Eur J Cancer, Vol. 28A, No. 8/9, pp. 1324–1328, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Pilot Study of High-dose Vincristine, Etoposide, Carboplatin and Melphalan with Autologous Bone Marrow Rescue in Advanced Neuroblastoma

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The efficacy and toxicity of a high-dose multiagent consolidation regimen, OMEC (vincristine, melphalan, etoposide and carboplatin), with autologous bone marrow rescue was studied in patients with poor-prognosis neuroblastoma. 20 patients were treated with OMEC, 18 after induction chemotherapy and 2 following relapse. All patients received, per m^2, vincristine 4 mg, etoposide 1 g, carboplatin 1.0–1.75 g and melphalan 180 mg followed by bone marrow rescue. 4 patients (20%) died of treatment-related complications. Severe gastrointestinal toxicity occurred in all of these patients, and in 75% of patients overall. 1 of 5 patients with evaluable disease achieved complete remission. 13 patients (65%) have relapsed a median of 10 months (range 3–26) after receiving OMEC. Thus, OMEC was not more effective, yet more toxic, than high-dose melphalan given alone, and the use of similar multiagent regimens with overlapping toxicities in advanced neuroblastoma appears inadvisable.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1324–1328, 1992.

INTRODUCTION

THE THERAPY of advanced neuroblastoma in children over 1 year of age presents clinicians with a considerable challenge. Complete remission (CR) or partial remission (PR) is achieved in up to 74% of these patients using combination chemotherapy. However, remission is usually of short duration with median disease-free survival of 16 months, and only 15–20% of patients surviving long-term [1, 2].

The high incidence of relapse in patients believed to be in CR after initial chemotherapy implies the presence of residual disease which is undetected by conventional investigations. Recently, therapy strategies have been directed towards the eradication of 'minimal residual disease'. Prolonged conventional chemotherapy (over 24 months) appears to offer no advantage over shorter regimens [1, 2].

An alternative approach is the use of high-dose chemotherapy with autologous bone marrow rescue as consolidation treatment in an attempt to eradicate minimal residual disease. A randomised European Neuroblastoma Study Group (ENSG) trial showed that patients receiving high-dose melphalan (HDM) had a significantly longer progression-free survival (PFS) than those who did not receive HDM [3, 4]. Although numbers were small, the study suggested that there may be a survival advantage for the HDM-treated group.

The present study questions the hypothesis that multiagent high-dose consolidation chemotherapy will result in survival rates superior to that achieved by HDM alone. We examined the efficacy and toxicity of a high-dose 4-drug combination (vincristine, melphalan, etoposide and carboplatin) as conditioning therapy in poor-prognosis neuroblastoma.

PATIENTS AND METHODS

Patients greater than 1 year of age with stage 3 or 4 neuroblastoma [International Neuroblastoma Staging System (INSS) classification] who had responded to initial chemotherapy were considered for entry into the study [5]. Informed parental consent was obtained in all cases. Between July 1987 and June 1989, 20 patients (12 males and 8 females), ranging in age from 2.5–12 years (median age 4 years) at the time of bone marrow rescue, were treated.

Clinical details and initial treatments are shown in Table 1. 18 patients were stage 4 at diagnosis and 2 patients were stage 3. As initial treatment, the standard OPEC regimen (vincristine, cisplatin, etoposide or teniposide and cyclophosphamide) was administered to 17 patients 3–4 weekly over 20–30 weeks [6]. 2 patients received high-dose OPEC in a rapid schedule (rapid OPEC) every 10 days over 70 days [7]. Patient 13 received a variety of drugs as initial therapy (see Table 1). 16 children had surgery to the primary tumour prior to receiving OMEC, and 2 patients had received external beam radiotherapy. Patient 1 was treated with [^{131}I]metaiodobenzylguanidine (mIBG) 7 days before receiving OMEC.

Bone marrow was harvested from the iliac crests under general anaesthetic, aiming to achieve a minimum nucleated cell count of 2×10^8/kg. No purging procedures were used. The bone marrow harvests were cryopreserved in DMSO. 11 patients were in CR (10 first CR, 1 second CR following relapse) at the time of bone marrow rescue; 3 had achieved a very good partial response (VGPR) and 3 PR (INSS criteria) [5]. Patients 1 and 18 were treated after relapse; the latter was treated as detailed in Table 1 and had achieved CR at the time of megatherapy. 2 patients (numbers 5 and 7) were not evaluable in terms of disease remission status because of insufficient investigation prior to OMEC.

The schema for the administration of OMEC and bone

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Received 13 Dec. 1991; accepted 31 Dec. 1991.

Table 1. Clinical details, initial treatment, responses and outcome in 20 patients who received OMEC

Patient No.	Sex	Sites of primary and metastatic disease at diagnosis: Primary	Bone	Bone marrow	Other	Treatment prior to OMEC	Status at ABMT	Age at ABMT (yr)	Response to OMEC	Subsequent course (months after ABMT)	Outcome (months after ABMT)
1	M	R adrenal	−	−	LN	OPEC × 5, Surgery, HDM → CR. Relapse → mIBG × 3 → CR	In relapse	12	CR	Relapse (10)	DOD (13)
2	F	L adrenal	+	+	—	OPEC × 7 Surgery	VGPR	4	CR	Relapse (3)	DOD (5)
3	M	L adrenal	+	+	—	OPEC × 6 Surgery	CR	3	NE	Relapse (6)	DOD (8)
4	F	R adrenal	+	+	—	OPEC × 8 IVAD × 2	CR	2½	NE	—	TRD (13 days)
5	F	L adrenal	+	+	—	OPEC × 7 Surgery	NE	3	NE	—	NED (35)
6	F	L adrenal	+	+	LN	OPEC × 9 Surgery	CR	2½	NE	—	TRD (16 days)
7	M	Thorax	+	+	LN	OPEC × 9 Surgery	NE	5½	NE	Relapse (10)	DOD (11)
8	F	L adrenal	+	+	—	OPEC × 9 Surgery, RT	CR	6½	NE	Relapse (5)	DOD (8)
9	M	L adrenal	+	+	—	OPEC × 8 Surgery	CR	3½	NE	Relapse (9)	DOD (12)
10	M	L adrenal	+	+	LN	OPEC × 8 Surgery	CR	7	NE	Relapse (21)	AWD (24)
11	F	R adrenal	−	−	—	OPEC × 8	PR	3	NR	Relapse (4)	DOD (6)
12	M	L adrenal	+	+	—	OPEC × 6 Surgery	CR	3½	NE	CRA Relapse (12)	DOD (13)
13	M	L adrenal	+	−	—	CVA × 3, EP × 4 Surgery	CR	3	NE	Relapse (20)	DOD (27)
14	M	Pelvis	+	+	—	OPEC × 8 Surgery	VGPR	8	NR	CRA Relapse (4)	DOD (5)
15	M	R adrenal	+	−	LN	OPEC × 6 Carbo × 2	PR	2½	NR	Surgical VGPR	Died of postoperative complications (4)
16	M	L adrenal	+	+	—	OPEC × 8 Surgery	CR	4½	NE	—	NED (31)
17	M	L adrenal	+	+	—	Rapid OPEC × 8 Surgery	CR	3	NE	Relapse (12)	DOD (16)
18	F	Pelvis	−	−	LN	OPEC × 10, Surgery→CR Relapse→Surgery, RT, Carbo × 6	Second CR	4	NE	—	TRD (7 days)
19	F	Rp	+	−	LN	Rapid OPEC × 5 mIBG × 2	PR	9½	NR	CRA	AWD (26)
20	M	L adrenal	+	+	—	OPEC × 8 Surgery	VGPR	9½	NE	—	TRD (42 days)

IVAD = Ifosfamide, vincristine, doxorubicin; Carbo = carboplatin; CVA = cyclophosphamide, vincristine, dactinomycin; EP = epipodophyllotoxin, cisplatin; HDM = high-dose melphalan; OPEC = vincristine, cisplatin, VP16/VM26, cyclophosphamide; mIBG = [^{131}I] metaiodobenzylguanidine therapy; RT = external beam radiotherapy; CRA = *cis*-retinoic acid; LN = lymph node; Rp = retroperitoneal; R = right; L = left. Responses [5]: CR = complete remission; VGPR = very good partial remission; PR = partial remission; NR = no response; NE = not evaluable; NED = no evaluable disease; TRD = treatment-related death; DOD = died of disease; AWD = alive with disease.

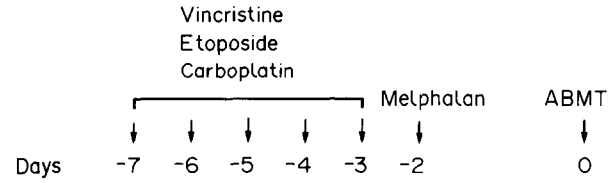

Fig. 1. Administration of OMEC.

Table 2. Total administered doses (/m²) of OMEC

Patient No.	Vincristine (mg)	Etoposide (g)	Carboplatin (g)	Melphalan (mg)
1–10	4	1	1	180
11–17	4	1	1.25	180
18	4	1	1.25	140
19	4	1	1.4	180
20	4	1	1.75	180

marrow rescue is depicted in Fig. 1; drug dosages are recorded in Table 2. All children received a loading bolus of 1.5 mg/m² vincristine, followed by a continuous infusion of 0.5 mg/m² daily for 5 days. Carboplatin, diluted in 5% dextrose, was infused over 1 h for 5 consecutive days. As the study progressed, the dose of carboplatin was increased as part of a dose-escalation/toxicity assessment. Etoposide (200 mg/m²) was infused over 3 h for 5 consecutive days. 19 patients were given intravenous melphalan, 180 mg/m² (patient 18 received 140 mg/m²) over 5 min in its own diluent. Intravenous fluids and diuretics were administered before, and for 24 h after the melphalan infusion to ensure an adequate diuresis.

RESULTS

Toxicity

4 patients (20%) died of treatment-related toxicity (Table 3). All suffered severe enteritis and infection. Patient 6 developed aspergillus pneumonia and an unexplained encephalopathy. Patient 18 died from systemic aspergillosis; the causes of sepsis in the remaining 2 patients who died were not identified. Patient 15 died 4 months after marrow rescue following surgical removal of his intra-abdominal primary tumour. The postoperative course was complicated by hypovolaemia and cardiac failure, which were attributed to fluid loss into the peritoneal cavity and possible endotoxic shock.

Table 3. Details of toxic deaths

Patient No.	Infection	Haemorrhagic enteritis	Other toxicities	No. days post OMEC to death
4	Serious*	Severe*	Multiorgan failure	13
6	Serious*	Severe	Encephalopathy	16
18	Serious*	Severe*	Liver dysfunction	7
20	Serious*	Severe*	Multiorgan failure	42

*WHO grade IV.

Table 4. Morbidity induced by OMEC

Nature of toxicity	% Patients with WHO grade III or IV toxicity
Infection	90
Mucositis	85
Diarrhoea	75
Hepatic	20
Renal	15

Details of morbidity are documented in Table 4. Neutrophils rose above 0.5 × 10⁹/l 12–60 days (median 27 days) after OMEC. Platelets took a median of 30 days to exceed 20 × 10⁹/l. Only patient 1, who had previously received mIBG therapy, failed to engraft adequately and required haematological support until death from disease 13 months after megatherapy.

4 patients suffered severe hepatic dysfunction, 3 as part of multiorgan failure (numbers 4, 18 and 20) and 1 (number 15) recovered from suspected veno-occlusive disease. Outside the setting of multiorgan failure, acute renal failure was not encountered. Glomerular filtration rate (GFR), evaluated by [^{51}Cr]EDTA clearance, was assessed before and after therapy in 4 patients and none suffered a sustained diminution. Pre- and post-therapy audiometry was performed on 5 patients; only patient 17 developed significant hearing loss (grade 0 pre-treatment to grade 2 after OMEC) [8]. 6 patients developed reversible vincristine toxicity (painful limbs, inappropriate anti-diuretic hormone secretion or paralytic ileus).

Responses and survival

15 patients were not evaluable in terms of disease reponse to OMEC on the basis of CR prior to megatherapy (11), inadequate pretreatment assessment (2), treatment-related death (1) or additional therapy (1). Patient 2 achieved CR with OMEC but relapsed 3 months later. No reduction in disease volume was noted after megatherapy in patients 15 and 19, and both underwent surgery. Surgical CR was attained in patient 19, and VGPR in patient 15 who died of postoperative complications. Patients 11 and 14 were in PR and VGPR, respectively, prior to OMEC; neither responded and both progressed 4 months later. Overall, 1 of 5 evaluable patients (number 2) responded to OMEC.

13 of 20 patients (65%) have relapsed 3–26 months (median 10 months) after marrow rescue. Overall, 4 patients are alive 24–35 months after receiving OMEC; 2 of these patients (numbers 10 and 19) have disease.

Dose-escalation of carboplatin

A comparison of patients 1–10 who received 1g/m² carboplatin, and patients 11–20 who were given more than 1 gm/m², shows no difference in relapse, survival or toxic death rates. The incidence of severe enteritis and renal dysfunction was similar in the two groups.

DISCUSSION

Multiagent high-dose therapy should ideally include agents which are individually active against neuroblastoma, exhibit a steep dose–response curve, are non-cross resistant, preferably synergistic and produce tolerable, yet different, non-myelotoxic side-effects at the administered dose.

Melphalan maintains fractional tumour cell kill with increas-

ing dose *in vitro* [9]. Myelosuppression is the major side-effect, making HDM an appropriate agent to include in a myeloablative regimen [10]. The side-effects of etoposide (2.4–3.6 g/m^2) are tolerable when followed by autologous bone marrow rescue [11, 12]. Etoposide, in combination with cisplatin, produced a 55% response rate in patients with progressive neuroblastoma, providing a rationale for its inclusion in a multiagent conditioning regimen [13].

A five-day continuous infusion of vincristine (total dose 4 mg/m^2) has documented efficacy in patients with solid tumours, and, in combination with HDM and total body irradiation (TBI), was relatively well tolerated [14, 15]. In contrast to cisplatin, the dose-limiting side-effect of carboplatin is myelosuppression [16]. A phase II study undertaken by the United Kingdom Children's Cancer Study Group (UKCCSG) showed that 44% (12/27) of patients with relapsed or refractory neuroblastoma responded to carboplatin (550–750 mg/m^2) given 3 weekly. All patients had previously received cisplatin, suggesting a lack of cross resistance between the two agents [17]. When bone marrow rescue is used, the maximum tolerated dose of carboplatin in adults is 2 g/m^2 [18]. These data indicate that the second generation platinum analogue is more suited to inclusion in a pretransplant regimen than cisplatin.

In studies of HDM alone, the incidence of treatment-related death was 3–6% [3, 4, 19], and has been higher if HDM is combined with carmustine and teniposide (8%), or vincristine and TBI (19%) [20, 21]. In our study, 20% (4/20) died of treatment-related toxicity. All suffered severe enteritis. A comparison of patients in our study who received 1 g/m^2 or more than 1 g/m^2 carboplatin showed a similar incidence of severe enteritis. However, a dose-escalation study of carboplatin (in combination with 1.2 g/m^2 etoposide and bone marrow rescue) in adult germ cell cancer showed that enteritis was dose-limiting when the dose of carboplatin exceeded 1.35 g/m^2 [22]. Etoposide, carboplatin and melphalan in combination caused severe enteritis in the majority of our patients, and probably accounted for the high mortality rate.

Only 2 patients remain disease-free 31 and 35 months, respectively, after bone marrow rescue. Vincristine and etoposide were included in the initial chemotherapy regimens of all our patients. It seems likely that these drugs contributed to toxicity, but had little effect on already resistant disease. It is apparent that OMEC is no more effective than HDM alone, yet considerably more toxic. In view of these data, it is unlikely that other high-dose agents (e.g. busulphan, thiotepa or cyclophosphamide) in combination with HDM will have a significant impact on survival, whilst inevitably increasing toxicity [23]. Retrospective analysis of the European Bone Marrow Transplantation group data showed no advantage if high-dose chemotherapy is combined with TBI compared with high-dose therapy alone, or if patients undergo two high-dose procedures rather than one [24]. As melphalan alone is the only regimen with proven efficacy we would advise against a continued trend to empirically add agents at high dose to the basic melphalan regimen, particularly when this involves drugs with overlapping non-myelotoxic side-effects. Alternative strategies are needed.

Neuroblastoma is an extremely radiosensitive tumour *in vitro* [25]. TBI, in combination with megatherapy, is associated with considerable toxicity in patients with neuroblastoma [21, 26]. In the absence of bone marrow involvement at the time of consolidation therapy, [^{131}I]mIBG treatment in combination with high-dose chemotherapy and bone marrow rescue may offer an alternative means of intensifying consolidation therapy [27]. A different approach is to concentrate on the initial chemotherapy regimen. To this end, a dose-intensive, rapid scheduling of agents, individually active in neuroblastoma, offers potential to improve outcome [28]. The ENSG is presently conducting a randomised, multicentre trial comparing a conventional schedule of a 5-drug combination (cisplatin, carboplatin, vincristine, etoposide and cyclophosphamide) with rapid, dose-intense scheduling in children with poor-prognosis neuroblastoma to test this hypothesis.

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Acknowledgements—R. Corbett is funded by the Royal Marsden Hospital Clinical Research Fund, and J. Pritchard in part by the Imperial Cancer Research Fund.

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1328–1330, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Can Karnofsky Performance Status be Transformed to the Eastern Cooperative Oncology Group Scoring Scale and Vice Versa?

Eugenia Verger, Manel Salamero and Carlos Conill

There is no consensus regarding the equivalence of performance status between the Karnofsky (KPS) and the Eastern Cooperative Oncology Group (ECOG) scales. In the present study KPS and ECOG scores were compared in 150 consecutive cancer patients. An empirical relation was established through regression analysis in a subsample of 75 patients and the results tested in the second subsample. Transformation tables including 95 and 66% confidence intervals were calculated. Both performance scales are highly correlated, but inferences about individual patients were subject to a high level of error. These results stress the difficulty of translating one score to another, especially in the range of lower performance status where a wide spread is observed.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1328–1330, 1992.

INTRODUCTION

THE KARNOFSKY performance status (KPS)[1] and the Eastern Cooperative Oncology Group (ECOG) [2] scales are the most widely used methods of assessing functional status in cancer patients. Both scales have been shown to correlate well with patient survival [3–7]. They have also been used as an outcome measure to compare differences in the functional abilities of patients before and after treatments, as well as patient selection and stratification of cancer clinical trials.

In the last 5 years according to Medline database, 227 (34.1%) of the 666 papers published regarding performance status assessment mention in the abstract the scale used. Of these, 114 (50%) employed the KPS scale and 113 (50%) used the ECOG scale.

In spite of the widespread use of these scales, data regarding the relationship between scores are limited. Oncologists usually use one of the two scales in clinical practice, and only seldom have both scales been referred to in the same study.

We have found no prospective study regarding the relationship between the two scales in the literature and there is no agreement in different equivalences derived from clinical experience. In fact, the equivalence proposed by the American Joint Committee of Cancer (AJCC) [8, 9] differs from that published in oncology text books [10, 11] (Table 1).

As KPS has more categories and is more specific than ECOG scoring, each ECOG value should correlate with more than one KPS scale value. Location of patients in high and low performance status does not represent a major problem. There is considerable disagreement concerning the intermediate valis, which are used as a cut off point to recruit patients in clinical trials. For instance, for a KPS between 30 and 50, the corresponding ECOG will vary from 3 to 2 in the AJCC equivalence to a 4–3 in Minna *et al.* [10, 11] correlation. This may produce bias in patient selection criteria and could contribute to the differences found between studies.

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Revised 3 Feb. 1992; accepted 19 Mar. 1992.