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Short communication

Prohibitive toxicity of a dose-intense regime for metastatic neuroblastoma containing ifosfamide, doxorubicin and cisplatin

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Summary. Three patients with stage 4 neuroblastoma were treated with a schedule comprising alternating modules of myelosuppressive (ifosfamide, etoposide, doxorubicin) and less myelosuppressive (vincristine, cisplatin) drugs given every 10 days regardless of the neutrophil count. A partial response was seen in two patients, and a very good partial response, in one patient. Extensive blood-component support was required. Non-haemopoietic toxicity was severe and led to treatment delays in two patients. Ifosfamide-related encephalopathy was seen in one patient and nephrotoxicity, in two patients. Mucositis was severe in two patients, may have contributed to the high rate of sepsis observed, and precluded the use of doxorubicin in one patient. As ifosfamide and doxorubicin were felt to be responsible for much of the toxicity, a subsequent schedule did not include these agents.

Introduction

Stage 4 neuroblastoma in patients over the age of 1 year has a poor prognosis despite initial tumour response rates of up to 70%–80% [7, 15, 16]. Failure to eradicate tumour cells and emergence of resistant disease are the usual reasons for treatment failure. Drugs known to have activity against neuroblastoma include cisplatin, etoposide, doxorubicin, vincristine, cyclophosphamide and ifosfamide [6, 8, 9, 17, 20]. Given a significant dose-response relationship for most chemotherapeutic drugs, dose escalation offers one way in which antitumour efficacy may be improved [6]. Administration of treatment at 21-day (or longer intervals, allowing bone marrow regeneration before each successive cycle of chemotherapy, may also enable tumour-cell repopulation and emergence of drug-resistant cells; hence, rapid administration of a number of agents at or near their maximum tolerated doses may further improve the therapeutic effect. Attempts have therefore been made to design such a protocol by maximising dose intensity. For minimisation of anticipated toxicity, myelotoxic combinations alternating with relatively non-myelotoxic combinations are required. Vincristine and cisplatin given at a dose of 80 mg/m^2 are the least myelotoxic drugs active in this disease [1]. The inclusion of ifosfamide allows the administration of high doses of alkylating agent. Combination of this drug with etoposide or doxorubicin forms active and anticipated myelotoxic modules. We report on the severe gastrointestinal and renal toxicity encountered in three patients treated with this approach, which led to the incorporation of major modifications into the successor to this regime [14].

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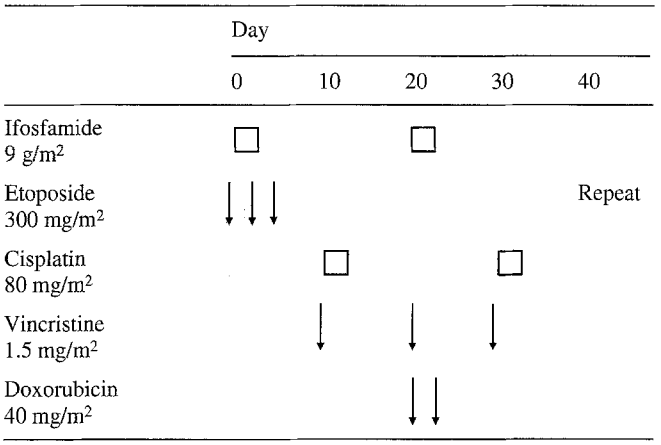
Patients and methods

Three children between the ages of 9 and 70 months who presented with stage 4 neuroblastoma were treated. The primary tumour was adrenal in two patients and thoracoabdominal in one child. All had extensive infiltration of bone marrow by neuroblastoma, and two had bone involvement. All three showed raised urinary catecholamine excretion.

An outline of the protocol is given in Table 1. Etoposide was given as an infusion in normal saline at a concentration of 0.25 mg/ml over 1 h. Ifosfamide was infused over 24 h with 3 g/m^2 mesna and hydration at 3 l/m^2 daily for 3 days. Cisplatin was infused after 3 h pre-hydration (500 ml/m^2) over 48 h with hydration at 3 l/m^2 daily. Each module was repeated on either two or three occasions until the occurrence of a complete bone-marrow remission and a partial response overall.

Where possible, chemotherapy was carried out despite myelosuppression or infection, and blood products and antibiotic/antifungal drugs were given when clinically indicated. All patients were assessed prior to treatment by a full blood count, determinations of plasma electrolytes, urea and creatinine, calcium, phosphate and magnesium, ionized calcium and albumin and by liver-function tests. The glomerular filtration rate (GFR) was measured by the plasma clearance of [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA). Patients' weight, height, full blood count and electrolytes were measured before each course of therapy. Tumour response was assessed at four and eight cycles after the commencement of treatment and at the end of therapy if this was prolonged. Response was assessed by ultrasound scan or computerised tomography of the primary tumour, by bone marrow aspiration and trephine at four separate

Table 1. Outline of the treatment protocol



Restaging was done after 4 cycles, and cycles 1–4 were repeated. Restaging was then carried out after 8 cycles, and if a complete bone-marrow response had occurred, surgery and high-dose chemotherapy with autologous bone marrow rescue were performed. In the case of evidence of a response in the face of tumour persistence, cycles 1–4 were repeated

sites, by ^{99}Tc bone scan and by measurement of urinary catecholamines. The International Neuroblastoma Response Criteria were used to classify response [3].

Table 2. Haematological and infective complications and dose intensities of chemotherapeutic agents

	Patient number		
	1	2	3
Duration of administration of 8 cycles (days)	73	109	115
Days in hospital	54	81	77
Number of tranfusions:			
Blood	5	6	11
Platelets	0	3	3
Total days of neutropenia (x, $<1.0 \times 10^9$/l)	34	23	63
Total episodes of febrile neutropenia	3	4	4
Episodes of septicaemia (bacteriologically confirmed)	1	0	3
Percentage of anticipated dose-intensity-received:			
Etoposide	74	65	128
Ifosfamide	73	67	48
Vincristine	86	75	70
Cisplatin	71	66	48
Doxorubicin	106	104	0

Dose-intensity calculations were made according to the method of Longo et al. [10]

Results

Toxicity

Myelosuppression. A summary of the myelosuppression encountered is given in Table 2. Myelosuppression was seen in all three patients and was particulary severe in patient 3, who was neutropenic for 63 of the 115 days of treatment. This patient received extensive blood, platelet and albumin support and experienced three episodes of proven bacterial infection.

Infection. Patients required admission for a respective total of three, four and four episodes of fever requiring intravenous antibiotics. Septicaemia was proven on four occasions and was due to an enterococcus (2), *Staphylococcus aureus* (1) and a diphtheroid (1). In addition, two patients had urinary tract infections (*Klebsiella*), (*Escherichia coli*). *Clostridium difficile* was grown repeatedly from patient 3.

Mucositis and gastrointestinal toxicity. Patient 3 developed severe (grade 4) [12] mucositis at an early stage of treatment and required prolonged admission to hospital for supportive care and total parenteral nutrition. She received no doxorubicin because of the severity of mucositis and myelosuppression. Grade 3 mucositis developed in patient 2 after seven cycles of chemotherapy, in association with recurrent episodes of abdominal pain over a period of 5 days.

Renal toxicity. Nephrotoxicity was observed in two patients and affected therapy in one case. After six cycles, the GFR of patient 3 had fallen to 52 ml min^{-1} 1.73 m^{-2}. This was attributed to combined cisplatin and ifosfamide toxicity, and both drugs were therefore withheld, resulting in subsequent recovery of the GFR. Renal function deteriorated in patient 2, but not until after the eighth course, and recovered subsequently.

Central nervous system toxicity. Patient 2 became drowsy and unwell during ifosfamide infusion on two occasions (cycles 7 and 9), once in association with a convulsion. The drowsiness improved after ifosfamide withdrawal on both occasions. One patient developed mild unilateral high-tone deafness (Brock grade 1) [2] after receiving a single dose of cisplatin.

Response

Responses (at individual sites and overall) are summarised in Table 3. Patient 1 showed an overall partial response (PR) both after four courses and at the end of treatment [bone marrow and urinary catecholamines, complete response (CR); primary site, PR] but relapsed shortly after the completion of treatment and died of disseminated disease. Patient 2 showed no response after four cycles and a PR at the end of therapy. Patient 3 showed a mixed response after four cycles and a very good partial response (VGPR) at the end of treatment (bone marrow, bone and primary tumour, CR; catecholamines, VGPR).

Table 3. Response to chemotherapy determined after 4 cycles and at the end of treatment according to International neuroblastoma Response Criteria

	Primary		Bone marrow		Catecholamines		Bone scan		Overall	
Patient	Cycle 4	End	Cycle 4	End	Cycle 4	End	Cycle 4	End	Cycle 4	End
1	PR	PR	CR	PR	CR	CR	NI	NI	PR	PR
2	NR	PR	NR	PR	PR	PR	PR	PR	MR	PR
3	PR	CR	NR	CR	NR	VGPR	PR	CR	MR	VGPR

CR, Complete response; VGPR, very good partial response; PR, partial response; MR, mixed response; NR, no response; NI, not involved

Discussion

The aim of this report is to document the toxicity of pilot combinations of drugs given on a high-dose, rapid schedule for the treatment of disseminated neuroblastoma. Too few patients were studied to allow meaningful assessment of antitumour efficacy, but a VGPR was seen in one patient.

As expected, myelosuppression was severe in all patients and required substantial support. Neutropenia was particularly severe after cycles containing ifosfamide, doxorubicin and etoposide. Mucositis occurred in two patients and was severe in one case. Mucosal toxicity has been reported in patients treated with rapid-schedule doxorubicin [18, 19], which may have been the agent responsible in one of these patients. The interaction of direct drug-induced and neutropenia-associated mucosal damage may have contributed to the high sepsis rate observed in these patients. Deterioration of renal function led to the withdrawal of cisplatin and ifosfamide in one patient. Neurological toxicity in a second patient, who might have been expected to have a low risk of developing encephalopathy (normal plasma albumin and creatinine, not principally pelvic disease, drug administration via continuous infusion [4, 11]) led to the withdrawal of ifosfamide.

Although the use of haemopoietic growth factors might improve the myelosuppressive side effects of this regime, it was non-haematological toxicity that led to delays in treatment. The high levels of toxicity encountered, particularly mucosal, renal and infective, meant that administration within the intended time was possible for only one patient (see Table 2).

Doxorubicin seems most likely to cause a high incidence of mucosal toxicity, and its inclusion in dose-intense protocols may make administration on time impossible. Ninane et al. [13] found that the addition of doxorubicin conferred no survival advantage to patients with stage 3 and 4 neuroblastoma. It would therefore seem advisable to avoid the use of doxorubicin in such regimes. Increased dose intensity of this drug has been related to higher response rates by Cheung et al. [5], although this was weaker for doxorubicin than for cisplatin and etoposide.

A high risk for encephalopathy would appear to be associated with ifosfamide administration in this regimen, and a more acceptable agent might therefore be cyclophosphamide. Taken together, the responses of these patients to the new, high-dose-intensity schedule indicated that toxicity was likely to be unacceptable for subsequent patients, and no further patients were treated with this regime. Subsequent rapid-schedule high-dose intensity protocols containing no doxorubicin and using cyclophosphamide rather than ifosfamide have produced acceptable levels of toxicity and encouraging early survival rates [14].

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