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The Feasibility of Using Glycosylated Recombinant Human Granulocyte Colony-stimulating Factor (G-CSF) to Increase the Planned Dose Intensity of Doxorubicin, Cyclophosphamide and Etoposide (ACE) in the Treatment of Small Cell Lung Cancer

N. Thatcher, H. Anderson, N.M. Bleehen, D.J. Girling, G. Lallemand, D. Machin and R.J. Stephens on behalf of the Medical Research Council Lung Cancer Working Party

This study was conducted to test the feasibility of reducing the interval between cycles of doxorubicin, cyclophosphamide, etoposide (ACE) chemotherapy to 2 weeks, thereby increasing dose intensity, by adding granulocyte colony-stimulating factor (G-CSF) to reduce the duration of neutropenia following a cycle. 20 patients with small cell lung cancer (SCLC) were prescribed six cycles of 2-weekly ACE, with G-CSF on the intermediate days. 3 patients died during the treatment period and a further 5 had ACE terminated, 3 for toxicity and 2 for progressive disease. Of the 71 intervals between cycles, 42 (59%) were of the prescribed 14 days, 9 (13%) of 15–20 days, 15 (21%) of 21 days and five (7%) longer, but during the first four cycles, 36 (77%) of 47 intervals were of 14 days. The main reason for delay was haematological toxicity. All 20 patients experienced WHO grade 3 or 4 neutropenia, but at 2 weeks after a cycle only 3 had grade 4 and 1 grade 3. 17 patients required blood transfusion and 12 platelet transfusion. The only potentially serious adverse reaction to G-CSF was an episode of rash with facial oedema. Adding G-CSF allows ACE chemotherapy to be intensified by reducing the interval between cycles.
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INTRODUCTION

SMALL CELL lung cancer (SCLC) is sensitive to chemotherapy, and one widely used regimen is the combination of doxorubicin, cyclophosphamide and etoposide (ACE) given intravenously every 3 or 4 weeks [1–3]. The ACE regimen is, however, associated with substantial neutropenia. This contributes to infection, morbidity, and mortality [4], and can often prevent chemotherapy being given without delay in full dosage.

Correspondence to D.J. Girling.
N. Thatcher and H. Anderson are at the CRC Department of Medical Oncology, Wythenshawe Hospital, Manchester; N.M. Bleehen is at the MRC Clinical Oncology and Radiotherapeutics Unit, Addenbrooke's Hospital, Cambridge; and D.J. Girling, G. Lallemand, D. Machin and R.J. Stephens are at the MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge, U.K.
The following are members of the Medical Research Council Lung Cancer Working Party: N.M. Bleehen, J.J. Bolger, P.I. Clark, D.J. Girling, P.S. Hasleton, P. Hopwood, F.R. Macbeth, D. Machin, K. Moghissi, M.I. Saunders, R.J. Stephens, N. Thatcher (Chairman) and R.J. White.
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Two randomised placebo-controlled trials have examined the prophylactic value of granulocyte colony-stimulating factor (G-CSF) in reducing neutropenia. In the first trial, G-CSF reduced both febrile neutropenia and the associated need for hospitalisation and intravenous antibiotics [5]. In the second, it also enabled a higher proportion of patients to receive their full protocol dosages of chemotherapy and reduced the number of infection-associated deaths [6]. However, neither trial was designed to assess a survival benefit from giving G-CSF or to address the important dose intensity question, as the interval between cycles of chemotherapy was not reduced.

As a first step towards elucidating whether survival can be improved by increasing the planned dose intensity by means of G-CSF support [7–9], the present study was conducted to test the feasibility of using G-CSF to enable ACE chemotherapy to be given at 2-week instead of the usual 3-week or 4-week intervals. The intention then was to follow it with a randomised trial comparing the ACE plus G-CSF regimen against the standard regimen of ACE at 3-week intervals without G-CSF.

PATIENTS AND METHODS

Eligibility

Patients of either sex, aged less than 75 years, were eligible for the study if they had previously untreated, microscopically confirmed SCLC. Their disease could be either limited or extensive, but they had to have a good performance status (WHO grade 0–2 [10]). Their plasma alkaline phosphatase and alanine (or aspartate) aminotransferase and serum creatinine concentrations had to be not more than 1.25 times the upper limit of normal and their blood count normal. They were required not to be receiving any other unlicensed drug or corticosteroids pretreatment and to have no contraindication to the study regimen; no known intolerance to any recombinant drug, and no other previous or concomitant malignant disease, except basal cell carcinoma or *in situ* carcinoma of the cervix. Female patients were either not of child-bearing potential or stated that they were using adequate contraception. Local ethics committee approval of the protocol and individual patient consent were required.

Treatment

All patients were prescribed six cycles of chemotherapy plus G-CSF, with prophylactic anti-emetics, each cycle of chemotherapy being given over 3 successive days at 2-week intervals followed by G-CSF for 11 days.

On day 1, doxorubicin 50 mg/m^2 and cyclophosphamide 1 g/m^2 were given by intravenous injection, and etoposide 120 mg/m^2 by intravenous infusion in 250 ml of 0.9% sodium chloride over 30 min. On days 2 and 3, etoposide 240 mg/m^2 was given orally. On days 4–14 inclusive, G-CSF 5 μg/kg was given by subcutaneous injection. A cycle of chemotherapy was only to be given if the total white blood cell (WBC) count was ≥3000/μl, the neutrophil count ≥1000/μl and the platelet count ≥100 000/μl; otherwise, G-CSF administration was to be continued and chemotherapy delayed until the aforementioned levels were reached. The next cycle was then to be given without dose reduction. If the WBC count rose above 50 000/μl, G-CSF administration was to be stopped until it fell below 10 000/μl. Prophylactic antibiotics were not given routinely.

Patients with limited disease on admission were given thoracic radiotherapy starting 3 weeks after the last cycle of chemotherapy. The dosage, fractionation and field size were decided by the local radiotherapist.

G-CSF preparation

The glycosylated G-CSF used was lenograstim and was donated by Chugai-Rhône-Poulenc. It is a glycoprotein, the structure of which is indistinguishable from native human G-CSF.

Reports and investigations

Assessments were made and reported before treatment, at the time of each cycle of chemotherapy and after the final cycle. They included details of the patient's general condition, WHO performance status and degree of breathlessness, according to the categories shown in Table 1. The presence and severity (mild, moderate or severe) of cough, haemoptysis, chest pain, other pain, nausea, vomiting, hoarse voice, sore mouth, numbness, anorexia, dysphagia and other symptoms (to be specified) were also recorded. The pretreatment assessments included, in addition, chest radiography and measurement of the plasma alkaline phosphatase, alanine (or aspartate) aminotransferase and creatinine concentrations. Subsequent assessments included evidence of infection and response to treatment [10]. A daily diary was used to record details of treatment, blood counts, transfusions, intravenous antibiotics, inpatient stay and serious adverse events.

Table 1. Characteristics of the 20 patients on admission

Characteristic	No. of patients
Sex	
Male	13
Female	7
Age (years):	
≤49	5
50–59	3
60–69	9
≥70	3
Extent of disease	
Limited	13
Extensive	7
Overall condition	
0 Excellent	4
1 Good	8
2 Fair	7
3 Poor	1
4 Very poor	0
WHO performance status [10]	
0 Normal activity without restriction	3
1 Strenuous activity restricted, ambulatory, can do light work	9
2 Up and about ≥50% of waking hours, capable of all self-care, unable to carry out any work	8
Degree of breathlessness	
0 Climbs hills or stairs without dyspnoea	2
1 Walks any distance on the flat without dyspnoea	7
2 Walks over 100 yards without dyspnoea	9
3 Dyspnoea on walking 100 yards or less	2
4 Dyspnoea on mild exertion, e.g. undressing	0

Definitions

Palliation of a symptom was defined as disappearance of the symptom or improvement by one or more categories at one or more assessments. Where appropriate, 95% confidence intervals (CI) are given.

RESULTS

Patients in the study

Between June 1992 and April 1993, 20 patients were entered into the study from two centres in the U.K. Of these, 13 were male and, on admission, 8 were aged less than 60 years (median 61) and 13 had limited disease (Table 1). All except 1 were in excellent, good or fair overall condition; 12 had WHO grade 0 or 1 performance status and all except 2 could walk over 100 yards without dyspnoea.

As reported by clinicians, on admission, 16 of the patients had cough, 7 haemoptysis, 11 chest pain, 5 hoarse voice, 5 dysphagia and 8 anorexia, but in only one instance, hoarse voice, was a symptom severe. Together with breathlessness, these were the commonest symptoms reported by clinicians of those listed on the assessment forms.

Treatment and response

12 patients (Table 2) received all six cycles of their chemotherapy. Of the 8 who did not, 3 died during the treatment period and 5 had chemotherapy terminated, 3 because of adverse effects and 2 for progressive disease. A partial response was reported in 13 patients and a complete response in 4, giving a total response rate of 17 (85%) of 20 (CI 35–98%).

The policy was that doses of chemotherapy should be delayed rather than reduced in the management of toxicity. Only 2 patients (numbers 13 and 20) had their dosages reduced, both to 50% for the sixth cycle because of cumulative haematological toxicity.

Intervals between cycles of chemotherapy

Of the 71 intervals between consecutive cycles of chemotherapy (Table 2), 42 (59%) were of the prescribed 14 days, 9 (13%) of 15–20 days, 15 (21%) of 21 days and the remaining five (7%) were longer. The main reason for delay was haematological toxicity in 26 of the 29 instances, including thrombocytopenia in 22. These delays were concentrated towards the end of the period of chemotherapy. Thus, 16 (89%) of the 18 intervals between cycles one and two were of 14 days, falling to two (17%) of 12 between cycles five and six. During the first four cycles, 36 (77%) of the 47 intervals were of 14 days.

Deaths

3 patients died during the treatment period (Table 2). Patient 1 had grade 3 anaemia and grade 4 neutropenia with diarrhoea after the second cycle of chemotherapy. He died at home 8 days later having declined hospital admission. Patient 7, despite supportive care with intravenous antibiotics and blood and platelet transfusions, died in hospital 11 days after the start of second-line chemotherapy. Patient 16 died with *E. coli* septicaemia 16 days after the first day of the second cycle of chemotherapy with grade 4 neutropenia and thrombocytopenia. In all 3 cases, cytotoxic chemotherapy, but not G-CSF, was considered a contributory cause of death. Since the study period, 5 more patients (numbers 4, 6, 8, 14 and 18) have died 13, 6, 9, 5 and 7 months after the start of treatment, respectively, and the remaining 11 have been followed up for between 7 and 16 months from the beginning.

Intravenous antibiotics and inpatient care

The total number of days of observation during administration of the study chemotherapy regimen and G-CSF for all 20 patients combined was 1492. Inpatient care was required for 492 (33%) of the 1492 days. This included 233 (16%) during which antibiotics were given intravenously.

Palliation of main thoracic symptoms

The main thoracic symptoms were, in general, palliated in high proportions of patients, particularly haemoptysis (100%), chest pain (82%) and hoarse voice (100%). Symptoms such as cough and breathlessness, likely to have been present in a number of patients before the development of lung cancer because of chronic obstructive airways disease, were palliated in smaller proportions, 69 and 44% respectively. Palliation included disappearance of a symptom in substantial proportions of instances, ranging from 33% for breathlessness to 100% for haemoptysis.

Neutropenia

The worst WHO grade of neutropenia recorded at any time was grade 4 (Table 3) in 18 patients and grade 3 in the remaining 2 patients. Of the 91 cycles of chemotherapy, 36 (40%) were followed by grade 4 neutropenia and 13 (14%) by grade 3. There was no evidence of increasing risk of grade 4 or 3 neutropenia following succeeding cycles of chemotherapy.

Table 2. Number of days between consecutive cycles of chemotherapy, performance status, disease extent and response to treatment

Patient no.	Performance status	Disease extent	Number of days between cycles 1–2	2–3	3–4	4–5	5–6	Response	Reason treatment not completed
1	1	Limited	14	—	—	—	—	Partial	Sudden death at home
2	2	Limited	—	—	—	—	—	Nil	Progressive disease
3	2	Extensive	14	17	15	19	19	Partial	
4	1	Extensive	14	14	14	14	14	Partial	
5	1	Limited	14	14	14	21	21	Partial	
6	2	Limited	14	14	14	14	21	Complete	
7	2	Limited	21	21	—	—	—	Partial	Death
8	1	Limited	14	14	14	17	17	Partial	
9	1	Extensive	14	14	21	28	42	Partial	
10	0	Extensive	14	14	14	14	25	Complete	
11	1	Limited	—	—	—	—	—	Nil	Drug reaction
12	2	Extensive	14	21	—	—	—	Partial	Toxicity
13	2	Limited	21	21	21	35	35	Partial	
14	0	Extensive	14	14	14	17	20	Partial	
15	2	Limited	14	14	14	14	14	Partial	
16	2	Limited	14	—	—	—	—	Partial	Death
17	1	Limited	14	16	—	—	—	Stationary	Progressive disease
18	1	Extensive	14	14	14	—	—	Partial	Toxicity
19	1	Limited	14	14	21	21		Complete	
20	0	Limited	14	14	14	21	21	Complete	
Total intervals between cycles			18	16	13	12	12		
Percent are given at day 14			89	69	69	33	17		

Table 3. The worst WHO grades of neutropenia, anaemia and thrombocytopenia following each cycle of chemotherapy

	Neutropenia cycle						Anaemia cycle						Thrombocytopenia cycle					
Patient no.	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	4	N	—	—	—	—	N	3	—	—	—	—	N	N	—	—	—	—
2	4	—	—	—	—	—	N	—	—	—	—	—	3	—	—	—	—	—
3	4	4	N	4	2	N	N	2	3	3	3	N	N	2	3	4	4	N
4	2	4	N	N	N	4	N	N	N	3	3	3	N	N	N	N	N	3
5	4	4	2	N	N	3	N	N	2	3	3	3	N	N	2	2	3	4
6	N	3	2	N	3	N	N	N	2	2	N	2	N	N	N	N	2	N
7	4	2	4	—	—	—	3	N	2	—	—	—	3	3	N	—	—	—
8	4	N	N	4	N	4	N	N	2	4	2	4	N	2	3	4	2	4
9	4	4	N	4	N	4	N	2	3	3	4	3	2	2	2	4	4	4
10	4	4	3	N	N	3	N	N	N	2	2	2	N	N	N	N	N	4
11	3	—	—	—	—	—	N	—	—	—	—	—	N	—	—	—	—	—
12	4	4	N	—	—	—	N	2	2	—	—	—	4	4	2	—	—	—
13	N	2	N	3	4	N	N	3	3	2	3	2	2	4	4	4	4	2
14	3	N	N	N	N	4	N	N	N	2	N	3	N	N	N	N	4	4
15	4	4	2	N	2	N	2	2	N	2	2	3	2	N	N	N	N	N
16	N	4	—	—	—	—	N	2	—	—	—	—	3	4	—	—	—	—
17	4	3	N	—	—	—	N	N	3	—	—	—	2	N	4	—	—	—
18	3	4	N	N	—	—	N	N	2	2	—	—	N	N	2	3	—	—
19	3	4	N	N	3	4	N	N	2	3	2	4	N	2	N	3	4	4
20	4	4	3	4	4	4	N	N	N	3	3	2	N	N	N	4	4	2
Total	20	18	16	13	12	12	20	18	16	13	12	12	20	18	16	13	12	12
No. 3 or 4	16	13	3	5	4	8	1	2	4	7	6	7	4	4	4	7	7	7
% 3 or 4	80	72	19	38	33	67	5	11	25	54	50	58	20	22	25	54	58	58

N, grade 0 or 1.

At 14 days after the first day of each cycle, only 3 patients had grade 4 and 1 patient grade 3, each on only a single occasion. Many of the results were well above 2000/μl, showing vigorous responses to G-CSF.

Anaemia and thrombocytopenia

The worse WHO grade of anaemia at any assessment (Table 3) was grade 4 in 3 patients and grade 3 in 10. Of the 91 cycles of chemotherapy, four (4%) were followed by grade 4 anaemia and 23 (25%) by grade 3. 17 patients were treated with blood transfusion.

The worst grade of thrombocytopenia was grade 4 in 12 patients and grade 3 in 4. Of the 91 cycles of chemotherapy, 23 (25%) were followed by grade 4 and 10 (11%) by grade 3. 12 patients were treated with platelet transfusion.

The proportions of patients with grade 4 or 3 anaemia or thrombocytopenia increased with succeeding cycles of chemotherapy. Thus, 5% of patients had grade 4 or 3 anaemia after the first cycle, rising to 58% after the sixth and 20% had grade 4 or 3 thrombocytopenia after the first cycle, rising to 58% after the sixth.

Adverse effects of treatment

The adverse effects of myelosuppression ranged from fever alone to septicaemia, which was reported in 4 patients. The only bleeding episode was a subfoveal haemorrhage during a period of pancytopenia in 1 patient; this was associated with impaired vision in one eye. 8 patients had nausea without vomiting and 11 vomiting, this being mild in 8. Mucositis was a troublesome adverse reaction; it affected 15 patients and was severe in 6 and moderate in 2. G-CSF was considered possibly responsible for two of five cutaneous reactions and highly probably responsible for one other. In addition, 4 patients complained of diarrhoea; G-CSF was considered a possible cause in 1 patient.

Only one serious reaction, affecting patient 11, was attributed to G-CSF. On the third day of G-CSF injections, following the first cycle of chemotherapy, there was a rash accompanied by severe facial and periorbital oedema. G-CSF administration was terminated forthwith; the symptoms then completely resolved and did not recur.

DISCUSSION

The importance of this study lies in its demonstration that the addition of G-CSF to cytotoxic chemotherapy with the ACE regimen, makes feasible the policy of reducing the interval between cycles from the usual 3 or 4 weeks to 2 weeks, thereby permitting an increase in dose intensity. Moreover, this policy was particularly successful during the first four cycles of chemotherapy, when 77% of the intervals were of the prescribed 14 days. This is a useful finding because randomised trials have shown that in the treatment of SCLC, multi-drug chemotherapy achieves almost all of its beneficial effect during the first three to four cycles [11, 12].

G-CSF greatly shortens the duration of transient drug-induced neutropenia following a cycle of cytotoxic chemotherapy [13], and a number of studies have indeed shown that it can reduce the risks of symptomatic myelosuppression, and the need for hospitalisation and intravenous antibiotic administration when chemotherapy is given in the usual 21-day cycles [5, 6]. Nevertheless, when dose intensity is increased, these potential advantages could be reduced or reversed. G-CSF cannot be expected to have any effect on the acute adverse effects of cytotoxic chemotherapy other than those related to neutropenia. Thus, when it is used, as in the present study, to increase the planned

dose intensity of cytotoxic chemotherapy and not just to reduce the associated risks of neutropenic toxicity, there is a potential risk that other adverse effects will become more frequent and more severe. In the present study, 3 patients died during the treatment period. Treatment was considered to be a contributory cause of all three deaths, but one might have been prevented had the patient remained in hospital as advised and another can probably be attributed to second-line chemotherapy—not the study regimen. Neutropenia had largely resolved by the end of the 14-day period and did not significantly interfere with the 14-day policy, although there was symptomatic myelosuppression in 18 patients, including septicaemia in 4 and subfoveal haemorrhage in 1 patient. In contrast to the rapid resolution of neutropenia, both anaemia and thrombocytopenia became progressively more severe with successive cycles of chemotherapy. The European group [6] reported similar findings. In the present study, 17 of the 20 patients required blood transfusion and 12 platelet transfusion. The numbers of patients requiring such supportive treatments should be reported in published papers; comparisons between standard and intensive chemotherapy policies in this respect have yet to be made. Mucositis was also a troublesome adverse reaction, being severe in 6 patients.

Only one serious adverse event was attributed to G-CSF, an episode of rash and severe facial and periorbital oedema that resolved rapidly when G-CSF administration was terminated. The other patients tolerated their G-CSF well. Other groups are also finding that G-CSF is a safe biological preparation to give to patients with cancer, the commonest reactions being musculoskeletal pain and fever [6, 13]. Nevertheless, *E. coli*-derived G-CSF is thought to have been responsible for liver damage in a young girl receiving vincristine, dacarbazine, ifosfamide and doxorubicin for neuroblastoma [14], and vasculitis has been reported in 2 patients receiving it on a long-term basis for chronic neutropenia [15].

As in a previous MRC Lung Cancer Working Party trial, the adverse effects of chemotherapy were offset by its palliative effects [16]. Of the main thoracic symptoms, all except breathlessness were palliated in more than half of the patients. Measuring both the palliative and the adverse effects of treatment policies is an important component of their clinical assessment in terms of the quality of patients' survival.

There is now a clear need for a randomised trial comparing the policy of the present study—ACE chemotherapy given at 14-day intervals with G-CSF—versus standard ACE chemotherapy given, without G-CSF, at the usual 21-day intervals, in the treatment of SCLC. Only in this way will it be possible to reliably measure the difference in dose intensity achievable between these two policies, to determine whether this difference results in an improvement in median or long-term survival, to document the differences in haematological toxicity, to find out whether other forms of toxicity become dose-limiting, to compare the other supportive measures required and to assess the effects of all of the above on the quality of life of the patients. The MRC Lung Cancer Working Party has recently opened the intake into such a trial (protocol LU19).

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