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Toxicity of Single-day High-dose Vincristine, Melphalan, Etoposide and Carboplatin Consolidation with Autologous Bone Marrow Rescue in Advanced Neuroblastoma

Susan J. Gordon, Andrew D.J. Pearson, Michael M. Reid and Alan W. Craft

16 unselected patients with advanced neuroblastoma were given high-dose consolidation chemotherapy with vincristine, melphalan, etoposide and carboplatin over 5 h followed by autologous bone marrow rescue. 3 patients died from treatment-related toxicity, 2 from disease, 1 is alive with disease and 10 are alive and disease-free a median of 12.5 months (range 2–38 months) after bone marrow rescue. All had bone marrow toxicity, most mucositis and 6 had seizures. Renal failure was unexpectedly severe. In the last 3 patients, administration of carboplatin was delayed by 18 h in an attempt to reduce renal damage. The results show that this regimen produces significant morbidity and has a high mortality. Although the overall outcome is encouraging, too few patients have been studied to gauge its efficacy. Whether such aggressive consolidation is necessary in heavily pretreated children with neuroblastoma remains unknown.
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INTRODUCTION

THE OUTCOME for patients who present with disseminated neuroblastoma after the age of 1 year is dismal, and with conventional chemotherapy, radiotherapy and surgery most centres report 2-year survival figures of only 10–15% [1].

In the 1980's, high-dose chemotherapy, followed by autologous bone marrow rescue (ABMR) as consolidation therapy emerged as a promising approach for patients with poor prognosis, chemosensitive malignancies, including neuroblastoma [2].

High-dose melphalan has been shown to improve event-free and overall survival [3, 4]. However, even when patients in complete remission receive this therapy, the relapse rate remains high. The need for more effective high-dose regimens therefore remains great in order to decrease the postbone marrow transplant relapse rate [5].

In attempts to improve the efficacy of treatment, research into different approaches to both induction and consolidation chemotherapy continues. For induction, these include administration of high-dose chemotherapy every 3 weeks and rapid schedule protocols [6]. For consolidation, various combinations of chemotherapy and radiotherapy have been studied, including melphalan and total body irradiation (TBI) [7], vincristine, melphalan and TBI [8], teniposide, carmustine and melphalan [9], teniposide, doxorubicin, melphalan, cisplatin and TBI [10] and carmustine, cisplatin, etoposide and melphalan or thiotepa [11] followed by ABMR, often with purged bone marrow. These combinations gave response rates varying from 30 to 50%; however, the two-year progression-free survival from the time of consolidation, irrespective of which high-dose regimen is used, remains around 40%.

Most recently, the Royal Marsden Hospital [12] has used a regimen containing vincristine, melphalan, etoposide and carboplatin (OMEC) given over 5 days. This has the potential advantage of using a combination of drugs which are not cross resistant. This combination has been modified in Newcastle to be given over 24 h, thus avoiding the need for cyropreservation of the harvested marrow.

Despite uncertainty about the relative contributions to survival of modern induction and consolidation regimens, the likelihood that investigations of both of these aspects of management will be pursued in different centres makes it important to establish a picture of the toxicity which children with this disease will face. This report describes the outcome and toxicity of a modified version of the Royal Marsden's regimen when applied to a group of children who had already received a high-dose, rapid schedule induction regimen [6].

PATIENTS AND METHODS

From January 1988 to March 1991, 16 consecutive unselected patients with stage 3 or 4 neuroblastoma over the age of 1, who achieved a partial response or better to initial chemotherapy and no longer had detectable tumour in the bone marrow, received high dose chemotherapy followed by ABMR. All patients were staged and had their response assessed using the International Neuroblastoma Response Criteria [13]. Their median age at consolidation was 2 years 9 months (range 16 months–14 years 3 months). 15 patients were stage 4, 1 patient was stage 3.

The primary tumour involved the adrenal in 10 patients, the sympathetic chain in 4, the kidney in 1 and, in 1, the primary site was unknown. All except patient 1 had received induction therapy with high-dose, rapid schedule chemotherapy [6] followed by surgery to the residual tumour (Table 1). Patient 1 received a pilot protocol in which high-dose ifosfamide, etopo-

Correspondence to A.D.J. Pearson.
S.J. Gordon, A.D.J. Pearson and A.W. Craft are at the Department of Child Health, The Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH, U.K.; and M.M. Reid is at the Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, U.K.
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Table 1. *Presenting features, response to induction therapy and outcome*

Patient	Primary	Metastases LN	Bones	BM	Pleura	Stage	Response to induction	Age at transplant	Hospital days	Outcome	Survival from transplant to May 1991
1	R. adrenal	+	+	+	+	4	PR	16 months	—	TRD	15 days
2	Unknown	−	+	+	−	4	CR	3 years 2 months	19	DOD	27 months
3	Abdominal sympathetic chain	−	+	+	−	4	CR	2 years 5 months	19	ADF	38 months
4	R. adrenal	−	+	+	−	4	VGPR	2 years 6 months	43	ADF	37 months
5	L. adrenal	+	+	+	−	4	CR	2 years 9 months	25	ADF	35 months
6	R. adrenal	−	+	+	−	4	CR	4 years	26	DOD	15 months
7	L. adrenal	+	−	+	−	4	CR	2 years 7 months	45	ADF	28 months
8	Abdominal sympathetic chain	−	−	+	−	4	CR	5 years	19	ADF	12 months
9	L. adrenal	+	−	−	−	4	PR	6 years 8 months	25	ADF	16 months
10	R. adrenal	+	−	−	−	4	PR	2 years 7 months	—	TRD	20 days
11	Abdominal sympathetic chain	+	+	+	−	4	CR	3 years 1 month	—	TRD	5 days
12	L. adrenal	−	+	+	−	4	VGPR	5 years	46	AWD	9 months
13	L. adrenal	−	−	−	−	3	CR	2 years 3 months	158	ADF	8 months
14	R. kidney	−	+	−	−	4	CR	2 years 9 months	28	ADF	7 months
15	L. adrenal	+	+	−	−	4	CR	2 years 3 months	21	ADF	3 months
16	Abdominal sympathetic chain	+	−	+	−	4	VGPR	14 years 3 months	28	ADF	2 months

R = right, L = left, LN = lymph nodes, BM = bone marrow, CR = complete remission, PR = partial remission, VGPR = very good partial remission, TRD = treatment related death, DOD = died of disease, ADF = alive disease free, AWD = alive with disease (after Brodeur *et al.* INRC[13])

side and doxorubicin were alternated with the non-myelotoxic combination of vincristine and cisplatin.

6 weeks after surgery, patients underwent bone marrow harvest, folowed by high-dose, marrow ablative chemotherapy using vincristine, melphalan, etoposide and carboplatin modified from the Royal Marsden Hospital's regimen [12]. This was given over a single day. A summary of the regimen is shown in Fig. 1. Vincristine was given as a 1.5 mg/m^2 intravenous bolus, followed by melphalan at 180 mg/m^2 as a fast infusion, followed by etoposide in a dose of 500 mg/m^2 in the first 4 patients and 250 mg/m^2 thereafter, over 4 h; carboplatin was then given at 1 g/m^2 over 1 h. In the last 3 patients, carboplatin was given 18 h after the first three drugs in an attempt to reduce renal toxicity.

At least 2 × 10^8 nucleated cells/kg of harvested, unpurged marrow (stored at 4°C) were infused 48 h later.

Patients were nursed in a cubicle without laminar air flow. Prophylactic cotrimoxazole, nystatin, acyclovir and ranitidine were started on day 3. All received total parenteral nutrition and platelet transfusions were given if there was a platelet count

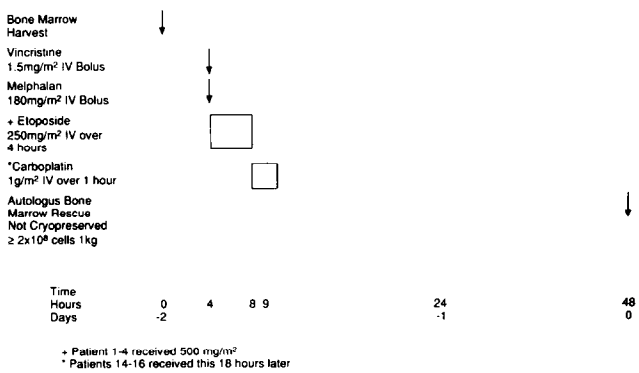

Fig. 1.

of less than 20 × 19^9/l, even in the absence of bleeding. Broad spectrum antibiotics were given empirically if there was febrile neutropenia.

Glomerular filtration rate (GFR), as measured by clearance from the plasma of ^{51}chromium EDTA, was determined before high-dose chemotherapy on day 3 and at a mean of 7 months after chemotherapy.

Toxicity was graded according to the World Health Organisation System. All parents gave consent to the proposed management.

RESULTS

Clinical details of the extent of the disease at diagnosis in 16 children, their initial response to induction therapy, length of hospital stay associated with consolidation and eventual outcome are shown in Table 1. 10 of 16 are alive and disease-free with a median of 12.5 months (range 2–38 months) after consolidation. 3 died of toxicity (see below, mortality) and 3 have relapsed. Only 1 patient spent longer than 46 days in hospital after consolidation. This case had chronic renal failure and required dialysis resulting in a stay of 158 days.

Toxicity

Haematological toxicity shown in Table 2 was as expected. All 16 required systemic antibiotics, 6 of whom had bacteriologically proven septicaemias. 14 received anti-fungal treatment, 1 of whom had *Candida albicans* detected in the blood. 9 had serious bleeding problems, though in no case was haemorrhage the sole or major cause of death.

Gastrointestinal toxicity is shown in Table 3. All received prophylactic total parenteral nutrition. 6 required morphine infusion to stop painful mucositis. Though all had some diarrhoea and *Clostridium difficile* was isolated from the stools of 4 children, in no case was enterocolitis formally diagnosed.

Renal toxicity is shown in Table 4. 15 had a rise in serum creatinine, 2 of whom already had an impaired GFR before consolidation. 1 developed high output renal failure, which was

Table 2. Haematological toxicity

Patient	Nucleated cells $\times 10^8$ cells/kg	Febrile neutropenia: Days to neutrophils $>1\times10^9$/l	Days of antibiotics	Days of anti-fungals	Baterial fungal or viral isolates	Days to platelets: $>20\times10^9$/l	$>50\times10^9$/l	$>100\times10^9$/l	Last platelet day transfusion	Significant episodes of bleeding	Days of last blood transfusion
1	3.2		15	5		—	—	—	15	—	14
2	3.9	58	11	7		14	11	58	14	—	17
3	3.5	17	16	6	Streptococcus, blood; *E. coli*, urine	15	8	53	15	—	14
4	4	21	30	14	Enterococcus, blood; Candida + blood, stool; Pneumococcus, blood + respiratory tract	40	47	79	40	Gums Jejunostomy stoma	16
5	7	14	19	15	Candida and adenovirus, stool	20	40	83	20	Haematemesis	20
6	2.9	25	21	8	Streptococcus, Staphylococus, and enterococcus, blood	26	47	75	23	Haematemesis	24
7	5.1	19	16	10		20	22	83	23	Haematuria Subconjunctivae	18
8	2	68	7	—	Streptococcus, blood; Clostridium, stool	23	6	68	23	Haematochezia melaena	41
9	5.3	13	14	7		47	70	154	24	Haematemesis	167
10	8.8	18	17		K. *oxytoca*, blood	—	—	—	—	Haematemesis Epistaxis Subconjunctivae	102
11	4.5		3	1		5	—	—	5	Gums Venepuncture sites	3
12	3.4	12	19	14	Clostridium, stool	38	93	—	53	Haematuria Subconjunctivae	102
13	5	24	60	7		5	—	—	31	—	100
14	5.5	26	14	12	Clostridium, stool	19	—	—	53	—	24
15	4.9	17	10	10	Clostridium, stool; S. *albus*, blood	21	—	—	21	—	22
16	2.3	45	10	8	*E. coli*, urine	42	47	—	42	—	20
Median (excluding TRD)		21	16	9		21	44.5	77.5	23	—	22
Range		12.68	7–60	0–15		5–47	6–93	53–154	14–53		14–167

managed conservatively. 3 with low output acute renal failure required peritoneal dialysis. 2 of these had fatal multi-system organ failure (see below, mortality). 1 patient developed chronic renal failure and currently has a serum creatinine between 200 and 300 μmol/l off dialysis. 9 of 10 whose GFR was measured a mean of 7 months after transplant showed a further deterioration of 24%.

Central nervous system toxicity was important. 6 experienced seizures, 3 of whom died. In these 3 (see below, mortality), the seizures were associated with multi-system organ failure. In one, convulsions were associated with a low serum magnesium (0.3 mmol/l, normal range 0.7 to 1.0 mmol/l). 6 patients had agitation or obtundation. In 3, these signs preceded death.

Important respiratory complications were not common and were infective. 3 patients experienced pulmonary infection and 2 of these required artificial ventilation. *Klebsiella oxytoca* and *Streptococcus pneumoniae* were cultured from 2 patients. The patient from whom the pneumococcus was cultured did not require artificial ventilation, but did require oxygen support.

Mortality

3 patients died at 5, 15 and 20 days post-transplant. Patient 1 had severe gastrointestinal toxicity, with abdominal distension, hepatomegaly, ascites and possible portal vein thrombosis leading to coagulopathy, respiratory failure, cardiac arrest and encephalopathy with seizures.

*Table 3. Gastrointestinal toxicity**

	Days total parentral nutrition	Days morphine for mucositis	Oral grade	Vomiting grade	Diarrhoea grade
1.	9	—	1–2	1–2	1–2
2.	20	—	1–2	1–2	1–2
3.	20	—	1–2	1–2	1
4.	45	28	3–4	3–4	2†
5.	26	—	1–2	2–3	2†‡
6.	22	—	1–2	1–2	2
7.	25	—	1–2	2–3	2
8.	19	8	3–4	1–2	2§
9.	26	12	3–4	1–2	1–2
10.	20	—	1–2	1–2	2
11.	2	—	1–2	1–2	1
12.	43	—	1–2	1–2	2§
13.	85	—	1–2	1–2	2
14.	23	7	3–4	3–4	2§
15.	21	19	3–4	2–3	2§
16.	21	17	3–4	3–4	1

*WHO grading system of acute and subacute toxic effects.
†*Candida albicans* cultured.
‡Adenovirus cultured.
§*Clostridium difficile* cultured.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Oral	No change	Sorento/ erythema	Erythema + ulcer; can eat solids	Ulcers; requires liquid diet only	Alimentation not possible Intractable vomiting
Nausea/ vomiting	None	Nausea	Transient vomiting	Vomiting requiring therapy	Haemorrhagic
Diarrhoea	None	Transient < 2 days	Tolerable level > 2 days	Intolerable requiring therapy	dehydration

Patient 10 had severe gram negative sepsis with resultant shock, acute renal failure, encephalopathy and pneumonitis. He had recovered from neutropenia at the time of death.

Patient 11 had acute renal failure, requiring peritoneal dialysis and ventilatory support until death. This was preceded by encephalopathy, seizures and a coagulopathy. He had experienced an episode of renal impairment several months before transplant, associated with haemolytic uraemic syndrome, during which he required peritoneal dialysis for 35 days. However, his GFR was 93 ml/min/1.73^2 before consolidation therapy.

All 3 had postmortem examination but no obvious cerebral lesions were found which could account for the seizures.

DISCUSSION

Despite considerable advances in the treatment of neuroblastoma, children with disseminated disease still have one of the worst prognoses of all childhood malignancies. Conventional therapy involves initial chemotherapy, followed by surgical removal of any residual tumour, and finally, high-dose consolidation chemotherapy to eradicate minimal residual disease followed by ABMR.

Recently, the role of high-dose chemo-radiotherapy and ABMR has been questioned [14, 15]. The efficacy and need for intensive consolidation will be difficult to assess, not least because of the variations in induction therapy. This report does not address this issue. However, it is important that detailed knowledge of the toxicity of consolidation programmes is available for those planning such studies. This report provides some of this information.

10 patients (62.5%) have remained disease-free after a median of 12.5 months after ABMR (range 2–38 months). This compares favourably with outcomes from studies using other high-dose chemotherapy combinations [3, 4, 7–11, 16]. 3 patients (19%) died from toxicity secondary to the conditioning. This toxic death rate is high [3, 4, 7, 9–11, 16], but very similar to the rate following vincristine, melphalan and TBI [8].

Apart from the expected myelosuppression, the predominant non-haematologic toxicity was renal, followed by mucositis and seizures. Renal toxicity was the most serious, and in some cases permanent, side effect of the consolidation regime in this study. Although only 3 of the 16 patients already had a GFR below 80 ml/min/1.73m^2 following induction chemotherapy, in 9 of 10 evaluable children, a further fall was seen. Of those most severely affected, 1 still has an impaired GFR and 1 is in chronic renal failure with a serum creatinine between 200 and 300 μmol/l off dialysis. Despite apparent complete recovery from an earlier episode of renal impairment, patient 11 developed severe acute renal failure after consolidation which directly led to his death.

Renal toxicity, previously documented after high-dose carboplatin therapy [17] may be exacerbated by prior cisplatin therapy. In the present series, most patients had received a cumulative dose of 720 mg/m^2 cisplatin (data not shown) and renal function may have already been impaired before consolidation treatment was given. In the last 3 patients, the carboplatin was given 18 hours after the other three drugs in an attempt to minimise the renal toxicity. Although none of these 3 patients had important clinical renal problems, too few have received this modification to determine whether it is of value in reducing renal toxicity.

Both melphalan alone and the combination of high-dose carboplatin and etoposide are enterotoxic. In this series, although diarrhoea was common, only the first patient in this study developed gastrointestinal toxicity so severe as to be the initiating event in her ultimate multi-organ failure and death. She, and the next 3 patients received 500 mg/m^2 of etoposide, rather than the 250 mg/m^2 the following 12 patients received. The dose was reduced in an attempt to decrease gastrointestinal toxicity, and this did appear to be successful.

Important central nervous system symptoms, encephalopathy and seizures, occurred in 6 patients. In only 1 was a cause readily identifiable, i.e. a low serum magnesium level. In the remaining patients, impaired clearance of acyclovir may have contributed. Cisplatin can cause convulsions [18], but to date carboplatin has not been implicated though some neurological symptoms occur after high dose [19]. It is possible that renal damage by one cytotoxic drug may have affected the clearance of another and thus increased neurotoxicity.

Respiratory problems were significant in only 3 patients, with infection being the likely cause in all, although organisms were only cultured from 2 of them.

Thus, this single-centre study has shown that single day OMEC consolidation with autologous marrow rescue when given to heavily pretreated children is toxic, consumes substantial resources both in investigation and support and has a significant mortality.

Although the overall outcome is encouraging, greater experience with this combination of drugs is required and a reduction

Table 4. Renal toxicity

Patient	Creatinine (μmol/l) *Day −3	1st day of rise (day)	Max creatine (μmol/l)	Day maximum creatinine	% increase	Type renal failure	Days dialysed	Pretransplant GFR (mls/min/1.73m²)	Post-transplant GFR	% change
1	36	7	98	9	172	—	—	109	NE	
2	38	1	53	1	39	—	—	187	125	−33
3	38	0	40	14	5	—	—	136	148	+ 9
4	21	8	134	13	538	—	—	141	89	−37
5	41	1	125	16	205	—	—	100	86	−14
6	31	0	321	3	935	High output	—	113	88	−22
7	40	1	173	2	333	—	—	99	74	−25
8	55	−1	71	−1	29	—	—	115	107	− 7
9	63	−3	213	5	238	—	—	67	56	−16
10	40	4	62	4	55	—	—	107	NE	
11	50	−2	316	2	532	Low output	3	93	NE	
12	53	−1	356	5	324	Low output	14	59	37	−37
13	63	−2	412	5	554	Low output	136	85	NE	
14	31	−1	111	1	258	—	—	96	69	−28
15	52	−1	72	−1	38	—	—	88	NE	
16	90	−2	127	2	41	—	—	70	NE	
Mean	46	1	167.7	5	268.5		—	104	88	−24
Range	21–90	−1–8	40–412	−1–16	5–935			59–187	37–148	

*OMEC given on day −2, NE = not evaluated.
Mean 7 months between pre- and post-transplant measurements.

in toxicity, particularly renal, is necessary before this regimen can be considered a safe approach to consolidation in heavily pretreated children with disseminated neuroblastoma. If the apparently improved survival of these children proves genuine, the toxicity of this regimen is great enough that some consideration be given to substituting it with a substantially less toxic approach to consolidation, rather than decreasing the intensity of induction treatment.

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