

# Etoposide compared with the combination of vincristine, doxorubicin, and cyclophosphamide in the treatment of small cell lung cancer

M B McILLMURRAY, R J BIBBY, B E TAYLOR, L P ORMEROD, J R EDGE, R J WOLSTENHOLME, R F WILLEY, J F O'REILLY, N HORSFIELD, C E JOHNSON, C P MUSTCHIN, D BRISCOE

*From the Royal Lancaster Infirmary, Lancaster; Victoria Hospital, Blackpool; Royal Preston Hospital, Preston; Blackburn Royal Infirmary, Blackburn; Marsden Hospital, Burnley; Furness General Hospital, Cumbria; Cumberland Infirmary, Carlisle; and Royal Albert Edward Infirmary, Wigan*

**ABSTRACT** One hundred and three patients with small cell lung carcinoma were stratified according to stage of disease (47 limited disease, 56 extensive disease) and then randomised to receive etoposide 300 mg/m<sup>2</sup> alone for two days or a combination (VAC) of vincristine 1 mg/m<sup>2</sup>, doxorubicin (Adriamycin) 50 mg/m<sup>2</sup>, and cyclophosphamide 1000 mg/m<sup>2</sup>. The drugs were given at three week intervals. Patients were assessed after three cycles of treatment and continued with the same regimen if in complete remission and with the alternative regimen if in partial remission; they were withdrawn if the disease had progressed. Twenty four patients (23%) achieved complete remission and this occurred more often when patients were receiving VAC (19 of 82) than etoposide (5 of 75). There was no difference, however, in overall survival between those initially treated with etoposide and those having combination chemotherapy, whether for limited disease (both 8 months) or extensive disease (7 and 5.5 months). Toxicity was less with etoposide. Survival was disappointing, especially with limited disease, even in patients who showed a complete response to treatment.

## Introduction

Small cell lung cancer disseminates early and is generally treated with chemotherapy rather than surgery or radiotherapy. Widely varying chemotherapeutic regimens have been used and response rates are high.<sup>1</sup> Relapse is common, however, and most patients die from their disease. A complete response to treatment is associated with prolonged survival and treatment regimens have become more complex and aggressive in the hope of increasing the proportion of patients achieving a complete response. The toxicity of these regimens, however, is such that their use is questionable for all but a few selected patients; for most patients treatment offers palliation rather than cure. Small cell lung cancer is therefore often treated with less toxic, easily manageable, outpatient

regimens. We have evaluated the response and survival of patients with small cell lung cancer using two simple treatment regimens in a comparative study: a combination of vincristine, doxorubicin (Adriamycin), and cyclophosphamide (VAC), which is relatively safe but unpleasant because of gastrointestinal side effects and hair loss<sup>2</sup>; and a single agent regimen using the podophyllotoxin derivative etoposide, one of the most active drugs against small cell lung cancer,<sup>3</sup> which may be less toxic. The comparison was made in a randomised study with a crossover design, so that patients not responding completely to one treatment were not denied the possibility of a response to the other.

## Methods

Ethical approval was granted by the district ethical committees and informed consent was obtained from patients participating in the study.

Patients were eligible if they had histologically

Address for reprint requests: Dr M B McIllmurray, Royal Lancaster Infirmary, Lancaster LA1 4RR.

Accepted 9 December 1988

confirmed small cell lung cancer not previously treated with drugs or radiotherapy, were aged less than 70 years, and had a Karnofsky performance score of more than 40.<sup>4</sup> Patients with evidence of cerebral metastases were not included.

Patients were stratified into two groups according to the extent of their disease after clinical, biochemical, radiological and bronchoscopic evaluation. Computed tomography and bone marrow examinations were not carried out. Patients with tumour limited to one hemithorax, the mediastinum, or the ipsilateral supraclavicular lymph nodes or any combination of these were defined as having limited disease. Patients not fulfilling these criteria were defined as having extensive disease.

Patients were randomly allocated either to a group receiving etoposide 300 mg/m<sup>2</sup> in 0.9% saline given intravenously over one hour on day 1 and the same dose orally on day 2 or to a group receiving the combination of vincristine 1 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, and cyclophosphamide 1000 mg/m<sup>2</sup> given intravenously on day 1. Treatment was repeated at three weekly intervals, with dose adjustments for bone marrow toxicity based on pretreatment blood counts (reduction to 75% dose for leucocyte count < 3000/mm<sup>3</sup> or platelet count < 100 000/mm<sup>3</sup>; reduction to 50% dose for leucocyte count < 2500/mm<sup>3</sup> or platelet count < 75 000/mm<sup>3</sup>; delay in treatment of one week for leucocyte count < 2000/mm<sup>3</sup> or platelet count < 50 000/mm<sup>3</sup>).

All patients were assessed for response in the week before the fourth cycle of treatment. Patients in complete remission—that is, no detectable tumour on chest radiograph or at bronchoscopy—were given the same regimen until relapse or for a total of 12 courses of treatment. Patients in partial remission—that is, over 50% reduction in all measurable features of the tumour—and patients with stable disease were given the alternative regimen for three further courses of treatment and were then reassessed. If they were then in complete remission the same regimen was continued for a further six cycles or until relapse. Doxorubicin was dropped from the combination when the maximum recommended doses had been reached. Patients showing disease progression were withdrawn. Metoclopramide 20 mg intravenously was given as standard antiemetic treatment with chemotherapy, followed by prochlorperazine suppositories. No patient was treated with radiotherapy.

## Results

One hundred and three patients were recruited to the study from eight treatment centres in North West England from April 1983 to April 1986. Their characteristics are shown in table 1. The two treatment

Table 1 Patients' characteristics

	Etoposide	VAC
Number	51	52
Extent of disease		
Limited	25	22
Extensive	26	30
Age (y): mean	62	58
range	38–75	37–70
Sex (M:F):	28:23	24:28
Performance score (Karnofsky)		
mean	84	83
range	40–100	50–100

VAC—vincristine, doxorubicin, cyclophosphamide.

groups were evenly matched for age, sex, performance score, and extent of disease.

### LIMITED DISEASE

Of the 47 patients with limited disease, 25 were initially randomised to receive etoposide. After three courses of treatment three patients were in complete and 13 in partial remission (combined response rate 64%). Five patients with progressive disease were withdrawn. Of the remaining 20 patients, 17 were given VAC and three of these were in complete remission after three courses of treatment.

Twenty two patients with limited disease were initially randomised to receive VAC. After three courses of treatment five patients were in complete and 10 in partial remission (combined response rate 68%). Four patients with progressive disease were withdrawn. Of the remaining 18 patients 13 were given etoposide and one of these patients was in complete remission after three courses of treatment.

Complete remission was attributable to VAC in eight patients and to etoposide in four, the overall rate being 25%. The median survival for both treatment groups was eight months. Actuarial survival curves are shown in figure 1.

### EXTENSIVE DISEASE

Of the 56 patients with extensive disease, 26 were initially randomised to receive etoposide. After three courses of treatment one patient was in complete and six in partial remission (combined response rate 27%). Twelve patients with progressive disease were withdrawn. Of the remaining 14 patients, 13 were given VAC and a further four patients were in complete remission after three courses of treatment.

Of the 30 patients initially randomised to receive VAC, seven patients were in complete and nine in partial remission (combined response rate 53%) after three courses of treatment. Twelve patients with progressive disease were withdrawn. Eleven of the remaining 18 patients were given etoposide but none had achieved a complete response after three courses of treatment.

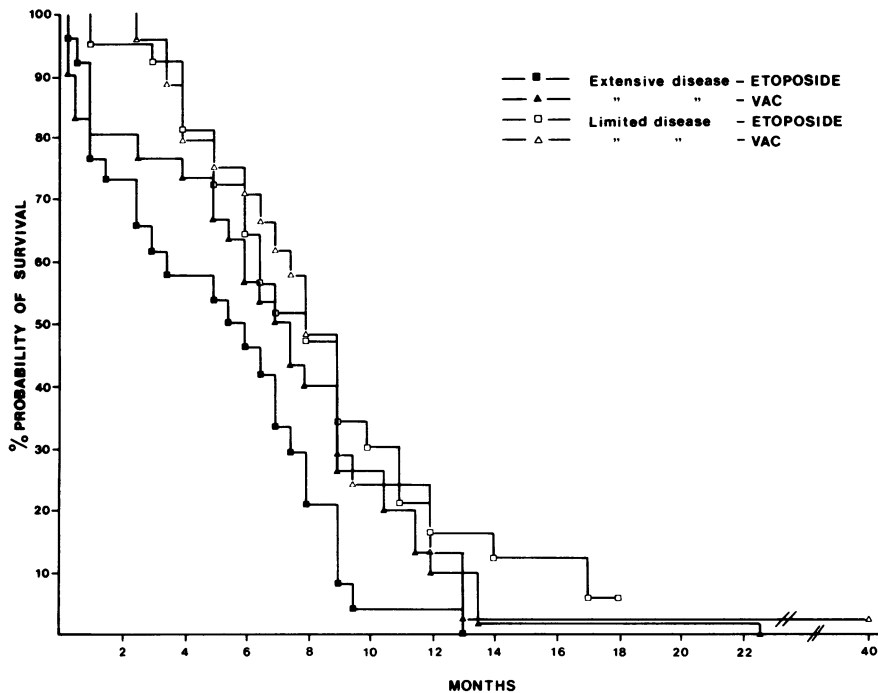


Fig 1 Actuarial survival rates in patients with limited disease and extensive disease treated by vincristine, doxorubicin, and cyclophosphamide (VAC) or by etoposide.

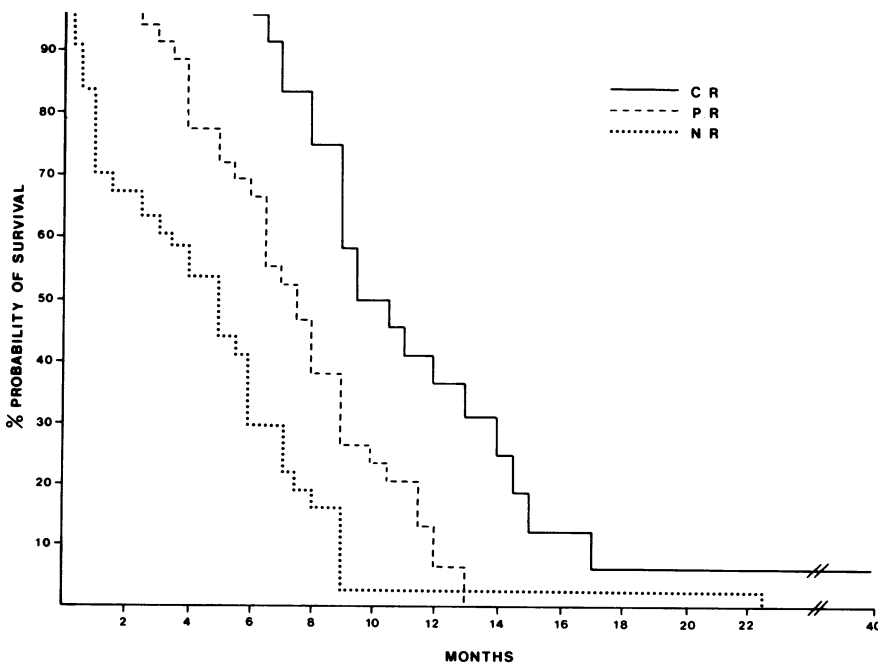


Fig 2 Actuarial survival rates in all patients according to response to chemotherapy. CR—complete response; PR—partial response; NR—no response.

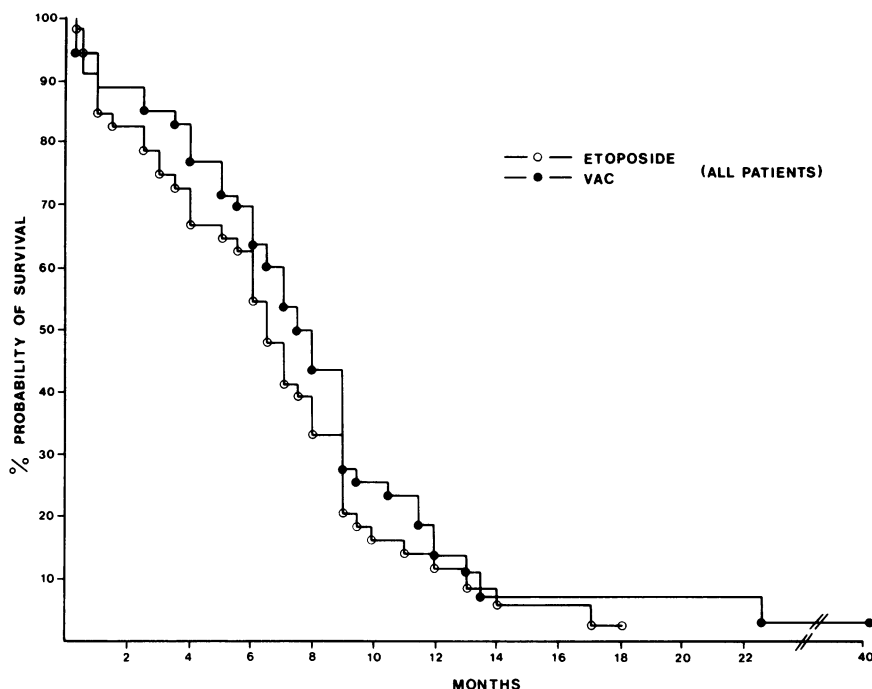


Fig 3 Actuarial survival rates for all patients according to initial treatment. VAC—vincristine, doxorubicin, and cyclophosphamide.

Complete remission was attributable to VAC in 11 patients and to etoposide in one patient, the overall rate being 21%. The median survival times for the two treatment groups were 7 months and 5.5 months respectively (fig 1).

#### OVERALL RESPONSE

Combining the results for limited and extensive disease gives a complete remission rate for all patients of 23%. Actuarial survival curves according to response are shown in figure 2 and according to initial treatment in figure 3. Complete response was seen in 19 of 82 patients treated with VAC and five of 75 treated with etoposide ( $p < 0.05$ ).

Table 2 Number (%) of episodes of toxicity caused by treatment

	Etoposide	VAC	<i>p</i>
Number of evaluable courses	140	159	—
Nausea (moderate/severe)	27 (19)	44 (28)	< 0.05
Vomiting (moderate/severe)	11 (8)	18 (11)	NS
Alopecia (moderate/severe)	53 (38)	121 (76)	< 0.00005
Neurotoxicity	—	3 (2)	—
Haematological toxicity requiring dose modification	—	8 (5)	—
Atrial fibrillation	—	1	—

VAC—vincristine, doxorubicin, cyclophosphamide.

#### TOXICITY

There were no drug related deaths. The toxicity of the two treatment regimens used initially is shown in table 2. Data referring to the first regimens were analysed. Haematological toxicity (as judged by pretreatment blood counts), alopecia, and nausea and vomiting were all significantly less with etoposide than with VAC.

#### Discussion

Small cell lung cancer is an aggressive disease with a median survival time for untreated patients of six weeks for extensive disease and three months for limited disease.<sup>5</sup> Surgery and radiotherapy have little effect on the outcome, for dissemination occurs early and patients die from systemic disease. Cytotoxic chemotherapy offers the only effective form of treatment. With the use of chemotherapy median survival times have increased considerably (7–9 months for extensive disease, and 12–18 months for limited disease) and a small proportion of patients have survived for several years.<sup>1</sup> Treatment regimens vary in effectiveness and toxicity but, because complete remission is a prerequisite for cure, drug combinations have become more intensive to increase complete response rates. Inevitably, treatment toxicity and drug related deaths have increased too.<sup>6</sup> Taken overall,

improvements in survival have been disappointingly small; treatment for most patients is palliative, and cures are rare. This study examines a less aggressive approach to the treatment of small cell lung cancer comparing one of the most active drugs, etoposide, given alone with a combination regimen of vincristine, doxorubicin, and cyclophosphamide. Single agent treatment is a departure from conventional practice in the treatment of small cell lung cancer because response rates have been inferior to those seen with a combination of drugs.<sup>7</sup> For this reason a crossover design was introduced so that patients not responding satisfactorily to etoposide were not denied treatment with combination chemotherapy. This also allowed an evaluation of etoposide as second line treatment. The crossover interval was chosen because a complete response to chemotherapy will usually have occurred by the time the fourth treatment is due.<sup>8</sup>

Complete response and survival rates in the patients with limited disease were disappointing. Indeed, the median values were nearer those expected in patients with extensive disease. A likely explanation is that patients were "understaged," because the proportion of patients with limited disease was higher than expected—50% compared with 30% in most studies. The definition of disease stage in use when this study was initiated is now known to be unsatisfactory. Modern staging definitions take account of biochemical measurements and other prognostic factors.<sup>9</sup> One of these, performance status, is very important. This study included patients with a wide range of scores but we did not take these into account in the stratification schedule. An alternative or additional explanation for the poor results is that the doses of the drugs in the VAC combination and the dose and schedule adopted for etoposide may have been sub-optimal. We now know that etoposide may be safely prescribed in higher doses and is probably more effective if given over three to five days. An optimal regimen would be expected to cause some myelotoxicity, which in this study was particularly low.

The overall survival rates in the two randomised groups of patients were similar regardless of whether VAC or etoposide was given first. Thus patients were probably not at a disadvantage by being initially allocated to receive single agent chemotherapy. Survival was longest in patients showing a complete response to either treatment and, when the responses to first and second line treatment were combined, this occurred more frequently with VAC than with etoposide (19 of 82 patients treated with VAC, five of 75 patients treated with etoposide). The survival of patients achieving a complete response was disappointingly short and only one patient is alive 40 months after treatment. This contrasts with the claims of others, who report a two year survival rate of over

20% in early stage patients treated with more intensive combination regimens,<sup>10</sup> though 10–15% may be a more realistic figure.<sup>11</sup> Thus neither etoposide nor VAC would appear to be justified for patients defined as having early disease by modern staging criteria.

This study did not include measurements of quality of life though a response to treatment, whether partial or complete, was generally associated with an improvement in symptoms. When palliation is the best that may be expected, simply administered and less toxic regimens such as etoposide or VAC may be justified, at least until more effective drugs are available.

We wish to acknowledge the valued assistance of Mr I Fleming, pharmacist at the Royal Lancaster Infirmary, and Miss M Hickman for the secretarial work.

## References

- Comis RL. Small cell carcinoma of the lung. *Cancer Treat Rev* 1982;9:237–58.
- Livingstone RB, Moore TN, Heilbrun L, *et al.* Small cell carcinoma of the lung: combined chemotherapy and radiation: a Southwest Oncology Group study. *Ann Intern Med* 1978;88:194–9.
- Radice PP, Bunn PA Jr, Ihde DC. Therapeutic trials with VP-16-213 and VM26: active agents in small cell lung cancer, non-hodgkin's lymphoma and other malignancies. *Cancer Treat Rep* 1979;63:1231–9.
- Karnofsky DA, Abelman WH, Craven LF, Burchenal JH. Use of nitrogen mustard in the palliative treatment of cancer. *Cancer* 1948;1:634–56.
- Zelen M. Keynote address: Biostatistics and data retrieval. *Cancer Chemother Rep* 1973;4:31–42.
- Catane R, Lichter A, Lee YJ, Brerton HD, Schwade JG, Glatstein E. Small cell lung cancer. Analysis of treatment factors contributing to prolonged survival. *Cancer* 1981;48:1936–43.
- Lowenbraun S, Bartolucci A, Smalley RV, *et al.* The superiority of combination chemotherapy over single agent chemotherapy in small cell lung cancer. *Cancer* 1979;44:406–13.
- Daniels JR, Chak LY, Sikic BI, *et al.* Chemotherapy of small cell carcinoma of lung: a randomized comparison of alternating and sequential combination chemotherapy programs. *J Clin Oncol* 1984;2:1192–9.
- Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring systems in 407 small cell lung cancer patients. *Int J Cancer* 1987;39:146–9.
- Oldham RK, Greco FA. Small cell lung cancer: a curable disease. *Cancer Chemother Pharmacol* 1980;4:173–7.
- Hansen HH, Roth M. Small cell carcinoma of lung. In: Flenley DC, Petty DC. *Recent advances in respiratory medicine*. Edinburgh: Churchill Livingstone, 1983: 193–202.