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High-dose etoposide with granulocyte colony-stimulating factor for mobilization of peripheral blood progenitor cells: efficacy and toxicity at three dose levels

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Summary High-dose etoposide (2.0–2.4 g m^{-2}) with granulocyte colony-stimulating factor (G-CSF) is an effective strategy to mobilize peripheral blood progenitor cells (PBPCs), although in some patients this is associated with significant toxicity. Sixty-three patients with malignancy were enrolled into this non-randomized sequential study. The majority (55/63, 87%) had received at least two prior regimens of chemotherapy, and seven patients had previously failed to mobilize following high-dose cyclophosphamide with G-CSF. Consecutive patient groups received etoposide at three dose levels [2.0 g m^{-2} ($n = 22$), 1.8 g m^{-2} ($n = 20$) and 1.6 g m^{-2} ($n = 21$)] followed by daily G-CSF. Subsequent leukaphereses were assayed for $CD34^+$ cell content, with a target total collection of 2.0×10^6 $CD34^+$ cells kg^{-1}. Toxicity was assessed by the development of significant mucositis, the requirement for parenteral antibiotics or blood component support and rehospitalization incidence. Ten patients (16%) had less than the minimum target yield collected. Median collections in the three groups were 4.7 (2 g m^{-2}), 5.7 (1.8 g m^{-2}) and 6.5 (1.6 g m^{-2}) $\times 10^6$ $CD34^+$ cells kg^{-1}. Five of the seven patients who had previously failed cyclophosphamide mobilization achieved more than the target yield. Rehospitalization incidence was significantly lower in patients receiving 1.6 g m^{-2} etoposide than in those receiving 2.0 g m^{-2} ($P = 0.03$). These data suggest that high-dose etoposide with G-CSF is an efficient mobilization regimen in the majority of heavily pretreated patients, including those who have previously failed on high-dose cyclophosphamide with G-CSF. An etoposide dose of 1.6 g m^{-2} appears to be as effective as higher doses but less toxic.

Keywords: etoposide; progenitor cell; mobilization

Currently, high-dose therapy with peripheral blood progenitor cell (PBPC) support is increasingly utilized in the treatment of patients with haematological or non-haematological malignant disease. The mobilization of sufficient numbers of these progenitor cells from bone marrow into the circulation for leukapheretic harvest may be achieved by either a haemopoietic growth factor [at present usually granulocyte colony-stimulating-factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF)] or cytotoxic chemotherapy alone (Richman et al, 1976; To et al, 1990; Rosenfeld et al, 1996; Diaz Mediavilla et al, 1996). However, the combination of cytotoxic chemotherapy with a growth factor may be more effective (Gianni et al, 1989; Schwartzberg et al, 1992; Pettengell et al, 1993).

Two previous reports have indicated that high-dose etoposide with growth factor may be employed for this purpose. Gianni et al (1992) studied an etoposide dose of 2.0–2.4 g m^{-2} with G-CSF or GM-CSF, and in most patients minimal toxicity was experienced, allowing the regimen to be given as an outpatient procedure. However, none of these patients was heavily pretreated. More recently, a study using etoposide at a dose of 2.0 g m^{-2} with G-CSF reported that nearly all patients, including those who had received more than two prior chemotherapy regimens, mobilized PBPCs successfully (Copelan et al, 1997). A proportion of these latter patients developed toxicity requiring hospitalization.

We have evaluated whether reducing the dose of etoposide might lessen the toxicity experienced without significantly affecting the effectiveness of the mobilization procedure. The patient group studied was predominantly heavily pretreated and included some that had previously failed to mobilize adequately with high-dose cyclophosphamide and G-CSF.

PATIENTS AND METHODS

Between September 1994 and September 1997, 63 patients with malignant disease were enrolled into this non-randomized sequential study. The first 22 patients received an etoposide dose of 2.0 g m^{-2}, the next 20 patients a dose of 1.8 g m^{-2} and the final 21 patients a dose of 1.6 g m^{-2}. The total dose of undiluted etoposide (Mross et al, 1994) was given on day 1 as a continuous intravenous infusion via a central vein over 10 h using a syringe driver. Patients were hospitalized for the first 48 h of the mobilization procedure. All patients received prophylactic antiemetic therapy, acetazolamide (250 mg orally every 6 h for four doses) and methylprednisolone (40 mg m^{-2} intravenously every 8 h for three doses) peri-infusion (Gianni et al, 1992). G-CSF (300 µg if body

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Table 1 Patient characteristics and results of mobilization

Patient	Age, years (sex)	Diagnosis	Disease status	Etoposide dose (g m^{-2})	$CD34^+$ cells collected ($\times 10^6$ kg^{-1})	Number of leukaphereses
1	54 (M)	AML	CR2	2.0	1.4	2
2	22 (F)	ChC	Prim ref	2.0	5.2	2
3	31 (M)	GCT	Rel 1	2.0	3.4	2
4	25 (M)	GCT	CR3(+)	2.0	5.9	2
5	17 (F)	GCT	Rel 1	2.0	5.8	2
6	28 (M)	GCT	Prim ref	2.0	4.1	1
7	60 (M)	GCT	Rel 1	2.0	3.7	1
8	45 (M)	GCT	CR3(+)	2.0	3.0	2
9	30 (M)	GCT	Rel 1	2.0	27.1	1
10	23 (M)	GCT	Rel 1	2.0	13.9	1
11	26 (M)	GCT	Prim ref	2.0	26.1	1
12	42 (M)	GCT	CR3(+)	2.0	3.6	3
13	27 (M)	LYM-HD	CR3(+)	2.0	3.4	2
14	35 (M)	LYM-HD	Rel 1	2.0	17.2	1
15	36 (F)	LYM-HD	Rel 1	2.0	11.5	1
16	53 (M)	LYM-NHL	CR3(+)	2.0	0.0	0
17	51 (M)	LYM-NHL	Rel 2	2.0	9.9	1
18	39 (M)	LYM-NHL	CR3(+)	2.0	5.8	2
19	44 (M)	LYM-NHL	CR3(+)	2.0	0.3	1
20	41 (F)	LYM-NHL	Rel 1	2.0	12.0	2
21	41 (M)	LYM-NHL	Rel 1	2.0	2.6	2
22	46 (M)	MM	Rel 2	2.0	2.9	4
23	27 (M)	ALL	CR1	1.8	3.5	2
24	52 (M)	GCT	Rel 2	1.8	11.2	1
25	32 (M)	GCT	CR3(+)	1.8	5.1	1
26	32 (M)	GCT	CR3(+)	1.8	60.1	1
27	26 (M)	GCT	CR2	1.8	27.6	1
28	28 (M)	GCT	CR3(+)	1.8	40.8	1
29	28 (M)	GCT	Rel 1	1.8	15.2	1
30	23 (M)	GCT	CR2	1.8	6.0	1
31	34 (M)	GCT	Rel 1	1.8	6.4	1
32	26 (F)	LYM-HD	Rel 1	1.8	27.9	1
33	29 (M)	LYM-HD	CR2	1.8	2.6	1
34	52 (M)	LYM-HD	CR2	1.8	8.4	1
35	49 (M)	LYM-HD	CR2	1.8	2.4	1
36	26 (M)	LYM-NHL	CR1	1.8	5.3	1
37	44 (M)	LYM-NHL	CR3(+)	1.8	4.1	1
38	55 (F)	LYM-NHL	Rel 1	1.8	2.0	2
39	70 (M)	LYM-NHL	CR2	1.8	16.0	1
40	31 (F)	LYM-NHL	CR1	1.8	2.2	1
41	43 (F)	LYM-NHL	Rel 1	1.8	2.0	2
42	47 (F)	LYM-NHL	CR3(+)	1.8	1.9	4
43	16 (F)	ALL	CR1	1.6	3.1	3
44	36 (M)	GCT	CR3 (+)	1.6	14.6	1
45	46 (M)	GCT	CR2	1.6	14.1	1
46	27 (M)	GCT	Rel 1	1.6	20.5	1
47	34 (M)	GCT	CR3(+)	1.6	18.1	1
48	24 (M)	GCT	CR1	1.6	4.9	1
49	36 (M)	GCT	Rel 1	1.6	2.3	2
50	19 (M)	LYM-HD	Rel 1	1.6	19.9	1
51	30 (F)	LYM-HD	CR2	1.6	2.5	2
52	42 (M)	LYM-HD	Rel 2	1.6	6.5	1
53	16 (F)	LYM-HD	CR1	1.6	24.2	1
54	65 (F)	LYM-HD	CR3(+)	1.6	2.4	1
55	48 (M)	LYM-NHL	CR2	1.6	14.3	1
56	44 (M)	LYM-NHL	Prim ref	1.6	21.0	1
57	44 (M)	LYM-NHL	Rel 1	1.6	25.5	1
58	32 (M)	LYM-NHL	CR1	1.6	0.0	0
59	42 (M)	LYM-NHL	CR1	1.6	26.6	1
60	32 (F)	LYM-NHL	Rel 1	1.6	0.2	2
61	67 (M)	MM	Prim ref	1.6	0.0	0
62	54 (F)	MM	Rel 1	1.6	3.7	2
63	57 (F)	MM	Rel 1	1.6	0.1	1

AML, acute myeloid leukaemia; ChC, choriocarcinoma; GCT, germ-cell tumour; LYM-HD, Hodgkin's disease; LYM-NHL, non Hodgkin's lymphoma; MM, myeloma; ALL, acute lymphoblastic leukaemia; CR1, first remission; CR2, second remission; Prim ref, primary refractory disease; Rel 1, first relapse; Rel 2, second relapse; CR3(+), third remission or more advanced disease.

weight < 70 kg, 480 μg if ≥ 70 kg) was started on day 3 and given daily subcutaneously until leukapheresis was completed. Patients were discharged from hospital on day 3, taking prophylactic ciprofloxacin (500 mg twice daily). Toxicity of the mobilization procedure was assessed by the development of significant (WHO grade 2–4) oropharyngeal mucositis, the requirement for blood or platelet transfusions, the development of sepsis necessitating parenteral antibiotic therapy and the rehospitalization incidence.

Leukapheresis was commenced when the preceding day's circulating $CD34^+$ cell concentration predicted that an adequate collection would be obtained the following day, as previously described (Elliott et al, 1996). Assays for circulating $CD34^+$ cell concentrations were initiated from the twelfth day following etoposide administration. All collections were harvested using a Cobe Spectra (Cobe Laboratories, Quedgeley, UK), with a target processing of 2.5 times the estimated patient blood volume. If an insufficient $CD34^+$ yield resulted from the first leukapheresis further collections were obtained on subsequent days.

$CD34^+$ concentrations in both blood samples and leukapheretic products were measured flow cytometrically by dual staining for CD45 and CD34. The $CD45^+$ cell population was gated and then analysed for the percentage of $CD34^+$ cells (Sutherland et al, 1994). The $CD34^+$ concentration was derived by reference to the white cell count of the sample.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. Thirty-one (49%) of the 63 patients had lymphoma [Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL)], 24 (38%) germ cell tumour (GCT) and the remaining eight patients (13%) had myeloma (n = 4), acute leukaemia (n = 3) or choriocarcinoma (n = 1). All patients with lymphoma had received first-line therapy with either BEMOP-CA (bleomycin, etoposide, methotrexate, vincristine, prednisolone, cyclophosphamide, doxorubicin) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and second-line therapy with MOPP (mustine, vincristine, procarbazine, prednisolone) if relapsed HD or DHAP (dexamethasone, cytosine arabinoside, cisplatinum) if relapsed NHL. All patients with GCT had received first-line therapy with POMB-ACE (cisplatinum, vincristine, methotrexate, bleomycin, actinomycin, etoposide, cyclophosphamide), and second-line therapy with an alternating cisplatinum/taxol–etoposide/taxol schedule. The patients with myeloma had received as a minimum melphalan and/or VAD therapy (vincristine, doxorubicin, dexamethasone). Forty-seven patients (75%) were male, and patient age ranged from 16 to 70 years (median 36). Fifty-five patients (87%) had disease beyond first remission and had received two or more chemotherapy regimens before the mobilization procedure. Seven patients (four with myeloma, two with lymphoma and one with acute leukaemia) had previously failed mobilization therapy with cyclophosphamide (2–4 g m^{-2}) and G-CSF, based on actual yields obtained and also on peak blood $CD34^+$ concentrations of less than 6×10^6 l^{-1} (Elliott et al, 1996).

Toxicity

Significant oropharyngeal mucositis requiring opiate analgesia developed in four (6%) patients following etoposide. This complication was sufficiently severe in three patients to necessitate hospitalization. In total, 23 patients (37%) were readmitted to hospital during the mobilization procedure. In 20 (32%) cases this was due to sepsis requiring parenteral antibiotic therapy. Haematological toxicity requiring support with blood or platelet transfusion developed in 28 (44%) patients. There were no procedure-related mortalities observed in this study.

The incidences of these toxicities and rehospitalization appeared to be lowest in the group of patients who received 1.6 g m^{-2} etoposide (Table 2). In particular, 4 of these 21 (19%) patients required readmission to hospital compared with 8 of 20 (40%) and 11 of 22 (50%) patients in the 1.8 g m^{-2} and 2.0 g m^{-2} groups respectively. However, only the comparison between rehospitalization incidence in the 1.6 g m^{-2} and 2.0 g m^{-2} groups reached statistical significance (P = 0.03, two-tailed chi-square test); all other comparisons were non-significant.

Leukaphereses and PBPC yields

The number of leukaphereses performed and the $CD34^+$ cells collected are shown in Table 1. The first day of leukapheresis in these 63 patients was at a median of 13 days following etoposide therapy (range 12–19 days), and was not different in the three groups of etoposide dosage (data not shown). Three patients (1 in the 2.0 g m^{-2} and two in the 1.6 g m^{-2} etoposide groups) failed to mobilize (as indicated by the peripheral blood $CD34^+$ concentration) and were not leukapheresed. A further seven patients (two each in the 2.0 g m^{-2} and 1.6 g m^{-2} groups, three in the 1.8 g m^{-2} group) failed to achieve total yields of 2.0×10^6 $CD34^+$ cells kg^{-1}. Mobilization procedures that produced yields of greater than this target number were achieved in 53 (84%) patients. The median number of $CD34^+$ cells collected in all 63 patients was 5.3×10^6 kg^{-1}, in an average of 1.5 leukaphereses (Table 3). Median yields ($\times 10^6$ $CD34^+$ cells kg^{-1}) in the three etoposide dosage groups were 4.7 (2.0 g m^{-2}), 5.7 (1.8 g m^{-2}) and

Table 2 Toxicity

Toxicity [no. of patients> (%)]	Etoposide dose (g m^{-2}) 2.0 (n = 22)	1.8 (n = 20)	1.6 (n = 21)	Total (n = 63)
Grade 2–4 (WHO) mucositis	3 (14%)	1 (5%)	0 (0%)	4 (6%)
Blood or platelet transfusion	11 (50%)	10 (50%)	7 (33%)	28 (44%)
Parenteral antibiotics	10 (45%)	6 (30%)	4 (19%)	20 (32%)
Hospitalization[a]	11 (50%)	8 (40%)	4 (19%)	23 (37%)

[a]1.6 g m^{-2} vs 2.0 g m^{-2}, P = 0.03. All other comparisons non-significant.

Table 3 PBPC yields

	Etoposide dose (g m^{-2})			
	2.0 (n = 22)	1.8 (n = 20)	1.6 (n = 21)	All patients (n = 63)
CD34$^+$ cells (median) × 10^6 kg^{-1} collected (range)	4.7 (0.0–27.1)	5.7 (1.9–60.1)	6.5 (0.0–26.6)	5.3 (0.0–60.1)
Number (median) of leukaphereses (range)	2 (0–4)[a]	1 (1–4)	1 (0–4)[c]	1 (0–4)

[a]Including one patient who was not leukapheresed. [c]Including two patients who were not leukapheresed.

Table 4 Etoposide/G-CSF mobilization in patients previously failing cyclophosphamide/G-CSF

Diagnosis[a]	Cyclophosphamide/G-CSF (× 10^6 CD34$^+$ cells/kg^{-1})	Etoposide/G-CSF (× 10^6 CD34$^+$ cells kg^{-1})	Etoposide dose (g m^{-2})	Number of leukaphereses
LYM-NHL	0.3	5.8	2.0	2
MM	0.1	2.9	2.0	4
LYM-NHL	1.4	2.6	2.0	2
ALL	0.0	3.5	1.8	2
MM	0.1	0.0	1.6	0
MM	0.0	0.1	1.6	1
MM	1.1	3.7	1.6	2

[a]For abbreviations see Table 1.

6.5 (1.6 g m^{-2}), and the average number of leukaphereses required were 1.7 (2.0 g m^{-2}), 1.3 (1.8 g m^{-2}) and 1.5 (1.6 g m^{-2}).

Five of the seven patients who had previously failed cyclophosphamide with G-CSF mobilization achieved the target yield following etoposide/G-CSF (Table 4). The two patients in this group who did not mobilize successfully following etoposide/G-CSF had an underlying diagnosis of myeloma and both received 1.6 g m^{-2} etoposide.

DISCUSSION

Several studies have suggested that the use of PBPCs to support high-dose therapy has advantages compared with autologous bone marrow (Elias et al, 1992; To et al, 1992; Chao et al, 1993; Schmitz et al, 1996). These benefits may include shorter median duration of neutropenia and thrombocytopenia, fewer febrile episodes with reduced antibiotic requirement, shorter hospitalization and lower procedural costs.

The procurement of PBPCs for this purpose has most often been accomplished using a combination of cyclophosphamide with G-CSF, but not all patients mobilize successfully. In particular, leukapheretic yields may be suboptimal in patients who have received several preceding regimens of chemotherapy (Haas et al, 1994; Dreger et al, 1995). Strategies employed to improve the results of mobilization have included increasing the dose of cyclophosphamide administered or using combinations of cytotoxic drugs (Lie et al, 1996; Demirer et al, 1997; McQuaker et al, 1997). The majority of patients (87%) in the present study had received at least two prior schedules of chemotherapy, and the mobilization therapy was successful in 53 of 63 patients (84%). In addition, five of seven patients who had previously failed to achieve a target collection of 2.0 × 10^6 CD34$^+$ cells kg^{-1} with cyclophosphamide/G-CSF mobilization yielded an adequate harvest following etoposide/G-CSF. These data confirm that high-dose etoposide with G-CSF is an effective mobilization regimen in the majority of patients, despite substantial previous therapy or an initial failure to mobilize PBPCs with cyclophosphamide/G-CSF.

The percentage of patients who mobilized PBPCs adequately and the median number of CD34$^+$ cells kg^{-1} obtained were not different between the three groups of etoposide dosage. In contrast, the toxicity experienced was lowest in those who received 1.6 g m^{-2}, with only 4 of these 21 patients needing readmission to hospital. In general, however, the toxic complications and rehospitalization frequency appear to have been greater than in the two previous reports of high-dose etoposide with G-CSF/GM-CSF. In the first study none of the patients evaluated had been heavily pretreated (Gianni et al, 1992), and in the second approximately 50% of the patients studied had breast cancer (Copelan et al, 1997). In a separate study at this centre PBPCs have been collected from more than 50 patients with high-risk primary breast cancer following mobilization with combination chemotherapy and G-CSF, and in none of these has readmission to hospital been required, suggesting that both previous therapy and underlying diagnosis may impact on procedural complications.

The equivalent cell yields in the three groups of etoposide dosage may suggest that a further reduction might eliminate toxicity without impairing PBPC mobilization. However, although disease response was not specifically evaluated in this study, there is evidence that high-dose etoposide is an effective agent in a variety of tumours (Postmus et al, 1984; Marangolo et al, 1989; Herzig, 1991; Bezwoda et al, 1992). It may therefore be advantageous to employ an etoposide dose sufficient to exploit this potential anti-tumour activity. These data indicate that 1.6 g m^{-2} may represent a reasonable compromise for this purpose, enabling the successful mobilization of adequate PBPCs for the support of subsequent high-dose therapy but with acceptable toxicity.

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