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Accelerated Chemotherapy With or Without GM-CSF for Small Cell Lung Cancer: a Non-randomised Pilot Study

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Two series of five consecutive patients with small cell lung cancer were treated with an "accelerated" chemotherapy regimen of cyclophosphamide-doxorubicin-vincristine (CAV) and cisplatin-etoposide (PE) alternated possibly every week. In the first group of patients (median age 49 years, range 46–52) recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) was given as soon as grade IV leukopenia occurred, while in the second group (median age 59 years, 55–68) no growth factor was administered . The mean interval between chemotherapy courses and the mean duration of chemotherapy were 10 and 57 days, respectively, in the patients supported with GM-CSF compared with 13 and 72 days in the control group. One GM-CSF treated patient was withdrawn after the third cycle because of severe toxicity. The mean white blood cell and platelet nadirs were 600 and 46 000/μl in the first group vs. 840 and 105 000/μl in the controls. Overall chemotherapy dose-intensity was increased by two fold in the patients given GM-CSF compared with a 1.5 fold increase in the control patients. In all cases, irrespective of their treatment, there was an impaired colony forming capacity of circulating and marrow haemopoietic progenitor cells when grade IV leukopenia occurred, with recovery after the end of leukopenia. This pilot study suggests that accelerated CAV/PE chemotherapy is feasible both with and without GM-CSF. Different GM-CSF schedules as well as combinations of different haemopoietic growth factors may further improve dose-intensity.
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INTRODUCTION

TUMOUR SHRINKAGE is obtained in most patients with small cell lung cancer (SCLC) by initial chemoradiotherapy, but complete response is achieved in only half of those with limited disease (LD) and in only 10–20% of those with extensive disease (ED). Overall survival is still poor—less than 5% of patients are cured [1]. Cyclophosphamide-doxorubicin-vincristine (CAV) alternated with cisplatin-etoposide (PE) at 3 week intervals has been studied extensively and is superior to CAV alone, at least in ED patients [2].

The response to chemotherapy in SCLC may be dose-dependent. In addition, clinical outcome can be significantly correlated with "dose-intensity" [3]. Dose-intensity is the amount of drug administered per unit time and can be augmented either by increasing the chemotherapy dose or by reducing intervals between cycles. Myelosuppression is the dose-limiting toxicity for most drugs used for SCLC, which thus prevents optimum dose-intensity administration.

The genes coding for granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been cloned [4, 5]. These glycoproteins increase the function and the number of granulocytes and macrophages. GM-CSF reduces the duration and severity of leukopenia due to both conventional and high-dose chemotherapy [6].

We have investigated the feasibility of a chemotherapy regimen in which dose-intensity was increased by reducing the intervals between full-dose standard chemotherapy courses ("accelerated" chemotherapy) and evaluated the possible contribution of recombinant GM-CSF in this approach.

PATIENTS AND METHODS

Consecutive patients under 70 with newly diagnosed, histologically or cytologically confirmed SCLC of any stage were eligible. WHO performance status of 3 or under with normal hepatic, renal and cardiac functions was necessary. Informed consent was required. No concomitant corticosteroid treatment was allowed. Before starting chemotherapy, all patients underwent a complete examination including chest and brain computed tomography (CT), abdominal ultrasound or CT, bone scan and full blood count and chemistry with tumour markers (carcinoembryonic antigen and neuron-specific enolase). Patients had to receive a total of six courses of weekly alternating chemotherapy unless disease progressed or excessive toxicity occurred.

Treatment

Chemotherapy consisted of a rotation of cyclophosphamide 1000 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mg total dose given intravenously on day 1 (CAV), and cisplatin 60 mg/m^2 and etoposide 150 mg/m^2 intravenously on days 8 and 9 (PE). A blood count was done every other day during treatment.

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Chemotherapy was administered when white blood cell (WBC) count was over 2000/μl and platelets were over 100 000/μl.

In the first five patients, with the advent of grade IV leukopenia (WBC ≤ 1000/μl), human GM-CSF (Schering–Sandoz) was administered intravenously at 5 μg/kg per day as a 2 h infusion for at least 5 days until white cells reached 2000/μl; a rest period of 1 day was allowed before restarting chemotherapy. The GM-CSF dose was 5 μg for the first cycle and was increased up to 10 μg for the following cycles if, during the first course, WBCs required more than 5 days to recover. In the case of grade IV leukopenia without fever, patients were treated prophylactically with norfloxacin 400 mg every 12 h and amphotericin B every 4 h both orally. When granulocytopenic fever occurred, patients were admitted and the possible source of infection was investigated; empiric or specific intravenous antibiotics were started. Platelet transfusions were planned if the count fell below 30 000/μl and packed red cell transfusions were given when haemoglobin was below 9 g/dl.

Bone marrow and blood samples were obtained before starting chemotherapy (TO) and just before (T1) and after (T2) the first GM-CSF course.

Five additional control patients were treated according to the same regimen but without GM-CSF support. Each control patient was matched to a GM-CSF treated patient with respect to timing of haemopoietic progenitor studies. Bone marrow aspirates in the control group were performed at T0 and T1, as in the GM-CSF treated group; the third aspirate (T2) for each control was obtained after a number of days equal to the period necessary for recovery (T2 minus T1) in the matched GM-CSF treated patient.

Table 1. Patients' characteristics

Patient*	PS	Age	Stage	No. of courses	Response	Survival	Relapse
GM-CSF							
1	1	46	LD	6	CR	25†	Brain
2	3	49	ED	6	PR	13	Brain
3	1	46	ED	3*	PR	9	Brain
4	1	52	ED	6	PR	22†	Thorax
5	0	49	LD	6	CR	23†	—
Control							
6	3	55	ED	6	CR	5.5	Brain
7	1	63	LD	6	PR	12	Thorax
8	0	68	LD	6	PR	8	Thorax
9	1	55	LD	6	CR	11.5	Brain
10	1	59	LD	6	CR‡	17	Leptomeninges

*Stopped treatment because of haemorrhagic cystitis, mucositis grade IV and pulmonary abcess.
† = still alive.
‡ = negative CT scan with positive brushing cytology.
CR = complete response and PR = partial response. Surv = survival.
* = performance status.

Laboratory studies

Peripheral blood (PBMC) or bone marrow mononuclear cells were separated on Ficoll–Hypaque. Monocytes were partly removed by adherence. These cell fractions were used for the assessment of the clonogenic capabilities of hemopoietic progenitors.

Myeloid colony assay. 10^5 bone marrow cells or 5×10^5 PBMC were resuspended in a final volume of 1 ml of a mixture containing alpha medium (Gibco), 10% heat-inactivated fetal calf serum (FCS) and 0.3% agar and supplemented with non-essential aminoacids, L-glutamine and sodium pyruvate [7]. The following growth factors were used: firstly, the supernatant of the 5637 bladder carcinoma cell line, which contains G-CSF, GM-CSF and interleukin-1 alpha (IL1–α) together with additional factors that are not yet characterised [8] and secondly, rGM-CSF donated by Dr Steven Clark, Genetics Institute, Cambridge, MA. This GM-CSF preparation had a specific activity of 8×10^7 U/mg and was used at a final concentration of 1 ng to 100 μg. The 5637 conditioned medium gave the maximum stimulation of myeloid colony (CFU-GM colony forming units-granulocytes macrophages) formation at the final dilution of 10%. GM-CSF exerted optimal stimulation of myeloid colonies in the range 10–100 ng/ml. In this study rGM-CSF growth factor was used at 10 ng/ml. Control plates did not contain any exogenous growth factor. Cultures were incubated in 5% CO_2 in air at 37°C and scored for colonies after 7 and 14 days. A colony was defined as an aggregate of at least 40 cells.

Erythroid colony assay. 10^5 bone marrow cells or 5×10^5 PBMC were resuspended in a mixture containing 0.9% methylcellulose (Dow) alpha medium, 30% heat-inactivated, pooled human AB serum, 10^{-4} mol/l alpha-thioglycerol, sodium pyruvate, L-glutamine, non-essential aminoacids and 2 U/ml recombinant erythropoietin (Pharmacia). Cultures were incubated as in the myeloid colony assay and colonies were counted after 7 days (CFU-E, colony forming units-erythroid) and 12–14 days (BFU-E, burst forming units-erythroid) [9].

Cytokine assays. Different serum samples were obtained from each patient at various times and stored at −80°C. The sera were evaluated for IL-1β and tumour necrosis factor alpha (TNF-α) by ELISA (Cistron Biotechnology and T Cell Science, respectively).

Acute phase protein assays. Analysis of serum acute phase proteins was done with rate nephelometry (Assay Protein System, Beckman). Each protein was calibrated with constants provided by the antibody card (Beckman). The following acute phase proteins were measured: al-antitrypsin, haptoglobin, a2-macroglobulin, a1-glycoprotein and C3 (b1-C-globulin).

RESULTS

Clinical results

Of the five patients treated with alternating chemotherapy and GM-CSF (Table 1), only patient 3, with brain metastases at presentation, had to stop treatment after the third course of chemotherapy. While granulocytopenic, this patient had grade IV mucositis and haemorrhagic cystitis followed by gram negative and anaerobic pulmonary infection with mycotic superinfection. The remaining four patients completed the six planned courses of treatment in a mean time of 57 days. In the overall group, the mean interval between courses was 10 days (Table 2).

The mean WBC and platelet nadirs were 600 and 46 000/μl, respectively. The mean duration of grade IV leukopenia and thrombocytopenia were 4.8 and 1.4 days, respectively. Platelet transfusions were given to two patients and packed red cell transfusions to three patients on one occasion each (Table 2). The non-haematological chemotherapy-related toxicity was mild (nausea and vomiting grade III and anorexia grade III in one patient during a single cycle).

Thirteen courses of GM-CSF were administered at 5 μg and five at 10 μg; the mean duration of GM-CSF treatment was 7 days with 5 μg and 5 days with 10 μg. The GM-CSF related toxicity consisted of bone pain and abdominal discomfort in

Table 2. Clinical and haematological results

	With GM-CSF	Without GM-CSF
Chemotherapy intervals (days)	10(6–19)*	13(6–23)
Chemotherapy duration (days)	57(51–59)	72(64–94)
Mean WBC nadir (/μl)	600	840
Mean platelet nadir (/μl)	46 000	105 000
No. requiring platelet transfusion	2	0
No. requiring red cell transfusion	3	3

*Mean (range).

four patients, rash in one and headache in one. In three cases, serum cholesterol levels decreased compared with the pre-treatment values.

All five patients responded rapidly to chemotherapy. Two achieved complete remission; the other three had a partial response which was almost complete in two. Three patients were given subsequent chest and brain prophylactic irradiation. Survival is shown in Table 1.

All the control patients (Table 1) were able to complete the six planned cycles, in a mean time of 72 days. The mean interval between courses was 13 days (Table 2). The mean WBC nadir was 840/μl with grade IV leukopenia for a mean of 3 days; three patients, while granulocytopenic, experienced short febrile episodes of unknown origin that were cleared by empiric antibiotic therapy. The mean platelet nadir was 105 000/μl; no patient had grade IV thrombocytopenia requiring transfusion. Three patients needed red cell transfusions on a single occasion (Table 2). The non-haematological toxicity consisted of mucositis grade III in one patient, vomiting grade III in two and anorexia grade III in one.

All five patients responded; two achieved complete response (one with a persistently positive sputum cytology) and three had partial response. All LD patients were given prophylactic brain and chest radiotherapy after completion of chemotherapy. Patients' survival is shown in Table 1.

Laboratory results

The colony forming capacity of bone marrow and peripheral blood progenitors at T0 is shown in Tables 3 and 4. The baseline values displayed were different in the two groups of patients, which may be related to the intrinsic variability of the culture techniques. Also differences in the mean age of the two groups (the controls were older) may have contributed to the *in vitro* behaviours of myeloid progenitors. At T1, haemopoietic colony formation was almost completely impaired, with the exception of the bone marrow cultures containing the 5637 cell line supernatant, in which a small but definite number of both 7 day and 14 day CFU-GM was still present.

At T2, myeloid colony formation recovered both in the bone marrow and in the peripheral blood in all the patients, independently of whether or not they had received GM-CSF. The numbers of bone marrow myeloid colonies detected in the patients who had been treated with chemotherapy alone were higher than those found in patients who had received GM-CSF. Finally, at T2, circulating BFU-E were detected in all patients, but the number of BFU-E colonies was higher in those who had been treated with GM-CSF. Bone marrow CFU-E colonies were detected only in the controls, whereas little or no growth of marrow BFU-E colonies was observed in any of the patients.

Table 3. Bone marrow haemopoietic progenitors

	Mean no. of colonies per 10^5 cells					
	T0		T1		T2	
	With GM-CSF	Without GM-CSF	With GM-CSF	Without GM-CSF	With GM-CSF	Without GM-CSF
CFU-GM (7 days)						
Control	14	0	0	0	10	57.5
5637 medium	83.2	43	25.2	42.5	76	132.2
GM-CSF	31.2	20	1.5	37.5	73.6	189
CFU-GM (14 days)						
Control	9.4	0	0.8	0	15.6	29.7
5637 medium	89	57.5	34.6	28.5	83	173.5
GM-CSF	37.5	28	2	23.7	96	196
CFU-E (7 days)						
Control	0	73.3	0	0	0	12.5
EPO	27	126.6	3	2	4	54.5
BFU-E (14 days)						
Control	0	36.6	0	0	0.5	0.5
EPO	42.3	71.6	4	0	6.2	11.5

Treatment with GM-CSF can induce mononuclear cells to produce other cytokines [10, 11]. To investigate whether or not this occurred in our patients, sera were tested at T0, T1 and T2 for IL-1β and TNF-α. We rarely detected either. Patient 2 at T0 and T1 had 200 U IL-1β, and at T2, had 1000 U of IL-1β. Only patient 7 in the controls had 100 U TNF-α and 200 U IL-1β at T0; these cytokines were not detectable subsequently. Since both IL-1β and TNF-α can induce the hepatocyte to synthetize several acute phase reactants we tested some patients' sera [12, 13]. GM-CSF administration did not significantly modify these values compared with controls (data not shown).

DISCUSSION

Our aim was to explore the possibility of increasing the dose-intensity of an effective alternating chemotherapy regimen for SCLC. The rationale was suggested by the clinical experience with third-generation regimens in high-grade lymphomas. In these protocols, the maximum tolerated number of drugs is

Table 4. Peripheral blood haemopoietic progenitors

	Mean no. of colonies per 5×10^5 cells					
	T0		T1		T2	
	With GM-CSF	Without GM-CSF	With GM-CSF	Without GM-CSF	With GM-CSF	Without GM-CSF
CFU-GM (14 days)						
Control	12.2	0	0.5	0	14	14.7
5637	75.7	37.5	3.5	1.5	59	58
BFU-E (14 days)						
Control	0	0	0	0	0	1.7
EPO*	10	50	0	3.2	98.5	16

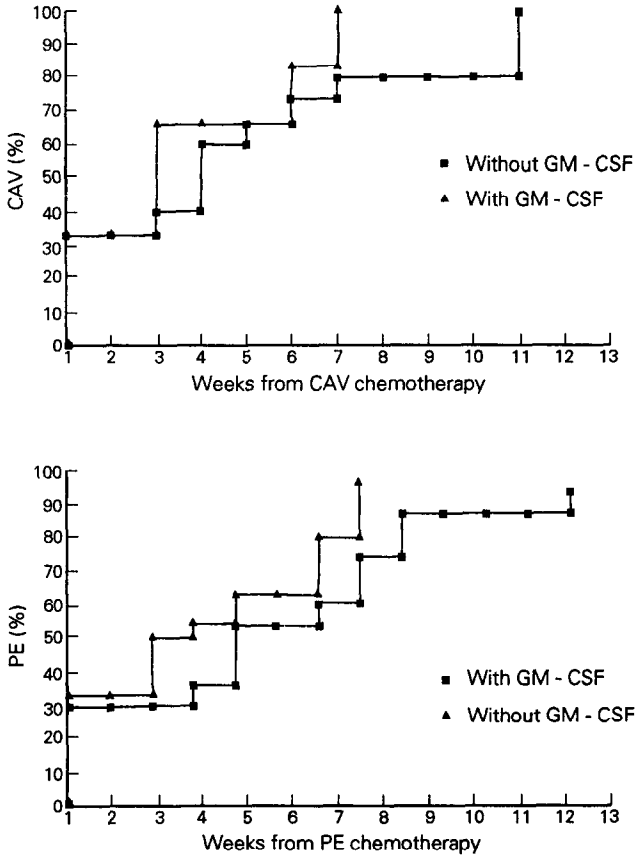

Fig. 1. Cumulative proportion of chemotherapy.

given in the shortest time [14] to fulfil the theoretical predictions of the Goldie and Coldman hypothesis [15] and to deliver the maximum dose of each single drug. Of the two strategies that may be used to increase the dose-intensity (i.e. to augment the dose of the drug or to shorten the intervals between cycles) we selected the latter.

Despite the limitations given by the small number of patients, the absence of a randomised design and the imbalance of the two groups in terms of age, our study suggested that it is possible to shorten the intervals between the cycles of the CAV/PE regimen with or without GM-CSF support. In fact, the average number of days required to recycle was 10 and 13 days, respectively; the standard interval is 20 days. Thus, although no patient was able to receive the planned weekly chemotherapy, the treatment duration was limited to 57 and 73 days, respectively (instead of the usually projected 107 days), with a concomitant 1.5–2 fold increase in dose-intensity (Fig. 1) compared with the standard schedule. The increase in dose-intensity was not associated with a worsening of the usual non-haematological side-effects or with the appearance of additional ones. In particular, gastrointestinal side-effects and mucositis were not dose-limiting except in one patient.

Although the decrease of the mean interval between chemotherapy courses observed in patients receiving GM-CSF was higher than that seen in the patients treated without the growth factor, this difference was not as large as expected. In addition no significant difference was detected in the two patient groups in mean WBC nadirs, red cell transfusion requirement, overall frequency of infection, fever and mucositis. Although the difference is small, the nadir platelet count and platelet transfusion requirement were worse in the GM-CSF group, which might reflect the higher chemotherapy dose-intensity in these patients. However, the number of patients was small and these comparisons would require larger numbers to be studied.

The prophylactic use of haematopoietic growth factor may be more suitable to reduce or even prevent the severe leukopenia induced by "acclerated" chemotherapy. In this respect, Bronchud *et al.* were able to give high-dose doxorubicin (75–150 mg/m^2) fortnightly to seventeen patients with advanced breast and ovarian cancer with G-CSF prophylactically for 11 days between chemotherapy courses. The neutrophil count rose over 2500/μl by day 14 at all doxorubicin doses when G-CSF was given, whereas a normal count was not reached until days 19–21 in the two control patients receiving 75 mg/m^2 doxorubicin only [16].

Furthermore, there is the possibility that the route of administration of GM-CSF that we used was suboptimal, as indicated by the low toxicity observed in our patients. Subcutaneous or continuous infusion of GM-CSF may be more effective than bolus infusion [17].

The behaviour of myeloid progenitors was similar in the two groups; however the numbers of bone marrow myeloid colonies in the patients treated with chemotherapy and GM-CSF were even lower than in patients receiving chemotherapy alone. This suggests that treatment with GM-CSF, at least in these conditions, has a modest effect on bone marrow CFU-GM, as already reported [18]. Conversely, some differences were observed in the *in vitro* behaviour of erythroid progenitors. In fact, at T2, BFU-E progenitors gave rise to colonies predominantly in the circulating compartment, with a higher number of colonies in the patients who had received GM-CSF treatment. This finding is in accordance with previous results [18] and suggests that the combination of GM-CSF and chemotherapy mobilises immature erythroid progenitors from the bone marrow to the peripheral blood.

The somewhat unexpected poor response to GM-CSF of CFU-GM not only in the bone marrow but also in the peripheral compartment may be related in part to the timing of sampling at T1. At this time, the haematopoietic progenitors may have been already damaged by intensive chemotherapy as indicated by the fact that, at this time, the colony-forming capacity was severely impaired.

Whereas no myeloid colonies were observed at T1 in all of the culture combinations stimulated with GM-CSF, a small but definite number of colonies was consistently detected at T1 in the cultures supplemented with the 5637 conditioned medium. This supernatant contains, in addition to GM-CSF, G-CSF, IL-1α and other poorly characterised factors, which suggests that a better prevention of chemotherapy-related myelosuppression would be achieved with a combination of different growth-factors.

Our study supports the feasibility of delivering an "accelerated" chemotherapy with high dose-intensity. This goal has been achieved with and without the use of GM-CSF as soon as severe leukopenia occurs. The final impact of the prophylactic use of GM-CSF in delivering higher dose-intensity regimens and in preventing severe leukopenia has still to be investigated. Moreover, the issue of whether this intensive schedule will give a better clinical outcome in SCLC patients requires randomised trials.

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Diagnostic and Treatment Procedures Induced by Cervical Cancer Screening

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The amount of diagnostic and treatment procedures induced by cervical cancer screening has been assessed prospectively and related to mortality reduction. Assumptions are based on data from Dutch screening programmes and on a scenario for future developments. With 5 invitations for screening, between ages 37–70 every eight years, 13 deaths are avoided per million women per screening year. Each death avoided is balanced by 2800 preventive smears, 9 women referred to a gynaecology department and 4 minor treatment procedures (conserving treatment or exconisation). 25 invitations in a life-time avoids 27 deaths per million women per screening year but with 7300 preventive smears, 22 referrals and 8 small treatment procedures. Thus intensifying screening will not only result in diminishing returns of extra screening efforts, but also in increasing risk for women to undergo unnecessary (no invasive disease or death avoided) diagnostic and treatment procedures. The balance between beneficial and adverse effects deteriorates strongly when hysterectomies play an important part in the management of cervical intraepithelial neoplasia.
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INTRODUCTION

THE APPROPRIATENESS of screening for cervical cancer should be balanced between beneficial health effects and adverse effects and costs. As the avoidance of death is the principal aim, most evaluations have concentrated on the relation between life-years saved and costs, which shows a diminishing return for the extra efforts involved in screening women more frequently [1–3]. Although unnecessary referrals and diagnostic and local therapeutic procedures are often discussed as the major adverse effect of cervical cancer screening, reports on this effect are scarce. Treatments of advanced cancer will be reduced by early detection. But due to follow-up of false positive smears and of lesions that would have regressed spontaneously, there will be a considerable increase in the number of diagnostic and minor therapeutic procedures. We have assessed this increase and related it to the number of life-years gained.

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