Phase I Study of Topotecan and Cisplatin in Patients with Small Cell Lung Cancer

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Objective: A single-agent topotecan has an indication for the treatment of small cell lung cancer in Japan. Previous studies demonstrated that topotecan combined with a platinum agent could provide additional antitumor efficacy. This study was to find the recommended dose of topotecan in combination with cisplatin and preferred administration sequence in untreated patients with extensive disease small cell lung cancer for Phase II study.

Methods: Patients received topotecan as a 30 min infusion for 5 days in escalating doses (starting at 0.5 mg/m²/day), and cisplatin at a fixed dose of 60 mg/m² 3 weeks cycle. This study employed the following stages: cisplatin was given before topotecan on day 1 to previously treated patients (Stage 1). After the maximum-tolerated dose level was achieved, the same schedule was applied for untreated patients (Stage 2). Subsequently, cisplatin was given after topotecan on day 5 to untreated patients (Stage 3). The recommended doses of cisplatin on day 1 and 5 schedules were estimated by considering results obtained from Stages 2 and 3, respectively.

Results: A total of 34 patients were enrolled. The maximum-tolerated doses in Stages 1–3 were estimated at 0.65, 0.65, and 1.4 mg/m², respectively. The recommended doses of cisplatin on day 1 and 5 schedules in untreated patients were determined at 0.65 and 1.0 mg/m², respectively. The major toxicity in this combination was hematological events.

Conclusions: For treatment-naïve patients, the combined use of 0.65/60 mg/m² topotecan/cisplatin with cisplatin on day 1 schedule or 1.0/60 mg/m² topotecan/cisplatin with cisplatin on day 5 schedule is recommended for Phase II study.

Key words: small cell lung cancer — combination chemotherapy — topotecan — cisplatin

INTRODUCTION

Small cell lung cancer (SCLC) is often diagnosed at the extensive disease (ED) stage due to lesion location and rapid disease progression (1). Multiagent chemotherapy is the mainstay of treatment for SCLC, and combination regimens such as cisplatin + etoposide are being used as the standard therapy for ED cases (2). Topotecan, a topoisomerase-I inhibitor, has a favorable toxicity profile compared with most other agents that are active in SCLC. Topotecan has a well-characterized and predictable hematologic toxicity profile that includes neutropenia, which is manageable, short-lived and reversible. The non-hematologic effects of topotecan are generally mild and include manageable gastrointestinal toxicities (3). A single-agent topotecan showed significant activity in SCLC, particularly in patients sensitive to prior chemotherapy; therefore, the incorporation of topotecan in combination chemotherapy regimens for the future treatment of SCLC was warranted (3). Although single-agent topotecan has already an indication for the treatment of SCLC in Japan, previous preclinical and clinical studies have demonstrated that the combination of topotecan with a
platinum agent, such as cisplatin, could provide additional antitumor efficacy (4–9). In addition, one study addressed the impact of cisplatin scheduling and showed that the sequence of cisplatin before topotecan induced significantly worse hematological toxicity than the alternate sequence (10). To improve the therapeutic effect of this combination, the granulocyte colony-stimulating factor (G-CSF) was employed as concomitant therapy in our study.

Thus, we designed the present study to evaluate both administration sequences. The prime objective of the study was to determine the recommended dosage for a subsequent Phase II study from the estimation of maximum-tolerated dose (MTD) of topotecan in combination with 60 mg/m² cisplatin on day 1 or 5 in previously untreated patients with SCLC.

METHODS

Eligibility

Written informed consent was obtained from all patients prior to treatment. The protocol and informed consent procedures were reviewed and approved by the Institutional Review Board of each participating institute. Eligibility criteria were as follows: histologically or cytologically proven SCLC; 20–74 years old; previously treated with single-regimen chemotherapeutic and/or radiotherapy, or previously untreated patients with ED; no prior treatment with biological response modifiers within 2 weeks; adequate organic function (hemoglobin level ≥ 9.5 g/dl, leukocyte count of 4000–12 000/mm³, neutrophil cell count ≥ 2000/mm³, platelet count ≥ 100 000/mm³, aspartate aminotransferase and alanine aminotransferase levels < 2.5 times the upper limit of normal, total bilirubin value < 1.5 mg/dl, serum creatinine below the upper limit of normal, partial pressure of arterial oxygen ≥ 60 mmHg); performance status of 0–1 on the Eastern Cooperative Oncology Group scale; a life expectancy of at least 3 months; and hospitalized patients.

Exclusion criteria included the following: serious infection or other serious concurrent disease; massive pleural effusion or ascites; interstitial pneumonia or pulmonary fibrosis; symptomatic central nervous system metastasis; concomitant malignancies; patients who received bone marrow or peripheral blood stem cell transplantation; a past history of drug allergy; actual or potential pregnancy, marrow or peripheral blood stem cell transplantation; a past history of drug allergy; actual or potential pregnancy, calculated life expectancy of less than 3 months; and hospitalized patients.

ASSESSMENT OF TREATMENT

Toxicities were assessed according to the US National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. The severity of other events not listed in the
NCI-CTC was graded as follows: Grade 1, slight; Grade 2, moderate; Grade 3, severe; and Grade 4, life threatening. During the study, complete blood cell counts and biochemistry tests were repeated at least twice weekly, whereas other investigations were repeated as needed to evaluate marker lesions. Response was evaluated according to the modified World Health Organization (WHO) criteria (11).

RESULTS

ESTIMATION OF MTD

Between March 2000 and February 2005, 34 patients were enrolled in this study and all of them received chemotherapy. The characteristics of these patients are shown in Table 1 and the occurrence of DLTs is shown in Table 2.

STAGE 1: CISPLATIN ON DAY 1 AND TOPOTECAN ON DAYS 1–5, FOR PREVIOUSLY TREATED PATIENTS

No DLT occurred at the first cycle in three patients who received a topotecan dose level of 0.5 mg/m², and the dose of topotecan was increased to 0.65 mg/m². Since one of the three patients displayed a DLT of thrombocytopenia (<20 000/mm³), another three patients were treated at the same dose. One of the additional three patients indicated Grade 4 neutropenia lasting 4 days or more as DLTs. No more increase in dose in this stage was, however, decided by Extramural Evaluation Committee (EEC) since in three out of six cases indicated DLTs at the second cycle, although the DLTs were observed in two out of six cases in the first cycle. The MTD of this stage was estimated as 0.65 mg/m².

STAGE 2: CISPLATIN ON DAY 1 AND TOPOTECAN ON DAYS 1–5, FOR UNTREATED PATIENTS

The starting dose of topotecan in Stage 2 was 0.65 mg/m² based on Stage 1 results. As one of three patients showed Grade 4 neutropenia lasting 4 days or more as DLTs, additional three patients were treated at the same dose. One out of the three cases indicated thrombocytopenia (<20 000/mm³) and Grade 4 neutropenia lasting 4 days or more as DLTs. Although two out of the six cases indicated DLTs at the first cycle, three of the six cases indicated thrombocytopenia (<20 000/mm³) only or thrombocytopenia (<20 000/mm³) and Grade 3 non-hematological toxicity.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin injection</td>
<td>On day 1</td>
<td>On day 1</td>
<td>On day 5</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>(+)³</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>57</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>23–70</td>
<td>50–74</td>
<td>48–74</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
³Cases previously treated with single-regimen chemo- and/or radiotherapy.

Table 2. DLTs during the first cycle or other cycles at different dose levels

<table>
<thead>
<tr>
<th>Topotecan (mg/m²)</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5a</td>
<td>0.65a</td>
<td>0.65b</td>
<td>0.8b</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>1.2b</td>
</tr>
<tr>
<td>1.4b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of assessable patients</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Toxic effects with first cycle/other cycles

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia ≥4 days</td>
<td>0/0</td>
<td>1/0</td>
<td>1/0</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;20 000/mm³)</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Grade 4 neutropenia ≥4 days and thrombocytopenia (&lt;20 000/mm³)</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0</td>
</tr>
<tr>
<td>Grade3 non-hematological toxicity²</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

²Intravenous antibiotic injection for infection.
and Grade 4 neutropenia lasting 4 days or more after the second cycle or later. EEC decided that no more proceed at this stage. Topotecan 0.65 mg/m² was estimated as the MTD of Stage 2, same with Stage 1.

STAGE 3: TOPOTECAN ON DAYS 1–5 AND CISPLATIN ON DAY 5, FOR UNTREATED PATIENTS

The first four patients, including one case who was decided as not evaluable from infection due to retaining needle, were treated with 0.65 mg/m² based on the results obtained in Stage 2, and no DLT appeared. At the next dose level of 0.8 mg/m², one of three patients experienced DLTs, Grade 3 of infection as intravenous antibiotic injection. Then, additional three patients were enrolled at the same dose level, and none of the additional three patients had DLT. The dose of topotecan was increased as 1.0, 1.2 and 1.4 mg/m² in the protocol sequence. Three patients given 1.0 mg/m² and three patients given 1.2 mg/m² tolerated their dose level without DLT. Of the three patients given 1.4 mg/m², one patient developed Grade 4 neutropenia lasting 4 days. Following the hematological symptom, this patient also experienced Grade 3 gait disturbance. Furthermore, one case indicated an atrial fibrillation on day 3, although the relation between atrial fibrillation and topotecan was not clearly evidenced. Dose escalation was terminated at 1.4 mg/m²; thus, we estimated the MTD of topotecan in this stage at 1.4 mg/m².

Gait disturbance occurred on day 10 of the first cycle following Grade 4 neutropenia. Twenty days later, in this patient, a cerebral infarction around the right lateral ventricle was observed by head magnetic resonance imaging diagnosis. This symptom has taken the medical history of cerebral hemorrhage without aftereffect and complications of hyperlipidemia and hyperuricemia into account. Then, this adverse event was observed for recovery tendency. Atrial fibrillation in a patient, who had a history of slight supraventricular arrhythmia without concomitant medication (not conflicted to exclusion criteria), noted at 1.4 mg/m² topotecan dose level, appeared just after completion of topotecan administration on day 3 in the first cycle and disappeared by oral anti-arrhythmic agent on the day 4 of the first cycle.

TOXICITIES

All 34 patients of 85 cycles were fully assessable for toxicity. Grade 3/4 toxicities during the overall cycles are summarized in Table 3. The most common hematological toxicity was neutropenia, followed by thrombocytopenia, leukopenia and anemia. On total comparison between the first cycle and overall cycles in hematological toxicity, at 0.65 mg/m² of Stage 1, 0.65 mg/m² of Stage 2 and 1.0 mg/m² of Stage 3, the occurrences of anemia and thrombocytopenia were increased. Leukopenia cases in 0.65 mg/m² of Stage 2 and anemia cases in over 1.2 mg/m² of Stage 3 were also increased. Average administration cycles in each dose

### Table 3. Grade 3/4 toxicities in 85 cycles

<table>
<thead>
<tr>
<th>Topotecan (mg/m²)</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>6</td>
<td>23</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Mean of cycles</td>
<td>2.2</td>
<td>3.8</td>
<td>1.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Hematological toxicities

- **Anemia**: 0 (0) 3 (1) 4 (0) 0 (0) 0 (0) 2 (0) 1 (0) 1 (0) 32.4%
- **Leukopenia**: 1 (1) 4 (4) 6 (5) 0 (0) 0 (0) 1 (1) 0 (0) 1 (1) 38.2%
- **Neutropenia**: 2 (2) 4 (4) 6 (6) 0 (0) 0 (0) 1 (1) 1 (1) 1 (1) 44.1%
- **Thrombocytopenia**: 0 (0) 3 (2) 5 (3) 0 (0) 0 (0) 1 (0) 1 (1) 1 (1) 41.2%

Non-hematological toxicities

- **Nausea**: 0 (0) 1 (1) 3 (2) 0 (0) 1 (1) 0 (0) 0 (0) 1 (1) 17.6%
- **Vomiting**: 0 (0) 1 (1) 2 (1) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 8.8%
- **Anorexia**: 0 (0) 1 (1) 3 (2) 0 (0) 1 (0) 0 (0) 0 (0) 0 (0) 17.6%
- **Interference with daily activity**: 0 (0) 1 (1) 0 (0) 0 (0) 1 (1) 0 (0) 0 (0) 0 (0) 8.8%
- **Infection febrile**: 0 (0) 1 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 2.9%
- **Increased amylase**: 1 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 2.9%

Grade by the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Grade 3/4 toxicities in 85 cycles

- Topotecan (mg/m²)
- Stage 1: 0.5
- Stage 2: 0.65
- Stage 3: 0.65
- Overall: 0.65

- Neutropenia
- Stage 1: 0.8
- Stage 2: 1.0
- Stage 3: 1.2
- Overall: 1.4

- Thrombocytopenia
- Stage 1: 1.0
- Stage 2: 1.2
- Stage 3: 1.4
- Overall: 1.4

- Non-hematological toxicities
- Nausea
- Stage 1: 17.6%
- Stage 2: 17.6%
- Stage 3: 17.6%
- Overall: 17.6%

- Vomiting
- Stage 1: 8.8%
- Stage 2: 8.8%
- Stage 3: 8.8%
- Overall: 8.8%

- Anorexia
- Stage 1: 17.6%
- Stage 2: 17.6%
- Stage 3: 17.6%
- Overall: 17.6%

- Interference with daily activity
- Stage 1: 8.8%
- Stage 2: 8.8%
- Stage 3: 8.8%
- Overall: 8.8%

- Infection febrile
- Stage 1: 2.9%
- Stage 2: 2.9%
- Stage 3: 2.9%
- Overall: 2.9%

- Increased amylase
- Stage 1: 2.9%
- Stage 2: 2.9%
- Stage 3: 2.9%
- Overall: 2.9%
level in each stage were less than two cycles in 0.5 and 0.65 mg/m² of Stage 1 and 0.65 and 0.8 mg/m² of Stage 3, and over two cycles in other doses of Stages 2 and 3.

Principal non-hematological toxicities were observed in six cases of nausea and anorexia, three cases of vomiting and interference with daily activity and one case of infection febrile and increased amylase, excluded as DLT events.

**Clinical Response**

Clinical response is shown in Table 4. Twelve (63%) of 19 patients in Stage 3 yielded partial response (PR), whereas out of nine patients administered 1 mg/m² and more than 1.0 mg/m², seven (78%) showed PR.

**Recommended Dose**

The MTD of topotecan on days 1–5 for therapy-naive patients in combination with cisplatin on day 1 administration was estimated as 0.65 mg/m². The RD for Phase II was decided as 0.65 mg/m² by considering clinical response and toxicity. The MTD of topotecan in the case of cisplatin on day 5 administration was estimated as 1.4 mg/m². The DLTs of this dosage level were atrial fibrillation and gait disturbance in non-hematological toxicity. Since unexpected/serious non-hematological adverse events were observed at topotecan 1.4 mg/m² dose level, the RD was tentatively considered at 1.2 mg/m², in which dose level, no DLT cases were observed. However, after the first course of 1.0 mg/m² dose level, frequencies of Grade 3/4 anemia and thrombocytopenia, as hematological toxicities, indicated increased tendency. Thus, the RD for Phase II was decided at 1.0 mg/m², to secure adequate safety.

**DISCUSSION**

The combination of topotecan and cisplatin has been investigated in several studies. Boabang et al. (5) reported an *in vitro* study result indicating synergistic antitumor activity between topotecan and cisplatin presumably due to the inhibition of DNA repair mechanisms. Since this drug is categorized as an inhibitor against topoisomerase-I, a previous administration of a DNA-injuring drug seems to be useful (12). An *in vitro* combination effect with cisplatin to topotecan was, however, recognized either pre- or post-administration for topotecan. Compared with day 5 administration of cisplatin, day 1 administration indicated an increase in hematotoxicity from the pharmacokinetic mechanism caused by renal dysfunction suspected as subclinical renal tubular damage (10). From this consideration, a Phase I clinical study in therapy-naive SCLC patients aiming at RD finding was planned from the safety and efficacy of cisplatin day 1 and 5 administration schedules, under the G-CSF concomitant use for the prevention of leukopenia/neutropenia.

The MTD of topotecan in this study was 0.65 mg/m² for cisplatin day 1 administration schedule and 1.4 mg/m² for cisplatin day 5 administration schedule. The DLTs which lead these MTDs were hematological toxicities. At the first course, neutropenia was observed at two of six in the cisplatin day 1 administration group and one of three in the day 5 administration scheduled group. One out of six patients in the cisplatin day 1 group also experienced thrombocytopenia. As for neutropenia, the incidence was similar to the DLT in topotecan monotherapy Phase I (7,13,14). In combination therapy of cisplatin and topotecan, the DLT of thrombocytopenia was reported associated with neutropenia (7,15). In this study, toxicity data on the second and further courses were also evaluated. In this evaluation, no discrepancy was found between the first course and further courses, which established the DLT in this study as neutropenia and thrombocytopenia.

The non-hematological DLTs were gait disturbance and atrial fibrillation, which were observed in the cisplatin day 5 administration group at 1.4 mg/m² of topotecan. No non-hematological DLT was observed in the cisplatin day 1 administration group. Grade 3 non-hematological toxicities of nausea, vomiting, anorexia, fatigue and interference with daily activity were observed as similar to other studies such as topotecan monotherapy and cisplatin combination in which Grade 3/4 non-hematological toxicities of nausea, vomiting, anorexia, fatigue and so on were recorded (7,13,15). These DLTs seem not to be this drug specified from clinical observation on occurrence and progress. Furthermore, no occurrence of Grade 3/4 diarrhea was observed, as different from the similar drug of irinotecan (16).

The MTDs of Stages 1 and 2 were estimated by taking not only the DLTs during the first cycle but hematological toxicity after the second cycle or further cycles into account. The RD for cisplatin on day 1 schedule was estimated from

### Table 4. Response to treatment

<table>
<thead>
<tr>
<th>Cisplatin injection (fixed at 60 mg/m²)</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Topotecan (mg/m²)</td>
<td>0.5 0.65 0.65 0.65 0.8 1.0 1.2 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>3 6 6 4 6 3 3 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.
In conclusion, the RDs of topotecan for 5 consecutive days in combination with 60 mg/m² cisplatin in a 3-week cycle were 0.65 mg/m² with cisplatin on day 1 with G-CSF and 1.0 mg/m², a maximum of 1.2 mg/m², with cisplatin on day 5 with G-CSF. Further Phase II study of this combination chemotherapy for advanced/metastasis SCLC as first-line therapy is ongoing.

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Conflict of interest statement
None declared.

References