Carboplatin Calculated with Chatelut’s Formula Plus Etoposide for Elderly Patients with Small-Cell Lung Cancer

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Abstract

Objective This dose escalation was conducted to evaluate the applicability of Chatelut’s dosing, and to determine the efficacy and toxicity of carboplatin with etoposide in previously untreated elderly patients (>70 years) with small cell lung cancer.

Patients and Methods Seventeen patients were treated with etoposide for 3 days and carboplatin calculated dose using Chatelut’s formula on day 1 intravenously. The starting doses of etoposide on days 1 to 3, and carboplatin using the area under the concentration versus time curve (AUC) were 90 mg/m² and 4 mg/ml-min, respectively.

Results The median age was 77 years (range 71 to 87). Dose-limiting toxicity (DLT) was seen at level 4 (AUC 5 mg/ml-min of carboplatin and etoposide 100 mg/m²). Hematologic toxicity was the primary DLT. Grade 4 thrombocytopenia and Grade 4 leukopenia were observed at level 4. Non-hematologic toxicity was insignificant. The overall response rate was 94%.

Conclusion Etoposide at 100 mg/m² and AUC of carboplatin of 4.5 mg/ml-min as calculated using Chatelut’s formula every four weeks is the recommended dose for further phase II trials for elderly patients with small cell lung cancer.

Key words: combination chemotherapy, lung cancer, dose escalation, area under the concentration curve

Introduction

Many elderly patients with small cell lung cancer (SCLC) receive less chemotherapy with more dose reductions and fewer cycles because they may have a lesser ability to tolerate these therapies (1, 2). Although an age-related decrease in physiologic functions including the glomerular filtration rate is well known (3), increased age is not always associated with reduced function (4).

The combination of carboplatin and etoposide has been proven synergistic against animal tumor models (5, 6). Chatelut’s carboplatin calculation dosage formula (Fig. 1) is useful for elderly patients, as it includes age, sex, body weight and serum creatinine as the parameters, and excludes 24-hour creatinine clearance (7).

Patients and Methods

Patient eligibility

Patient selection was restricted to those over 70 years of age with no prior chemotherapy or radiotherapy, with histologically or cytologically proven SCLC. Eligibility stipulated measurable or evaluable disease, performance status of 0–3 on the ECOG scale, adequate hepatic function with serum transaminases <2 times upper limit of normal and normal total bilirubin, adequate renal function with normal serum creatinine, adequate pretreatment bone marrow reserve (leukocyte count >4,000/μl, and platelet count >100x10³/μl), and adequate cardiac functions. Written informed consent was obtained from all patients.

Dose calculation and administration

Patients were treated in cohorts of at least three individuals. The study was designed to escalate the doses of both etoposide and carboplatin until the maximum tolerated dose (MTD) was reached. Decisions to escalate the doses were based upon acute toxicities in cycle 1. Dose escalation continued with the following dose levels of carboplatin (mg/ml-min)/etoposide (mg/m²) evaluated: 4/90, 4/100, 4.5/100, 5/100 (Table 1). Toxicities were graded according to the World Health Organization (WHO) criteria (8). Dose limiting-toxicity (DLT) was defined as at least one of the following: 1) Absolute neutrophil count (ANC) of <500/μl for >3 days or associated with fever exceeding 38°C; 2) platelet count of ≤25,000/μl; or 3) grade 3 non-

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Received for publication April 11, 2000; Accepted for publication October 30, 2000

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Internal Medicine Vol. 40, No. 7 (July 2001) 603
Figure 1. Chatelut’s formula. Carboplatin (CBDCA) dosage were calculated with target AUC by CBDCA clearance. Body weight is expressed by the kilogram (kg). As for “sex”, Chatelut et al substituted zero for male and one for female.

Table 1. Dose Escalation Scheme and Dose Limiting Toxicity on the First Course at Each Level

<table>
<thead>
<tr>
<th>CBDCA</th>
<th>ETP</th>
<th>No. of patients</th>
<th>Plts. nadir grade</th>
<th>ANC nadir grade</th>
<th>Neutropenic fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1. AUC 4</td>
<td>90 mg/m²</td>
<td>5*</td>
<td>2 1 0 0 0</td>
<td>1 2 1</td>
<td>1</td>
</tr>
<tr>
<td>Level 2. AUC 4</td>
<td>100 mg/m²</td>
<td>3</td>
<td>0 0 1 0</td>
<td>0 1 1</td>
<td>0</td>
</tr>
<tr>
<td>Level 3. AUC 4.5</td>
<td>100 mg/m²</td>
<td>5**</td>
<td>3 0 2 0</td>
<td>0 0 3 0</td>
<td>0</td>
</tr>
<tr>
<td>Level 4. AUC 5</td>
<td>100 mg/m²</td>
<td>4</td>
<td>0 1 2 1</td>
<td>0 0 3 1</td>
<td>0*</td>
</tr>
</tbody>
</table>

CBDCA: carboplatin, ETP: etoposide, Plts.: platelets, ANC: absolute neutrophil count. *One: massive pleural effusion, **One: bone marrow infiltration. *One patient who received level 4 chemotherapy experienced neutropenic fever and grade 4 neutropenia continuing more than three days using recombinant colony stimulating factor. Another one patient experienced grade 3 thrombocytopenia and neutropenia.

hematologic toxicities excluding nausea/vomiting and alopecia. The MTD was defined as the dose at which >33.3% of the patients experienced DLT during the first cycle of chemotherapy.

The carboplatin dose which was determined based on Chatelut’s formula (7) was administered on day 1 intravenously over one hour in a 500 ml dextrose solution. The use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was allowed only for patients who developed grade 3 or worse leukopenia. Chest irradiation at a dose of 45 Gy in 30 accelerated hyperfractionations over three weeks was given for patients with limited disease (LD) after four cycles of chemotherapy.

Dose modification

Etoposide dose was reduced on the next cycle to 80 mg/m²/day when grade 4 hematologic toxicities were observed during the previous chemotherapy course, and if the platelet count was under 2.5x10⁹/µl, only 90% of the calculated dose carboplatin was injected. If grade 2 non-hematologic toxicities excluding nausea/vomiting and alopecia were observed, chemotherapy was to be discontinued.

Response, and response duration

Tumor responses were classified in accordance with the WHO criteria (8). The duration of the response was measured from the start of the treatment to disease progression. Patients who did not achieve a complete response (CR) or partial response (PR) after a second course were removed from the study.

Results

Characteristics of patients

Between March 1995 and December 1998, 17 patients were enrolled. There were 13 men and four women with a median age of 77 years (range 71–87). Eleven patients had limited disease and six had extensive disease. The ECOG performance status (PS) was 0–1 in twelve patients and 3 in one patient. A patient with a PS of 3 was treated at dose level 2, and his condition got better with a PS 2 after the first course.

The study was approved in advance by our hospital's Institutional Review Board.

Treatment received

Three to five patients were enrolled at each dose level. All
17 patients received at least two courses. Carboplatin doses calculated with Chatelut’s formula were 242 mg/m² (193 to 305 mg/m²) in level 1, 192 mg/m² (190 to 245 mg/m²) in level 2, 363 mg/m² (286 to 363 mg/m²) in level 3 and 297 mg/m² (280 to 316 mg/m²) in level 4.

Three patients (2 LD and one ED) received three courses and 13 received four or more courses. Seven of 11 (63.4%) LD patients received chest irradiation after chemotherapy. One LD patient experienced no change with chemotherapy and received chest irradiation after two courses of chemotherapy. Another patient who achieved a partial response received chest irradiation after three cycles of chemotherapy. Four LD patients did not receive chest irradiation because of poor respiratory function, and/or patient’s refusal.

### Hematologic toxicity and dose-limiting toxicity

One of the major clinical toxicities observed during this study was bone marrow suppression, principally neutropenia (Table 1). Grade 4 neutropenia was observed already at the first dose level; however, in all such occurrences, at levels 1–3, grade 4 neutropenia recovered within 3 days and those were thus not considered DLTs. The MTD was reached at dose level 4 because three of four patients experienced DLTs (grade 4 neutropenia; grade 4 thrombocytopenia; and neutropenic fever). Grade 3 anemia was noted at levels 3 and 4.

Because of dose modification, the hematologic toxicities were relatively infrequent in all courses. Grade 4 thrombocytopenia was experienced in only one course in level 4 (Table 2). Grade 3/4 neutropenia was seen in 90% and 86% of courses on level 3 and level 4, respectively.

### Non-hematologic toxicity

Non-hematologic toxicity was of minor importance in all patients. Grade 3 alopecia and nausea/vomiting were seen in two patients at levels 3 and 4.

### Efficacy

Sixteen of 17 patients achieved objective response with 4 CRs and 12 PRs with an overall response rate of 94% (95% Confidence Interval; 81.6% to 100%). The response duration was 223 days (range 79 to 121+ days), and overall survival was 375 days (range 132 to 1213+ days).

### Discussion

The age-specific incidence rate for lung cancer increases dramatically with age and specific treatment decisions must be made for elderly patient with lung cancer (9, 10). Despite the documented potential for survival benefit with treatment, elderly patients are frequently excluded from clinical trials and there is no standard chemotherapy for elderly patients with SCLC. Shepherd et al (1) reported no significant differences between the three age groups aged 70 to 74, aged 75 to 80 and aged over 80 years. The survival of patients who received chemotherapy is significantly longer than that of untreated patients even though frequent dose reductions for toxicity may be required. The elderly patients who received chemotherapy experienced toxicity more frequent, especially myelosuppression than younger patients. Chemotherapy with oral etoposide was recommended for elderly patients at several phase II trials (11, 12). On the contrary, Miller et al (13) compared three-day oral etoposide plus cisplatin with 21-day oral etoposide plus cisplatin. In their study, more toxicities especially nausea and appetite loss were experienced on 21-day oral etoposide plus cisplatin regimen although the two regimens had equivalent activity for SCLC. The combination of carboplatin and etoposide seems effective and less toxic than the combination of cisplatin and etoposide (6, 14, 15). Carboplatin plus etoposide was generally used at a dose of 320 to 450 mg/m² of carboplatin and 80 mg/m² to 100 mg/m² of intravenous etoposide for three days (16) but for elderly patients the carboplatin dosage was reduced to 150–300 mg/m² (6, 9, 17).

The renal clearance of anticancer agents is highly variable in elderly patients; this is one of the biggest problems for treatment (18, 19). Calvert’s carboplatin calculation dosage formula (20) is useful and simple but it includes glomerular filtration rate (GFR). GFR is often substituted by 24-hour creatinine clearance which necessitates hospitalization to measure and increases aberration in elderly patients. Chatelut’s carboplatin calculation dosage formula (20) is useful for elderly patients, as it excludes 24-hour creatinine clearance (7).

Using Chatelut’s formula, the carboplatin dosage determined with target area under the concentration versus time curve (AUC) and carboplatin clearance, we performed dose escalation study with carboplatin dosing based on Chatelut’s formula and intravenous three-day etoposide.
This study has shown that the MTD was reached at an AUC of 5.0 mg/ml/min by Chatelut’s formula for carboplatin and etoposide of etoposide on days 1–3. DLTs were leukopenia, neutropenia, thrombocytopenia, and neutropenic fever. In 17 elderly SCLC patients, we observed encouraging 12 (71%) partial responses and 4 (23%) complete responses, with an overall response rate of 94%. For future phase II studies, the recommended doses are carboplatin at an AUC of 4.5 mg/ml/min on day 1 and etoposide 100 mg/m² of etoposide on days 1–3 at 4-week intervals.

Recent studies for LD-SCLC that included thoracic irradiation, especially concurrent use reported superior response rates, time to progression, and overall survival rates (21). However, elderly patients over age 70 years or over age 75 years were excluded in such studies (22, 23), and the meta-analysis performed by Pignon et al (24) did not demonstrate the benefit of chest irradiation for elderly patients over age 70 years. To confirm the efficacy of thoracic irradiation for elderly patients, a randomized study is needed.

Acknowledgements: We wish to thank Mr. Seiji Ito, Oncology Department staff, Bristol-Myers Squibb K.K., Tokyo, Japan, for his help in the data collection and analysis and Dr. Nydia E.C. Cotelly, Executive Director, Medical Affairs, Intercontinental, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey, U.S.A., for critically reviewing multiple drafts of the manuscript.

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