

How curable is relapsed Wilms' tumour?

J J Groot-Loonen, C R Pinkerton, P H Morris-Jones, J Pritchard
on behalf of the United Kingdom Children's Cancer Study Group

Abstract

Three hundred and eighty one children with Wilms' tumour were treated on the United Kingdom Children's Cancer Study Group WT1 Study (1980/6). Seventy one patients relapsed during or after treatment, which included surgery and chemotherapy, with irradiation depending on stage and histology. Despite treatment with various combinations of chemotherapy, surgery, and radiotherapy there were only 17 survivors. For unfavourable histology, any stage, only two of 20 survive. We conclude that, after relapse, even for patients who have had localised disease and favourable histology, the 'salvage' rate is little more than 50% and for all others the likelihood of cure is very small. Three of 41 children who relapsed less than 12 months from diagnosis survive, compared with 14 of 30 who relapsed later. It is essential that even with this 'good prognosis' tumour initial treatment is optimal and given by centres experienced in management of children's cancer. Furthermore, there is a clear need for additional effective chemotherapeutic agents for relapsed patients.

Over 85% of patients with Wilms' tumours are cured by conventional combinations of treatment including surgery, radiotherapy, and chemotherapy.¹⁻³ Most recurrences are within two years of diagnosis, although metastases have developed as long as 11 years after initial treatment.^{4,5} Wilms' tumour can recur locally or in several other sites including elsewhere in the abdomen, the contralateral kidney, lungs, liver, bone, and brain. However, the most frequent site of recurrent disease is the lung.⁶ Although successful treatment of recurrent disease has been reported for patients with pulmonary metastases^{7,8} and for patients with a solitary metastasis in liver or brain,⁹⁻¹¹ the prognosis after abdominal recurrence or unresectable metastatic disease is still poor.¹²

Because most previous reports have not clearly defined their population, it is difficult to draw conclusions regarding the overall efficacy of second line treatment. An exception to this is a recent study of relapsed disease from the National Wilms' Tumour Study Group.¹³ In that series a number of adverse features were evident: unfavourable histology, relapse outside the lung (especially in the previously irradiated abdomen), high initial stage, and more than two drugs given initially. Details of the second line chemotherapy were not given but it was sug-

gested that in those patients who relapsed off treatment, the same standard drugs, such as vincristine, actinomycin D, doxorubicin, and cyclophosphamide, could be used to good effect. This report describes the outcome after 'second line' treatment in an unselected group of patients who relapsed after receiving the United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour regimen (WT1).

At relapse the treatment approach was determined by the individual centre, with no formal guidelines from the UKCCSG. In general early surgical resection of operable disease was performed and adjuvant chemotherapy given, which where possible usually included agents that the patient had not already received. Local recurrences at previously unirradiated sites received 35-40 Gy.

Patients and methods

The UKCCSG Wilms' tumour WT1 study was started in January 1980 and closed to patient entry in May 1986. During this period 381 eligible patients were registered on the study: 118 patients with stage I disease, 67 with stage II, 126 with stage III, 50 with stage IV, and 20 with stage V. The histological subgroup was documented in 358 cases: favourable in 317 and unfavourable in 41 patients.¹⁴

First line treatment included surgery in all patients and irradiation depending on stage and histology. The radiation policy was as follows: stage I—nil, stage II favourable—20 Gy to flank; and stage III—20 Gy to flank or whole abdomen. Chemotherapy was given every three weeks and comprised vincristine 1.5 mg/m² for six months for stage I favourable, vincristine and actinomycin D 1.5 mg/m² for six months for stage II favourable, vincristine, actinomycin D, and doxorubicin 40 mg/m² for 12 months for stage III and stage IV favourable, and vincristine, actinomycin D, doxorubicin, and cyclophosphamide 600 mg/m² for 12-15 months for stage IV favourable and all stages with unfavourable histology. All received vincristine weekly (10 doses initially) either alone or in combination.³ Stage IV treatment was individualised.

At the time of relapse, disease in the lungs was assessed by posterior-anterior and lateral radiography or computed tomography of the chest, or both; in the abdomen by computed tomography or ultrasound examination, or both; in the skeleton by radiography or bone scan, or both; and disease in the brain was detected by computed tomography.

The Royal Marsden
Hospital, Sutton
J J Groot-Loonen
C R Pinkerton

Royal Manchester
Children's Hospital
P H Morris-Jones

The Hospital for Sick
Children, Great Ormond
Street, London
J Pritchard

Correspondence to:
Dr C R Pinkerton,
Royal Marsden Hospital,
Sutton, Surrey SM2 5PT.

Accepted 3 May 1990

Table 1 Stage of disease at presentation, initial histology, and survival of the 71 patients who relapsed on the UKCCSG WT1 protocol

Stage of disease	No of patients	No with favourable histology	Survival (No patients)	No with unfavourable histology	Survival (No patients)
I	11	9	6	2	1
II	11	10	5	1	0
III	23	11	0	12	1
IV	21	16	3	5	0
V	5	5	1	—	0
Total	71	51	15	20	2

Table 2 Treatment given after relapse (n=71)

Treatment	No of patients
Surgery	2
Radiotherapy	3
Chemotherapy	22
Surgery/chemotherapy	12
Surgery/radiotherapy	1
Chemotherapy/radiotherapy	18
Chemotherapy/radiotherapy/surgery	7
No treatment	6

Results

Seventy one patients relapsed on the UKCCSG WT1 protocol (table 1). At initial presentation histology was favourable in 51 of the relapsed patients and unfavourable in 20. Seventeen patients (24%) have survived disease free for 20–70 months (median 36).

The management of patients at relapse is summarised in table 2. Two patients died soon after relapse without treatment and in four no further treatment was given electively. Two had surgery alone: one had complete removal of lung metastases and the second a contralateral nephrectomy. In most children a combination of treatments was used; however, in 30% chemotherapy alone was used as second line treatment.

Table 3 shows treatment given to the 17 survivors. The majority had many types of treatment. In only two patients was chemotherapy alone used, and in one surgery alone (nephrectomy) was curative.

Table 3 Clinical details of patients who survived

Stage at presentation	Histology	Site of recurrence	Time of relapse (months after diagnosis)	Treatment			Survival* (months)
				Chemotherapy	Radiotherapy	Surgery	
I	Favourable	Lung	24	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	—	+	35
I	Favourable	Kidney	17	Vincristine, actinomycin D, doxorubicin	—	+	52
I	Favourable	Lung	8	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	—	+	53
I	Favourable	Lung	12	Vincristine, actinomycin D, doxorubicin	+	—	40
I	Favourable	Lung	12	Ifosfamide, actinomycin D, doxorubicin	—	—	43
I	Favourable	Kidney	13	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	—	+	20
I	Unfavourable	Brain	58	—	+	+	28
II	Favourable	Lung+mediastinum	26	HDM, vincristine	+	+	70
II	Favourable	Lung+pericardium	20	Vincristine, actinomycin D	+	—	55
II	Favourable	Liver	16	Ifosfamide, vincristine, doxorubicin	—	—	26
II	Favourable	Pleura	13	Ifosfamide, etoposide, cyclophosphamide, vincristine, epirubicin	—	+	28
II	Favourable	Lymph node	4	Actinomycin D, ifosfamide, vincristine, teniposide	+	+	37
III	Unfavourable	Bone	33	Carboplatin, etoposide	+	—	25
IV	Favourable	Lung	54	Etoposide, cisplatin	+	—	29
IV	Favourable	Lung	19	Ifosfamide, HDM, vincristine	+	—	40
IV	Favourable	Lung+liver	5	Ifosfamide	—	+	40
V	Favourable	Kidney	13	—	—	+	64

*Survival at May 1989.

HDM, high dose melphalan.

Most patients initially presenting with low stage disease achieved a second complete remission (14/19) but three of these subsequently relapsed. It should be noted that most of the survivors had had late relapses occurring off treatment (table 3). In patients with stage III and IV disease who had previously received three drug regimens with or without irradiation, response to subsequent chemotherapy was poor and only three of 44 patients survived.

Discussion

Acquiring information about the cure rate after treatment of relapsed Wilms' tumour is difficult because numbers of patients are small due to the high cure rate after primary treatment. Moreover, interpretation of the published studies is complicated by differences in initial treatment and patient selection. Survival after relapse will depend on the initial stage of disease, histology, relapse site, and the timing of relapse.^{7 12 13 15}

Advantageous features generally include initial favourable histology, extra-abdominal metastases, and relapse occurring late, after cessation of treatment.

Treatment strategy at time of relapse will depend on the nature of initial treatment. In those patients who relapse off treatment having received only one or two agents, often vincristine alone or vincristine and actinomycin D, it is appropriate to use drugs such as doxorubicin and cyclophosphamide and, where suitable, radiotherapy. By contrast, patients who had more advanced disease will have initially received most conventional active agents, and may have also been irradiated, and new drugs were therefore required. This analysis demonstrates, however, that outcome was disappointing even in patients who originally had low stage disease and who had received only one or two drugs in their initial regimen, suggesting that some degree of cross resistance exists between the original and subsequently used drugs. It should be noted that all the stage I patients who failed

second line treatment had relapsed less than 12 months from diagnosis. Such 'multidrug resistance' in the absence of prior exposure is now well recognised and may involve vincristine, actinomycin D, and doxorubicin.¹⁶

Information regarding activity of drugs other than vincristine, actinomycin D, doxorubicin, and cyclophosphamide is scanty.¹⁷⁻¹⁹ Encouraging response rates with the cyclophosphamide analogue ifosfamide have been reported.²⁰⁻²² Unfortunately, the renal toxicity of this drug is causing increasing concern with reports of renal tubular dysfunction.^{23 24}

Because of its nephrotoxicity, there are few studies of cisplatin in Wilms' tumour and the results have been disappointing.²⁰ Carboplatin, the comparatively non-nephrotoxic analogue of cisplatin, is currently under evaluation.

Etoposide has been studied as a single agent and has clear activity in refractory Wilms' tumour.²⁵ The main toxicity of this drug is myelosuppression and it therefore has advantages over the alkylating agents and anthracyclines, which may have undesirable late effects on fertility and cardiac function, respectively.

The importance of children with cancer being managed at experienced centres has been demonstrated²⁶ and applies to Wilms' tumour as much as any other tumour.²⁷ The relative simplicity of the chemotherapy regimens and high cure rates do not mean that paediatricians, surgeons, or radiotherapists can afford not to refer children for specialist care.

Our study demonstrates that although second line treatment is moderately effective in a proportion of patients relapsing after treatment for localised Wilms' tumour, for most children there is no 'second chance'. There is clearly no room for complacency and new drugs or alternative ways to use conventional agents are required.

Patients with initial stage III and IV disease, those with unfavourable histology, or those relapsing less than 12 months after diagnosis should be considered for trials with initial single agent treatment. In this way antitumour activity is determined and the new drug can be included in subsequent combination regimens if effective. This strategy has been applied in the UK and Europe to ifosfamide, etoposide, and currently to carboplatin, and new front line combinations have been logically devised. Although the overall relapse rate is low, there may be scope for improving refinement of prognostic features so that more intensive treatment may be given to those patients at comparatively high risk of relapse.

The authors wish to thank the following for providing data on their patients: F Breatnach, JE Kingston, JR Mann, J Martin, A Oakhill, ADJ Pearson, A Craft, I Lewis, and C Bailey. Thanks also to Janet Barnes, statistician for UKCCSG and Tereza Gladwell for preparation of this manuscript.

JJ Groot-Loonen was supported by the Koningin Wilhelmina Fonds. The UKCCSG is supported by the Cancer Research Campaign.

- Lemerle J, Voute PA, Tournade MF. Effectiveness of preoperative chemotherapy in Wilms' tumour: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *J Clin Oncol* 1983;1:604-9.
- D'Angio GJ, Evans A, Breslow N, et al. The treatment of Wilms' tumor: results of the second national Wilms' tumor study. *Cancer* 1981;47:2302-11.
- Pritchard J, Barnes JM, Gough D, et al. Preliminary results of the first United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour study. *Med Pediatr Oncol* 1988;16:413.
- Clausen N. Late recurrence of Wilms' tumour. *Med Pediatr Oncol* 1982;10:557-61.
- Kisielius T, Bianco A, Merrill JM, et al. Bleomycin in combination chemotherapy of metastatic Wilms' tumour: a late recurrent case, refractory to conventional therapy. *Med Pediatr Oncol* 1979;6:11-4.
- Jereb B. Metastases and recurrences in nephroblastoma. *Acta Radiol [Ther] (Stockh)* 1973;12: 289-304.
- Wedemeyer PP, White JG, Nesbit ME, et al. Resection of metastasis in Wilms' tumour: a report of three cases cured of pulmonary and hepatic metastases. *Pediatrics* 1968;41: 446-51.
- Sutow WW, Breslow NE, Palmer NF, et al. Prognosis in children with Wilms' tumour metastases prior to or following primary treatment. *Am J Clin Oncol* 1982;5: 339-47.
- Smith WB, Wara WM, Margolis LW, et al. Partial hepatectomy in metastatic Wilms' tumour. *J Pediatr* 1974;84: 259-61.
- Mohammad AM, Meyer J, Hakami N. Long-term survival following brain metastases of Wilms' tumour. *J Pediatr* 1977;90:660.
- Morgan SK, Buse MG. Survival following brain metastases in Wilms' tumour. *Pediatrics* 1976;58:130-2.
- Burgers JMV, Tournade MF, Bey P, et al. Abdominal recurrences in Wilms' tumours: a report from the SIOP Wilms' tumour trials and studies. *Radiother Oncol* 1986;5: 175-82.
- Grundy P, Breslow N, Green DM, Sharples K, Evans A, D'Angio GJ. Prognostic factors for children with recurrent Wilms' tumour: results from the second and third national Wilms' tumour study. *J Clin Oncol* 1989;7:638-47.
- Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms' tumor. Results from the first national Wilms' tumor study. *Cancer* 1978;41:1937.
- Weeks DA, Beckwith JB, Luckey DW. Relapse-associated variables in stage I favourable histology Wilms' tumor—a report of the national Wilms' tumor study. *Cancer* 1987;60:1204-12.
- Kaye SB. The multidrug resistance phenotype. *Br J Cancer* 1988;58:691-4.
- Jereb B, Eklund G. Factors influencing the cure rate in nephroblastoma: a review of 335 cases. *Acta Radiologica* 1973;12:84-106.
- Sutow WW. Cyclophosphamide in Wilms' tumour and rhabdomyosarcoma. *Cancer Chemotherapy Reports* 1967; 51:407.
- Green DM. Wilms' tumour. *Diagnosis and management of malignant solid tumors in infants and children*. Boston: Martinus Nijhoff, 1985:129-86.
- de Kraker J, Voute PA. Ifosfamide, mesna and vincristine in paediatric oncology. *Cancer Treat Rev* 1983;10(suppl A): 165-6.
- Pinkerton CR, Rogers H, James C, et al. A phase II study of ifosfamide in children with recurrent solid tumours. *Cancer Chemother Pharmacol* 1985;15:258-62.
- Demeocq F, Tournade MF, Lemerle J, et al. Ifosfamide is an active drug in Wilms' tumour. A phase II study of the French Society of Paediatric Oncology. *Proceedings of the American Society of Clinical Oncology* 1986:204.
- Moncrieff M, Foot A. Fanconi syndrome after ifosfamide. *Cancer Chemother Pharmacol* 1989;23:121-2.
- Willems PHB, de Jong PE, Elema JD, Mulder NH. Severe renal failure following high-dose ifosfamide and mesna. *Cancer Chemother Pharmacol* 1989;23:329-30.
- Pein F, Tournade M-F, Brunat-Mentigny M, et al. A Phase II study of etoposide in the treatment of relapsed Wilms' tumors. *Proceedings of the American Society of Clinical Oncology* 1988:259.
- Stiller CA. Centralisation of treatment and survival rates for cancer *Arch Dis Child* 1988:63.
- Pritchard J, Stiller CA, Lennox EL. Overtreatment of children with Wilms' tumour outside paediatric oncology centres. *Br Med J* 1989;299:835-6.