkologie und Hämatologie	45 (15%)	45 (15%)	17%
Société Française des Cancers de l'Enfant	76 (26%)	74 (25%)	23%
International Society of Paediatric Oncology Netherlands	63 (22%)	65 (22%)	23%
Children's Cancer and Leukaemia Group	45 (15%)	44 (15%)	21%
Stage of Wilms' tumour at randomisation			
II	170 (58%)	171 (59%)	55%
III	121 (42%)	121 (41%)	45%

Data are n (%), %, or median (IQR). The final column shows the demographic characteristics of the estimated 262 patients with stage II or stage III tumours and intermediate-risk histology (after pathological review) who were not randomly assigned.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Treatment including doxorubicin (n=291)	Treatment without doxorubicin (n=292)
Stage of Wilms' tumour		
I	33 (11%)	42 (14%)
II	147 (51%)	133 (46%)
III	109 (37%)	113 (39%)
IV	1 (<1%)	4 (1%)
Information unavailable	1 (<1%)	0 (0%)
Low-risk group	4 (1%)	2 (<1%)
Completely necrotic	4 (1%)	2 (<1%)
Intermediate-risk group	276 (95%)	279 (96%)
Intermediate risk (not otherwise specified)	9 (3%)	3 (1%)
Epithelial	15 (5%)	14 (5%)
Stromal	35 (12%)	35 (12%)
Mixed	112 (38%)	90 (31%)
Regressive	102 (35%)	131 (45%)
Focal anaplasia	3 (1%)	6 (2%)
High-risk group	5 (2%)	9 (3%)
Blastemal	2 (1%)	9 (3%)
Diffuse anaplasia	3 (1%)	0 (0%)
Not assessed or non-Wilms	6 (2%)	2 (1%)

Data are n (%), analysed according to central pathological review.

Table 2: **Tumour stage and histological risk groups**

of random assignment to the date of death (all causes), and did several per-protocol analyses to test the robustness of the results. Our per-protocol analysis included only patients whose tumours were stage II or III, had intermediate-risk histology after a central pathological review, and who had received the treatment to which they had been randomly assigned. Stage III patients who received no radiotherapy were excluded from the per-protocol analysis. Long-term follow-up is in progress. We used the statistics programs SAS version 9.2 and R version 3.1.1 for all analyses.

This trial is registered with EudraCT, number 2007-004591-39.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 1, 2001, and Dec 16, 2009, we recruited 2243 children with unilateral, non-metastatic Wilms' tumour for the SIOP WT 2001 trial and study. Of 845 (80%) with documented intermediate-risk histology stage II–III Wilms' tumour after preoperative chemotherapy according to the protocol, 583 (69%) patients were randomly assigned to postoperative chemotherapy: 292 to treatment excluding doxorubicin and 291 to treatment including doxorubicin (figure 1). All 583 patients were included in the intention-to-treat analysis. Baseline characteristics were similar between groups (table 1), but slightly more patients than predicted from the previous trial[3] had stage III tumours.

580 cases (99%) were submitted for central pathological review, 555 (96%) of which were confirmed as intermediate-risk histology and 502 (87%) of which were confirmed as stage II–III (table 2). The distribution of the few patients who were ineligible because of adverse tumour factors (stage IV and high-risk histology) after pathological review did not differ significantly. For patients who had details available of postoperative treatment of the high-risk tumours, nine of 14 had their postoperative treatment intensified to take account of the review information.

Median follow-up was 60·8 months (IQR 40·8–79·8) for all randomly assigned patients. 39 events (including 36 relapses) occurred in the group without doxorubicin compared with 26 events (24 relapses) in the group with doxorubicin. The absolute difference in event-free survival at 2 years was 4·4% (95% CI 0·4–9·3), which did not surpass the predefined limit (table 3). The 2 year estimates of event-free survival were 88·2% (95% CI 84·5–92·1) without doxorubicin versus 92·6% (89·6–95·7) with doxorubicin. 22 patients would need to receive doxorubicin to prevent one relapse (appendix).

We noted no significant differences between the groups for 5 year event-free survival or 5 year overall survival (table 3, figure 2). The HR for any event was 1·55 (95% CI 0·94–2·54) and for death was 0·81 (0·35–1·89). Only three first relapses happened after 5 years, all in the group receiving doxorubicin.

424 patients met the criteria for the per-protocol analysis. We noted a small increase in the size of the absolute difference in 2 year event-free survival in the per-protocol population (table 3). The number needed to treat with doxorubicin to prevent one excess relapse remained at about 22 patients (figure 2).

When outcome was analysed separately by tumour stage, the differences in 2 year event-free survival (table 3) and corresponding increase in HR for any event were similar for stage II and stage III tumours. We also did Kaplan-Meier survival curve analyses for events over the entire time course (appendix).

17 (3%) patients had hepatic veno-occlusive disease, 11 during preoperative chemotherapy and eight during postoperative chemotherapy, with two patients having more than one episode of veno-occlusive disease. Four (<1%) children, all from Brazil, died after treatment-related toxic effects: three in first remission (one from neutropenic sepsis who received treatment including doxorubicin, and one each from varicella and metabolic seizure, both of whom received treatment excluding

	Treatment including doxorubicin	Treatment without doxorubicin	Difference (95% CI)
Intention-to-treat population (n=583)	n=291	n=292	
2 year event-free survival	92·6%, 89·6–95·7	88·2%,84·5–92·1	4·4 (0·4–9·3)
Number of events by 2 years	21 (7%)	33 (11%)	
5 year event-free survival	91·8%, 88·6–95·1	85·3%, 81·0–89·7	
Number of events between 2–5 years	2 (<1%)	6 (2%)	
5 year overall survival	96·5%, 94·3–98·8	95·8%, 93·3–98·4	
Pathology-reviewed stage II/III Wilms' tumour) (n=502)	n=256	n=246	
Stage II	n=147	n=133	
2 year event-free survival	92·5%, 88·3–96·8	88·1%, 82·7–94·0	4·3 (2·8 –11·4)
5 year event-free survival	91·6%, 87·1–96·3	84·8%, 78·4–91·7	
5 year overall survival	97·6%, 95·0–100·0	95·5%, 91·7–99·5	
Stage III	n=109	n=113	
2 year event-free survival	91·5%, 86·3–97·0	86·9%, 80·8–93·6	4·5 (3·8–12·8)
5 year event-free survival	90·5%, 85·0–96·3	85·1%, 78·3–92·6	
5 year overall survival	93·8%, 89·1–98·8	96·0%, 91·5–100·0	
Per-protocol analysis* (n=424)	n=221	n=203	
2 year event-free survival	92·7%, 89·3–96·2	87·8%, 83·3–92·5	4·9 (0·8–10·7)
5 year event-free survival	91·6%, 88·0–95·4	84·8%, 79·6–90·3	
5 year overall survival	96·9%, 94·5–99·4	96·0%, 93·0–99·2	

Data are %, 95% CI, or n (%). *Several per-protocol analyses are recommended in non-inferiority studies to test the sensitivity of any potential difference between two groups. Here, the analysis is restricted to only fully compliant patients who had the correct diagnosis of stage II or III and intermediate-risk histology tumour after a central pathological review, and who received the correctly assigned treatment. Patients with stage III tumours who did not receive radiotherapy were also excluded.

Table 3: **Event-free and overall survival for the intention-to-treat and per-protocol populations**

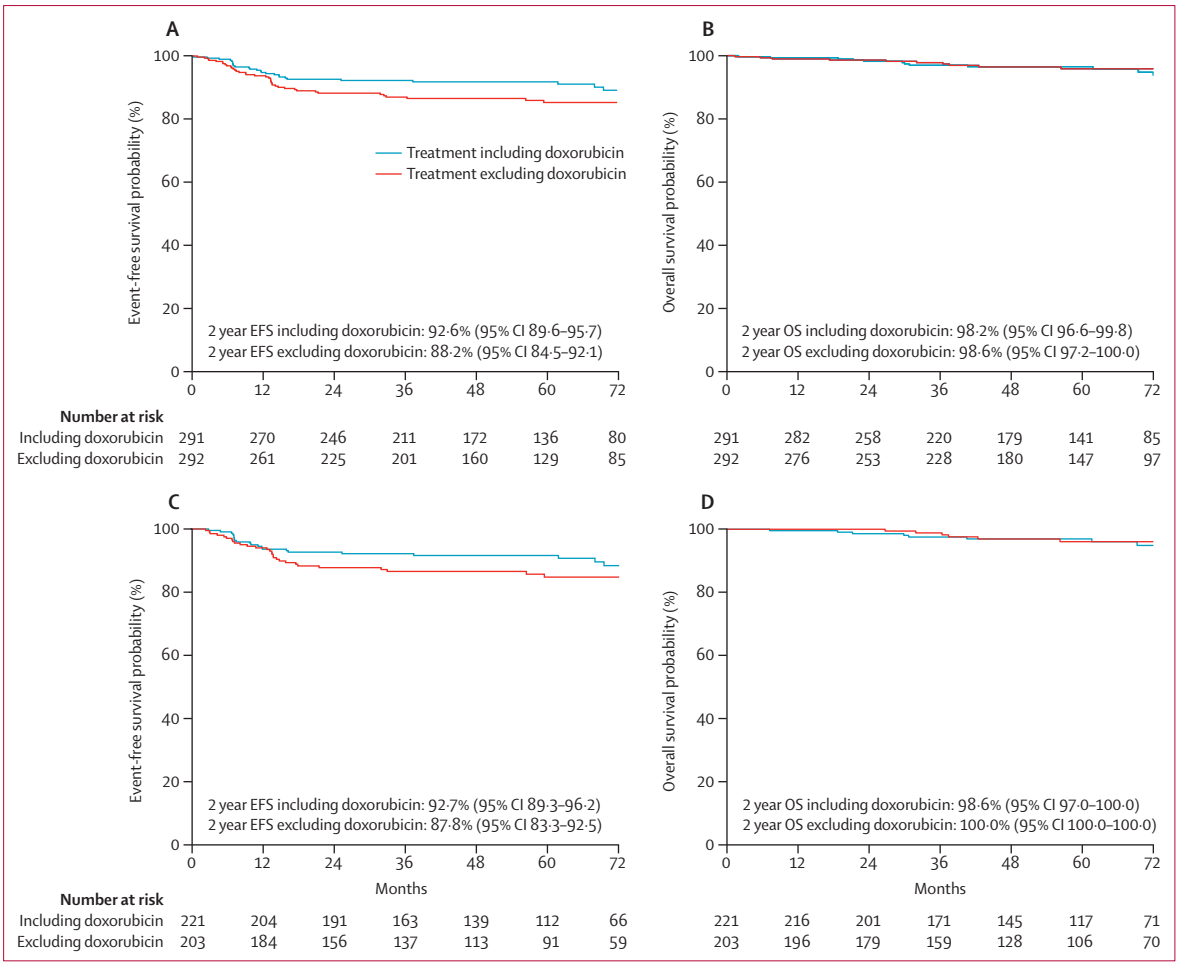

Figure 2: **Kaplan-Meier survival curves for event-free survival and overall survival**
Data from the intention-to-treat population for event-free survival (A) and overall survival (B) and from the per-protocol population for event-free survival (C) and overall survival (D). EFS=event-free survival. OS=overall survival. Per-protocol population includes patients who had eligible tumour stage and histology according to review pathology, and correctly received their assigned treatment.

	Treatment including doxorubicin (n=291)	Treatment excluding doxorubicin (n=292)
Relapses	24 (8%)	36 (12%)
Local recurrence only	3 (1%)	8 (3%)
Haematogenous relapse only*	17 (6%)	17 (6%)
Combined local and haematogenous relapses	2 (<1%)	8 (3%)
Relapses with a site missing	2 (<1%)	3 (<1%)

Data are number of patients (%). *23 lung only, three liver only, two lung and liver, four lung and other extra-abdominal sites, and two extra-abdominal sites only.

Table 4: **Sites of relapse in the intention-to-treat population**

doxorubicin) and one from sepsis during treatment for relapse (initially given treatment excluding doxorubicin). 15 children had cardiotoxic effects, maximum grade 1 in 11 cases and grade 2 in four cases, all in the group with doxorubicin.

Most relapses (83%) occurred within 2 years of diagnosis in both treatment groups (table 4). 85% of stage III tumours received irradiation, with equal distribution between the two groups (appendix). Details of relapse therapy were reported in 41 of 60 cases. No child received further doxorubicin after assigned treatment with doxorubicin, whereas doxorubicin was given to 11 children relapsing after the assigned treatment with no doxorubicin.

Discussion

Our results show that omission of doxorubicin from the postoperative chemotherapy regimen of vincristine and actinomycin D for patients with stage II and stage III Wilms' tumours of intermediate-risk histological subtype was not significantly worse in clinical terms than standard treatment with all three drugs, with only a small decrease in event-free survival (panel). 5 year overall survival was unaffected by omission of doxorubicin, and remained high.

Panel: Research in context

Systematic review

Much debate has been generated regarding treatment schedules that omit anthracyclines in Wilms' tumour; however there are few data. At the time of designing the SIOP WT 2001 trial in 2000–01, members of the steering committee undertook an extensive review of the scientific literature in English and several other European languages, on anthracycline cardiotoxicity in relation to dose scheduling and toxicity in all types of cancer in both children and adults (appendix). They concluded that there was probably no completely safe dosing schedule and a design that tested the omission of doxorubicin was preferred. The recognition of a new type of high-risk Wilms' tumour—blastemal type—enabled the definition of a group of intermediate-risk histology tumours with a lower risk of relapse.[14] This group might therefore be able to avoid doxorubicin without a higher relapse rate. A previous Cochrane review[24] that assessed treatment including anthracyclines versus treatment not including anthracyclines for childhood cancers identified two randomised trials that have been done for Wilms' tumour. One of the trials (SIOP-6)[25] was excluded from the formal analysis because a 25% difference was noted between the study groups in cumulative dose of treatments other than anthracyclines. In the other study (National Wilms Tumor Study Group 3),[19] children were randomly assigned with a 2×2 factorial design that compared treatment with or without doxorubicin, and included random assignment to different radiation doses of 10 or 20 Gy (K2 or DD2) in stage III, or 0 or 20 Gy in stage II Wilms' tumours, after immediate nephrectomy. None of the studies used histological assessment of the tumour as a stratification technique.

Interpretation

To our knowledge, ours is the first randomised study to test, in isolation, omission of doxorubicin from the postoperative treatment of stage II–III, intermediate-risk histology Wilms' tumour. Our results build on the long-term follow-up of the SIOP-6 and NWTSG 3 trials, add to the evidence base that doxorubicin is not necessary for optimum control of stage II or III Wilms' tumours without high-risk histological features after preoperative chemotherapy, and emphasise the need for further research into the molecular drivers of chemotherapy resistance in the blastemal component of Wilms' tumour.

Risk stratification that includes an individualised histological assessment of tumour response in vivo has allowed further optimisation of the overall burden of treatment for children with Wilms' tumours given preoperative chemotherapy followed by delayed nephrectomy, by reducing the proportion of patients for whom doxorubicin is indicated in their postoperative chemotherapy. The results of this trial have changed the practice of the SIOP Renal Tumours Study Group. However, patients with stage II–III Wilms' tumours of high-risk blastemal type should continue to be given doxorubicin.

Although doxorubicin has been included in standard chemotherapy regimens since the 1980s for patients with stage III Wilms' tumour, no conclusive evidence has shown that front-line doxorubicin treatment improves survival.[26] Two randomised trials begun in the 1980s (National Wilms Tumor Study Group 3 [NWTSG 3] and SIOP-6)[19,25] tested the removal of doxorubicin from post-nephrectomy chemotherapy for stage II and stage III Wilms' tumour. Randomisation in SIOP 6 was closed early because of an excess of relapses in the treatment groups without doxorubicin, but no difference in overall survival was found in the final analysis of stage II cases with lymph node involvement and stage III cases. In NWTSG 3,[19] a numerical survival advantage for doxorubicin was noted only in patients with stage III disease who were randomly assigned to a reduced dose (10·8 Gy) of flank radiotherapy. In both studies, few patients were included in the doxorubicin groups and no difference in overall survival was detected after long-term follow-up.

The absence of superior outcomes in previous trials that were restricted in statistical power, and the increasing recognition of the late adverse effects associated with doxorubicin therapy, suggested that the role of doxorubicin in the management of some patients with localised, non-anaplastic Wilms' tumour should be reassessed. Our trial incorporated new information about the risk of relapse, according to histological response, into the initial risk-stratification process. Although none of the survival endpoints reached significance in this treatment-reduction setting, reliable quantification of the potential risk of excess relapse from omission of a drug that might impair long-term quality of life and survival was important. We therefore did several per-protocol analyses to test the robustness of the results.

The most conservative included an analysis of patients whose eligibility of stage II–III, intermediate-risk histology Wilms' tumour was confirmed by central pathological review, taking account of the treatment received. By maximising any potential treatment effect, these analyses helped to support the robustness of our findings. The trial could not be adequately powered to analyse outcomes separately by tumour stage because of the few expected events, even in a large multinational trial. However, we did this analysis to explore any signs of a differential effect and showed that omission of doxorubicin was not significantly worse in clinical terms-for patients with stage II or stage III intermediate-risk histology. Our data for stage II tumours are similar to a longer-term analysis of outcome of stage II tumours staged after immediate nephrectomy in the NWTSG 4 trial,[27] for which two-drug (vincristine plus actinomycin D) chemotherapy without doxorubicin was the standard after the NWTSG 3 trial.[19] This previous analysis focused on mechanical factors (tumour spill) to stratify stage II patients, whereas our study used in-vivo histological responses and would have placed tumours with spill into stage III. Encouragingly, our data suggest that stage III tumours can be treated effectively without doxorubicin, whereas the Children's Oncology Group recommend that tumours with spill should receive doxorubicin.[28]

The applicability of our results is restricted to patients with Wilms' tumour given preoperative chemotherapy, which is standard clinical practice in most European and many other countries. Furthermore, the ultimate goal of showing avoidance of symptomatic cardiotoxicity needs more than 20 years of follow-up, which is in progress. However, the overall benefit of doxorubicin in the long-term outcomes of children with Wilms' tumour has

also been questioned by investigators in North America, who use an immediate nephrectomy approach as standard.[29] Nonetheless, doxorubicin is still thought to contribute to effectiveness in some settings, including high-risk blastemal-type Wilms' tumour[30] and metastatic disease, even when the metastatic volume is low and detectable only by CT.[31] Anthracyclines cause dose-related cardiotoxicity, and cause an additive effect in left-sided stage III tumours in which flank irradiation might encompass part of the heart muscle.[10,11] International follow-up guidelines suggest that survivors who receive at least 250 mg/m² of doxorubicin—the dose given in our three-drug regimen—need continual cardiac surveillance. Hence, omission of doxorubicin could remove a perpetual reminder of possible ill health as a result of treatment for Wilms' tumour survivors who are otherwise healthy.

Because of the complexity of the histological composition of Wilms' tumours, the personalised response of each tumour was not based only on the percentage of necrosis after preoperative chemotherapy, but also on the predominant cell type in the residual viable component.[13,30] When the percentage of viable tumour consists of more than two-thirds primitive blastemal cells, in the setting of less than two-thirds necrosis, the tumour is classified as high-risk blastemal-type Wilms' tumour. These patients were excluded from random assignment and continued to receive doxorubicin. However, this histological classification is subjective and the accuracy of risk stratification needs to be improved; a quantitative assessment of the total volume of residual blastema after preoperative chemotherapy might achieve such accuracy. Preliminary analyses suggest residual blastema might be an adverse prognostic factor in this solid tumour, akin to measuring low residual disease in childhood leukaemia.[30] Alternative avenues of research are characterisation of molecular biomarkers associated with chemotherapy-resistant blastema, with whole-exome sequencing and other assessments in progress.[32]

Our results show that incorporation of a measure of the in-vivo chemosensitivity of each child's tumour into risk stratification has allowed further reduction of treatment intensity for children with localised, stage II or III Wilms' tumour in a controlled way. Although the small excess of relapses in the reduced treatment arm did not lead to a rise in the number of deaths even in the long term, a few additional children might need treatment for relapse. More accurate prognostic risk predictors are needed, and the identification of novel molecular, histological, and clinical[33] risk factors is a priority to allow further stratification of treatment intensity.

Contributors

All authors contributed to study design, data collection and interpretation, management of the clinical trial, writing and review of the report and approval of the final version. HvT maintained and analysed the consolidated data from all participating study groups, did all statistical analyses, and advised on their clinical interpretation. KP-J, NG, CB, BdC, and TA were responsible for clinical oversight of the study in the UK, Germany, France, Brazil, and Spain, respectively. JdK undertook clinical oversight for all other countries in the study. JdK and MvdH-E provided clinical oversight of the main trial office at the Netherlands Cancer institute, Amsterdam, Netherlands. BS, IL, LB-G, and GV did the centralised pathology review at a national and international level. JG provided clinical oversight of the surgical panel. FO provided clinical oversight of the radiotherapy panel. KP-J and HvT drafted the initial report. Members of the SIOP Renal Tumours study group substantially contributed to the set-up, data acquisition, and clinical oversight of patient enrolment in their countries. The group consists of the lead clinicians (oncologists, surgeons, radiotherapists, pathologists, and radiologists) from each participating country and their supporting clinical trial unit, where relevant (full list in appendix).

Declaration of interests

We declare no competing interests.

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References

1 Pastore G, Znaor A, Spreafico F, et al. Malignant renal tumours incidence and survival in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006; **42:** 2103–14.

2 de Kraker J, Graf N, van Tinteren H, et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. *Lancet* 2004; **364:** 1229–35.

3 Graf N, van Tinteren H, Bergeron C, et al. Characteristics and outcome of stage II and III non-anaplastic Wilms' tumour treated according to the SIOP trial and study 93-01. *Eur J Cancer* 2012; **48:** 3240–48.

4 Green DM, Breslow NE, Beckwith JB, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1998; **16:** 3744–51.

5 Pritchard-Jones K, Moroz V, Vujanic G, et al. Treatment and outcome of Wilms' tumour patients: an analysis of all cases registered in the UKW3 trial. *Ann Oncol* 2012; **23:** 2457–63.

6 Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes *1p* and *16q* is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol* 2005; **23:** 7312–21.

7 Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol* 2013; **31:** 3673–80.

8 Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; **297:** 2705–15.

9 Mertens AC, Brand S, Ness KK, et al. Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study. *Psychooncology* 2014; **23:** 266–75.

10 Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. *J Clin Oncol* 2001; **19:** 1926–34.

11 van der Pal HJ, van Dalen EC, van Delden E, et al. High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol* 2012; **30:** 1429–37.

12 van Dalen EC, van der Pal HJ, Caron HN, et al. Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. *Cochrane Database Syst Rev* 2006; **4:** CD005008.

13 Vujanic GM, Sandstedt B, Harms D, et al. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol* 2002; **38:** 79–82.

14 Weirich A, Leuschner I, Harms D, et al. Clinical impact of histologic subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. *Ann Oncol* 2001; **12:** 311–19.

15 Reinhard H, Semler O, Burger D, et al. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms Tumor. *Klin Padiatr* 2004; **216:** 132–40.

16 UK Clinical Research Network Study Portfolio. The SIOP nephroblastoma clinical trial and study (WT2002-01). http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=1162 (accessed Dec 8, 2014).

17 Mitchell C, Pritchard-Jones K, Shannon R, et al. Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. *Eur J Cancer* 2006; **42:** 2554–62.

18 Tournade MF, Com-Nougue C, de Kraker J, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the ninth International Society of Pediatric Oncology Wilms' Tumor trial and study. *J Clin Oncol* 2001; **19:** 488–500.

19 Tournade MF, Com-Nougue C, Voute PA, et al. Results of the sixth International Society of Pediatric Oncology Wilms' Tumor trial and study: a risk-adapted therapeutic approach in Wilms' tumor. *J Clin Oncol* 1993; **11:** 1014–23.

20 Verschuur AC, Vujanic GM, Van Tinteren H, et al. Stromal and epithelial predominant Wilms tumours have an excellent outcome: the SIOP 93 01 experience. *Pediatr Blood Cancer* 2010; **55:** 233–38.

21 Rodary C, Com-Nougue C, Tournade MF. How to establish equivalence between treatments: a one-sided clinical trial in paediatric oncology. *Stat Med* 1989; **8:** 593–98.

22 Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and noninferiority testing. *Biol Blood Marrow Transplant* 2009; **15:** 120–27.

23 Machin D, Gardner MJ. Calculating confidence intervals for survival time analyses. *Br Med J (Clin Res Ed)* 1988; **296:** 1369–71.

24 van Dalen EC, Raphaël MF, Caron HN, Kremer LCM. Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer. *Cochrane Database Syst Rev* 2011; **19:** CD006647.

25 D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor: results of the Third National Wilms' Tumor Study. *Cancer* 1989; **64:** 349–60.

26 Breslow NE, Ou SS, Beckwith JB, et al. Doxorubicin for favorable histology, stage II–III Wilms tumor: results from the National Wilms Tumor Studies. *Cancer* 2004; **101:** 1072–80.

27 Green DM, Breslow NE, D'Angio GJ, et al. Outcome of patients with stage II/favorable histology Wilms tumor with and without local tumor spill: a report from the National Wilms Tumor Study Group. *Pediatr Blood Cancer* 2014; **61:** 134–39.

28 Fernandez C. Treatment of Wilms tumor in the Children's Oncology Group. In: Pritchard-Jones K, Dome J, eds. Renal tumors of childhood: biology and therapy. Berlin: Springer-Verlag, 2014: 77–99.

29 Green DM. The treatment of stages I–IV favorable histology Wilms' tumor. *J Clin Oncol* 2004; **22:** 1366–72.

30 van den Heuvel-Eibrink MM, van Tinteren H, Bergeron C, et al. Outcome of localised blastemal-type Wilms tumour patients treated according to intensified treatment in the SIOP WT 2001 protocol, a report of the SIOP Renal Tumour Study Group (SIOP-RTSG). *Eur J Cancer* 2015; **51:** 498–56.

31 Grundy PE, Green DM, Dirks AC, et al. Clinical significance of pulmonary nodules detected by CT and not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and 5: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 2012; **59:** 631–35.

32 Wegert J, Ishaque N, Vardapour R, et al. Mutations in the SIX1/2 pathway and the DROSHA/DGCR8 miRNA microprocessor complex underlie high-risk blastemal type Wilms tumors. *Cancer Cell* 2015; **27:** 298–311.

33 Blanco JG, Sun CL, Landier W, et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children's Oncology Group. *J Clin Oncol* 2012; **30:** 1415–21.