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The Use of Four-Drug Combination Chemotherapy (D.A.V.E.) in the Treatment of Advanced Wilms' Tumour

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Summary. *A study was begun in 1971 at St. Bartholomew's Hospital with a combination of 4 drugs, dactinomycin (actinomycin D), adriamycin, vincristine and Endoxan (cyclophosphamide) (D.A.V.E.), together with surgery and radiation, in the treatment of stage III and stage IV Wilms' tumour. Seventy-one percent of the children treated achieved complete response. The median survival from diagnosis was 19 months, and in those children achieving complete response the median disease-free survival has not yet been reached. Toxicity was not a serious problem.*

The study group is compared with a group of children treated at this hospital before 1971. There is an improved survival in the children treated with D.A.V.E. Children who have relapsed with stage I or stage II disease may also respond.

This four-drug combination was well tolerated and effective, and confirms recent experience suggesting that intensive multiple-drug regimens may be curative even in advanced disease.

Introduction

The overall outlook for children with Wilms' tumour has improved dramatically over recent years, and a cure rate of more than 80% for patients with localised disease is now a realistic aim [5]. The prognosis for children presenting with stages III and IV Wilms' tumour remains less favourable. Reports of the use of actinomycin D and vincristine with surgery and radiotherapy have been encouraging [9]. The addition of adriamycin to actinomycin D and vincristine gave an improved survival in the group III patients of the N.W.T.S. II study [5], but the outlook for the group IV patients remained comparatively poor [4]. That study emphasised the poor survival in all patients with an unfavourable histology. Cyclophosphamide is the fourth drug which has been shown to be effective in metastatic Wilms' tumour [13].

In the hope that combining drugs that are effective in Wilms' tumour would produce a higher response rate and a better survival, we designed a study using actinomycin D (dactinomycin), adriamycin, vincristine, and cyclophosphamide (Endoxan). The drugs in this order gave rise to the acronym D.A.V.E., and for convenience this term will be used for the rest of this report.

We report the results of using this four-drug combination in association with surgery and radiotherapy for the treatment of stage III and stage IV Wilms' tumour.

Patients and Methods

A study was begun in 1971 at St. Bartholomew's Hospital with a four-drug combination (D.A.V.E.) in histologically proven stages III and IV Wilm' tumour. Because of the predictably small numbers of patient referrals, a randomised study was not planned. Instead a comparison was made with a carefully assessed historical group consisting of consecutive patients treated at the same institution with similar surgical and radiotherapeutic techniques.

The staging used in all cases is shown in Table 1. No child under the age of 1 year was included in the study, in view of the better prognosis in that group [10] and concern about the toxicity of these combined agents in small infants. Histology in all the study cases and the majority of the historical control group was reviewed by a single pathologist (AGS). The criteria used were those of Beckwith and Palmer [1].

Statistical evaluation of comparative survival in the two groups has been made by the log rank test.

Study Group 1. There were 14 children in study group 1, five presenting in stage III and nine in stage IV. There were 8 boys and 6 girls and the median age was 6 years. Assessment at diagnosis included a CXR, lung tomograms, IVP, and lymphogram. Bone marrow examinations and inferior venocavogram were also performed in some cases.

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Table 1. Staging of Wilms' tumour

Stage I	Complete removal Encapsulated No spillage No para-aortic node involvement
Stage II	All macroscopic disease removed Extension beyond capsule Extension along renal vein (macroscopic or microscopic) Involvement of para-aortic glands
Stage III	Incomplete removal Extension of tumour beyond kidney Spillage at operation Peritoneal metastases Prior renal biopsy
Stage IV	Involvement of lungs, liver, brain, bones
Stage V	Bilateral disease

Stage III. All five patients had a laparotomy with nephrectomy. In one child laparotomy was delayed until reduction in the size of the tumour was achieved with two courses of D.A.V.E. chemotherapy. Surgery was followed by a course of radiotherapy, 3,000 rad given in 20 fractions over 4 weeks to the whole abdomen, with the healthy kidney protected after 1,200 rad. D.A.V.E. chemotherapy was then started after an interval of 2 weeks.

Stage IV. The nine children presenting with stage IV Wilms' tumour were assessed initially as to their response to one course of D.A.V.E. This was followed by nephrectomy with assessment of the extent of abdominal disease and tissue diagnosis. In 2 children, laparotomy was delayed until adequate reduction in the tumour size was obtained with a further course of D.A.V.E. All patients received radiotherapy, 3,000 rad in 20 fractions over 4 weeks, to the whole abdomen (normal kidney shielded at 1,200 rad). This was followed by sequential whole-lung irradiation to pulmonary metastases, up to 1,500 rad being given in ten fractions over 2 weeks. D.A.V.E. chemotherapy was then started.

Details of Drug Therapy. A single course of the combination chemotherapy D.A.V.E. was defined as follows:

Dactinomycin (actinomycin D)	0.6 mg/m^2	Days 1 and 8
Adriamycin	30.0 mg/m^2	Days 1 and 8
Vincristine	0.8 mg/m^2	Days 1 and 8
Endoxan (cyclophosphamide)	200.0 mg/m^2	Days 1 and 8

The drugs were given in two pulses separated by 7 days, so that toxicity could be minimised by omitting the second half of the course if necessary. Treatment was given on an out-patient basis.

The courses were repeated every 3–4 weeks, dependent on the level of the blood count. A total white cell count below 2.5×10^9/l or a platelet count below 100×10^9/l were indications for delaying a course. Liver function tests were performed before each course, and if abnormal, adriamycin and actinomycin D were reduced or stopped. Adriamycin was omitted from the courses when a total dose of 400 mg/m^2 was reached to avoid cardiotoxicity.

Up to eight courses of D.A.V.E. were given, representing 1 year of treatment.

Group 2. The study group are compared with a group of patients treated for stages III and IV Wilms' tumour at this hospital before the beginning of the study, between 1956 and 1971.

Staging was carefully reviewed in all cases. There are 41 children in this group, 26 presenting with stage III and 15 with stage IV, and the median age at diagnosis was 3 years.

Stage III. All the children had laparotomies and in 19 out of the total of 26, nephrectomy was performed. Twelve children received chemotherapy with actinomycin D, and four with a combination of actinomycin D and vincristine. Ten received no chemotherapy. All children received abdominal irradiation: 3,000 rad in 20 fractions over 4 weeks, with shielding of the normal kidney at 1,200 rad.

Stage IV. All children had laporotomies and in 11 out of a total of 15, nephrectomy was possible. Pulmonary metastases were present in all cases, and the children were given irradiation to the lungs (1,200–1,500 rad) in ten fractions over 2 weeks, plus either irradiation to the tumour bed, 1,700–1,900 rad in 12 fractions over $2^1/_2$ weeks (15 patients), or 3,000 rad to the whole abdomen as 20 fractions over 4 weeks with screening of the normal kidney at 1,200 rad (two children).

Eight children received chemotherapy with actinomycin D, four with a combination of actinomycin D and vincristine. Two children also received cyclophosphamide. Three received no chemotherapy.

Group 3. A further group of children will be reported on in the *Results* and the *Discussion*, but not considered in the statistical analysis of survival.

These children who presented with stages I and II Wilms' tumour were given D.A.V.E. at relapse, subsequent to initial treatment at diagnosis with radiotherapy, surgery, and vincristine or actinomycin D. All developed pulmonary metastases and were given radiotherapy to the whole lung to the considered limit of tolerance combined with D.A.V.E. chemotherapy. Surgical removal of localised disease was considered in all cases. There were 4 children in this group, 2 boys and 2 girls, and the median age was 3 years.

Results

In the study group a complete response (CR) is defined as the complete disappearance of all clinical and radiological evidence of disease, a partial response (PR), as a reduction in measurable disease by more than 50% for more than 1 month, and no response as a change of less than 50% tumour size.

Study Group 1

The details of the children in the study group with response and histology are shown in Tables 2 and 3.

All 5 children presenting with stage III disease responded to the D.A.V.E. therapy. Four had CR. One child had only a PR, dying after 18 months with a recurrence in the liver. One child, after an initial clearing of the disease, had an abdominal recurrence after 7 months and died. Three children are in continuing remission, 2 of them having now received

Table 2. D.A.V.E. chemotherapy: Stage III patients

Patient	Age/Sex	Histology	Response	Outcome	Survival from diagnosis (months)
L. C.	6/F	FH	CR	Continuing remission	63^+
D. B.	3/F	FH	CR	Continuing remission	39^+
A. G.	12/M	FH	PR	Relapsed in liver (18 months)	23
A. W.	6/M	FH	CR	Abdominal recurrence (7 months)	11
J. M.	7/M	FH	CR	Continuing remission	14^+

FH, favourable histology; CR, complete response; PR, partial response; +, still alive at time of analysis

Table 3. D.A.V.E. chemotherapy: Stage IV patients

Patient	Age/Sex	Histology	Type of metastases	Response	Outcome	Survival from diagnosis (months)
C. S.	2/M	FH	MP + colon	CR	Continuing remission	93^+
S. S.	1/F	FH	MP	CR	Continuing remission	73^+
C. P.	6/F	FH	MP	CR	Continuing remission	64^+
J. H.	4/M	FH	MP	CR	Continuing remission	41^+
K. S.	6/F	FH	MP	PR	Relapsed in CNS (14 months)	15
R. J.	13/M	FH	SP + liver	PR	Relapsed in liver (8 months)	9
J. M.	2/M	UH	MP	CR	Abdominal recurrence	8
G. D.	11/M	FH	MP	CR	Relapsed in liver (3 months)	8
E. S.	9/F	UH	MP	NR	–	2

FH, favourable histology; UH, unfavourable histology; CR, complete response; PR, partial response; MP, multiple pulmonary; SP, single pulmonary; $^+$, still alive at time of analysis

no treatment for 45 months and 21 months. The other child has just finished treatment after 1 year. The median disease-free survival for these children has not yet been reached.

Of the 9 children who presented with stage IV, one child failed to respond. Two had only partial responses and both died. Six have had a complete response as judged by clearing of the CXR. Two of these died after 3 months and 4 months with a recurrence of their abdominal disease. Four children are in continuing remission and have remained relapse-free for between 24 and 78 months since stopping all treatment.

The median disease-free survival in those children achieving CR has not yet been reached.

Group 2

Of those 26 presenting in stage III, only 6 responded to therapy and became disease-free. Four children are long-term survivors, and have been alive and well for more than 9 years from diagnosis.

Of those presenting in stage IV, 5 out of 15 became disease-free, and of these, 4 children are long-term survivors and are alive and well 9 years after diagnosis.

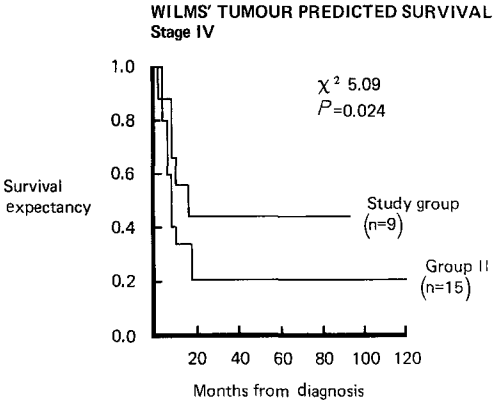

Fig. 1. Wilms' tumour, predicted survival in stage IV

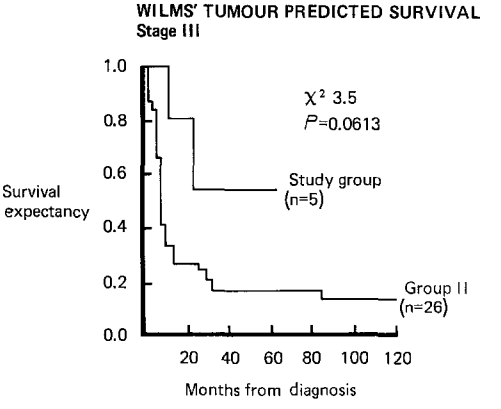

Fig. 2. Wilms' tumour, predicted survival in stage III

Table 4. D.A.V.E. chemotherapy: Stage IV relapse patients

Patient	Age/Sex	Initial stage	Initial treatment	Diagnosis to relapse (months)	Relapse site	Response	Duration (months)	Survival from diagnosis (months)
T. F.	1/M	II	RT VCR	16	MP	CR	34	50+
D. M.	2/M	I	RT AMD	34	MP Liver + bone	PR	21	55
S. W.	7/F	II	RT VCR	12	SP	PR	10	23
P. S.	5/M	I	RT AMD	11	MP	CR	5	22

SP, single pulmonary; MP, multiple pulmonary; CR, complete response; PR, partial response; RT, radiotherapy; VCR, vincristine; AMD, actinomycin D; +, still alive at time of analysis

Actuarial Analysis

Actuarial comparison between groups 1 and 2 shows a significant improvement in survival at 2 years in the study group if the two stages are considered together ($\chi^2 = 5.63$, $P = 0.0117$).

If the two stages are considered separately, the improved survival in the children of the study group presenting with stage IV reaches statistical significance ($\chi^2 = 5.09$, $P = 0.024$). In the smaller group with stage III, the improved survival failed to reach statistical significance ($\chi^2 = 3.5$, $P = 0.0613$) (Figs. 1 and 2).

Group 3

The details of children given D.A.V.E. at relapse are shown in Table 4. The mean interval between diagnosis and relapse was 18 months. Three relapsed with lung metastases and one with liver and bone marrow involvement. All 4 responded to D.A.V.E.; in two children response was partial, lasting 21 months and 10 months, respectively. In one child response was complete but he relapsed within 5 months. There was one long-term survivor.

Toxicity

In total, 67 courses of D.A.V.E. were administered during the study. In 15 courses the second pulse was delayed or dosage reduced because of a low total white cell count. Fifteen courses (22%) were modified by the omission of one or more drugs. The major problems of toxicity were diarrhoea, vomiting, and marrow suppression. A low total white cell count was the cause of modifications in 9 courses, vomiting and abdominal pain in 5. One patient developed hepatitis during her chemotherapy, and actinomycin D and adriamycin were excluded from further treatment. This patient received a preoperative course of D.A.V.E., but no chemotherapy during the period of radiotherapy. There were no drug-related deaths.

The total dose of drugs administered compared with those required by protocol was 88.7% of adriamycin, 89% of actinomycin D, 98% of vincristine, and 88% of cyclophosphamide.

Discussion

In recent years there have been dramatic advances in the treatment of children with Wilms' tumour. In 1950, radiotherapy was used with surgery and an overall survival of 50% was achieved [8]. D'Angio and Farber [3] showed that the effects of radiation could be potentiated by actinomycin D and Farber was the first to report significant increased survival with the use of this drug [3, 7]. Subsequent work has shown that permanent regression of lung metastases could be obtained with radiation combined with systemic actinomycin [6].

The second drug shown to be of value was vincristine [14], and subsequent studies have shown a definite effect on pulmonary metastases with the combination of radiation and vincristine [15]. In 1967, Sutow reported the use of cyclophosphamide in Wilms' tumour, and although it was shown to be less effective than either vincristine or actinomycin D, PR was obtained in several cases [13]. Adriamycin is the fourth drug which has been shown to have an effect in Wilms' tumour [2].

Several treatment combinations have been tried in metastatic Wilms' tumour. Farber reported a 36% survival in 86 children with metastatic disease treated with actinomycin D radiation [6], and Vietti reported a survival of 45% obtained with vincristine and radiation [15]. In 1976, Jenkin showed an improved disease-free survival with whole-lung irradiation and maintenance chemotherapy with actinomycin D and

vincristine in patients with pulmonary metastases, but he drew attention to the excessive toxicity of this regime. Five out of 11 patients developed acute diffuse pneumonitis, which was fatal in three of those affected [9]. The addition of adriamycin to vincristine and actinomycin D in the NWTS II study improved survival for stage III patients with favourable histology [5]. Stage III patients with unfavourable histology or stage IV disease showed poor survival, however, of between 33% and 53% [4].

In the present study CR was achieved in 71% of children with stage III and IV disease who were given D.A.V.E. There were no serious problems of toxicity. Compared with an historical control group, survival was significantly improved. Seven of the 10 patients who responded are in continuing remission, 6 of them more than 2 years after cessation of all treatment. These results confirm recent experience showing that intensive multiple-drug regimens may be curative even in advanced Wilms' tumour.

Multiple-drug regimens may have a place in the treatment of patients relapsing after intial treatment for stages I and II Wilms' tumour [11]. Useful remissions were obtained in three patients given D.A.V.E. and one is a long-term survivor.

The four-drug combination appears, therefore, to be a safe treatment which is effectve in advanced Wilms' tumour. The possibility that cyclophosphamide is not adding to the combination or that there is antagonism between actinomycin D and adriamycin, as suggested recently [12], can only be determined in large randomised studies.

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