Five-Day Oral Etoposide Treatment for Advanced Small-Cell Lung Cancer: Randomized Comparison With Intravenous Chemotherapy

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Background: **Oral etoposide is an active single agent in small-cell lung cancer (SCLC) and is widely prescribed as first-line treatment as an alternative to intravenous combination chemotherapy in patients with extensive disease.** ***Purpose:*** **The intention of this study was to determine if the effects of oral etoposide therapy on survival and quality of life are equivalent to those of intravenous chemotherapy.** ***Methods:*** **In a randomized trial of palliative treatment in advanced SCLC, oral etoposide (100 mg given twice daily for 5 days) was compared with intravenous chemotherapy consisting of alternating cycles of cisplatin and etoposide (PE) and cyclophosphamide, doxorubicin, and vincristine (CAV). Six cycles of chemotherapy were administered every 21 days in both regimens. Symptom control and quality of life were measured with the Rotterdam Symptom Checklist and a daily diary card. In January 1996, after 155 patients had been randomly assigned from a projected intake of 365 patients, an independent Data Monitoring Committee examined the interim results. Survival was determined by the Kaplan–Meier method, and the logrank test was used to compare treatments. For quality-of-life comparisons, average scores were calculated for each time point. The Mann–Whitney *U* test was used to determine any significant overall differences between treatments. For the Rotterdam Symptom Checklist, separate analyses were done for each subset (psychological well-being, physical symptoms, lung cancer symptoms, treatment symptoms, activity, and quality of life). Response rates and toxicity scores were compared by using χ^2. All statistical tests were two-sided.** ***Results:*** **Survival was inferior at 1 year in the oral etoposide group compared with intravenous therapy (9.8% for oral versus 19.3% for intravenous; difference = 9.5%; 95% confidence interval of difference = 0.3%-18.7%; *P*<.05), and there was a trend toward inferior overall survival. Median survival was 4.8 months for oral treatment and 5.9 months for intravenous therapy. Progression-free survival was worse in the oral etoposide arm (median = 3.6 months versus 5.6 months; *P*<.001), as well as overall response rate (32.9% versus 46.3%; *P*<.01). With the exception of acute nausea and vomiting associated with intravenous chemotherapy, all aspects of symptom control and quality of life were either the same or worse in the oral etoposide group. Study closure was recommended.** ***Conclusions:*** **These interim results show that this schedule of oral etoposide is inferior to intravenous chemotherapy in the treatment of advanced SCLC and should not be used as first-line treatment of this disease. [J Natl Cancer Inst 1997;89:577-80]**

The prognosis of extensive small-cell lung cancer (SCLC) remains very poor in spite of combination chemotherapy. Only 5%-10% of patients with this disease survive to 2 years (*1*,*2*). Some patients have adverse prognostic features at presentation and survive a median of only 6-8 months (*3*,*4*). In these patients, the use of oral etoposide would seem to have much to recommend it. In otherwise untreated patients, major tumor responses occur in approximately 70% of cases, and uncontrolled (not randomized) phase II studies have reported survival comparable to that seen with intravenous treatment (*5*-*8*). This treatment is now widely prescribed on the basis of the assumption that it will clearly be preferable to intravenous chemotherapy with respect to side effects and that there will be no clinically important difference in survival. Oral etoposide is not, however, a nontoxic treatment; it produces nausea, myelosuppression, and alopecia in a substantial proportion of patients (*5*,*8*,*9*). The toxicity and efficacy of the treatment have not been formally compared with those of conventional intravenous treatment.

The present trial was therefore designed as a randomized comparison between a widely used schedule of oral etoposide and a commonly used cyclical alternating combination of intravenous drugs (*see* ''Subjects and Methods'' section). Our intention was to determine if equivalent survival could be obtained with better quality of life using oral etoposide.

At the time that this trial began, the U.K. Medical Research Council Lung Cancer Working Party (*10*) had started a similar study, but they used a schedule of etoposide of 50 mg twice daily for 10 days and compared it with two different intravenous regimens. In December 1995, they informed us that their trial was to be terminated early on the recommendation of their Data Monitoring Committee. We therefore invited three of the members of this committee to examine the interim results of our trial. They began this examination in January 1996. The committee's analysis had not been specified in the original protocol. It was considered essential because of a significant difference in survival and toxicity revealed in the Medical Research Council trial. The interim results of the study and recommendations of the Data Monitoring Committee form the basis of this report.

Subjects and Methods

Eligibility Criteria

Eligible patients had untreated SCLC based on biopsy findings or on cytologic criteria. All patients entered into the study who were below the age of 75 years had extensive disease and either World Health Organization (WHO) (*11*) performance status grade 2 or 3 or serum alkaline phosphatase levels greater than 1.5 times the upper limit of normal according to

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See ''Notes'' following ''References.''

the participating institution. In addition, patients aged 75 years or more with any stage of SCLC were eligible. Participating physicians agreed to treat such patients with oral chemotherapy regardless of disease extent or performance status grade. Patients under age 75 with limited disease, performance status grade 0 or 1, were not considered to be candidates for palliative treatment. Patients had to have no medical contraindication to chemotherapy. Proof of extensive disease was obtained by isotope bone scan, liver ultrasound, and abdominal and thoracic computed tomography scans, where appropriate. Ethical committee approval was obtained for all centers, and all patients gave informed consent.

Treatment Regimens

Patients were randomly assigned to receive either oral etoposide or intravenous chemotherapy consisting of alternating cycles of cisplatin and etoposide and cyclophosphamide, doxorubicin, and vincristine. In the first treatment arm, oral etoposide was given at a dose of 100 mg twice daily for 5 days every 21 days for six cycles. In the second treatment arm, intravenous chemotherapy comprised alternating cycles of 1) cisplatin (60 mg/m^2 on day 1) and etoposide (120 mg/m^2 on day 1), with 100 mg etoposide given orally twice a day on days 2 and 3 (PE); and 2) cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (2 mg/m^2) all given on day 1 (CAV). Three alternating cycles of PE and CAV were given at 21-day intervals.

Doses were modified on the basis of pretreatment blood cell counts. Patients with a white blood cell (WBC) count of 3×10^9/L or higher and a platelet count of 100×10^9/L or higher received 100% of the dose; for patients with a WBC count lower than 3×10^9/L and a platelet count of 99×10^9/L or lower, treatment was delayed 1 week. After a 1-week delay, if the blood cell count was normal, the full dose was given; if the WBC count was 2.5-2.9 $\times 10^9$/L or the platelet count was 75-99 $\times 10^9$/L, the intravenous chemotherapy dose was reduced to 75% and oral etoposide was given for 4 days only. Toxicity was assessed according to the WHO criteria.

Palliative therapy was permitted to control symptoms associated with disease progression or for persisting symptoms such as pain.

Response Assessment

Patients were seen at 21-day intervals during chemotherapy and monthly after treatment. At each visit, a chest x ray was taken, with full blood cell count, liver function tests, and measurements of urea, creatinine, and electrolyte levels.

Response was based on clinical examination, chest x ray, and biochemistry. A complete response (CR) was defined as disappearance of all signs of tumor, including biochemistry and abnormal ultrasound scans reverting to normal. Abnormal bone scans rarely become normal in responders, and those subjects were considered not to have achieved a CR. A partial response was defined as a greater than 50% decrease in tumor size measured as the sum of two transverse diameters. Response had to be maintained for 3 weeks or more. Stable disease was defined as any response less than this (i.e., ⩽50% decrease in tumor size). Where bulky disease was indistinguishable from the mediastinum, the midline on the radiograph was taken as the medial site for measurement. Disease progression was defined as worsening of the condition, as shown by chest x ray, or development of clinical or other signs of tumor growth or metastasis.

Symptom Control and Quality-of-Life Measurements

The Rotterdam Symptom Checklist (*12*) was used. This checklist was subdivided into subsets relating to physical symptoms, lung cancer symptoms, treatment symptoms, physical activity, psychological well-being, and one general quality-of-life question. It was filled in by patients every 3 weeks at each treatment cycle and at the first two follow-up visits. The initial checklist was completed before the patient was randomly assigned to treatment but after written informed consent was obtained for study entry. The daily diary card that we previously used and described (*13*) was used by patients to record acute chemotherapy-related symptoms.

Statistical Considerations

Intravenous chemotherapy was considered to be the standard treatment, and oral etoposide was regarded as the preferred treatment if no clinically important difference in survival occurred and if quality of life and symptom control were similar. Therefore, the primary statistical end points were median survival and 1-year survival. To detect a difference in median survival of 3 months and a 9% improvement in 1-year survival (significance level, 5%; power, 90%), we needed 365 patients for treatment randomization. Randomization was by minimization stratification (*14*) by sex, age (⩾75 or <75 years old), Eastern Cooperative Oncology Group performance status, hospital center, and disease extent for those age 75 years or older.

Secondary end points were tumor response and progression-free survival. Comparisons between treatment groups were made for symptom control and quality of life, but sample size was not calculated on the basis of a difference between any of the several quality-of-life and symptom measurements.

At the time that the Data Monitoring Committee met, 155 patients had been randomly assigned to treatment; of these patients, 134 had completed chemotherapy. The median follow-up was 10.4 months. The present report is therefore an interim analysis of data currently available.

Statistical Analyses

Survival was determined by the Kaplan–Meier method using the logrank test for comparison between treatments. For quality-of-life comparisons, average scores were calculated for each time point. The Mann–Whitney *U* test was used to determine any significant overall differences between treatments. For the Rotterdam Symptom Checklist, separate analyses were done for each subset. Response rates and toxicity scores were compared by use of χ^2.

Results

From February 1993 through December 1995, 155 patients had been randomly assigned to one of the two treatment arms. The patients' characteristics are given in Table 1. Not all clinicians would stage the disease of patients 75 years old or older; therefore, disease extent in this group was sometimes unknown. Pretreatment variables were similar in both groups.

Table 2 summarizes tumor response to treatment for 134 patients having reached the end of treatment. There were fewer complete responses and substantially more patients with tumor progression while on treatment in the oral etoposide group. Upon review, one nonassessable patient was found not to have SCLC. All other patients died before their response could be evaluated.

Overall survival and progression-free survival are shown in Figs. 1, A and B, respectively. Survival was worse in the oral etoposide group. The proportion of survivors at 1 year was 9.8% in the oral therapy group and 19.3% in the group

Table 1. Pretreatment characteristics of patients randomly assigned to intravenous or oral therapy

	Intravenous chemotherapy (n = 80)	Oral etoposide (n = 75)
Age, y (range)	67 (49-80)	66 (50-86)
Male/female	42/38	42/33
Disease extent: LD/ED/UK*	4/72/4	7/66/2
Performance status†		
0	10	13
1	25	26
2	31	25
3	14	11
Alkaline phosphatase, IU/L‡	295 ± 279	411 ± 574
Albumin, g/L‡	35 ± 6.6	36 ± 5.3
Aspartate transaminase, IU/L‡	64.9 ± 95.2	73.6 ± 93.2
Hemoglobin, g/100 mL‡	12.5 ± 2.3	13.1 ± 1.8

*LD = limited disease; ED = extensive disease; UK = unknown.
†Eastern Cooperative Oncology Group.
‡Mean ± standard deviation.

Table 2. Tumor response at end of treatment in the two patient groups

Response data*	Intravenous chemotherapy (n = 67)†	Oral etoposide (n = 67)†
CR	14 (20.9)	6 (9.0)
PR	17 (25.4)	16 (23.9)
Stable disease	7 (10.4)	3 (4.5)
Progression	12 (17.9)	33 (49.3)
Nonassessable	17 (25.4)	9 (13.4)

*CR = complete response; PR = partial response. $P<.01$ for overall response rate (excluding nonassessable patients).

†Values in column = number of patients (%).

given intravenous treatment (difference = 9.5%; 95% confidence interval of the difference = 0.3%-18.7%; $P<.05$). The median survivals were 5.9 months with intravenous therapy and 4.8 months with oral etoposide. Progression-free survival was significantly worse with oral etoposide (Fig. 1, B). The values for median progression-free survival were 5.6 and 3.6 months for the intravenous and oral arms, respectively. When response rate and median survival were compared according to treatment in patients of performance status 0 and 1 and performance status 2 and 3 combined, no significant differences were demonstrated (data not shown), but these subgroups were small, and the analysis lacked power. The trend in each case was, however, toward worse survival in the oral etoposide group. Toxic effects, as measured by the WHO criteria, were similar in the two treatment arms, except that more patients with grade 3 or 4 nausea and vomiting were in the intravenous therapy group than in the oral therapy group (14 patients in the intravenous therapy group compared with two in the oral therapy group). There were five grade 3 or 4 infections in the intravenous therapy group and four in the oral therapy group as well as two grade 3 or 4 neutropenic episodes in both arms.

Results of the quality-of-life measurements for the two treatment arms are summarized in Table 3. Compliance among patients agreeing to complete the daily diary card and who survived longer than 21 days was 66.1% and 73.5% in the intravenous and oral therapy groups, respectively. The results showed that nausea was worse in those receiving intravenous therapy ($P<.001$) but that pain, appetite, general well-being, and mood (all $P<.001$) as well as sleep ($P<.02$) were worse in the patients on oral etoposide. The worse quality of life with the oral treatment was also supported by the Rotterdam Symptom Checklist, which showed that palliation of lung cancer symptoms was of shorter duration ($P<.01$) and that there was less improvement in quality of life ($P<.01$), although treatment-related symptoms were worse with the intravenous regimen ($P<.01$). The size of the differences between the two treatment regimens was small. Compliance was 70.5% and 84.8% at the time of first follow-up in the intravenous and oral therapy groups, respectively. More detailed analyses will be reported later, when follow-up is more complete.

Discussion

Several nonrandomized phase II studies (*5*,*6*) have suggested that oral etoposide might be a useful treatment in extensive stage SCLC, especially in the elderly and in patients with poor prognostic factors. The difficulty in interpreting these studies lies in the lack of randomized comparison with intravenous chemotherapy, which gives rise to results that are influenced by case selection. Thus, Carney and co-workers (*6*) treated 35 patients aged 70-93 years with 800 mg/m^2 etoposide in a 5-day schedule and observed a response rate of 71% and a median survival of 9 months for patients with extensive disease. In a subsequent report (*7*) on 63 patients, the response rate (for all patients) was 76% and the median survival was 38 weeks. Although these results are encouraging, the value of this approach can be tested only in a randomized comparison with intravenous chemotherapy, since case selection affects response rate and survival.

In our study, the very poor survival seen in both treatment groups is a consequence of selecting patients with known poor prognostic factors at presentation (*3*,*4*). Using very similar selection criteria, the U.K. Medical Research Council trial (*10*), posing the same question, reported similar survival figures. Questions of palliation and quality of life are of

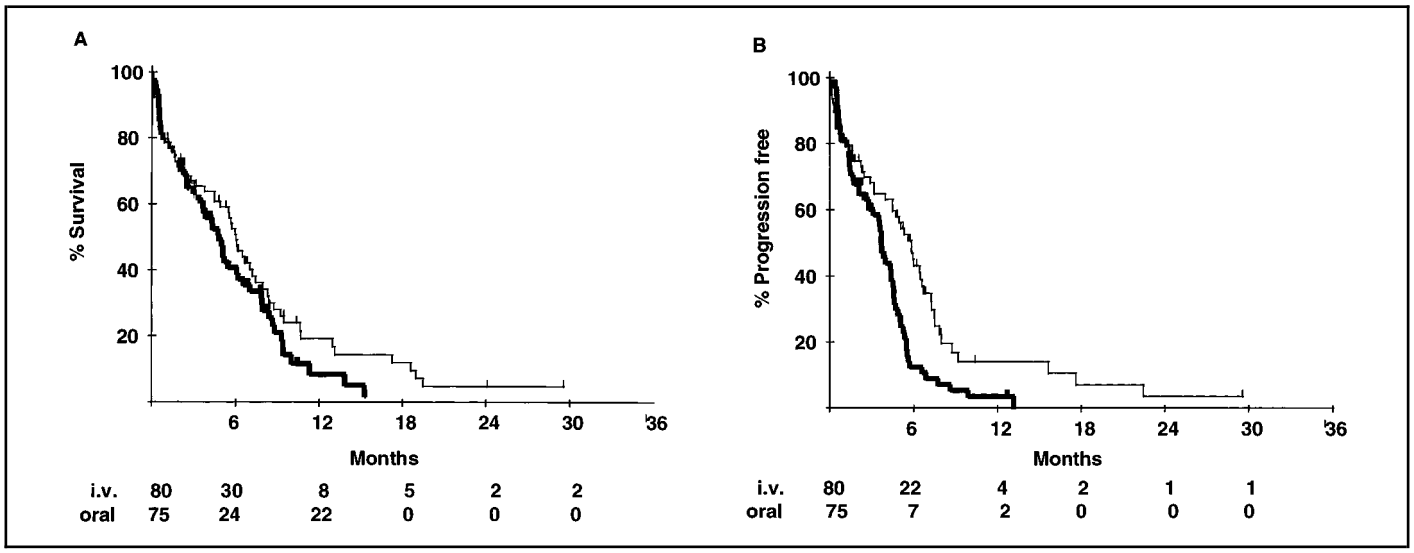

Fig. 1. Overall survival **(A)** and progression-free survival **(B)** in patients randomly assigned to receive oral etoposide (oral) treatment (dark lines) or intravenous (i.v.) treatment (light lines). The numbers of patients at risk at 6-month intervals are shown below the survival curves, and the *P* values for comparison of the curves in **(A)** and **(B)** are .134 and .001, respectively.

Table 3. Results of quality-of-life measurements for the two treatment arms

	Treatment arm comparisons*	*P*†
Daily diary card		
Nausea	IV worse than oral	<.001
Vomiting	Comparable	NS
Appetite	Oral worse than IV	<.001
Pain	Oral worse than IV	<.001
Sleep	Oral worse than IV	<.02
Mood	Oral worse than IV	<.001
General well-being	Oral worse than IV	<.001
Physical activity	Comparable	NS
Rotterdam Symptom Checklist		
Psychological well-being	Comparable	NS
Physical symptoms	Comparable	NS
Lung cancer symptoms	Oral worse than IV	<.01
Treatment symptoms	IV worse than oral	<.01
Activity	Comparable	NS
Quality of life	Oral worse than IV	<.01

*IV = intravenous chemotherapy; oral = oral etoposide.
†NS = not significant.

great importance in these very ill patients who have not long to live. Before the data were examined by the Data Monitoring Committee, although some participating clinicians were growing anxious about prescribing the oral therapy, most were not, and none had formed any clinical impression about differences in quality of life.

The bioavailability of oral etoposide varies (*15,16*), and this situation may, in part, limit its clinical usefulness as a palliative treatment, since some patients may be undertreated and others may have avoidable toxic effects. The 5-day schedule of etoposide administration that we used has been assessed in phase II studies (*5*). Other, more prolonged schedules of administration at lower dose have also been reported (*8*). The U.K. Medical Research Council trial used a 10-day regimen and compared this regimen with two other intravenous regimens (*8*). There are pharmacokinetic reasons for preferring low-dose, prolonged exposure (*17*), but response rates are similar to those obtained with the 5-day regimen employed here. There is considerable similarity of outcomes in the two randomized studies, with worse survival in both studies and, in the present study, worse overall response and poorer quality-of-life scores. The small difference in compliance with the quality-of-life measures is unlikely to account for the differences in the two arms, although it is possible that patients with poor quality of life may be more likely to be noncompliant. The difference in compliance with the use of the daily diary card was 7.4%, whereas there were highly significant and consistent differences in quality-of-life scores.

Taken together, the two trials constitute a strong argument against the use of single-agent oral etoposide in the treatment of advanced SCLC. The experience in our trial indicates the great importance of randomized comparison of treatments even when treatment is palliative.

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Notes

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