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High-dose Chemotherapy with Etoposide, Cyclophosphamide and Escalating Dose of Carboplatin Followed by Autologous Bone Marrow Transplantation in Cancer Patients. A Pilot Study

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25 patients with poor-prognosis malignancies were treated with a combination of fixed-dose etoposide (1750 mg/m²), cyclophosphamide (6400 mg/m²) and escalating doses of carboplatin (from 800 to 1600 mg/m²) followed by autologous bone marrow transplantation (ABMT). The median duration of granulocytopenia (< 500/mm³) and thrombocytopenia (< 20000/mm³) was 23 days and 20.5 days, respectively. The main non-haematological toxicity was gastro-intestinal, with moderate to severe diarrhoea in 15 patients. No significant renal toxicity was observed. 2 patients died early due to toxicity. The overall response rate was 58% including 42% having complete responses. 4 of the 25 patients are alive with no evidence of disease at 22, 27, 40 and 43 months after ABMT. The encouraging antitumoral activity of this regimen makes it a good candidate for intensified chemotherapy in patients with various malignancies. Toxicity is acceptable and may be reduced in the near future with the widespread use of haematopoietic growth factors.
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INTRODUCTION

IT IS now well established that high-dose chemotherapy (HDC) gives a higher rate of antitumoral responses than conventional chemotherapy in numerous malignancies [1].

The response rate to HDC among patients with breast cancer [2], ovarian carcinoma [3] and germ-cell tumours [4] is high, even after heavy pretreatment. Autologous bone marrow transplantation (ABMT) is increasingly used to reduce the duration of iatrogenic myelosuppression. Although the response is generally of short duration in this population of poor-prognosis patients, valuable information has been obtained on efficacy and toxicity with a view to prospective trials involving selected groups.

Significant experience has been gained at the Institut Gustave Roussy with HDC combining cisplatinum, etoposide and cyclophosphamide (PEC protocol) followed by autologous bone marrow transplantation [5], either as salvage therapy for responders and refractory patients, or as first-line treatment for patients with poor-prognosis non-seminomatous germ cell tumours [6].

Carboplatin, a platinum derivative, has shown similar efficacy to cisplatinum in ovarian cancer, both at normal doses [7] and at high doses [8]. The renal toxicity of cisplatinum is the major limiting factor, restricting the maximum dose per cycle to 200 mg/m². Cumulative dose-limiting toxicity is neurological [9, 10]. Carboplatin has less renal, gastrointestinal, neurological and cochlear toxicity than cisplatin; its dose-limiting toxicity is haematological, but this can be circumvented by autologous bone marrow transplantation [11].

In this study, we attempted to increase the antitumoral effect of the PEC protocol by replacing cisplatinum with carboplatin. The protocol was otherwise unchanged: the same doses of etoposide and cyclophosphamide were used. The dosage of carboplatin was increased stepwise in a 96-h continuous perfusion, as reported by Dana Farber investigators [12]. This schedule is different from that developed at the Memorial Hospital, where fixed doses of etoposide and carboplatin were used and the cyclophosphamide dosage was increased [13].

PATIENTS AND METHODS

Between November 1988 and March 1991, 25 patients were included in this prospective trial. There were 16 men and 9 women, with a median age of 30 years (range 18–54). Performance status, according to the WHO criteria [14], was < 2 in every case.

The patients gave their informed consent according to institutional guidelines. There were 8 ovarian carcinomas, 13 non-seminomatous germ cell tumours (NSGCT) (10 testicular, and 3 extragonadal), 3 rhabdomyosarcomas and 1 case of Hodgkin's disease. All of these patients were considered incurable by standard salvage therapy. 17 patients had never achieved complete remission and had progressive disease at the time of inclusion; these patients were considered refractory. 5 patients

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had previously relapsed and had responded to conventional salvage therapy [3 complete remission (CR) and 2 partial remissions (PR)]. 3 patients (one metastatic rhabdomyosarcoma, 1 non-seminomatous extragonadal tumour, 1 ovarian carcinoma) with initial bulky disease were considered to be at a high risk of relapse and received HDC in first CR/PR. The characteristics of the patients are summarised in Table 1.

The patients were initially evaluated in terms of their past history, physical examination, electrocardiogram (ECG), pulmonary function tests, and computer tomography (CT) scans (when carried out to evaluate the response). They were required to have no significant hepatic, renal or cardiopulmonary impairment. Histological samples were reviewed by pathologists at our institute.

All 25 patients had previously received platinum derivatives (cisplatinum, $n = 17$; carboplatin, $n = 2$; carboplatin + cisplatinum, $n = 6$). Cisplatinum doses ranged from 200 to 1830 mg/m^2 (median 800 mg). Carboplatin doses ranged from 900 to 3900 mg/m^2 (median 1600 mg).

In the HDC protocol, etoposide was administered at a fixed dose (1750 mg/m^2), as was cyclophosphamide (6400 mg/m^2); carboplatin was given in escalating doses. The modes of administration were as follows:

—Etoposide was given at the dose of 350 mg/m^2/day in 500 ml of normal saline solution as a 1-h infusion on 5 consecutive days (d-7–d-3).

—Cyclophosphamide was given at the dose of 1600 mg/m^2/day in 250 ml of 5% dextrose as a 1-h infusion on 4 consecutive days (d-6–d-3), associated with mesna and hyperdiuresis (3 l/m^2/day) to avoid haemorrhagic cystitis.

—The carboplatin dosage was increased in four successive steps: 800 mg/m^2 (4 patients), 1200 mg/m^2 (10 patients), 1400 mg/m^2 (4 patients), and 1600 mg/m^2 (7 patients). Carboplatin was administered as a 20-h continuous infusion on 5 consecutive days (d-7–d-4) in 1000 ml of 5% dextrose.

—Bone marrow was harvested by means of regular procedures and cryopreserved (10% dimethylsulphoxide, −196°C); it was thawed and reinfused on day 0. A median of 0.5×10^8 mononuclear cells/kg (range 0.3–1.5) were reinfused. The median number of colony forming units (CFU-GM) reinfused was 7.9×10^4/kg.

Usual infection-control measures for autologous bone marrow recipients were applied. They included isolation in laminar-airflow rooms, total parenteral nutrition, broad-spectrum antibiotics, and high microbiological quality food. Selective gut decontamination was used only when indicated. All blood products were irradiated (25 Gy).

Haematopoietic growth factors were not used, except in 1 patient HEB [compassionate administration of recombinant human granulocyte macrophage colony stimulating factor (Rhu GM-CSF), Hoecsht from day 6 to day 13 after ABMT].

Toxicity was evaluated according to the WHO criteria [14]. Responses were assessed as follows:

—Complete response: disappearance of all clinical evidence of disease and normalisation of serum tumour markers, when appropriate, for at least 4 weeks.

Table 1. Patients' characteristics and results of carbopec protocol

Patient number	Carboplatin dose (mg/m^2)	Diagnosis	Tumoral status before carbopec	Response	Follow-up
1	800	Ovary	Primary refractory	PD	DIP (8 m)
2	800	GCT	Secondary refractory	PD	DIP (9 m)
3	800	Ovary	Primary refractory	CR	Relapse (8 m) DIP (12 m)
4	800	Hodgkin's disease	PR	NE	Toxic death d + 22
5	1200	GCT (abdominal)	Primary refractory	Stable	DIP (8 m)
6	1200	GCT (mediastinum)	Primary refractory	NE	Toxic death d + 22
7	1200	Ovary	Primary refractory	CR	Relapse (24 m) DIP (38 m)
8	1200	GCT	Primary refractory	PR	DIP (11 m)
9	1200	GCT	2nd CR	NE	Relapse (9 m) DIP (20 m)
10	1200	GCT	Secondary refractory	Stable	DIP (7 m)
11	1200	GCT	Primary refractory	PR	DIP (7 m)
12	1200	GCT	2nd CR	NE	CCR (43 m +)
13	1200	GCT (mediastinum)	Primary refractory	Stable	DIP (6 m)
14	1200	Ovary	Primary refractory	Stable	DIP (18 m)
15	1400	Rhabdo	1st PR	CR	Relapse (4 m) DIP (5 m)
16	1400	GCT	Primary refractory	CR	CCR (40 m +)
17	1400	Rhabdo	PR	CR	Relapse (6 m) DIP (12 m)
18	1400	Ovary	Primary refractory	CR	Relapse (5 m) DIP (12 m)
19	1600	Ovary	Primary refractory	PD	DIP (21 m)
20	1600	Ovary	1st CR	NE	Relapse (9 m) DIP (12 m)
21	1600	Rhabdo	Primary refractory	PD	DIP (7 m)
22	1600	GCT	Primary refractory	PR	Relapse (5 m) alive in CR (27 m +) after surgery
23	1600	Ovary	2nd CR	NE	Relapse (12 m) DIP (26 m)
24	1600	GCT	1st PR	CR	Relapse (10 m) DIP (12 m)
25	1600	GCT	Primary refractory	CR	CCR (22 m +)

PD = progressive disease; DIP = died in progression; PR = partial remission; NE = non-evaluable; CR = complete remission. CCR = continuous complete remission. GCT = germ cell tumour; rhabdo = rhabdomyosarcoma; m = months.

—Partial response: more than 50% decrease in the product of the perpendicular diameters of all measurable lesions, for at least 4 weeks.
—No response, stable disease: less than 50% reduction for at least 4 weeks or less than 25% reduction for at least 8 weeks.
—Progression: appearance of new lesions or more than 25% increase in volume of known lesions. Time to progression was calculated from the start of high-dose chemotherapy to the documentation of progression.

In the case of non-seminomatous germ cell tumours, serum tumour markers (human chorionic gonadotropin and alphafetoprotein) were also taken into account.

RESULTS

Toxicity

All 25 patients were fully evaluable for toxicity. 2 patients died early, the first at day 22 (of adult respiratory distress syndrome due to undocumented septic shock during aplasia), and the second at day 22 (of intra-alveolar bleeding).

Haematological toxicity at each dose level is shown in Table 2. The median duration of granulocytopenia [< 500 ANC (absolute neutrophil count)/mm^3] was 23 days (range 14–52) for the 25 patients. Thrombocytopenia (< 20000 platelets/mm^3) lasted from 7 days to 57 days (median 20.5 days).

All the patients were febrile during the period of granulocytopenia. 8 patients had documented septicaemia (2 *Streptococcus pneumoniae*, 2 group D Streptococci, 2 *Escherichia coli*, 1 *Geotrichum* sp., and 1 *Candida pseudotropicalis*).

Non-haematological toxicity at each dose level is shown in Table 3. Gastrointestinal side effects were most frequent. Moderate to severe nausea and vomiting occurred in 22 of the 25 patients. Mucositis requiring morphine analgesia occurred in almost half the patients, but did not seem to be related to the dose of carboplatin. Moderate to severe diarrhoea occurred in 15 patients, and was dose-related: 6 of the 7 patients receiving 1600 mg/m^2 of carboplatin developed diarrhoea. Only 1 patient developed transient renal dysfunction (peak creatinine level 142 μmol/l; normal range, 53–115 μmol/l). Severe hepatic toxicity was observed in 5 patients, but was reversible in every case. 1 patient receiving 1200 mg/m^2 of carboplatin presented an isolated increase in the bilirubin level (> WHO grade 3). Increased transaminase levels (> WHO grade 3) were seen in 3 patients, all in the second and third dose-increment groups. 1 patient, in the second dose-increment group, has multinodular hepatic metastases of an embryonal rhabdomyosarcoma at the time of high-dose chemotherapy. She developed hepatic veno-occlusive disease documented clinically and histologically. It began on day 9 and was resolved favourably within 2 weeks. 2 patients developed rapidly reversible inappropriate secretion of anti-diuretic hormone.

Table 2. Haematological toxicity

	Carboplatin dose (mg/m^2)			
	800 (4 pts)	1200 (10 pts)	1400 (4 pts)	1600 (7 pts*)
Number of days with				
ANC < 500/mm^3	15,5	23	25	24
Platelets < 20000/mm^3	15	17	37	17,5
Platelets < 50000/mm^3	16	32	42	21
Infectious complication				
Number of pts:				
FUO	3	8	3	3
Sepsis	1	2	1	4
Septic shock	0	1	0	0

pts = patients; FUO = fever of unknown origin. * 1 patient received GM-CSF post-ABMT.

Table 3. Non-haematological toxicity (WHO ≥ 2)

	Carboplatin dose (mg/m^2)			
	800 (4 pts)	1200 (10 pts)	1400 (4 pts)	1600 (7 pts)
Nausea/vomiting	4	10	2	6
Mucositis	1	6	2	3
Diarrhoea	1	6	2	6
Renal	0	0	0	0
Hepatic	3	8	1	1
HVOD	0	0	1	0
Cutaneous	0	1	2	1
Neurological				
Motor	2	2	0	0
Sensitive	1	1	0	0
Encephalopathy	1	2	0	0

pts = patients; HVOD = hepatic veno occlusive disease.

4 patients developed reversible severe neurological disturbances, consisting of cognitive dysfunction with no signs of central nervous system involvement, systemic infection or a metabolic disorder. 2 patients (one in the first-step group, the other in the second-step group) developed generalised seizures and cerebellar dysfunction. 1 patient in the second-step group developed only cerebellar dysfunction. The fourth patient, in the third-step group, developed only cognitive abnormalities. All 4 patients had a normal EEG, cerebral CT scan and cerebrospinal fluid.

Peripheral neuropathy was already present before high-dose chemotherapy and was thus difficult to evaluate. Nevertheless, 4 patients had temporarily impaired peripheral motricity and sensitivity.

4 patients developed a maculopapular rash which lasted approximately 1 week. 1 patient in the third-step group developed reversible haemorrhagic cystitis during treatment.

Anti-tumoral effect (Table 1)

6 patients were not evaluable for response: 2 patients died of toxicity and 4 patients were in CR at the time of HDC.

19 patients, of whom there were 16 refractory and 3 responders, were evaluable for response. The overall response rate (CR + PR) was 58% (11 patients), and the complete remission rate was 42% (8 patients).

Of the 4 patients in CR before HDC, 1 is alive with no evidence of disease (NED) after 43 months, while 3 died of disease progression at 12, 20 and 26 months.

Among the 16 refractory evaluable patients, 5 achieved CR (3 ovarian cancer, 2 NSGCT), 3 achieved PR (3 NSGCT), and 8 did not respond. Of the 5 refractory patients achieving CR, 2 are alive with NED at 22 months and 40 months. The patient alive at 9 months received a second course of HDC (PEC protocol) [5] as consolidation. The other 3 patients died of progressive disease at 12 months, 12 months and 38 months. Of the 3 refractory patients who achieved PR, 1 is alive with NED at 27 months. This patient entered CR after surgical removal of a single lung metastasis (histologically positive) and received a second course

of PEC. The other 2 patients died of progressive disease at 7 and 11 months. The 8 refractory patients who did not respond died of progressive disease between 6 and 21 months after ABMT.

The 3 patients who received high-dose chemotherapy in PR and were considered as responders, died of progressive disease 5, 12 and 12 months after ABMT. However, 2 patients reached CR after HDC.

The median duration of CR in the 8 patients who attained CR was 14.5 months (range 6–29).

4 of the 25 patients are currently NED 22, 27, 40 and 43 months after ABMT.

Of the 13 NSGCT patients, 10 were refractory and 3 were responders before HDC. 3 of the 10 refractory patients have NED at 22, 27 and 40 months, together with 1 of the 3 responders at 43 months.

None of the 8 patients treated for ovarian carcinoma is alive.

DISCUSSION

High-dose chemotherapy combining cisplatin, etoposide and cyclophosphamide (PEC protocol) has been extensively used in our centre for the treatment of poor-prognosis non-seminomatous germ cell tumours [4].

As of April 1984, three successive generations of trials had been initiated at the Institut Gustave Roussy to investigate the place of this combination. Seventy-one cycles were performed for either relapsing or refractory germ-cell tumours as consolidation of salvage and/or first-time chemotherapy in 65 poor-risk patients.

Toxicity was acceptable: 5 toxic deaths occurred during the 71 procedures.

Haematological toxicity was acceptable, with a median duration of aplasia of 17 days (5–18). 16 patients had documented septicaemia.

The main extra-haematological toxicity was mucositis (in all procedures), and diarrhoea (50% of procedures). Renal dysfunction occurred in only six treatment cycles.

The principal objective of this prospective study was to determine whether cisplatin could be replaced by carboplatin in the PEC protocol.

Etoposide is a good candidate for high-dose chemotherapy. The optimal dose is 2.4 g/m^2 when used alone [15]. Dose-limiting toxicity is oro-pharyngal (mucositis), possibly related to metabolite excretion in the saliva [16].

Buckner *et al.* [17] reported 8 responses in 9 previously untreated patients with germ cell tumours, using cyclophosphamide at a dose of 60–120 mg/kg.

Carboplatin is a covalent platinum compound with toxic effects that differ from those of cisplatin : renal, otological, and neurological toxicity is mild but haematological toxicity is severe. This drug is thus a good candidate for high-dose chemotherapy. As a single agent, the standard maximum tolerated dose (MTD) is 400 to 500 mg/m^2 [18]. Ozols *et al.* reported that 800 mg/m^2 could be administered to ovarian cancer patients every 5 weeks with acceptable haematological toxicity [8].

With the aim of reducing the non-haemotological toxicity due to carboplatin we used a continuous infusion regimen based on the experience of the Dana Farber team. Shea *et al.* [12] published the results of a phase I trial with pharmacokinetic studies in which carboplatin was perfused at between 375 and 2400 mg/m^2 on 4 consecutive days. ABMT was required when the carboplatin dose exceeded 1200 mg/m^2. The maximal tolerated dose was 2000 mg/m^2 and there was a correlation between the dose administered and the area under the curve (AUC).

Postmus *et al.* [19] published the results of a phase I trial in which the cyclophosphamide dose was fixed at 7 g/m^2, and etoposide was given at increasing doses from 0.9 to 2.5 g/m^2. Bone marrow was infused 72 h after the last infusion of etoposide. Dose-limiting toxicity was mucositis, which occurred with more than 1.5 g/m^2 etoposide. The median duration of aplasia was 14 days.

Nichols *et al.* [20], using a fixed dose of etoposide (1.2 g/m^2) and increasing doses of carboplatin (0.9 g to 2 g/m^2) followed by ABMT, gave 53 cycles to 33 heavily pretreated patients with GCT. Myelosuppression was severe at all dose levels of carboplatin, with a median duration of granulocytopenia (< 500 ANC/mm^3) and thrombocytopenia (< 50 000 platelets/mm^3) of 24 and 26 days, respectively.

The former PEC protocol included a cisplatin dose of 200 mg/m^2. Some authors have estimated the equivalence ratio between cisplatin and carboplatin as 1:4 [21]. Thus, in this pilot study, we chose a carboplatin dose of 800 mg/m^2 for the first step. This is also the highest conventional dose so far studied. We then escalated the carboplatin dose to 1600 mg/m^2 in four steps of 200 mg/m^2. The need for ABMT following the PEC protocol has been questioned [22] but with a carboplatin dose of more than 1200/m^2 it appears to be beneficial [12].

The three drug regimen containing etoposide, cyclophosphamide and carboplatin has been extensively studied [13, 23, 24].

The reported toxic death rate varied, but encouraging results have been obtained. In our trial, the incidence of treatment-related deaths was 8% (2 patients), close to that reported by Motzer *et al.* [13]. Rates of treatment-related deaths as high as 20% have been reported in similar patients undergoing ABMT [13, 20]. In our series, myelosuppression was severe at all carboplatin dose levels, with a median duration of aplasia (< 500 ANC) and granulocytopenia (< 50 000 platelets) of 24 and 26 days, respectively. These results confirmed the recent study published by Motzer *et al.* [13] in which 29 patients with GCT received 44 cycles of high-dose carboplatin 1500 mg/m^2, etoposide 1200 mg/m^2 +/− cyclophosphamide 60–120 mg/kg, followed by ABMT. The median duration of aplasia (< 500 ANC) and thrombocytopenia (< 20 000 platelets) was 22 and 23 days respectively, in the group receiving cyclophosphamide and 16 and 15 days, respectively, in the group not receiving cyclophosphamide. Similar results have been reported by Rosti *et al.* [25] with an acceptable toxicity. Escalating doses of carboplatin (1350 to 1800 mg/m^2) and etoposide (1800 to 2400 mg/m^2) were used to treat 28 patients with refractory NSGCT. The mean duration of granulocytopenia and thrombocytopenia was 16 days.

In our series, the incidence of septicaemia was 32% (8 patients), a figure similar to that in trials of the same drugs in combination [13, 24].

We used cyclophosphamide instead of ifosfamide because of the major renal toxicity encountered with this drug in several three-drug regimens. Lotz *et al.* [26] reported that major renal impairment developed in 22 (50%) out of 44 patients. 2 of 3 patients developed grade 3–4 toxicity and died with renal failure. Ifosfamide was infused at a dose exceeding 2000 mg/m^2 in all 3 cases. A decrease in the ifosfamide dose markedly reduced nephrotoxicity. Siegert *et al.* [27] reported severe renal impairment in 3 out of 38 patients. 2 required haemodialysis and 1 died of acute renal failure. All 3 patients had received > 1500 mg/m^2 carboplatin and 10 g/m^2 of ifosfamide. Of the 6 patients with GCT initially treated by the Vancouver Group [24], 4 developed

severe renal impairment (2 required haemodialysis, 1 died of renal failure); ifosfamide 6 g/m^2 was combined with carboplatin 1.2 g/m^2 and etoposide 3 g/m^2. In this ongoing trial, ifosfamide was replaced by cyclophosphamide 7.2 g/m^2, and only 1 out of 13 patients subsequently developed severe renal toxicity. Despite the heavy pre-treatment of the majority of our patients, generally with regimens including cisplatin, we observed only 1 case of transient renal impairment (4%). This frequency is lower than that reported with protocols combining ifosfamide and carboplatin [13, 20, 23].

The most common non-haematological toxicity was gastrointestinal. Sixty per cent of the patients had moderate to severe diarrhoea. This side-effect appeared to be correlated with the dose of carboplatin, as it concerned 6 of the 7 patients at the highest dose level. Similar effects have been reported with high-dose carboplatin in the literature. Linkesch *et al.* [23] reported the results of a phase II study of 16 patients with refractory NSGCT, who received carboplatin 2000 mg/m^2, etoposide 1500 mg/m^2 and cyclophosphamide 120 mg/kg with ABMT rescue. Twenty-five per cent of the patients developed grade 3 or 4 diarrhoea.

We were unable to certify that the cases of cognitive dysfunction observed in 4 patients at the first two dose levels of carboplatin were directly related to the high-dose chemotherapy. However, we felt it warranted the inclusion of more patients than initially planned in the second dose level. No severe neurological toxicity occurred at the third and fourth dose levels.

4 patients (16%) developed moderate but transient hepatic toxicity. The only case of hepatic veno-occlusive disease was not unexpected since the patient had marked metastatic liver involvement. With a similar drug regimen, Motzer *et al.* [13] observed major reversible liver dysfunction in 3 patients (23%) out of 13, and reduced the dosage in subsequent cycles.

This three-drug combination is active: 3 of 10 cisplatin refractory NSGCT patients achieved a response (2 CR and 1 PR). These patients are NED 22, 27, 40 months after ABMT. 2 received a further PEC protocol as consolidation. Similar encouraging results have recently been reported in a comparable cohort of patients treated with the same drugs [13]. 7 of 13 patients reached CR, and 3 were still NED at 8, 20 and 24 months. Linkesh *et al.* [23] reported 3 long-term survivors in CR among 15 refractory patients.

In the 6 patients with ovarian carcinomas refractory to cisplatin, we observed three CR but of short duration. These results are comparable to those reported in the literature [8, 28, 29].

In a pilot study of breast cancer patients, investigators at the MD Anderson Hospital opened the way to a combination of cisplatinum (120–180 mg/m^2), etoposide (750–1 200 mg/m^2) and cyclophosphamide (4.5–5.25 g/m^2) [30], followed by ABMT. This protocol had good efficacy and low toxicity. Because of the MTD of carboplatin 2000 mg/m^2 used alone [12], the choice of the 1600 mg/m^2 dose in combination chemotherapy with etoposide and cyclophosphamide seemed more appropriate. The equivalence ratio between cisplatin and carboplatin has been reported as 1:4 in numerous studies [21]. Thus, 1600 mg/m^2 carboplatin may be equivalent to 400 mg/m^2 of cisplatin, i.e. twice the dose used in our former IGR PEC protocol [4].

Furthermore, the good antitumoral activity of our regimen makes it a good candidate for intensified chemotherapy in various solid tumours, e.g. germ cell tumours, ovarian carcinoma, and breast cancer. The toxicity is acceptable and may be reduced in the near future with the widespread use of haematopoietic growth factors.

1. Spitzer G, Velasquez W, Dunphy FR, Spencer V. Autologous bone marrow transplantation in solid tumors. *Curr Opin Oncol* 1992, **4**, 272–278.
2. Antman K, Corringham R, de Vries E, *et al.* Dose intensive therapy in breast cancer. *Bone Marrow Transplant* 1992, **10** (suppl 1), 67–73.
3. Viens P, Maraninchi D, Legros M, *et al.* High-dose melphalan and autologous marrow rescue in advanced epithelial ovarian carcinomas: a retrospective analysis of 35 patients treated in France. *Bone Marrow Transplant* 1990, **5**, 227–233.
4. Pico JL, Droz JP, Zambon E, *et al.* High-dose chemotherapy with haemotologic rescue for high risk non seminomatous germ cell tumors. In Banzet P, Holland JF, Khayat D, Weil M, ed. *Proceedings of the 3rd International Congress on Neoadjuvant Chemotherapy*. Springer, France, Paris, 1991, pp 311–314.
5. Droz JP, Pico JL, Ghosn M, Gouyette A, Baume D, Piot G. Long-term survivors after salvage high-dose chemotherapy with bone marrow rescue in refractory germ cell cancer. *Eur J Cancer* 1991, **27**, 831–835.
6. Droz JP, Pico JL, Biron P, Kerbrat P, Curé H, Heron JF. No evidence of a benefit of early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor-risk non seminomatous germ cell tumors: preliminary results of a randomized trial. *Proc Am Soc Clin Oncol* 1992, **11**, 197 (Abstr.).
7. Wiltshaw E. Ovarian trials at the Royal Marsden. *Cancer Treatment Review* 1985, **12** (suppl 1), 67–71.
8. Ozols RF, Ostchega Y, Curt G, Young RC. High-dose carboplatin in refractory ovarian cancer patients. *J Clin Oncol* 1987, **5**, 197–201.
9. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. *Ann Intern Med* 1981, **95**, 628–632.
10. Young RC, Myers CE, Ostchega Y, Zabell A, Ozols RF. CPR (cyclophosphamide, high-dose cisplatin and radiation): an aggressive short term induction regimen for advanced ovarian adenocarcinoma. *Proc Am Soc Clin Oncol* 1985, **4**, 119 (Abstr.).
11. Van Glabbeke M, Renard J, Pinedo HM. Iproplatin and carboplatin induced toxicities: overview of phase II clinical trials conducted by the EORTC Early Clinical Trials Cooperative Group (ECTG). *Eur J Cancer Clin Oncol* 1988, **24**, 255–262.
12. Shea TC, Flaherty M, Elias A, *et al.* A phase I clinical and pharmacokinetic study of carboplatin and autologous bone marrow support. *J Clin Oncol* 1989, **7**, 651–661.
13. Motzer RJ, Gulati SC, Crown JP, *et al.* High-dose chemotherapy and autologous bone marrow rescue for patients with refractory germ cell tumors. *Cancer* 1992, **69**, 550–556.
14. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer* 1958, **53**, 457–481.
15. Wolff SN, Johnson DH, Hainsworth JD, Greco A. High-dose VP16-213 monotherapy for refractory germinal malignancies: a phase II study. *J Clin Oncol* 1984, **2**, 271–274.
16. Gouyette A, Dencel A, Pico JL, *et al.* Clinical pharmacology of high-dose etoposide associated with cisplatin. Pharmacokinetic and metabolic studies. *Eur J Cancer Clin Oncol* 1987, **23**, 1627–1632.
17. Buckner CD, Rudolph RH, Fefer A, *et al.* High-dose cyclophosphamide therapy for malignant disease. Toxicity, tumor response and the effects of stored autologous marrow. *Cancer* 1972, **29**, 357–365.
18. Koeller JM, Trump DL, Tutsch KD, Earhart RH, Davis TE, Tormey DC. Phase I clinical trial and pharmacokinetics of carboplatin by single monthly 30 minute infusion. *Cancer* 1986, **57**, 222–225.
19. Postmus PE, de Vries EGE, de Vries-Hospers HG, *et al.* Cyclophosphamide and VP16-213 with autologous bone marrow transplantation. A dose escalation study. *Eur J Cancer Clin Oncol* 1984, **20**, 777–782.
20. Nichols C, Andersen J, Lazarus H, *et al.* High-dose carboplatin and etoposide with autologous bone marrow transplantation in refractory germ cell cancer : an eastern cooperative oncology group protocol. *J Clin Oncol* 1992, **10**, 558–563.
21. Canetta R, Rozencweig, Carter SK. Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985, **12**, 125–136.
22. Neidhart JA, Kohler W, Sitdley C, *et al.* Phase I study of repeated cycles of high-dose cyclophosphamide, etoposide and cisplatin administered without bone marrow transplantation. *J Clin Oncol* 1990, **8**, 1728–1738.
23. Linkesch W, Kuhrer I, Wagner A. Rhu-GM-CSF after ultra high-dose carboplatin, VP16, cyclophosphamide with ABMT in refractory germ cell cancer. *Proc Am Soc Clin Oncol* 1990, **9**, 141 (Abstr.).

24. Coppin CML, Barnett MJ, Murray N, *et al.* High-dose chemotherapy with autologous marrow rescue as consolidation for extreme risk non seminoma. *Proc Am Soc Clin Oncol* 1990, **9**, 139 (Abstr.).
25. Rosti G, Albertazzi L, Salvioni R, *et al.* High-dose chemotherapy supported with autologous bone marrow transplantation in germ cell tumors. A phase II study. *Ann Oncol* 1992, **10**, 809–812.
26. Lotz JP, Machover D, Malassagne B, *et al.* Phase I-II study of two consecutive courses of high-dose epipodophyllotoxin, ifosfamide and carboplatin with autologous bone marrow transplantation for treatment of adult patient with solid tumors. *J Clin Oncol* 1991, **9**, 1860–1870.
27. Siegert W, Beyer J, Weisbach V, *et al.* High-dose carboplatin, etoposide and ifosfamide with autologous sterm cell rescue for relapsed and refractory non-seminomatous germ cell tumors. *Proc Am Soc Clin Oncol* 1991, **10**, 163 (Abst.).
28. Mulder POM, Willemse PHB, Aalders JG, *et al.* High-dose chemotherapy with autologous bone marrow transplantation in patients with refractory ovarian cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 645–649.
29. Wallerstein R, Huan S, Spitzer G, Deisseroth AB. Autologous bone marrow transplantation for solid tumors. *Cancer Bull* 1990, **42**, 162–168.
30. Dunphy FR, Spitzer G, Buzdar AU, *et al.* Treatment of estrogen receptor-negative or hormonally refractory breast cancer with double high-dose chemotherapy intensification and bone marrow support. *J Clin Oncol* 1990, **8**, 1207–1216.

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Granulocyte Colony-stimulating Factor (G-CSF) With or Without a Quinolone in the Prevention of Infection in Cancer Patients

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59 patients who had earlier developed an infection following antineoplastic chemotherapy were randomised to receive either granulocyte colony-stimulating factor (G-CSF) alone or G-CSF + quinolone as prophylaxis during subsequent identical chemotherapy courses. 30 patients received 48 courses of G+CSF, while 29 patients received 44 courses of G-CSF + ofloxacin or ciprofloxacin. The overall infection rate was 23%. Patients with WHO grade IV leukopenia at the onset of prophylactic treatment developed infection in 61% of cases when on G-CSF, but only in 22% when on G-CSF+quinolone ($P = 0.002$). Patients with initial leukopenia of grade WHO III–I had only a 11% infection rate showing no significant difference between the treatment groups. The median duration of leukopenia $< 1 \times 10^9$/l was 4 days for patients receiving G-CSF alone and 3.5 days for those receiving additional quinolone. Patients developing infection had grade IV leukopenia for a median of 5 days. Both prophylactic treatments were well tolerated. We conclude that when prophylactic G-CSF is initiated at WHO grade IV leukopenia, addition of an oral quinolone reduces the risk of infection.
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INTRODUCTION

INFECTION IS the immediate cause of death in many cancer patients [1, 2]. When the peripheral blood granulocyte count falls below 0.5×10^9/l, the risk of serious infection and septicaemia increases rapidly, and when granulocytopenia falls below 0.1×10^9/l, practically all patients develop life-threatening infections [3].

The suppression of potentially pathogenic micro-organisms with prophylactic antibacterial treatment could result in protection against infection [4]. Several antibiotics have been used with variable success and various adverse effects [5]. Oral ofloxacin has also been used in neutropenic cancer patients resulting in low infection rates [6]. Quinolones given alone or in combination with other antibiotics have been found to be safe and well tolerated [7–9].

Granulocyte colony-stimulating factor (G-CSF) has proven its high activity on the neutrophils, increasing the number of peripheral neutrophils and reducing risk of infection [10].

The aim of the present pilot study was to establish whether a combination of G-CSF and an antibiotic, in this case a quinolone, could further reduce the incidence of infections in cancer patients receiving antineoplastic chemotherapy.

PATIENTS AND METHODS

59 patients, 18 men and 41 women, received either G-CSF alone (30 patients/48 courses) or G-CSF plus a quinolone (29 patients/44 courses). Their mean age was 55 years, range 17–83 years. All patients had developed febrile neutropenia during their preceding chemotherapy course and were enrolled in the present study as compassionate need cases. G-CSF 0.3 mg was given as subcutaneous injection during 7–10 days. Antibiotic prophylaxis was given as ofloxacin 200 mg twice daily, orally, or

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