Dose-escalation Study of Oral Etoposide and Carboplatin in Patients with Advanced Lung Cancer

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A dose-escalation study of daily etoposide and carboplatin was carried out on 23 patients with advanced lung cancer using a starting dose of 40 mg/m²/day etoposide given orally for 21 days and 250 mg/m² carboplatin given intravenously (IV) on day 1. A total of 41 courses were given. Myelosuppression was the major dose-limiting toxicity. The maximum tolerated dose was reached at the fourth level with 40 mg/m²/day etoposide for 21 days and 400 mg/m² carboplatin on day 1, once every 4 weeks. Non-hematological toxicities were generally mild or reversible. The recommended doses of this combination chemotherapy are 40 mg/m²/day etoposide for 21 days and 350 mg/m² carboplatin on day 1. The response rate for non-small cell lung cancer and small cell lung cancer was 16.7% and 60% (95% confidence intervals of 3.6% to 41.4%, and 14.7% to 94.7%), respectively. A phase II study is necessary to define the efficacy and safety of this combination chemotherapy.

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Key words: Lung Cancer—Etoposide—Carboplatin—Phase I Study

Introduction

Cisplatin-containing regimens show activity against both small cell (SCLC) and non-small cell (NSCLC) lung cancers.1,2 Although a reproducible response rate in the range of 30% can be obtained with cisplatin-containing combination regimens, these therapies have had little impact on the survival of patients with NSCLC.3

Carboplatin, an analogue of cisplatin, shows no nephrotoxicity, neurotoxicity or ototoxicity and is much less emesis-provoking than cisplatin.4-10 The dose-limiting toxicity is bone marrow suppression, thrombocytopenia being more marked than leukopenia. It has considerable activity against SCLC and modest activity against NSCLC.11-14

Etoposide, a semisynthetic derivative of podophyllotoxin, which has been demonstrated to have significant antitumor activity against SCLC, germ cell tumors, malignant lymphoma, and probably also NSCLC.15,16 In addition, recent studies have indicated that etoposide, a topoisomerase II inhibitor, is highly schedule-dependent and that prolonged administration may enhance its effectiveness against resistant tumors.17-19 Use of oral etoposide allows long-term administration without the need for repeated or continuous venous access. Prolonged oral administration of etoposide for 14 or 21 days has been extensively studied in patients with SCLC and NSCLC, non-Hodgkin's lymphoma, germ cell tumors, and ovarian cancer.19-23 Based on these studies, prolonged exposure to low concentrations of the drug is considered important for its antitumor efficacy.

There is evidence that etoposide in combination with cisplatin produces synergistic activity against experimental animal tumors.24 The combination of etoposide and carboplatin has also been proven to exert a synergistic effect against animal tumor models.25 Therefore, we considered it reasonable to combine oral etoposide and carboplatin in a phase I study of this combination regimen in patients with advanced lung cancer.
COMBINATION CHEMOTHERAPY FOR ADVANCED LUNG CANCER

Patients and Methods

Patient Selection

To be eligible for this study patients had to fulfill the following criteria: (1) cytologic or histologic proof of lung cancers that failed to respond to conventional chemotherapy or for which no standard therapy exists; (2) a minimum interval of 4 weeks since prior chemotherapy or radiation therapy (6 weeks for nitrosoureas or mitomycin C); (3) assessable lesion; (4) age of 75 yr or younger; (5) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; (6) adequate bone marrow function (leukocyte count ≥4000/μl, platelet count ≥150,000/μl, and hemoglobin concentration ≥10 g/dl), hepatic function (bilirubin level ≤1.5 mg/dl and GGT/ALP < 2 times upper limit of normal), and renal function (creatinine level ≤1.2 mg/dl and blood urea nitrogen concentration ≤25 mg/dl); (7) no coexisting complications severe enough to prevent compliance with the study or expose the patient to unnecessary risk; (8) written informed consent.

Dose Escalation Procedure and Evaluation

The purpose of this study was to determine the maximum tolerated dose (MTD) of oral etoposide plus carboplatin when given to patients with advanced lung cancer. Four dose levels were chosen (Table I). The starting doses of etoposide and carboplatin were 40 mg/m²/day orally for 21 days and 250 mg/m² intravenously (IV) on day 1 per course, respectively. Carboplatin was escalated from 250 mg/m² to 400 mg/m², combined with a fixed dose (40 mg/m²/day) of etoposide. We chose the dose of etoposide in accordance with a previous report by Fukuoka et al. At least three patients were included per dose level. Patients received IV carboplatin as a 1-h infusion with 500 ml of 5% dextrose. The full dose of etoposide was given before breakfast in the form of a soft gelatin capsule on days 1 through 21. After 21 days, etoposide was discontinued for 1 week. Because etoposide is only available in 25-mg or 50-mg capsules, it was necessary to make some approximations in the calculated daily dose. The method of approximation was the same as that reported previously by Hainsworth et al. Briefly, if a patient was calculated to receive 65 mg/day, etoposide was given as 75 mg, 75 mg, 75 mg, and 50 mg on 3 consecutive days, respectively, and the schedule was repeated for 21 days. During the 21-day course, etoposide was discontinued until recovery if the leukocyte count fell below 2000/μl or the platelet count fell below 50,000/μl. In SCLC patients, this regimen was discontinued after one course if a patient’s disease had not changed or was progressive. For these SCLC patients, another session of salvage chemotherapy or radiotherapy was planned, depending on the individual clinical situation. NSCLC patients who were stable or who had shown a response received a second course; treatment was discontinued after one course in those with disease progression. Before the next course was started, the leukocyte count had to be 3000/μl or higher and the platelet count 100,000/μl or higher.

Patients underwent a complete blood cell count, differential count, and platelet count before their first course of treatment and at least twice weekly thereafter. Serum renal and hepatic chemistry studies were done before therapy and once weekly, as well as studies of electrolytes, urinalysis, complete history, physical examination, and toxicity evaluation.
Plan of Phase I Study

The MTD was defined as the dose level at which at least 2 of 3 patients developed leukopenia and thrombocytopenia of WHO grade 4. Non-hematological toxicity at grade 3 except alopecia was also used as a criterion to establish the MTD. If at least 2 of 3 patients developed non-hematological toxicity, this level was considered to be the MTD. If the WBC count decreased to less than 1000/µl and/or the platelet count to less than 25,000/µl during the first course, both drugs had a 25% dose reduction for the next course.

Tumor response and drug toxicity were classified in accordance with the WHO criteria.

Results

Twenty-three patients were entered onto the study between February 1990 and October 1991, and their characteristics are listed in Table II. There were 19 men and 4 women, with a median age of 59 years (range, 43–75 yr). Five patients had SCLC and 18 had NSCLC. Eighteen patients had no previous therapy. A total of 41 courses were given; all were assessable for toxicity and response. The numbers of patients and courses per dose level are shown in Table III.

Toxicity

Hematological toxicity and non-hematological toxicity were analyzed during all the courses of therapy. Myelosuppression was the principal dose-limiting toxicity of this schedule (Table III). A dose-related reduction of complete blood cell count was noted. WBC and platelet count of WHO grade 4 were seen with step 4. Non-hematological toxicity was relatively mild (Table IV). There were no treatment-related deaths. We considered step 3 as the recommended dose for the phase II study.

Response

Response data for this study are shown in Table V. Five patients received one course of therapy, 16 patients two courses, 1 patient four courses, and 1 patient five courses. When analyzed by intent-to-treat policy, three of 18 patients with NSCLC achieved partial responses (16.7%, 95% confidence intervals of 3.6% to 41.4%). There were no complete responses. In SCLC patients, the response rate was 60% (95% confidence intervals of 14.7% to 94.7%).

Relative Dose Intensity of Oral Etoposide and Carboplatin Dose Administered

The actual doses of oral etoposide and carboplatin administered are presented in Table VI as per-
COMBINATION CHEMOTHERAPY FOR ADVANCED LUNG CANCER

Table IV. Non-hematological Toxicities of Oral Etoposide and Carboplatin

<table>
<thead>
<tr>
<th></th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total no. of courses</td>
<td>9</td>
<td>13</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>No. of courses with WHO grade ≥ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

Table V. Response by Histology

<table>
<thead>
<tr>
<th>No. of evaluated patients</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>Response rate (%)</th>
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<tbody>
<tr>
<td>Non-small cell patients</td>
<td>18</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Small cell patients</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>60</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table VI. Dose-escalation Scheme and Treatment Given to Patients Receiving Oral Etoposide and Carboplatin

<table>
<thead>
<tr>
<th>Step</th>
<th>No. of patients</th>
<th>Total no. of courses</th>
<th>Delivered dose/projected dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Etoposide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carboplatin</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>9</td>
<td>89.0</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>8</td>
<td>90.4</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>11</td>
<td>82.9</td>
</tr>
</tbody>
</table>

percentages of the projected dose and the interval between the courses in days. It was possible to give nearly all of the projected doses, and courses were delayed by a mean of 4.9 days (range, 0–18 days). Five patients were unable to receive 2 or more courses; three patients had progressive disease, one had worsening of PS, and one had leukocytopenia and thrombocytopenia of WHO grade 4.

Discussion

Etoposide has been shown to be a phase-specific cytotoxic drug and it is usually administered intravenously over 3 to 5 days. The clinical superiority of a 5-day schedule versus a 1-day schedule has been demonstrated in the treatment of SCLC. In vitro studies have clearly demonstrated that the duration of exposure of cells to etoposide dictates the degree of cytotoxicity. To achieve the same cell kill in SCLC lines, the concentration of etoposide required in a 1-h exposure is 100 times that of a continuous incubation. Slevin et al. reported that the duration of plasma drug levels greater than 1 μg/ml correlated with tumor response better than peak drug levels or the total area under the plasma concentration versus time curve (AUC). Recently, the prolonged oral administration of etoposide for 21 days has produced excellent results in patients with relapsed or refractory SCLC and NSCLC. Hainsworth et al. and Johnson et al. demonstrated the feasibility of administering oral etoposide at 50 mg/m² for 21 consecutive days, and reported a 46% response rate in the treatment of relapsed or refractory SCLC using this dose and schedule. Fukuoka et al. reported a phase I study of chronic daily dosing with oral etoposide in combination with cisplatin for patients with advanced cancer. He recommended that phase II
studies in patients with malignancies sensitive to etoposide be carried out using a daily oral etopo-
side dose of 40 mg/m² for 21 days plus 80 mg/m²
IV cisplatin.

The present study demonstrated that the MTD
was a dose of 40 mg/m²/day etoposide for 21
days and 400 mg/m² carboplatin on day 1. Oral
etoposide (50 mg/m²/day) and carboplatin (300,
350 or 400 mg/m²) in the same schedule was also
used previously by Johnson et al.\(^{35}\) In their
report, the response rate was 27% for NSCLC.

There has been one prospective, randomized
phase III trial comparing two-drug regimens of
etoposide with cisplatin or carboplatin for NSCLC.
In this trial the response rates (27% versus 16%)
and median survivals (30 weeks versus 27 weeks)
were similar, and differences were not statistically
significant.\(^{36}\) Less non-hematological toxicity was
seen in the patients treated with carboplatin. Over-
all hematological toxicity was similar in the two
regimens.

Lung cancer patients are often elderly and have
medical problems related to other organ sites, such
as chronic heart disease or renal functional impair-
ment. Therefore, carboplatin-based regimens may be
less toxic than cisplatin-based regimens for these
patients.

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