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High-dose Rapid Schedule Chemotherapy for Disseminated Neuroblastoma

Andrew D.J. Pearson, Alan W. Craft, C. Ross Pinkerton, Simon T. Meller and Michael M. Reid

In a high-dose schedule for disseminated neuroblastoma, eight courses of chemotherapy were administered every 10 days, regardless of myelosuppression, to eradicate tumour cells rapidly and reduce emergence of drug-resistant clones. Relatively non-myelotoxic vincristine and cisplatin were alternated with high-dose cisplatin–etoposide and cyclophosphamide–etoposide. Of 12 evaluable patients, there were 1 complete (CR), 3 very good partial (VGPR), 5 partial (PR) and 3 mixed responses (MR) 100 days after starting treatment. 6 out of 9 achieved a bone marrow CR at 40 days. 9 of 11 primary tumours were completely resected, after which 4 patients had CR, 3 VGPR (bone scan alone being abnormal), 4 PR and 1 mixed response (MR). Myelotoxicity was the major adverse effect. The only death was due to fungal infection. Clinically important renal dysfunction occurred in 3 patients. 4 had convulsions and 4 temporary hypertension. This schedule produced a rapid response and its toxicity, though serious, was manageable. Further evaluation is warranted.
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INTRODUCTION

DISSEMINATED NEUROBLASTOMA occurring after the first birthday continues to have a dismal prognosis [1]. Although high response rates of 70–80% can be obtained with a variety of chemotherapeutic regimens, there is almost invariably emergence of drug-resistant disease. Many of the drugs used have a significant dose response effect [2] and in order to exploit this, higher doses of chemotherapy, particularly cisplatin, have been given [3, 4]. In some studies high-dose chemotherapy has been followed by myeloablative chemo/radiotherapy with autologous marrow rescue [5–7]. Improvements in median survival have occurred, but these intensive therapeutic approaches have only increased long-term disease-free survival by 10–15% with the most optimistic reports being of 20% disease-free survival at 4 years [1]. All of these chemotherapeutic regimens have adhered to the convention that the bone marrow must be allowed to recover between courses to avoid unacceptable morbidity. This has led to 3-week or longer gaps between pulses of chemotherapy during which drug-resistant cell clones may develop.

Rapid administration of the maximum tolerable doses of drugs could lead to more rapid cell kill with less chance of emergence of resistance. In order to achieve the target of rapid administration it is inevitable that some drugs will need to be given when the marrow has been suppressed by previous chemotherapy. Of the drugs active against neuroblastoma (i.e. vincristine, cyclophosphamide, etoposide, tenoposide, doxorubicin, cisplatin, melphalan, ifosfamide and carboplatin), vincristine and cisplatin at a dose of 80 mg/m^2 are least myelotoxic [8]. An intensive chemotherapy protocol was therefore designed which was based on a 10-day interval between treatments, rather than the conventional 21 days. Relatively non-myelotoxic were alternated with myelotoxic drugs.

This report describes the use of such a high-dose rapid schedule regimen in 13 children with disseminated neuroblastoma, and documents the initial response and toxicity.

Correspondence to A.D.J. Pearson.
A.D.J. Pearson and A.W. Craft are at the Department of Child Health, University of Newcastle upon Tyne, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH; C.R. Pinkerton and S.T. Meller are at the Department of Paediatric Oncology, Royal Marsden Hospital, Sutton, Surrey; and M. M. Reid is at the Departments of Child Health and Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.
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PATIENTS AND METHODS

Patients

13, consecutively presenting, previously untreated children over the age of 1 year with stage 4 neuroblastoma were treated. Their ages ranged from 2 to 9.1 years (median 4.1). At diagnosis 12 children had bone marrow involvement and 9 had bone disease detected by ^{99}Tc isotope bone scan. The 4 without detectable bone disease had abdominal primary tumours crossing the midline, thus no case could be considered stage 4S. In 8 children there was both bone marrow and bone involvement, in 4 only bone marrow and 1 only bone metastases. Distant lymph node metastases were present in 4. The primary tumour was detected in 12/13 patients; in 8 it was adrenal in origin, in 3 abdominal and in 1 originated in the thoracic sympathetic chain.

Treatment regimen

A summary of the treatment protocol is shown in Fig. 1. Eight courses of chemotherapy were administered over 72 days. Courses 1–4 were repeated once.

Course 1 consisted of cisplatin at a dose of 40 mg/m^2 per day given as a 24 h continuous infusion for 5 consecutive days. Three hours prior to the administration of cisplatin, 0.5 l/m^2 every 3 h normal saline with 20 mmol/m^2 of potassium chloride was administered. During and for 24 h after cisplatin infusion, 3 l/m^2 every 24 h normal saline with 60 mmol/m^2 of potassium chloride, 10 mmol/m^2 every 24 h of magnesium sulphate and 2.5 mmol/m^2 every 24 h of calcium gluconate were given.

The 5-day cisplatin infusion was interrupted each day by an infusion of etoposide 100 mg/m^2 in 250 ml/m^2 normal saline given over 1 h.

Course 2 was administered 10 days after starting Course 1.

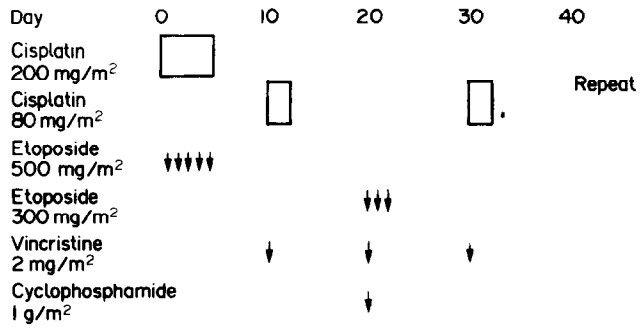

Fig. 1. Chemotherapy regimen. Chemotherapy was delivered regardless of neutrophil or platelet counts.

2 mg/m² (to a maximum 2 mg total dose) of vincristine was given by intravenous bolus followed by cisplatin by continuous infusion at 40 mg/m² every day for 2 consecutive days. The hydration regimen was the same as for Course 1.

Course 3 was administered a further 10 days later at day 20. Etoposide 100 mg/m² in 250 ml/m² of normal saline was given over 1 h daily for three consecutive days, i.e. days 20, 21 and 22. On day 20 vincristine 2 mg/m² (to a maximum 2 mg total dose) and cyclophosphamide 1 g/m² were given by intravenous bolus, followed by 0.75 l/m² of 4% dextrose in 0.18% saline over 6 h.

Course 4 (identical to Course 2) was administered 10 days after the start of Course 3.

The aim was to give the treatment in the doses and at the times prescribed, ignoring as far as possible all other clinical events and blood counts, accepting that a high level of supportive care would need to be given.

Four months after diagnosis surgical removal of the residual primary tumour was attempted in all responding children in whom the surgeon considered it might be successful.

Supportive care

The children were nursed on the open ward or in cubicles but not in protected environments. Subcutaneously tunnelled central venous catheters were inserted in all children. Red cell transfusions were given when necessary and platelet transfusions if there was bleeding and thrombocytopenia. Prophylactic antibiotics, white cell transfusions and gut decontamination were not used but systemic antibiotics were given to children with fever with a neutrophil count less than 10^9/l and antifungal and antiviral drugs when clinically indicated. Parenteral nutrition was given to those who lost more than 5% of their body weight. Appropriate management of metabolic disturbance was instituted when necessary.

Assessment of response

Evaluation of the tumour burden was carried out before and at 40 and 100 days after starting treatment. The urinary catecholamines, homovanillic acid (HVA) and vanillylmandelic acid (VMA), were measured in a random urine sample and their concentration related to creatinine. The plan was that both a bone marrow aspirate and trephine biopsy specimen should be taken from at least two iliac crests. Demonstration of malignant cells by light microscopy in the aspirate was recorded as "positive". For a complete bone marrow response to be recorded it was necessary that at least two bone marrow biopsies were evaluable. Bone marrow histology was assessed using the grading system previously described, in which grade 1 is normal histology, grade 2 increased reticulin, grade 3 distorted marrow with abnormal fibrous stroma and grade 4 the presence of identifiable malignant cells with or without the other abnormalities [9]. The overall grade at each assessment represented the worst appearance in any single marrow core. Trephine biopsies were all reviewed by a single haematologist (MMR). Bone involvement was assessed by a ^{99}Tc bone scan. The size of the primary tumour was assessed by ultrasound and/or computerised tomography (CT) from which three-dimensional measurements were obtained. Chest radiography and ultrasound examination of the liver or CT completed staging. Response to treatment was evaluated according to the International Neuroblastoma Response Criteria (INRC) [10]. Only histological grade 4 appearances or positive identification of tumour in smears was taken as evidence of persisting marrow infiltration for response evaluation and this was recorded even in cases when less than four evaluable bone marrow samples were obtained.

For the purpose of this report, surgery of the residual primary tumour along with the other staging procedures carried out at this time, constituted the final response assessment end-point.

Assessment of toxicity

Full blood count and measurement of serum electrolytes, calcium, magnesium, phosphate and alkaline phosphatase were obtained prior to treatment and at 10-day intervals until day 70 and then at day 100. Glomerular filtration rate (GFR), measured by the plasma clearance of ^{51}Cr EDTA, was determined before treatment and at days 10, 30, 40, 50, 70 and 100. Pure tone audiometry in children over the age of 4 years was carried out after treatment. Ototoxicity was graded according to the Brock criteria [11]. In 8 children echocardiographic assessment of left ventricular function was carried out before and after treatment. Children were weighed every 10 days at the beginning of each course of treatment.

The numbers of red cell and platelet transfusions, episodes of bleeding and febrile neutropenia, days of antibiotic, antifungal and antiviral drugs, days of parenteral nutrition, and numbers of in-patient days required for chemotherapy and/or supportive care were recorded.

RESULTS

Toxicity

During therapy, prior to surgery, children were admitted to hospital for a median of 37 (range 34–110) days. They received a median of five red cell transfusions (range 2–13). The absolute neutrophil count during therapy is shown in Fig. 2. A median of 3 (range 0–5) episodes of febrile neutropenia during treatment and a median of 1 (range 0–3) episodes of bacteriologically confirmed septicaemia per child were recorded. A total of 12 episodes of septicaemia occurred in the 13 patients. The central venous catheter was causally implicated in 4. The children received a median of 10 days of antibiotic therapy each (range 0–26), 5 days of antiviral therapy (range 0–12) and 3 days of antifungal therapy (range 0–12). The platelet counts during therapy are shown in Fig. 3. A median of three (range 0–12) episodes of significant bleeding with a platelet count less than 20×10^9/l were recorded and a median of 3 (range 1–7) platelet transfusions were given per patient. The theoretically more myelotoxic courses 1, 3, 5 and 7, were associated with more prolonged use of antibiotics (medians of 8, 5, 7 and 6 days per child) than courses 2, 4, 6 and 8 (medians of 2, 2, 1 and 1 days) per child, but no obvious trends were found in neutrophil or platelet counts or in septicaemias.

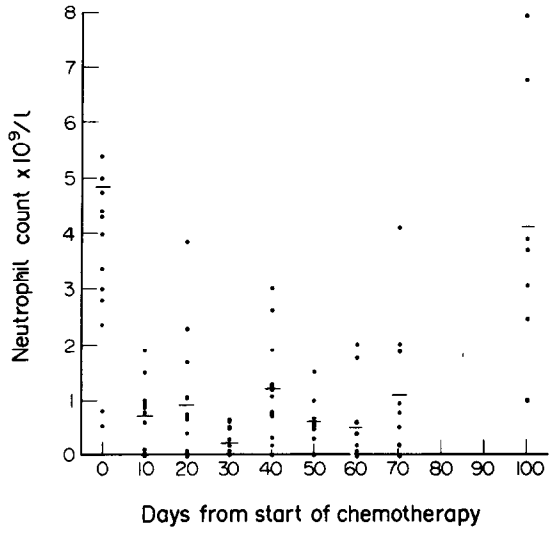

Fig. 2. Absolute neutrophil count (×10⁹/l) at commencement of each course of chemotherapy and 30 days after the final course of treatment. Individual and mean values are shown.

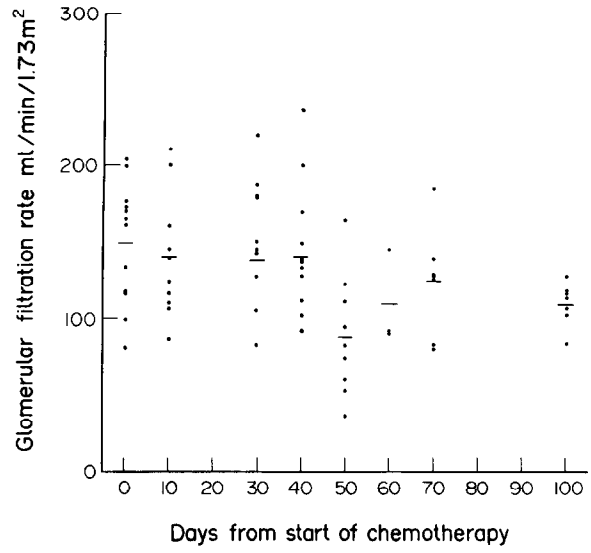

Fig. 4. Glomerular filtration rate (ml/min/1.73 m²) measured by the plasma clearance of ^{51}chromium EDTA at 0, 10, 30, 40, 60, 70 days after diagnosis (i.e. before cisplatin therapy) and 30 days after completing treatment. Individual and mean values are shown.

The GFR during therapy reached its nadir at day 50 (Fig. 4). There were no significant abnormalities of potassium, bicarbonate or phosphate. The serum magnesium fell below the normal range in 3 patients during therapy, but in all had returned to normal by the end of therapy. Pure tone audiograms were available from 10 of the 13 children. 9 were abnormal, 6 with a grade 2 and 3 with a grade 3 deficit. In 1 child hearing was unaffected. No abnormality in left ventricular function was detectable in the 8 children tested. Anorexia and vomiting were common and the maximum weight loss during therapy was a median of 4% of body weight (range 2–15% body weight). A median of 10 days parenteral nutrition (range 4–28) was required per child. Severe mucositis or other significant gastrointestinal problems were not seen. 4 patients had convulsions occurring at days 40, 50, 61 and 90, respectively. These convulsions were not associated with hypomagnesaemia or any other detected metabolic abnormality. Only 1 child had a convulsion after completion of chemotherapy and this occurred at day 90. She had no further fits. Hypertension requiring therapy occurred in 4 patients. All subsequently became normotensive and did not require continued therapy.

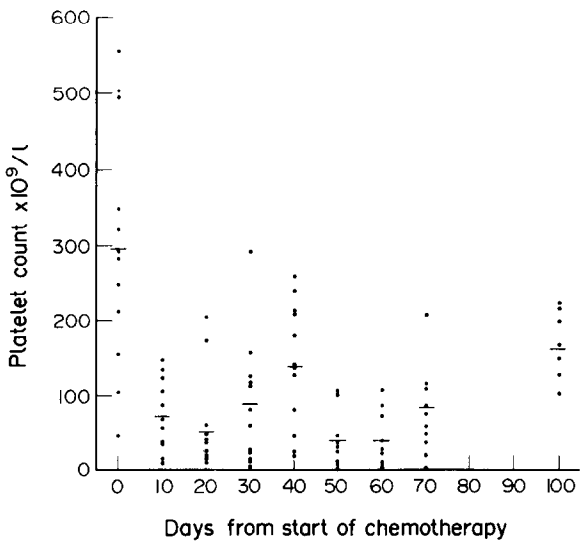

Fig. 3. The platelet count (×10⁹/l) at commencement of each course of chemotherapy and 30 days after the final course of treatment. Individual and mean values are shown.

The aim was to complete administration of courses 1–8, over a 72-day period. The actual period of administration of chemotherapy ranged from 70 to 81 days with a median of 72 days. In 3 children therapy was modified. In 1 child it was stopped after 50 days when her GFR fell to 37 ml/min/1.73 m² but it later rose to 98 ml/min/1.73 m². In another, course 6 was omitted when the GFR fell to 61 ml/min/1.73 m² and was replaced by course 7; subsequently the GFR recovered to 90 ml/min/1.73 m². In the final patient the last course was omitted due to a GFR of 24 ml/min/1.73 m². The other 10 patients received 100% of the target drug dose.

Response

Details of the response to therapy, at 40 days and 100 days after start of treatment according to INRC are shown in Table 1. 6 out of 9 evaluable patients achieved complete bone marrow response at day 40 and 7 out of 10 at day 100. Grading of the bone marrow response [9] is shown in Table 2. The catecholamine complete response (CR) rate was 6 out of 10 at day 40, 8 out of 12 at day 100. The primary tumour showed a partial response (PR) in 6 out of 8 at day 40, and at day 100 a very good partial response (VGPR) in 4 out of 11 and PR in 6 out of 11. There were 3 CR and 4 VGPR on bone scan in 7 evaluable patients at day 100. Using INRC criteria at day 100, of 12 evaluable patients, there was 1 CR, 3 VGPR, 5 PR and 3 mixed response (MR). No patient failed to respond or had progressive disease.

Details of the operability of the primary tumour and histology of the tumour specimen are shown in Table 3. Only 2 patients had unresectable tumour. In 6 out of 9 resected tumours there was less than 10% viable tumour tissue on histological examination. Following surgery of 12 evaluable patients, there were 4 CR, 3 VGPR, 4 PR and 1 MR. In those patients with a VGPR the only remaining abnormality was on bone scan.

Table 1. INRC response 40 and 100 days after start of treatment

Days after start of treatment	Primary		Bone marrow		Catecholamine		Bone scan		Other		Overall	
	40	100	40	100	40	100	40	100	40	100	40	100
Patient no.												
1	No Primary		CR	CR	CR	CR	PR	CR	NI	NI	VGPR	CR
2	PR	PR	CR	CR	CR	CR	PR	PR	NI	NI	PR	PR
3	PR	NE	NR	NE	PR	NE	PR	NE	NI	NI	MR	NE
4	PR	VGPR	CR	CR	CR	CR	NI	NI	NI	NI	PR	VGPR
5	PR	VGPR	CR	CR	CR	CR	NE	PR	NI	NI	PR	VGPR
6	PR	PR	NR	CR	CR	CR	PR	PR	NI	NI	MR	PR
7	NE	PR	NE	NE	NE	NR	NE	NE	NE	CR	NE	PR
8	NE	NR	NI	NI	NE	PR	NE	CR	NE	PR	NE	MR
9	NE	PR	NE	PR	NR	CR	NE	PR	NI	NI	NR	PR
10	NE	PR	NE	NR	NE	PR	NE	CR	NI	NI	NE	MR
11	NR	VGPR	NR	NR	NR	PR	NI	NI	NI	NI	NR	MR
12	PR	VGPR	CR	CR	PR	CR	NI	NI	PR	CR	PR	VGPR
13	NR	PR	CR	CR	CR	CR	NI	NI	PR	PR	MR	PR

CR = complete response; VGPR = very good partial response; PR = partial response; MR = mixed response; NR = no response; NI = not involved; NE = not evaluated.

DISCUSSION

Despite improvements in understanding the biology of neuroblastoma and the use of combination chemotherapy, most children over the age of 1 year who have distant metastases die from the disease. The initial, but often incomplete, response followed by progressive disease, suggests the emergence of drug-resistant cells. Studies in experimental cell lines have revealed multiple simultaneous mechanisms of drug resistance [12]. Strategies designed to overcome single specific mechanisms may therefore fail to result in improved cure rate. An alternative approach is to eradicate rapidly maximum numbers of tumour cells before drug-resistant clones can emerge. The potential value of increased dose intensity, the delivery of more drug per unit time, is supported by the higher remission rate achieved in breast [13] and ovarian cancer [14], Hodgkin's disease [15], small cell lung cancer [16] and multiple myeloma [17]. Similarly, shortening intervals between courses of chemotherapy has improved event-free survival in B cell lymphoma and leukaemia [18], germ cell tumours [19] and acute myeloid leukaemia [20].

A recent review showed a correlation between dose intensity and response, median survival and median progression free survival in metastatic neuroblastoma [21]. This was most significant with cisplatin and etoposide. The dose intensity in the 44 clinical trials included in this analysis ranged from 5.8 to

*Table 2. Bone marrow histological grade**

Patient no.	Days after start of treatment	
	40	100
1	3	3
2	3	3
3	4	NE
4	3	3
5	1	3
6	4	3
7	NE	NE
8	NI	NI
9	3	4
10	3	4
11	4	4
12	1	3
13	3	3

*Grade 1 = normal, grade 2 = increased reticulin, grade 3 = distorted architecture with fibrosis, grade 4 = obvious tumour.
NI = not involved; NE = not evaluated.

Table 3. Primary tumour resection

Patient number	Tumour removed*	Presence of viable tumour cells in resected specimen or biopsy†	Post surgery overall response status
1	No primary tumour		CR
2	+	−	VGPR‡
3	Died before surgery		
4	+	−	CR
5	+	−	VGPR‡
6	+	+	VGPR‡
7	+	−	PR
8	−	No histology	PR
9	+	+	PR
10	−	No histology	PR
11	+	−	MR
12	+	+	CR
13	+	−	CR

*+ = total macroscopic surgical removal; − = unresectable. There were no partial resections.
†+ = > 10% viable tumour cells detected; − = < 10% viable tumour cells detected.
‡in those with VGPR, only persisting abnormality was in bone scan.

33.3 mg/m^2 per week for cisplatin and 4.6–64 mg/m^2/week for etoposide or teniposide. The dose intensity for both cisplatin and etoposide in the present schedule (70 mg/m^2 per week and 155 mg/m^2 per week, respectively) is more than double the maximum in those studies.

The major anticipated problem with shortening the time intervals between courses of high-dose chemotherapy was myelotoxicity so it was important that alternate courses were relatively non-myelotoxic. Studies of vincristine indicate no myelotoxicity [22] and cisplatin given at 80 mg/m^2 has little myelotoxicity [8]. Therefore a combination of vincristine and cisplatin was used as a relatively non-myelotoxic module in courses 2 and 4. Pilot studies in Newcastle upon Tyne (unpublished) had shown that the inclusion of doxorubicin in courses 1 and 3 caused severe intestinal mucosal damage, and that the combination of ifosfamide and cisplatin was too nephrotoxic.

Doxorubicin and ifosfamide were therefore avoided in this regimen. High-dose cisplatin (200 mg/m^2) can be administered without prohibitive side effects if given in divided doses [23] and continuous infusion may further reduce nephrotoxicity [24]. Because there is evidence, in murine tumours, of synergy between cisplatin and etoposide [25], these two drugs were combined in Course 1. The remaining module, course 3, combined etoposide and cyclophosphamide, both myelotoxic agents, with vincristine. Thus a regimen of non-cross-resistant drugs was designed, comprising alternating myelotoxic and relatively non-myelotoxic courses given at 10-day intervals, regardless of neutrophil or platelet counts.

The first aim was to eradicate tumour rapidly. This approach produced a rapid response at metastatic sites. Even with larger numbers of patients it would remain difficult, because of lack of uniform response criteria, to compare initial rates of response with those previously reported apart from the ENSG 3c study [4]. The bone marrow CR and overall response rates compare favourably with those of ENSG 3c, 7/10 and 10/12 vs. 50 and 51%, respectively. Wide use of the INRC should permit meaningful comparisons in the future.

Bone marrow metastases provide the most accessible source of tumour in which the effects of treatment can be monitored. However, there has been great variation in the methods used to assess bone marrow response. The quality of the biopsy core is important. A centimetre of bone marrow will yield more information than a few millimetres of cartilage and traumatised cores are difficult to interpret. While tumour infiltration is usually easily detectable on smears at diagnosis, once treatment has started, examination of bone marrow histology is probably the best way of identifying tumour in the marrow. The role of immunological detection of neuroblastoma cells in marrow remains unclear [26–28], and the routine use of such techniques was not incorporated in this study.

In addition to aspirates, between 2 and 4 (median 3) cores of marrow were obtained at each assessment. The INRC recommend a minimum of two cores. 6 out of 9 children achieved a bone marrow CR after only 40 days. For comparison, in ENSG 3c, 50% of children had bone marrow CR after 120 days [4]. The difficulties in interpretation are illustrated by the more detailed histological grading which showed how rare it was to achieve truly normal marrow appearances. Most of the children with bone marrow CR still had abnormal marrow with persisting fibrous tissue, often containing unidentifiable mononuclear cells, distorting the marrow architecture. Whether these grade 3 appearances imply failure to eradicate tumour remains unknown, and the study was not designed to answer this question.

Urinary catecholamine levels and bone scans are poor indicators of response because the former may rise early in treatment or fall when disease is obvious elsewhere and bone abnormalities may take a long time to resolve. Disappearance of primary tumour after chemotherapy is unusual. Many feel that total resection of the primary tumour may contribute to survival. In the present study 9 out of 11 primary tumours were completely removed. This compares favourably with 55% reported in ENSG 3c [4]. The possibility that more effort was made to remove residual primary tumour in the present study cannot be excluded. In 3 of these 9, viable tumour cells were still detectable. However the value of this practice remains unproven and the implication of detecting viable tumour cells in this material is unknown.

The second aim was to assess the toxicity of a high-dose rapid schedule. As expected, myelosuppression was the major side-effect but the module of vincristine and cisplatin (Courses 2 and 4) was associated with less severe myelosuppression. Neutrophils and platelets tended to rise following these courses. There was 1 toxic death, due to fungal pneumonia. This occurred in the first patient treated who deviated from the protocol. At day 50 a non-myelotoxic course, Course 6, was omitted because her renal function deteriorated, and was replaced by the myelosuppressive Course 7. Although the GFR fell in several children, none required dialysis and all recovered despite the administration of 720 mg/m^2 of cisplatin. Hypomagnesaemia, noted in other cisplatin containing protocols, was rare, perhaps because it was infused continuously, the maximum daily dose being 40 mg/m^2.

Hypertension, possibly caused by cisplatin, was unexpected. However, it has been reported as a late effect in cisplatin-treated survivors of germ cell cancer [29] and the drug increases serum renin and aldosterone concentrations [30]. Convulsions, not apparently associated with metabolic disturbance, hypertension or intracranial haemorrhage, also occurred. There were no long-term sequelae. Their cause is unknown but they have previously been associated with cisplatin [31]. Nausea and vomiting caused by cisplatin caused weight loss in some children. Nasogastric tube feeding was not possible as the tubes were frequently vomited. Parenteral nutrition was the most practical method of managing this problem. No detectable peripheral neuropathy occurred, despite high cisplatin dosage. Gastrointestinal toxicity was not a major problem.

If expectations of the improved antitumour activity of this approach are realised then the toxic side-effects, whilst serious, are manageable and within the capacity of specialist centres accustomed to treating children with acute leukaemia or carrying out bone marrow transplantation. Nonetheless there is still a need and potential for reducing toxicity. Myelosuppression, the major toxicity, might be reduced by haemopoietic growth factors. The major non-haemopoietic side-effects, renal dysfunction, hypertension, convulsions and persistent nausea, were presumed to be caused by cisplatin. A recent study has documented activity of carboplatin in neuroblastoma [32]. Although it is myelotoxic, renal dysfunction and ototoxicity are not common. Substitution of carboplatin for cisplatin in Courses 1 and 5 might reduce these side-effects. Ultimately, the value of this novel approach to the treatment of poor prognosis neuroblastoma will be determined by its impact on long-term event-free survival. Although the present study did not attempt to evaluate this, the initial response rates are sufficiently encouraging that a modified high-dose schedule, in which the only

variable will be dose intensity, will form one arm of a prospective randomised study of the management of disseminated neuroblastoma to be carried out by the European Neuroblastoma Study Group.

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