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PAEDIATRICS

Doxorubicin is not necessary in postoperative chemotherapy for Wilms tumour

Doxorubicin can be safely omitted from the postoperative chemotherapy regimen for selected children with stage II–III intermediate-risk Wilms tumour. This finding has the potential to eliminate doxorubicin-related cardiotoxicity, further reduce treatment and improve long-term outcomes in this patient group.

Doxorubicin can cause clinically significant cardiac disease that can manifest up to 20 years after receiving the treatment. Kathy Pritchard-Jones and colleagues undertook the SIOP WT 2001 noninferiority phase III trial to assess whether removing doxorubicin from the postoperative treatment regime in patients with stage II or stage III intermediate-risk Wilms tumour was feasible.

> “...there is no detriment to survival at 5 years if doxorubicin is omitted”

The team recruited 583 patients between the ages of 6 months and 18 years at 215 hospitals in 26 countries. Children who had received 4 weeks of preoperative vincristine and actinomycin D and also had histologically confirmed stage II–III intermediate-risk Wilms tumour, assessed at delayed nephrectomy, were included. Participants were randomly allocated 1:1 to receive postoperative chemotherapy consisting of intravenous vincristine and actinomycin D with or without doxorubicin.

The primary end point of the trial was the noninferiority of 2-year event-free survival of treatment including doxorubicin compared with treatment excluding it, with a 10% margin. Secondary end points were 5-year event-free survival and 5-year overall survival. Median follow-up duration was 60.8 months. The absolute difference in 2-year event-free survival was 4.4%, which did not meet the predefined 10%

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noninferiority limit. Analysis showed that in order to prevent one relapse, 22 patients would need to receive doxorubicin. With regards to secondary end points, no significant differences in 5-year event-free or overall survival were observed. Analysis of outcomes separately, by tumour stage, showed that the 2-year event free survival and corresponding increase in the hazard ratio for any event were similar for both stage II and stage III tumours. Relapses occurred in both treatment groups (8% in the group receiving doxorubicin and 12% in the group where it was excluded from the therapy regime) and most happened within 2 years of diagnosis. In the group who received doxorubicin, 15 children experienced cardiotoxic effects, 11 had a maximum grade 1 effect and four had a grade 2 effect.

These results show that removing doxorubicin from the postoperative treatment regime of children with stage II–III intermediate-risk Wilms tumour is clinically safe. Importantly, individualized histological assessment needs to be added to the risk stratification of patients to identify those who need not receive doxorubicin. Pritchard-Jones told *Nature Reviews Urology* “The trial has shown is that there is no detriment to survival at 5 years if doxorubicin is omitted. If children are not exposed to doxorubicin, then they also do not need to have lifelong monitoring for potential heart problems due to this drug”.

In his commentary on this report for the *Lancet,* Daniel M. Green highlights some limitations concerning this trial that need consideration, stating that the findings “...apply only to children who receive prenephrectomy chemotherapy...” continuing “...many children in North America and elsewhere routinely undergo immediate nephrectomy...” and that “...prenephrectomy chemotherapy might have altered the accuracy of pathological staging...”. However, Green continues “Pritchard-Jones and colleagues interpretation of their results is appropriately cautious.” He adds “They have taken a much-needed step that has application in other paediatric oncology settings.”

Pritchard-Jones concluded “The results of this trial have highlighted the need to better understand the biological subgroups of Wilms tumour that drive adverse clinical behaviour. To date, collaborative biomarker studies have found that a number of changes, in particular gain of 1q and of the region containing *MYCN* on chromosome 2p, are associated with adverse-event-free survival.”

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Original article Pritchard-Jones, K. *et al*. 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. *Lancet* doi:10.1016/S0140-6736(14)62395-3

Further reading Green, D. M. Doxorubicin in stage II—III, intermediate-risk Wilms' tumour. *Lancet* doi:10.1016/S0140-6736(15)60686-9 | Waters, A. M. & Pritchard-Jones, K. Long-term effects of Wilms tumour therapy on renal function. *Nat. Rev. Urol.* 10.1038/nrurol.2015.167