

A phase II study of oral etoposide in elderly patients with small cell lung cancer

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ABSTRACT Thirty five previously untreated patients with small cell lung cancer older than 70 years were treated with oral etoposide (800 mg/m² over five consecutive days) every four weeks. Twenty two patients had extensive disease and 13 limited disease. The overall response rate was 71%. The median survival for patients with limited diseases was 16 (range 6-32) months and for patients with extensive disease nine (range 4-17) months. There was mild haematological toxicity and alopecia but no major toxicity. It is concluded that etoposide in this dose regimen is an effective and well tolerated treatment for elderly patients with small cell lung cancer.

Introduction

For most patients with small cell lung cancer the introduction of combination chemotherapy has considerably prolonged median survival¹ in addition to improving the quality of life. For elderly patients, however, aggressive combination chemotherapy is often associated with life threatening toxicity, especially myelosuppression.² For these reasons elderly patients often have been and still are excluded from most clinical phase II trials. Treatment of these patients, however, is often indicated.

One of the most active agents for small cell lung cancer is the epipodophyllotoxin derivative etoposide (VP 16-213), which has been associated with response rates of up to 65% when used as a single agent in previously untreated patients.³ It is associated with relatively mild toxicity, mainly myelosuppression. Etoposide has clearcut dose and schedule related activity; a five day regimen has been shown to be superior to a single infusion of the same total dose in patients with small cell lung cancer.⁴

Etoposide is available for oral administration, after which bioavailability is about half, though there is considerable interpatient and inpatient variability.⁵ We have evaluated the activity and toxicity of orally administered etoposide as palliative treatment in elderly patients with small cell lung cancer.

Methods

Thirty five consecutive patients (33 of them male) with previously untreated small cell lung cancer were treated from August 1985 to October 1987 with the same protocol (for their characteristics see table). All met the following criteria: cytologically or histologically proved small cell lung cancer, age over 70 years, ECOG performance score 0-3. The extent of their disease was assessed on the basis of findings at physical examination, biochemical profile, and chest radiograph. If there was clinical suspicion or biochemical or radiological evidence of further extension, isotope bone scanning or liver ultrasonography or both were performed. Limited disease was defined as evidence of disease within one hemithorax and supra-

Characteristics of the 35 patients

Male:female	33:2
Age (median (range), y)	73 (70-95)
ECOG performance score:	
0	2
1	10
2	10
3	13
Extent of disease:	
Limited (LD)	13
Extensive (ED)	22
Response rate (%)	71
Remissions:	
Complete	5 LD, 1 ED
Partial	5 LD, 14 ED
Stable disease	3 LD, 5 ED
Early deaths	2 ED
Survival (median (range), mo):	
LD	16 (6-32)
ED	9 (4-17)

ECOG—Eastern Cooperative Oncology Group.

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Accepted 25 April 1989

clavicular fossa and extensive disease as evidence of disease beyond these borders. Twenty two patients had extensive disease and 13 limited disease.

Each cycle of etoposide consisted of a total dose of 800 mg/m² body surface area, divided over five consecutive days. Etoposide was given orally, in 50 or 100 mg capsules (Vepesid, Bristol Myers) supplied by the patient's pharmacist or general practitioner, individual doses being rounded up or down to the nearest 50 or 100 mg. Treatment was repeated every four weeks on an outpatient basis. Chemotherapy was discontinued if there were signs of progressive disease; patients who responded received a maximum of 12 courses.

Toxicity and response were scored according to WHO criteria⁶ three weeks after each treatment. This was usually the only hospital visit during the treatment cycle. Patients were considered evaluable if they had completed at least one treatment cycle. Response was assessed by physical examination and chest radiography. Bronchoscopy was not repeated. A complete remission was defined as complete regression of evaluable tumour, and a partial response as a decrease of 50% of the product of two perpendicular diameters of measurable lesions or a 30% decrease of one diameter of an evaluable lesion. Adjustment of the dose to 75% of the previous dose was carried out if full haematological recovery had not occurred three weeks after the previous cycle.

Survival time was determined from the start of treatment.

Results

The total number of cycles was 205 and the median number of cycles given was six (range 1–12).

RESPONSE AND SURVIVAL

Thirty three patients were evaluable for their response (table); two patients died during the first cycle owing to progression of the tumour. The overall response rate was 71%, six patients showing complete regression and 19 partial regression (five limited disease, 14 extensive disease). Median survival was 16 months (range 6–32 months) for the limited disease group of patients and nine months (range 4–17 months) for those with extensive disease. One patient is still alive 22 months after the start of treatment.

TOXICITY

As expected, bone marrow suppression was the predominant form of toxicity, though the incidence was low. There were no hospital admissions for drug related toxicity, including neutropenia, thrombocytopenia, or anaemia. Only one patient needed adjustment of the dose and no deaths were related to treatment.

All patients experienced alopecia, usually complete. Gastrointestinal toxicity was easy to handle. Only a few patients needed symptomatic treatment.

Discussion

The proportion of patients with small cell lung cancer who are over 70 years is not clear. In a report by Kreyborg in 1969⁷ only 4% of the patients with small cell lung cancer were over 70, though in a recent large American survey 26% were over 70.⁸ In our institutions about 15% of patients presenting with small cell lung cancer are older than 70. Concerns about increased toxicity of combination chemotherapy in elderly patients may be the reason why physicians tend to avoid this approach.⁹

Various reports are available on palliative treatment of elderly patients or those with a poor prognosis (by virtue of their performance score or extent of disease). In two studies using a two drug regimen including etoposide^{10,11} response rates were around 70%. The results for our patients with extensive disease—a 70% response rate and a median survival of nine months—are in agreement with the results of these studies. For the patients with limited disease the median survival was somewhat longer than in the study of Allan *et al*¹⁰: 16 versus 12.5 months. We had less toxicity and no drug related deaths, and apart from alopecia no important non-haematological side effects. In these two studies the other drug in the combination, vindesine or vincristine, probably contributed to the observed toxicity. A major advantage of our treatment is that it may be given on an outpatient basis with minimal investigations and hospital visits.

The median survival for the patients in this study is very reasonable both for those with extensive disease (nine months) and for those with limited disease (16 months). Though some series report better survival for the latter group, this might be only at the cost of more treatment related toxicity. Certainly for elderly patients, who are less able to tolerate or survive standard chemotherapy regimens, a shorter median survival with the alleviation of symptoms may be considered as an acceptable goal.

We conclude from our data that orally administered etoposide at a dose of 800 mg/m² divided over five consecutive days is a well tolerated and effective regimen for palliation in elderly patients with small cell lung cancer.

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