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 survival in addition to improving the quality of life. For elderly patients, however, aggressive combination chemotherapy is often associated with life threatening toxicity, especially myelosuppression. 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. 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 lung cancer.

Etoposide is available for oral administration, after which bioavailability is about half, though there is considerable interpatient and intrapatient variability. 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 suprathoracic region.

Characteristics of the 35 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>33:2</td>
</tr>
<tr>
<td>Age (median, range, y)</td>
<td>73 (70–95)</td>
</tr>
<tr>
<td>ECOG performance score:</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Extent of disease:</td>
<td></td>
</tr>
<tr>
<td>Limited (LD)</td>
<td>13</td>
</tr>
<tr>
<td>Extensive (ED)</td>
<td>22</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>71</td>
</tr>
<tr>
<td>Remissions:</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>5 LD, 1 ED</td>
</tr>
<tr>
<td>Partial</td>
<td>3 LD, 14 ED</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 LD, 5 ED</td>
</tr>
<tr>
<td>Early deaths</td>
<td>2 ED</td>
</tr>
<tr>
<td>Survival (median, range, mo):</td>
<td></td>
</tr>
<tr>
<td>LD</td>
<td>16 (6–32)</td>
</tr>
<tr>
<td>ED</td>
<td>9 (4–17)</td>
</tr>
</tbody>
</table>

ECOG—Eastern Cooperative Oncology Group.

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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 criteria a 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 radiogra-
phy. 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 regres-
sion 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, thrombo-
cytopenia, 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 1969 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 institu-
tions about 15% of patients presenting with small cell
lung cancer are older than 70. Concerns about in-
creased toxicity of combination chemotherapy in
elderly patients may be the reason why physicians
tend to avoid this approach.

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 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;9
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, vin-
desine 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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