Management of nephroblastoma in childhood

Clinical study of two forms of maintenance chemotherapy

MEDICAL RESEARCH COUNCIL'S WORKING PARTY ON EMBRYONAL TUMOURS IN CHILDHOOD*

SUMMARY This report presents results of the first multicentre study of the treatment of nephroblastoma in the United Kingdom. Of 114 children entered in the trial, 108 with localised tumours and without identified metastases were treated by nephrectomy and a 4-day course of actinomycin D, followed by radiotherapy: they were then allocated randomly either to receive further courses of actinomycin D or to receive vincristine for a period of 2 years from diagnosis. The children have so far been followed for periods of between 27 and 69 months; at this stage the superiority of vincristine (in the dose given) to further actinomycin D in preventing local recurrence and metastasis borders on significance; the difference between survival rates also suggests an advantage for vincristine but is not statistically significant. The actuarial survival and continuous disease-free rates at 2 years were 77.7% and 53.6% respectively in the actinomycin D group compared with 87.8% and 79.4% in the vincristine group.

Nephroblastoma accounts for 5% of all malignant disease in childhood in the UK and affects 1 in 200 000 children under the age of 15 years (Marsden and Steward, 1968). Treatment has traditionally been by nephrectomy. The first major advance in treatment followed the introduction in 1931 of nephrectomy by an anterior transperitoneal and trans-abdominal approach. Over the next 20 years in the Boston Children's Hospital, where all children with a diagnosis of nephroblastoma were treated in this way, there were no deaths from operation (Gross, 1953). When, in 1950, in the same hospital, radiotherapy was added, an overall survival rate of 50% was achieved (Gross and Neuhauser, 1950). Interest in chemotherapy was stimulated when the enhancement

of radiation by actinomycin D was reported by D'Angio *et al.* (1959), and later when Farber and others reported improved survival (Farber *et al.*, 1960; Colebatch *et al.*, 1964; Farber, 1966; Fernbach and Martyn, 1966; Burgert and Glidewell, 1967). Vincristine was shown to be of value by Sutow (1965) and Sullivan and Sutow (1969).

The first randomised trial in the treatment of nephroblastoma was that of the Children's Cancer Study Group A (Wolff *et al.*, 1968); nephrectomy was followed by radiotherapy and the children then received *either* a single course of actinomycin D, 15 µg/kg daily for 5 days immediately after surgery, *or* continued with repeated maintenance courses of that dosage at 6 weeks and 3 months after operation and then every 3 months until 15 months from diagnosis. Early results reported in 1968 suggested that the multiple-course regimen was superior in preventing local recurrence and metastatic disease, but a later report (Wolff *et al.*, 1974) showed that many children who developed metastases after the single course of chemotherapy had been cured by further chemotherapy. The survival rates in the two groups were not statistically different.

When Ledlie *et al.* (1970) reviewed the results of treatment in the UK between 1962 and 1966 the overall survival was only 32% at 3 years; and only about one-third of patients had received chemotherapy. It was against this background that the Medical Research Council Nephroblastoma Study was designed to determine whether actinomycin D or

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vincristine was the better adjuvant maintenance chemotherapeutic agent in the prevention of recurrent and metastatic disease after primary treatment by nephrectomy, paraoperative actinomycin D, and radiotherapy. The study began in August 1970; entry terminated in March 1974 because preliminary results from the US National Wilms's Tumour Study indicated that, for maintenance, single-agent chemotherapy was not as effective as the combination of vincristine and actinomycin D (D'Angio *et al.*, 1976).

Methods

Patient selection. Any child between 1 and 14 years with a nephroblastoma diagnosed at operation was eligible for inclusion in the study if there was no spread outside the abdominal cavity or to the liver. Children aged under one year were excluded because of the better prognosis (Margolis *et al.*, 1973) and the dangers of cytotoxic chemotherapy at this age.

Investigations. Standard investigations were full blood count, measurement of blood urea and electrolyte levels, urine microscopy and culture, chest x-ray—posteroanterior and lateral films, and intravenous pyelogram. Although it was suggested that further investigations such as liver scan, lung tomogram, and inferior venacavogram might be helpful, they were not mandatory.

Operative treatment. A transabdominal, transperitoneal approach was suggested: the renal vessels were to be exposed and ligated as soon as possible and before mobilisation of the kidney. Macroscopically abnormal lymph nodes were to be removed, but routine formal retroperitoneal dissection was not advocated.

Staging of disease. The same classification as in the National Wilms's Tumour Study Group (D'Angio, 1972) was used. The three stages included in the present study were identical with groups I, II, and III of the American study.

Stage I Tumour confined to the kidney and completely resected.

Stage II Tumour extending beyond the capsule of the kidney either by local infiltration, extension along the renal vein or involvement of the para-aortic nodes, but complete macroscopical removal achieved.

Stage III Tumour extending beyond the capsule of the kidney and not completely resected or the

operative field contaminated with tumour spilled at operation.

The other two groups, not included in the MRC trial are:

Stage IV Haematogenous metastases—deposits in liver, lung, bone, and brain or other distant sites.

Stage V Bilateral renal involvement either initially or subsequently.

Staging was determined by the surgeon at the time of operation and subsequently confirmed or adjusted by the pathologist's report.

Paraoperative chemotherapy. All patients were given a course of actinomycin D 15 µg/kg per day for 4 days; the first dose was given on the day of operation as soon as diagnosis was confirmed, then daily for the next 3 days provided that the total white cell count was $>2.5 \times 10^9/l$ and platelet count $>100 \times 10^9/l$. Otherwise the doses were spaced over 6 days.

Radiotherapy. Because previously some radiotherapy centres had treated the whole abdomen and others only the affected side, two treatment schedules were devised for stage I cases. Each centre adopted a single schedule (see below) for all its stage I cases and randomised comparison of the two was not possible. It was agreed that radiotherapy should start as soon as possible after surgery but always before the 15th postoperative day.

Stage I cases—schedule A (Fig. 1 (i)). At centres where treatment had customarily been given to the whole abdomen, but not including the true pelvis, this practice was continued, and the volume treated was from the sacral promontory to the level of the ninth dorsal vertebra with shielding of the unaffected kidney throughout. Megavoltage radiation was recommended and the tumour doses given were: (i) 3000 rads in 20 fractions in 4 weeks; (ii) 3250 rads in 25 fractions in 5 weeks, (iii) 3500 rads in 30 fractions in 6 weeks. In a few centres kV had to be used and the dose was adjusted to be radiobiologically equivalent.

Stage I cases—schedule B (Fig. 1). At those centres which considered schedule A to be too extensive the following alternative was given: the volume to be treated extended from the flank on the affected side to 1 cm lateral to the spine on the contralateral side. The vertical limits were from the level of the iliac crests to the dome of the diaphragm. The field was sufficiently large to include the tumour bed and the immediate primary lymphatic drainage; the tumour dose was as for schedule A (Fig. 1, schedule B).

Fig. 1 Diagram of the three different suggested radiotherapy fields.

Stage II and III cases. The treatment was as in schedule A, except that in stage III patients in whom 'spill' had occurred or there was thought to be disease in the true pelvis, the volume was extended downwards to the pelvic floor. It was accepted that where complete shielding of the opposite kidney was considered impossible, the dose of radiation received by that kidney would be safe provided that it was shielded throughout from the back-field (Fig. 1—schedule A (ii)).

Maintenance chemotherapy. Patients were allocated at random to one of two treatment regimens, each starting 6 weeks after completion of radiotherapy (Fig. 2). (i) Repeated 4-day courses of actinomycin D 15 µg/kg per day at 12-week intervals for a total of eight courses; or (ii) vincristine 1.5 mg/m² weekly for 6 weeks and then alternate weeks until 2 years from diagnosis.

Pathology. Initial pathological investigation was carried out at the participating centre. Specimens were examined to ascertain whether there was renal vein involvement. The histological sections were also examined by a panel of pathologists to confirm the diagnosis and to correlate histology with spread of disease and prognosis.

Statistical comparisons. Throughout this paper 'disease-free' is defined as free of both metastatic and recurrent disease. Comparisons of percentage disease-free and percentage survival curves have been made using the logrank test (Peto and Pike, 1973).

Patients

114 patients from 19 centres were notified for inclusion; of these, 108 were randomised for chemotherapy, and 6 were excluded (3 of whom were found subsequently to have stage IV tumours and 3 of whom died shortly after operation and before randomisation for maintenance therapy). There were 61 boys and 47 girls; 57 tumours were on the left side and 51 on the right. The stage of tumour and age of the patients are shown in Table 1. 37 children presented with abdominal swelling and 35 with haematuria as their only complaint. 16 children had

Table 1 Distribution of patients by age and tumour stage

Stage	Age (years)				Total
	1.0—	2.0—	3.0—	4.0+	
I	9	9	9	18	45
II	8*	9	8	10	35
III	5	5	5*	15	30
IV	2	1			3
Unstaged				1*	1
Total	24	24	22	44	114

*The 3 postoperative deaths occurred in these groups.

Fig. 2 Diagram of the plan of the trial.

abdominal pain. Dysuria, anorexia, diarrhoea, vomiting, weight loss, and lethargy were less frequent presenting symptoms.

Deviations from protocol

The period between operation and starting x-ray therapy was longer than the recommended 15 days for 21 patients; 3 of these had definite postoperative complications. Other deviations from the protocol occurred for 54 patients; 18 of these had their treatment stopped or modified because of deterioration in their condition. In the remainder the differences were only minor and judged to be of no significance.

Results

Results have been assessed up to 1 May 1976, giving a follow-up period of between 27 and 69 months. All the surviving children will be followed up indefinitely.

Freedom from metastases and survival in all patients randomly allocated for maintenance chemotherapy. The distribution of the 108 patients is shown in Table 2 together with actuarial percentages of those disease-free and surviving at 1 year, 2 years, and 3 years. The corresponding curves are shown in Figs. 3 and 4 respectively. A comparison of the percentage disease-free curves in Fig. 3, using the logrank test, indicates after adjustment is made for tumour stage that the difference between them borders on statistical significance at $P = 0.05$ ($\chi^2 = 3.66$, $df = 1$, $P = 0.056$). Similarly, Fig. 4 suggests a better percentage survival for the vincristine patients, but the difference

Fig. 3 Actuarial percentage disease-free curves for all patients allocated chemotherapy.

Fig. 4 Actuarial percentage survival curves for all patients allocated chemotherapy.

between the two curves is not significant at $P = 0.05$ ($\chi^2 = 2.70$, $df = 1$, $P = 0.100$). Comparison of the disease-free and survival percentages for the three tumour stages after adjustment for chemotherapy indicates that patients with stage I tumours have a better prognosis than patients with stage II or III tumours.

Results in patients actually receiving maintenance chemotherapy. Of the 108 randomised patients, 7 (1 actinomycin D, 6 vincristine) did not receive their allotted chemotherapy, for reasons shown in Table 3, and a further 11 patients (5 actinomycin D, 6 vincristine) developed metastases before chemotherapy was started; thus 90 disease-free patients started the randomly allocated course of maintenance chemotherapy. 12 (1 actinomycin D, 11 vincristine) of these 90 were withdrawn for reasons other than progressive disease. The intervals to withdrawal, the current status, and the reasons for withdrawal are given in the lower part of Table 3.

The percentage disease-free and survival curves for the 90 patients are shown in Figs. 5 and 6 respectively: the vincristine group has a higher percentage disease-free survival than the actinomycin D group ($\chi^2 = 7.05$, $df = 1$, $P = 0.008$) and a higher percentage survival ($\chi^2 = 4.54$, $df = 1$, $P = 0.033$). These comparisons, which assess the difference between the two chemotherapies in those patients who are disease-free at the start of maintenance chemotherapy, are less reliable than those in all patients as a result of the selective elimination of 18 patients (6 actinomycin D, 12 vincristine) from the analysis.

There was no association between the stage of the tumour and age (Table 1), nor any important difference in the disease-free or survival percentages

Table 2 Actuarial percentages, disease-free and surviving, at 1 year, 2 years, and 3 years from entry to the trial by chemotherapy and tumour stage

Tumour stage	Total no. of patients	Actuarial percentages						Patients not starting allocated CT	Patients with metastases before CT	Total no. of disease-free patients starting CT	Actuarial percentages														
		Disease-free at (yr)			Surviving at (yr)						Disease-free at (yr)			Surviving at (yr)											
		1			2						1			2			1			2			3		
		I	2	3	I	2	3				I	2	3	I	2	3	I	2	3						
<i>Actinomycin D</i>																									
I	23	77.3	72.7	72.7	72.7	95.5	90.9	86.1	1	1	21	81.0	76.2	76.2	100.0	95.2	90.2								
II	17	58.8	52.9	41.2	88.2	76.5	52.3	0	3	16	62.5	56.3	43.8	93.8	81.3	55.6									
III	15	46.7	40.0	40.0	86.7	66.7	59.3	0	3	12	58.3	50.0	50.0	91.7	83.3	74.1									
Total	55	61.1	53.6	53.6	88.9	77.7	67.9	1	5	49	67.3	59.0	59.0	93.9	85.6	74.8									
<i>Vincristine</i>																									
I	22	100.0	100.0	90.9	100.0	100.0	100.0	4	0	18	100.0	100.0	90.9	100.0	100.0	100.0									
II	17	79.5	70.7	70.7	84.6	76.2	76.2	1	2	14	90.9	80.8	80.8	100.0	90.0	90.0									
III	14	69.6	61.9	61.9	92.3	84.6	69.2	1	4	9	100.0	88.9	88.9	100.0	88.9	88.9									
Total	53	82.0	79.4	76.4	93.0	87.8	81.9	6	6	41	94.1	91.1	87.7	100.0	93.8	93.8									

CT = chemotherapy.

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Table 3 Patients withdrawn from the trial for reasons other than progressive disease

Allocated chemotherapy	Reasons for withdrawal (n)	Interval from diagnosis to withdrawal (m)	Tumour stage	Current status*
Patients never receiving allocated chemotherapy				
Actinomycin D	Clinician's decision, vincristine used instead (1)	1	I	A
	Postoperative complications (1)	1	I	A ⁺
Vincristine	Hypertension after radiation (2)	1,1	I,III	A,A
	Clinician's decision (2)	1,1	I,II	A,D ⁺
	Postoperative complications and liver toxicity (1)	1	I	A
Patients withdrawn from allocated chemotherapy				
Actinomycin D	Toxic reaction to actinomycin D (1)	14	III	A
Vincristine	Clinician's decision (5)—(severe retardation, dislike of I.V. injection, family problems, unwell, psychological distress)	2,2,3,7,8	I,II,II,I	D,A,A,A,A
	Vincristine neuropathy (4)	4,7,9,15	II,I,II,I	D ⁺ ,A,A,A
	Anaemia with repeated courses of vincristine (1)	22	I	A
	Developed pulmonary tuberculosis (1)	23	I	A

*A = alive; D = dead; + = developed metastases subsequent to withdrawal.

Fig. 5 Actuarial percentage disease-free curves for all 'disease-free' patients receiving allocated chemotherapy.

Fig. 6 Actuarial percentage survival curves for all 'disease-free' patients receiving allocated chemotherapy.

for (1) age groups; (2) right-sided and left-sided tumours; (3) patients for whom the delay between diagnosis and operation was 10 days or more, compared with the remainder; (4) patients for whom the duration of x-ray therapy exceeded 5 weeks, and the remainder; and (5) the two x-ray schedules in stage I patients.

Metastatic disease and death. 39 out of the 108 patients developed metastases; 11 between 5 and 12 weeks from diagnosis, i.e., before starting maintenance chemotherapy; of these, 10 have died despite further therapy; 23 while on maintenance chemotherapy (18 in the first year, 5 in the second); of these, 14 have died. All 14 had evidence of progressive disease, although the immediate cause of death in one case was intestinal obstruction. 3 children developed metastases after withdrawal from maintenance chemotherapy; of these, 2 have died from progressive disease and the third has a tumour in the remaining kidney. 2 children developed metastases after completion of maintenance chemotherapy more than 2 years from diagnosis, both have had further therapy and are now free of disease.

Three patients developed bone metastases as the first manifestation of further disease and 2 other patients (each of whom had a second laparotomy) developed liver metastases. Clinical evidence of liver metastases appeared in 2 other patients. In the remaining 32 patients the spread of progressive disease was detected first in the lungs. The 13 survivors who have developed metastases, all of whom have had further treatment either with surgery, radiotherapy, or chemotherapy, have been off treatment for periods varying between 10 and 36 months. There has been one further death in a child removed from therapy, who developed pneumonia.

Complications of therapy (Table 3).

Paraoperative chemotherapy and radiotherapy. 2 patients developed hypertension with evidence of renal damage considered to be radiation nephritis due to the enhancing effect of paraoperative actinomycin D. These 2 patients have been previously reported (Arneil *et al.*, 1974). Another patient developed a postoperative abscess which delayed radiotherapy, and later had liver damage with ascites and thrombocytopenia after radiation for a right-sided tumour. This syndrome has also been ascribed to the enhancement of radiation by actinomycin D (Tefft *et al.*, 1970; McVeagh and Akert, 1975).

Maintenance chemotherapy.

(a) **Actinomycin D (49 patients).** One patient developed a severe toxic reaction to actinomycin D therapy and treatment was stopped at 14 months.

(b) **Vincristine (41 patients).** 4 patients showed vincristine neuropathy. One of these patients was changed to actinomycin D and a full treatment schedule was completed. One patient developed intractable anaemia after 22 months of vincristine therapy; the bone marrow showed hypoplastic changes which have now resolved. Another patient developed pulmonary tuberculosis. 2 other patients, one of whom has since died of progressive disease, were said to be unwell on vincristine but no specific pathological changes were reported.

Most of the 90 patients who received maintenance chemotherapy suffered hair loss, usually after the first course of treatment, but normal regrowth was seen despite subsequent courses of drug treatment. Significant leucopenia and thrombocytopenia were not a problem. No late toxicity or other complication has so far been reported.

Conclusions

After a paraoperative course of actinomycin D, vincristine in the dose given appears to be marginally more effective both in preventing the development of metastases and in prolonging survival than does further actinomycin D. But the study shows no clear advantage of either therapy alone and, indeed, the report of the US National Wilms's Tumour Study suggests that maintenance with a combination of vincristine and actinomycin D is superior to the use of either drug alone when used in the regimen described (D'Angio *et al.*, 1974).

The results obtained from the present practice for the management of the disease show a useful advance over the results reported by Ledlie *et al.* (1970) for a period some 8 years earlier, and the fact

that they have already been overtaken is encouraging in the hope it offers for continuing progress.

The study leaves unanswered some questions which, notwithstanding the US results, merit investigation. (1) Could the paraoperative course of actinomycin D be with advantage omitted or replaced by vincristine? (2) Is such an intensive and prolonged course of vincristine necessary? (The present study suggests that such a course is difficult to maintain, although this was not the experience of all centres participating in the trial.) (3) Should chemotherapy be introduced at an earlier stage or be given for a longer period of time to prevent the development of the early metastases found in 11 of the children in this study?

The introduction of new drugs may bring still further improvements, particularly in the management of poor-risk patients. Patients with metastatic disease have already been shown to respond to doxorubicin and this drug is being tested in combination with vincristine and actinomycin D in stage II and III patients in the US and the MRC studies in progress.

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