A phase II study of amrubicin combined with carboplatin for elderly patients with small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0405


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Received 22 April 2009; revised 29 June 2009; accepted 30 June 2009

Background: Amrubicin, a new anthracycline agent, has shown high activity for small-cell lung cancer (SCLC) in previous studies. However, a combination regimen with amrubicin and platinum has been investigated little. On the basis of previous phase I study, we conducted this study to evaluate the efficacy and the safety of amrubicin and carboplatin for elderly patients with SCLC.

Methods: Chemotherapy-naive elderly patients with SCLC received amrubicin (35 mg/m², days 1–3) and carboplatin [area under the curve (AUC) 4.0, day 1] every 3 weeks. The primary end point was overall response rate (ORR), and secondary end points were progression-free survival (PFS), overall survival and toxicity profile.

Results: From January 2005 to November 2007, 36 patients were enrolled [median age 76 (range 70–83); ECOG performance status of zero and one in 17 and 19 patients, respectively]. One complete response and 31 partial responses were observed (ORR 89%). Median PFS was 5.8 months and median survival time was 18.6 months. Grade 3–4 neutropenia was observed in 97% of the patients and six patients (17%) suffered from grade 3–4 febrile neutropenia. Other toxic effects were moderate and treatment-related death was not observed.

Conclusions: Amrubicin combined with carboplatin is quite effective for SCLC with acceptable toxic effects even for the elderly population. Further evaluation of this regimen is warranted.

Key words: amrubicin, carboplatin, chemotherapy, elderly, phase II study, small-cell lung cancer

introduction

Lung cancer is currently a leading cause of cancer death in many countries [1, 2], and small-cell lung cancer (SCLC) accounts for 15%–20% of all lung cancer cases. Over 50% of patients newly diagnosed as SCLC are >70 years old, and the number of elderly patients is expected to increase because the geriatric population is also rapidly growing [3–5]. There has been a general tendency among physicians to consider that elderly patients often have poor tolerance for cisplatin-containing regimens and carboplatin is widely used alternatively because of its mild, non-hematological toxicity [6]. Okamoto et al. [7] had reported that carboplatin plus etoposide is similarly effective as cisplatin plus etoposide in elderly SCLC patients in the Japan Clinical Oncology Group (JCOG) 9702 trial; however, results of the study [the overall response rate (ORR) of 73% and median survival time (MST) of 10.6 months] are not satisfactory, thus it is important to establish a superior treatment regimen for elderly SCLC patients.

Amrubicin is a new anthracycline agent that yielded an extremely high response rate of 79% and MST of 11 months by a dose of 45 mg/m² on days 1–3 in chemotherapy-naive SCLC with extensive disease (ED)-SCLC, which was comparable to the results of JCOG 9702 [8]. As to the combination therapy with amrubicin and platinum agent, a phase II study of amrubicin (40 mg/m²) combined with cisplatin (60 mg/m²) has also shown promising activity for ED-SCLC; however, most of the enrolled patients in the study were <70 years old [9]. We had previously tried a new combination with amrubicin and...
carboplatin for elderly population as a phase I study that revealed the recommended dose of amrubicin (35 mg/m² on days 1–3) and carboplatin (AUC 4.0 on day 1) [10].

Subsequently, we conducted this phase II study to evaluate the efficacy and safety of this regimen for elderly SCLC patients.

methods

patient selection

Patients aged 270 years with histologically confirmed SCLC who had never received chemotherapy or radiotherapy were enrolled in this study. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero or one and estimated life expectancy ≥12 weeks. Laboratory requirements included hemoglobin ≥29 g/dl, white blood cell count ≥4000/mm³, absolute neutrophil count ≥20000/mm³, platelets >100 000/mm³, serum bilirubin ≤1.5x the institutional upper limit of normal, aspartate aminotransferase and alanine aminotransferase ≤150 IU/l, and creatinine clearance ≥40 ml/min. Ejection fraction >260% by echocardiogram and PaO₂ > 60 torr were also required. Patients with symptomatic brain metastasis or severe comorbidity were excluded. Each hospital’s institutional review board approved the study, and written informed consent was obtained from all enrolled patients.

treatment schedule

Amrubicin was diluted in 20 ml of normal saline and administered as a bolus during a drip infusion of normal saline on days 1–3 of each treatment cycle. Carboplatin was diluted in 250 ml of 5% glucose solution and administered after amrubicin by 1-h i.v. infusion on day 1. The treatment schedule was repeated on a 21-day cycle. Premedication with corticosteroid and antiemetic 5-HT3 antagonist was recommended. No prophylactic granulocyte colony-stimulating factor (G-CSF) or prophylactic antibiotic support was planned. G-CSF support was recommended in cases of neutrophil count decrease <1000/mm³ or febrile neutropenia. All patients received at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after disease progression were not prohibited by the protocol.

The study permitted the enrollment of patients with limited disease (LD)-SCLC as well as ED-SCLC because concurrent chemoradiotherapy was not a standard of care for elderly SCLC patients. LD-SCLC patients who were medically feasible for irradiation were recommended to receive sequential thoracic radiotherapy (total 50–60 Gy in 25–30 fractions) after three to four cycles of the protocol treatment.

The starting doses were 35 mg/m² of amrubicin and AUC 4.0 of carboplatin according to the result of previous phase I study [10]. When severe toxic effects such as grade 3 or more non-hematological toxic effects except nausea/vomiting, thrombocytopenia <20 000/mm³, grade 4 neutropenia lasting 24 days, or febrile neutropenia occurred, the dose of amrubicin was reduced to 30 mg/m² in subsequent cycles.

treatment assessment

Baseline assessment included a physical examination, complete blood counts (CBC) with differential and platelet count, hepatic and renal function tests, urine analysis, 12-lead electrocardiogram, echocardiogram, and chest X-ray. Measurement of visible and palpable tumors was carried out in the baseline assessment by chest X-ray, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans (when clinically indicated). During the study, the medical history and results of physical examination, weight, vital signs, ECOG PS, CBC, and blood chemistry were monitored weekly, and urinalysis was carried out every 3 weeks. Radiographic evaluation (CT, MRI, or chest X-ray) by extramural review was carried out to assess the response to the treatment. Unidirectional measurements were undertaken using the RECIST criteria. Tumor response assessment was carried out at least every two cycles while the patients were in the study. For the confirmation of response according to the RECIST criteria, a response ≥4 weeks duration was needed for a complete response (CR) or partial response (PR) and ≥6 weeks from the initiation of chemotherapy was needed to determine the disease as stable. Toxic effects were assessed according to National Cancer Institute—Common Toxicity Criteria version 3.0.

statistical analysis

The primary end point of this study was an ORR defined as the proportion of the patients whose best response was CR or PR among all per-protocol patients. Simon’s two-stage minimax design was used to determine the sample size and interim decision criteria. Assuming that an ORR of 60% in eligible patients would indicate potential usefulness, whereas an ORR of 40% would be the lower limit of interest, with α = 0.10 and β = 0.20, the estimated accrual number was 30 patients. Secondary end points of this study were progression-free survival (PFS), overall survival, and toxicity profiles. Survival estimation was carried out using the Kaplan–Meier method. Patients alive without disease progression at the data cut-off point (December 2008) were censored at the last point when the patients were assessed to be progression free.

results

patient characteristics and treatment administration

From January 2005 to November 2007, 36 patients were enrolled from 11 institutions. The patients’ characteristics are listed in Table 1. Fifty-eight percent (21 of 36) of the patients were ≥75 years. The median number of treatment cycles was 4 (range 2–7 cycles) and 89% (32 of 36) of patients could receive three cycles or more. All patients were assessable for toxicity, tumor response, and survival. Fifteen patients with LD were enrolled and 10 patients (67%) received thoracic radiotherapy after the protocol treatment. For these 10 patients, all response evaluations were confirmed before the initiation of radiotherapy. The other five patients with LD did not receive thoracic irradiation because of the following reasons: one was...
due to pericardial effusion, two were considered intolerable to radiation by radiation oncologists because of too large irradiation fields, and two were considered intolerable to radiation by attending physicians. Twenty-one patients (62%) received second-line chemotherapy after disease progression, in which the objective response was achieved in eight patients.

**response and survival**

The numbers of objective responses were as follows: CR 1, PR 31, stable disease (less than a 30% reduction and less than a 20% increase in the sum of the products of one longest diameters of pre-defined measurable lesions and the appearances of no new lesions) 2, and progressive disease 2 (Table 2). The ORR was 89% [95% confidence interval (CI) 79–99]. The final survival assessment was carried out in December 2008 (>1 year after the last patient enrollment). The median PFS was 5.8 months (95% CI 5.1–6.2) and MST was 18.6 months (95% CI 16.1–19.4) (Figure 1). One-year survival rate was 67%. MST of 21 patients with ED was 12.8 months (range 2.6–37.6) and that of 15 patients with LD was 18.6 months (range 8.6–30.1).

**toxicity**

Regarding the hematological toxic effects, 97% of patients experienced grade 3 or more neutropenia and febrile neutropenia was observed in 17% of patients. Twenty-two patients (61%) were treated with G-CSF for 2–10 days during their first treatment cycle due to neutropenia and 11 patients (31%) needed dose reduction in subsequent cycles. Although one patient suffered from sepsis after severe neutropenia, she recovered and serious complications were not observed in any other patients (Table 3). Four patients experienced grade 4 thrombocytopenia and two needed platelet transfusion, although no serious hemorrhagic event was observed. Two patients experienced grade 4 anemia and one received a blood transfusion.

The common non-hematological adverse events were nausea, infection, fatigue, diarrhea, and stomatitis, most of which were mild or moderate and recovered within a short period (Table 3). Ten patients who received thoracic radiation after this study did not experience any radiation recall phenomenon.

**discussion**

The prospective studies for elderly patients with SCLC have been very limited. Since most of those studies consisted of heterogeneous populations such as elderly patients with good PS and younger patients with poor PS, their treatment outcomes varied from report to report [11]. Recently, elderly patients with good PS and normal organ functions tend to be treated with similar regimens to those of younger patients, but some reports indicated that even with good PS and normal organ functions, elderly patients had a higher risk of severe toxic effects than younger patients [12–14]. Although the carboplatin and etoposide combination has become one of the standard chemotherapies for elderly SCLC according to JCOG 9702 [7], the ORR (73%) and MST (10.6 months) of this regimen were inferior to those of the standard chemotherapy for younger SCLC patients (ORR 87% and MST 12.8 months by cisplatin and Irinotecan) [15]. In this context, a prospective study to investigate a more effective regimen for elderly SCLC patients is still warranted.

In the current study, a new regimen of amrubicin combined with carboplatin achieved high efficacy (ORR of 89%, MST of 18.6 months) for elderly SCLC patients and met its primary statistical end point. Even in patients with ED, more than half of the patients could live >1 year, which is quite a better result compared with previous reports. Since the sample size of this study was too small to draw any valid conclusion, further investigation of this regimen in larger comparative study (e.g. current regimen versus carboplatin plus etoposide) is warranted.

**Table 2. Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>31</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Overall response rate</strong></td>
<td><strong>32</strong></td>
<td><strong>89</strong></td>
<td><strong>79–99</strong></td>
</tr>
<tr>
<td>Disease control rate</td>
<td><strong>34</strong></td>
<td><strong>94</strong></td>
<td><strong>86–100</strong></td>
</tr>
</tbody>
</table>

CI, confidence interval.
Table 3. Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>&gt;Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>9</td>
<td>26</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>–</td>
<td>5</td>
<td>1</td>
<td>6 (17)</td>
</tr>
<tr>
<td><strong>Non-hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hiccups</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

*Includes one grade 2 depression, one grade 3 abdominal pain, and one grade 3 duodenal ulcer.

The dosage of carboplatin (AUC 4.0) in this study is lower than that used in other studies [6, 7]; however, recent large comparative studies also used carboplatin with AUC of 4.0 even for younger SCLC patients [16]. The hematological toxic effects described below as well as the efficacy observed in this study also support its appropriateness. Regarding the eligibility criteria, the current study permitted an enrollment of LD-SCLC patients, which is a different patient population from that with ED in terms of survival. Because concurrent thoracic irradiation is not a standard of care for elderly SCLC patients with LD, we considered that chemotherapy followed by radiotherapy was a proper strategy for such patients and tumor response, a primary end point of this study, could be assessable for those patients. So far, this regimen is incompatible with concurrent chemoradiation because there has been no safety data of amrubicin under the concurrent irradiation.

The principal toxicity of the amrubicin and carboplatin combination was myelosuppression, which is a similar profile to the results of previous studies of amrubicin alone, standard carboplatin plus etoposide, or our previous phase I study [7]. The hematological toxic effects described below as well as the efficacy observed in this study also support its appropriateness. Regarding the eligibility criteria, the current study permitted an enrollment of LD-SCLC patients, which is a different patient population from that with ED in terms of survival. Because concurrent thoracic irradiation is not a standard of care for elderly SCLC patients with LD, we considered that chemotherapy followed by radiotherapy was a proper strategy for such patients and tumor response, a primary end point of this study, could be assessable for those patients. So far, this regimen is incompatible with concurrent chemoradiation because there has been no safety data of amrubicin under the concurrent irradiation.

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In conclusion, amrubicin combined with carboplatin is quite effective for SCLC with acceptable toxic effects even for the elderly population. Further evaluation of this regimen is warranted.

**disclosure**

The authors indicated no potential conflicts of interest.

**references**