Chemotherapy of advanced neuroblastoma: does adriamycin contribute?

JACQUES NINANE, JON PRITCHARD, AND JAMES S MALPAS

The Hospital for Sick Children, and St Bartholomew's Hospital, London

SUMMARY Between 1970 and 1977, 69 children with newly diagnosed stage III or IV neuroblastoma were treated with pulses of either cyclophosphamide and vincristine (CV) (n=23), or cyclophosphamide, vincristine, and adriamycin (CVA) (n=46). The 'complete' and partial response rates were 35 and 22% to CV, and 43 and 26% to CVA. For 'complete' responders the median time to relapse was 18 months for those treated with CV, and 17 months for those treated with CVA; for partial responders the times were 5 and 7 months respectively. At 2½ years only 17% of the CV patients and only 13% of the CVA patients were alive and free of disease, giving a 15% overall survival rate. The addition of adriamycin to cyclophosphamide and vincristine did not significantly improve the response rate, duration of response, or survival in these children with advanced neuroblastoma. The previously noted favourable effects of age less than 1 year at diagnosis and of female sex were confirmed. The equally poor survival for stage III and stage IV patients justifies the inclusion of stage III patients in a bad prognosis group.

Despite the use of chemotherapy the treatment of advanced neuroblastoma has remained unsatisfactory and the overall disease-free survival rate for children aged >1 year still does not exceed 10 to 15% 2 years after diagnosis.¹⁻³ Cyclophosphamide and, to a lesser extent, vincristine, gave fairly good responses when used singly.^{4,5} When used together, the therapeutic response seemed to be increased⁶ but did not achieve the results obtained in other solid tumours in childhood.^{7,8} In two studies on single agents, some patients with stage IV neuroblastoma showed some response to adriamycin, even patients who had been treated with cyclophosphamide and vincristine previously.^{9,10} Gasparini *et al.*¹¹ added adriamycin to vincristine and cyclophosphamide in an attempt to increase the overall survival rate of stage IV patients but, although the number of patients reported was small, the results were discouraging. Between January 1970 and June 1977, 69 patients with newly diagnosed advanced neuroblastoma were treated in our two hospitals with pulses of either vincristine and cyclophosphamide (CV), or vincristine, cyclophosphamide, and adriamycin (CVA). Because a retrospective survey showed that the two groups were well matched for age, gender, site of the primary tumour, distribution of metastases, and duration of treatment, it was possible to analyse the effect of adriamycin

on the response rate, response duration, and overall survival. In addition, we analysed the series for the effects on prognosis of age, gender, and stage (that is III or IV). Our paper reports the results of this analysis.

Patients and stage

Patients. All children in this study had been newly diagnosed between January 1970 and June 1977. None had received prior chemotherapy or radiotherapy. At least two of the following three criteria were fulfilled to establish diagnosis: raised level of urinary vanillyl-mandelic acid (VMA), presence of tumour cells in the bone marrow, histological confirmation of the primary tumour. A skeletal survey or an isotopic bone scan (technetium-^{99m}), and sometimes both, was performed in each case. Other radiological, biochemical, and haematological studies were performed as necessary.

The Evans *et al.* classification¹² was used. Stage I, II, and IV-S tumours were excluded. Stage III tumours were tumours without overt metastases, which extended in continuity beyond the mid-line with or without affecting the lymph nodes; in each instance, stage III tumours were initially deemed surgically unresectable. Stage IV patients were those with overt metastatic disease.

Chemotherapy regimens

Cyclophosphamide and vincristine (n=23)

Patients were treated with pulses of cyclophosphamide (300–600 mg/m²) and vincristine (1.5 mg/m² intravenously, maximum dose 2.0 mg). The regimen was repeated every 14 days if possible. The number of pulses given was between 2 and 24 (median 8).

Cyclophosphamide, vincristine, and adriamycin (n=46)

Patients were treated with pulses of cyclophosphamide (600 mg/m² intravenously), vincristine (1.5 mg/m² intravenously, maximum dose 2.0 mg), and adriamycin (40 mg/m²). The regimen was repeated every 21 days if possible. The number of pulses given was between 2 and 12 (median 7). When the cumulative dose of adriamycin reached 480 mg/m², the drug was stopped. Some patients still in their first remission were then given CV for up to 12 further courses.

Additional treatment. Of the 21 patients who had surgery, only 5 (2 in the CV group, 3 in the CVA group) had complete resections of the primary tumour at diagnosis (Table 1). Forty (56%) children (16 in the CV group, 24 in the CVA group) received radiotherapy with a cumulative dose range of 400 to 4000 rad. Radiotherapy was given to reduce bulk tumours in 22 patients (10 (43%) in the CV group, 12 (26%) in the CVA group), and to control any residual disease after a partial excision in 18 other patients (6 (26%) in the CV group, 12 (26%) in the CVA group). We did not try to analyse the effects of surgery or radiotherapy on the response or survival rates.

Definition of responders

'Complete' response

'Complete' disappearance of all evidence of primary and metastatic disease with a normal level of VMA.

Partial response

Disappearance of all evidence of metastatic disease, apart from 'residual' bone changes, more than 50% shrinkage of primary and more than 50% decrease in VMA excretion.

No response

Less than 50% shrinkage of primary or persistence of metastases or new metastases.

The response to treatment was evaluated after 3 or 4 courses by physical findings, repeated bone

Table 1 *Treatment*

	Total (n=69)		Cyclophosphamide and vincristine (n=23)		Cyclophosphamide, vincristine, and adriamycin (n=46)	
	No	(%)	No	(%)	No	(%)
Chemotherapy alone	26	(38)	7	(30)	19	(41)
Chemotherapy and radiotherapy	22	(32)	9	(39)	13	(28)
Chemotherapy and surgery	3	(4)	0		3	(6.5)
Chemotherapy, surgery, and radiotherapy	18	(26)	7	(30)	11	(24)

marrow examination, urinary levels of VMA, and radiological surveys. Because the study ended in 1977, few patients had abdominal ultrasonography or computerised tomography. Therefore, the definition of 'complete' response is clinical rather than the result of exhaustive imaging investigations.

Results

Characteristics of patients and tumours at diagnosis.

The sex and age distribution of patients in the CV and CVA groups were similar. The two groups were also comparable in terms of the proportions with stage III and IV tumours, sites of primary disease, and, for stage IV patients, distribution of metastatic disease (Table 2); in particular, bone metastases were present in all patients. VMA level was significantly raised in 82% of both groups of patients.

Primary site—stage (Table 2). In most patients, the primary tumour was found to arise within the abdomen, mainly from the suprarenal gland. No primary site could be found in 9% of cases. Stage IV disease (88%) was more common than stage III (12%). Among the 61 patients with stage IV disease, there was similar distribution of metastases in bone, bone marrow, lymph nodes, liver, and skin.

Response rate (Table 3). As defined above, 66% of patients responded to chemotherapy, 41% completely and 25% partially. The number of responders, complete and partial, was higher in the CVA than in the CV group but did not reach statistical significance ($P>0.50$, χ^2 test, 2 df).

Relapses. Table 4 gives the time to relapse and the site of relapse for complete and partial responders. All patients with partial responses 'relapsed' within

a median time of 6 months, most of them at the primary site. Sixty-four per cent of the complete responders relapsed with a median time to relapse of 17 months. In these patients, relapse occurred much less often at the primary site; 6 (2 in the CV group, 4 in the CVA group) relapsed in both sites. These results are almost identical in the CV and CVA groups.

Table 2 *Primary site, stage, metastases*

	Total (n=69)		Cyclophosphamide and vincristine (n=23)		Cyclophosphamide, vincristine, and adriamycin (n=46)	
	No	(%)	No	(%)	No	(%)
Primary site						
Mediastinum	9	(13)	3	(13)	6	(13)
Abdomen	50	(73)	15	(65)	35	(76)
(Suprarenal gland)	44	(64)	12	(52)	32	(70)
Pelvis	4	(6)	2	(9)	2	(4)
Unknown	6	(9)	3	(13)	3	(7)
Stage						
III	8	(12)	2	(9)	6	(13)
IV	61	(88)	21	(91)	40	(87)
Metastases (stage IV)						
Total	61		21		40	
Bones	61	(100)	21	(100)	40	(100)
Bone marrow	40	(66)	13	(62)	27	(68)
Lymph nodes	32	(52)	10	(48)	22	(55)
Liver	22	(36)	7	(33)	15	(37)
Skin	6	(10)	2	(10)	4	(10)

Table 3 *Response rate*

	Total (n=69)		Cyclophosphamide and vincristine (n=23)		Cyclophosphamide, vincristine, and adriamycin (n=46)	
	No	(%)	No	(%)	No	(%)
Complete responders	28	(41)	8	(35)	20	(43)
Partial responders	17	(25)	5	(22)	12	(26)
Complete and partial responders	45	(66)	13	(57)	32	(69)

Table 4 *Relapses*

	Total	Cyclophosphamide and vincristine	Cyclophosphamide, vincristine, and adriamycin
After complete response	28	8	20
Primary site	7 (25%)	1 (13%)	6 (30%)
Metastases	16 (57%)	4 (50%)	12 (60%)
Time to relapse (months)			
Median	17	18	17
Range	(6-24)	(6-24)	(7-24)
After partial response	17	5	12
Primary site	15 (88%)	5 (100%)	10 (83%)
Metastases	15 (88%)	5 (100%)	10 (83%)
Time to relapse (months)			
Median	6	5	7
Range	(3-9)	(3-6)	(4-9)

Survival rate. Because no patient died from disease later than 30 months after diagnosis the survival rate was analysed at 2½ years (Fig. 1). The total survival rate free of disease was found to be between 15 and 17% for CV-treated patients, and 13% for patients receiving CVA. Among the 28 complete responders, this survival rate was between 36 and 50% in the CV group, and 30% in the CVA group.

Fig. 1 *Survival rate and the effect of adriamycin.* Fig. 2 *Effect of age on the survival rate.*

The prognosis for stage III patients was, surprisingly, as poor as for those with stage IV disease with 13 and 15% respectively, for 2½-year survival. Two parameters, other than the initial response to chemotherapy, were found to affect the prognosis—age at presentation, and gender. Children aged <1 year fared significantly better than older children (Fig. 2), in the CV (33%) and the CVA (60%) groups. However, the prognosis for patients aged >6 years was no better than for those between 1 and 6 years old, their survival rate being only 9%.

As far as gender was concerned, there was a trend in favour of girls (27%) and this was true in the CV- (40%) and CVA- (20%) treated patients. The difference was not statistically significant ($P>0.10$).

Discussion

In this series of 69 children with advanced neuroblastoma, 46 (69%) patients treated with pulses of CVA responded to chemotherapy but only 23 (57%) treated with pulses of CV responded. However, this higher incidence of responses attributable to adriamycin was not statistically significant ($P>0.50$). In addition, the use of adriamycin did not prolong the duration of the remission nor did it increase the number of survivors. These data confirm the results published in 1974 by Gasparini *et al.*¹¹ who, in a small series of 19 patients, found a response rate to CVA of 57%, a median survival time of 17.5 months in patients who responded, and a 2-year survival rate of 17%. More recently, Finklestein *et al.*¹³ showed that the addition of adriamycin to cyclophosphamide, vincristine, and imidazole carboxamide influenced neither the response rate nor the duration of response. In the present series, only patients who responded completely after at least 3 pulses of chemotherapy had a long duration of response which suggests that patients who do not fulfil our criteria for a complete response should be given other treatment. Moreover, criteria for complete response should now include a normal abdominal ultrasound or normal computerised tomography, and even a surgical exploration—since one-quarter of 'complete' responders still relapsed in the primary site when assessed by standard radiological investigations.

It has been suggested that children aged >6 years at the time of diagnosis have a better prognosis than younger patients.¹³ This could not be confirmed as only 9% of our patients were alive and free of disease 2½ years after diagnosis. However, our data confirm that children aged <1 year fared significantly better, with a survival rate of 50% (Fig. 2).^{13 14}

The prognosis for survival was worse in boys; this trend has been noted before.¹⁵

It is concluded that adriamycin did not change the outlook for patients with advanced disease when added to cyclophosphamide and vincristine in this particular 'pulsed' schedule. Before stopping the use of this drug, which is undoubtedly active as a single agent in 30 to 40% of neuroblastomas,⁹ other schedules should be tried. It has been claimed, for example, that if adriamycin were to be administered on the day after 6 consecutive days of oral cyclophosphamide, the response rate would be higher than if the drugs were given simultaneously.¹⁶ This clinical effect has been successfully correlated with laboratory studies of the kinetic behaviour of human neuroblastoma¹⁷ and clearly should be investigated further. Are there other chemotherapeutic agents which show any promise in the treatment of this lethal neoplasm? Response rates of 20 to 66% have been reported to cis-Platinum^{18 19} and of 23% to VM-26.²⁰ We have investigated the effect of high-dose melphalan chemotherapy combined with autologous bone marrow grafting and preliminary results²¹ are encouraging for some patients. We feel that the activity of cis-platinum, VM-26, and melphalan warrants their inclusion in the 'induction' therapy of newly-diagnosed cases of advanced neuroblastoma; analysis of the results of such treatment must examine the contribution of individual agents so that children are not treated unnecessarily with drugs that, while giving respectable response rates as single agents, do not contribute favourably to response, duration, or ultimate survival and which may have significant toxicity.⁹

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Correspondence to Dr Jon Pritchard, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

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gluten challenge. The findings suggest that this automated method of tissue analysis is of value in the routine examination of small intestinal biopsies.

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Correspondence to Dr D N Challacombe, Somerset Children's Research Unit, Taunton and Somerset Hospital, Musgrove Park, Taunton, Somerset TA1 6DA.

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Erratum

Chemotherapy of advanced neuroblastoma: does adriamycin contribute?

Jacques Ninane, Jon Pritchard, and James S Malpas.
We apologise for the fact that Fig. 1 (*Arch Dis Child* 1981; **56**: 544-8) was incorrect. The correct version is shown below.

Fig. 1 Survival rate and the effect of adriamycin.