EUROPEAN JOURNAL OF CANCER 43 (2007) 2453–2456

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Controversies in the management of Wilms tumour – Immediate nephrectomy or delayed nephrectomy?

*Daniel M. Green**

School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York, USA

ARTICLE INFO

Article history:
Received 18 July 2007
Accepted 25 July 2007
Available online 6 September 2007

Keywords:
Wilms tumor
Immediate nephrectomy
Pre-nephrectomy chemotherapy

ABSTRACT

Wilms tumour is the paradigm for the treatment of a malignant solid tumour of children and adolescents. Dramatic improvements in survival have occurred as the result of advances in anaesthetic and surgical management, radiation therapy technique and the availability of several very effective chemotherapeutic agents. Despite these successes, controversy exists regarding the initial management of children with unilateral, favourable histology Wilms tumour. Two different approaches have been recommended by different investigators – immediate nephrectomy or pre-nephrectomy chemotherapy followed by delayed nephrectomy. The results of randomised trials will be reviewed and the benefits and risks of each approach discussed.

1. Immediate nephrectomy

Immediate nephrectomy has been recommended by the National Wilms Tumour Study (NWTS) Group (NWTSG). The NWTSG conducted four randomised clinical trials between 1969 and 1994. Patients were eligible for randomisation if they had undergone initial nephrectomy. Patients who had pre-operative tumour rupture were eligible for randomisation as they underwent immediate nephrectomy and such patients comprised 4.4% (19/427) of those randomised on NWTS-1.[1] Intra-operative rupture complicated nephrectomy for 17.8% (76/427) of randomised NWTS-1 patients,[1] 12.1% (76/626) of randomised or followed NWTS-2 patients[2] and 13.3% (195/1466) of randomised or followed favourable histology NWTS-3 patients.[3]

Post-operative chemotherapy and radiation therapy were administered based on the surgical pathological stage. The results of NWTS-2 and NWTS-3 suggested that the addition of doxorubicin to the combination of vincristine and actinomycin D improved relapse-free, but not overall, survival of children with stage III favourable histology Wilms tumour, and improved neither the relapse-free nor the overall survival of those with stage II favourable histology Wilms tumour.[4,5] Prolonged follow-up of these children confirmed the absence of an improved overall survival rate among those children with stage III favourable histology Wilms tumour treated with the doxorubicin containing regimen compared to those treated without doxorubicin.[6,7]

2. Pre-nephrectomy chemotherapy

To decrease the need for post-operative abdominal radiation therapy to treat patients who have tumour rupture during nephrectomy, the investigators of the International Society of Paediatric Oncology (SIOP) conducted a series of trials in which all patients received pre-nephrectomy chemotherapy or abdominal radiation therapy. Patients classified as a surgical emergency were not eligible for the randomised study, but

* Present address: Department of Paediatrics, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14263, USA. Tel.: +1 716 845 2334; fax: +1 716 845 8003.
E-mail address: daniel.green@roswellpark.org
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.07.022

underwent immediate nephrectomy. The frequency of tumour rupture observed among the unirradiated SIOP patients was higher than reported among patients without metastases entered on NWTS studies 1, 2 or 3 (see above) but in the first SIOP study, pre-nephrectomy abdominal irradiation decreased the percentage of nephrectomies complicated by tumour rupture from 33% (20/60) to 4% (3/72).[8] In a subsequent randomised trial, the frequency of tumour rupture was nearly the same for patients treated with pre-nephrectomy abdominal irradiation and dactinomycin (8%, 7/76) and for those treated with pre-nephrectomy chemotherapy with vincristine and dactinomycin (6%, 5/88).[9]

3. Risks and benefits of immediate and delayed nephrectomy

The administration of pre-nephrectomy chemotherapy is associated with several actual or theoretical risks, including: a) administration of combination chemotherapy to a patient with a benign disease; b) administration of combination chemotherapy to a patient with a different histological type of malignant tumour; c) modification of tumour histology; and d) loss of staging information, whereas delayed nephrectomy is associated with a lower risk of intra-operative tumour spillage, and hence in the requirement for abdominal radiation therapy.

The early results of both the NWTS and the SIOP Nephroblastoma Trials demonstrated that between 7 and 10%[8,10] of patients with a pre-nephrectomy diagnosis of Wilms tumour have a benign or malignant condition other than Wilms tumour. More recent data suggest that, even with the use of modern imaging techniques, an incorrect diagnosis will be made in 4.8% of patients.[11]

The effect of pre-nephrectomy chemotherapy on tumour histology was evaluated in 140 patients with unilateral Wilms tumour registered on the NWTS. The percentage of patients in this group with anaplastic tumours was 9.2% (11/119)[12] compared to 3.4% among the first 1700 patients entered on NWTS - 3.[13] The percentage of patients who received pre-nephrectomy chemotherapy using the SIOP-9 protocol with anaplastic histology was 7.5% (33/440).[14] These results may represent non-significant statistical variation, but could also reflect the induction of cytologic changes consistent with anaplasia in tumours which, prior to treatment, may have had favourable histology, or the occurrence of an increased frequency of rapidly growing, invasive tumours within the anaplastic category.

The major concern regarding the management of children who receive pre-nephrectomy chemotherapy is the potential for loss of important staging information. This concern is exemplified by the experience reported by the investigators in SIOP who conducted a clinical trial in which patients treated with pre-nephrectomy combination chemotherapy who had post-chemotherapy stage II Wilms tumour without regional lymph node involvement by tumour were randomised to receive or not receive post-nephrectomy abdominal irradiation. All received post-nephrectomy adjuvant chemotherapy which included vincristine and dactinomycin. The trial was discontinued because an unexpected, statistically significant excess of intraabdominal recurrences occurred in the unirradiated patients.[15] This result might suggest that pre-nephrectomy chemotherapy produced sufficient tumour response to obscure the detection of perinephric tumour extensions and/or tumour deposits which were present in regional lymph nodes.[16]

The NWTS - 4[17,18] and SIOP Nephroblastoma - 9 Trials[14,19] employed abdominal irradiation and/or treatment with a combination chemotherapy regimen which included an anthracycline, for specific groups of patients. Those with stage II, lymph node positive Wilms tumour on SIOP Nephroblastoma Trials were included in stage III in the NWTS. Employing the staging system developed by the NWTSG Study Committee, and placing SIOP patients with stage II, lymph node positive Wilms tumour in stage III, one can demonstrate, using the stage distributions of patients entered on NWTS - 3 and SIOP Nephroblastoma Trial - 6, that approximately fifty percent more European Stage I–III, favourable histology Wilms tumour patients would be treated with an anthracycline (SIOP - 6 - 45.5%,201/442; NWTS - 3 - 29.3%,449/1528), whereas approximately fifty percent more North American patients would be treated with abdominal irradiation (SIOP - 18.0%,80/442; NWTS - 29.3%,449/1528).[4,15]

4. Randomised study of immediate *versus* delayed nephrectomy

The United Kingdom Children's Cancer Study Group (UKCCSG) conducted a trial (United Kingdom Wilms (UKW) 3) in which patients were randomised to either immediate nephrectomy or pre-operative chemotherapy followed by delayed nephrectomy.[20] The investigators randomised 205 patients representing 39% (205/525) of the incident eligible cases. Although the increase in the proportion of stage I patients was not statistically significant ($p = 0.13$), the authors recommended that pre-nephrectomy chemotherapy be adopted as the standard for the management of most children with non-metastatic unilateral favourable histology Wilms tumour. There are, however, a number of methodological criticisms which should be considered in interpreting their results.

This study redefined stage I disease to include necrotic tumour that was outside the renal capsule but was completely excised. Although the investigators stated that this corresponded to the staging systems employed by the NWTSG and other UKW studies, it is not clear this was the case.[4,21,22] Furthermore, it has been suggested that early systemic relapse occurs more frequently in patients with non-differentiated tissue within the renal capsule and only non-viable tissue or traces of the former tumour in the perirenal fat.[23]

The authors reported outcome by randomised treatment, and did not indicate in their report whether analysis of outcome by actual treatment led to the same conclusions. One of the underlying assumptions of analysis by 'intent to treat' is that there are no significant differences in the distribution of patients with adverse risk factors between the two (or more) randomised treatment arms. The paper did not report the distributions by gender, age at diagnosis, tumour size (or volume), diagnostic imaging evaluation of tumour 'invasion' of adjacent structures, etc. of the 320 patients who were not randomised and it is therefore difficult to confirm that the randomised group was representative of the total group of pa-

tients seen at the participating centres. In particular, the report is unable to determine if patients with large tumours, extensive tumour necrosis or retroperitoneal lymphadenopathy on diagnostic imaging, or those referred to particular institutions and/or particular surgeons, were less likely to be randomised.

Local relapses were reported more commonly among those patients treated with delayed nephrectomy: the proportion of patients with abdominal involvement in a relapse, with or without concurrent distant relapse, was 5.3% (5/94) for those who underwent immediate nephrectomy versus 10.9% (10/92) for those who underwent delayed nephrectomy. This is a disturbing trend, and is in the same direction as that previously reported by the International Society of Paediatric Oncology.[15]

The authors suggested that their results demonstrated an 11.4% reduction in the percentage of patients who required post-operative actinomycin D, based on the assumption that monotherapy with vincristine was adequate for the post-nephrectomy management of those with stage I tumours. However, this conclusion was not based on a comparison with the results of a randomised trial, but rather on a single arm study in which the reported design did not include a formal stopping rule.[22] A subsequent report of the results for a subgroup of these patients suggested that monotherapy was in fact not sufficient treatment for those stage I, favourable histology patients with pulmonary nodules identified only on CT scan.[24] In addition, as stated by the authors, two drug chemotherapy was recommended for this group of patients in their current trial. The investigators also concluded that the overall burden of treatment was considerably reduced and resulted in the avoidance of doxorubicin for stage II tumours but, as discussed above, it is not yet clear that this reduction in therapy is safe. Are there yet sufficient data to reassure that this therapeutic approach does not in fact lead to an increase in the morbidity of therapy due to the more intensive therapy required for management of relapse?

Importantly, the authors stated that they did not observe biopsy track relapse among 102 patients who underwent closed biopsy. This requires clarification as a recurrence of this nature has been reported elsewhere in a patient randomised to have a needle biopsy and preoperative chemotherapy according to the same UKCCSG protocol.[25,26] Another report in the literature demonstrates that this risk is more than theoretical.[27]

Although the UKCCSG study was undertaken to resolve the controversy regarding the risks and benefits of immediate versus delayed nephrectomy in the management of children with Wilms tumour, the study, as reported, does not resolve this controversy and the data do not support the statement in the Abstract that all children with non-metastatic Wilms tumour should receive chemotherapy prior to tumour resection.

5. Summary

Based on prior data from the NWTSG, the only patients with a unilateral Wilms tumour who should undergo delayed nephrectomy are those with extension of tumour thrombus into the inferior vena cava.[28] In addition, those who are poor surgical candidates due to malnutrition, parasitic infestation or other reasons should receive appropriate correction of these problems prior to nephrectomy. Administration of pre-nephrectomy chemotherapy to additional patients with unilateral Wilms tumour still requires careful assessment of the risks and benefits of this approach, compared to those associated with immediate nephrectomy.

Conflict of interest statement

None declared.

Acknowledgement

The author thanks the investigators of the Paediatric Oncology Group and the Children's Cancer Group and the many pathologists, surgeons, paediatricians, radiation oncologists and other health professionals who managed the children entered on the National Wilms Tumour Studies, and Mrs. Diane Piacente for preparation of the manuscript.

Supported in part by USPHS Grant CA-42326.

REFERENCES

1. Breslow NE, Palmer NF, Hill LR, et al. Wilms' tumor: Prognostic factors for patients without metastases at diagnosis. *Cancer* 1978;**41**:1577–89.
2. Breslow N, Churchill G, Beckwith JB, et al. Prognosis for Wilms' tumor patients with nonmetastatic disease at diagnosis - Results of the Second National Wilms' Tumor Study. *J Clin Oncol* 1985;**3**:521–31.
3. Breslow N, Sharples K, Beckwith JB, et al. Prognostic factors in nonmetastatic, favorable histology Wilms' tumor. Results of the Third National Wilms' Tumor Study. *Cancer* 1991;**68**:2345–53.
4. 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.
5. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor: Results of the Second National Wilms' Tumor Study. *Cancer* 1981;**47**:2302–11.
6. Breslow NE, Ou S-S, 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.
7. Green DM. The treatment of stages I – IV favorable histology Wilms tumor. *J Clin Oncol* 2004;**22**:1366–72.
8. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single versus multiple courses of actinomycin D in the treatment of Wilms' tumor. *Cancer* 1976;**38**:647–54.
9. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms' tumor: Results of an International Society of Paediatric Oncology (SIOP) clinical trial. *J Clin Oncol* 1983;**1**:604–9.
10. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor. Results of the National Wilms' Tumor Study. *Cancer* 1976;**38**:633–46.
11. Zoeller G, Pekrun A, Lakomek M, et al. Wilms tumor: The problem of diagnostic accuracy in children undergoing

preoperative chemotherapy without histological tumor verification. *J Urol* 1994;**151**:169–71.
12. Zuppan C, Beckwith B. Pretreated anaplastic Wilms' tumor. *Lab Invest* 1988;**58**:108A. abstract.
13. Zuppan CW, Beckwith JB, Luckey DW. Anaplasia in unilateral Wilms' tumor. *Hum Pathol* 1988;**19**:1199–209.
14. Weirich A, Ludwig R, Graf N, et al. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. *Ann Oncol* 2004;**15**:808–20.
15. Tournade MF, Com-Hougue 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.
16. Green DM, Breslow NE, D'Angio GJ. The treatment of children with unilateral Wilms' tumor. *J Clin Oncol* 1993;**11**:1009. editorial.
17. Green D, Breslow N, Beckwith J, et al. A comparison between single dose and divided dose administration of dactinomycin and doxorubicin. A report from the National Wilms Tumor Study Group. *J Clin Oncol* 1998;**16**:237–45.
18. Green DM, Breslow NE, Beckwith JB, et al. The effect of duration of treatment on outcome and cost of the treatment for Wilms tumor. A report from the National Wilms Tumor Study Group. *J Clin Oncol* 1998;**16**:3744–51.
19. Tournade MF, Com-Hougue C, deKraker 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.
20. 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 randomized trial (UKW3) by the UK Children's Cancer Study Group. *Eur J Cancer* 2006;**42**:2554–62.
21. Pritchard J, Imeson J, Barnes J, et al. Results of the United Kingdom Children's Cancer Study Group (UKCCSG) first Wilms' tumor study (UKW - 1). *J Clin Oncol* 1995;**13**:124–33.
22. Mitchell C, Morris Jones P, Kelsey A, et al. The treatment of Wilms' tumour: results of the United Kingdom Children's Cancer Study Group (UKCCSG) second Wilms' tumour study. *Br J Cancer* 2000;**83**:602–8.
23. Weirich A, Leuchsner I, Janig U, et al. Discrimination between SIOP stage (ST) and stage IIN- with respect to regressive tumor in localized non-anaplastic Wilms tumor (WT). *Med Pediatr Oncol* 2000;**35**:212. abstract.
24. Owens CM, Veys PA, Pritchard J, et al. Role of chest computed comography at diagnosis in the management of Wilms' tumor: A study by the United Kindgom Children's Cancer Study Group. *J Clin Oncol* 2002;**20**:2768–73.
25. Aslam A, Foot ABM, Spicer RD. Needle track recurrence after biopsy of non-metastatic Wilms tumour. *Pediatr Surg Int* 1996;**11**:416–7.
26. Vujanic GM, Kelsey A, Mitchell C, et al. The role of biopsy in the diagnosis of renal tumors of childhood. Results of the UKCCSG Wilms tumor study 3. *Med Pediatr Oncol* 2003;**40**:18–22.
27. Lee IS, Nguyen S, Shanberg AM. Needle track seeding after percutaneous biopsy of Wilms tumor. *J Urol* 1995;**153**:1074–6.
28. Shamberger RC, Ritchey ML, Haase GM, et al. Intravascular extension of Wilms tumor. *Ann Surg* 2001;**234**:116–21.