Clinical Trial Note

A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201)

Junko Eba, Tsuneo Shimokawa*, Kenichi Nakamura, Taro Shibata, Yuki Misumi, Hiroaki Okamoto, Noboru Yamamoto, and Yuichiro Ohe, on behalf of the Lung Cancer Study Group of the Japan Clinical Oncology Group

1JCOG Data Center/Operations Office, Center for Research Administration and Support, National Cancer Center, Tokyo, 2Department of Respiratory Medicine, Yokohama Municipal Citizen’s Hospital, Kanagawa, and 3Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo

*For reprints and all correspondence: Tsuneo Shimokawa, Department of Respiratory Medicine, Yokohama Municipal Citizen’s Hospital, 56 Okazawa-cho, Hodogaya-ku, Yokohama, Kanagawa 240-8555, Japan. E-mail: ts00-shimokawa@city.yokohama.jp

Received 10 July 2014; Accepted 2 October 2014

Abstract

A randomized Phase II/III trial commenced in Japan in December 2013. Carboplatin plus etoposide is the current standard treatment for elderly extensive-disease small-cell lung cancer. The purpose of this study is to confirm the superiority of carboplatin plus irinotecan in terms of overall survival over carboplatin plus etoposide for elderly extensive-disease small-cell lung cancer patients in a Phase II/III design. A total of 370 patients will be accrued from 38 Japanese institutions within 5 years. In the Phase II part, the primary endpoint is the response rate of the carboplatin plus irinotecan arm and the secondary endpoint is adverse events. In the Phase III part, the primary endpoint is overall survival and the secondary endpoints are progression-free survival, response rate, adverse events, serious adverse events and symptom score. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000012605 (http://www.umin.ac.jp/ctr/index.htm).

Key words: small-cell lung carcinoma, extensive-disease, elderly, chemotherapy, Phase II/III

Introduction

Lung cancer is the leading cause of cancer-related deaths in Japan (1). Approximately 70% of lung cancer-related deaths occur in patients aged 70 years or older (1). Small-cell lung cancer (SCLC) accounts for 13–15% of all lung cancers and 60–70% of these patients present with extensive disease (ED) (2).

The standard treatment for extensive-disease small-cell lung cancer (ED-SCLC) is combination chemotherapy including a platinum agent, which is a key drug for SCLC. Cisplatin is widely used in non-elderly patients, but causes severe renal and gastrointestinal toxicities. Therefore, the Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG) previously conducted a Phase III trial (JCOG9702) and evaluated the efficacy and safety of carboplatin,
which is known to cause milder renal and gastrointestinal toxicities than cisplatin.

JCOG9702 was a Phase III trial that compared split doses of cisplatin plus etoposide (SPE) and carboplatin plus etoposide (CE) in elderly or poor-risk patients with ED-SCLC. The CE regimen consisted of four courses of carboplatin, area under the curve (AUC) 5, on Day 1 and etoposide 80 mg/m²/day on Days 1–3, repeated every 3–4 weeks. The SPE regimen consisted of four courses of cisplatin 25 mg/m²/day on Days 1–3 and etoposide 80 mg/m²/day on Days 1–3, repeated every 3–4 weeks. Survival curves almost overlapped (median survival of 9.9 months versus 10.6 months, \( P = 0.54 \)) and most of the toxicities observed were equivalent (3). Based on these results and the usefulness of carboplatin, which did not require hydration and was easily administered in an outpatient setting, the JCOG Lung Cancer Study Group concluded that CE should be the standard regimen for elderly ED-SCLC.

In 2002, JCOG9511 demonstrated the superiority of irinotecan over etoposide in combination with cisplatin for the treatment of ED-SCLC patients who were 70 years or younger. This was a randomized Phase III trial that planned to accrue 230 patients and terminated early after accruing 154 patients because an interim analysis showed overall survival was significantly longer in the irinotecan plus cisplatin (IP) arm than in the etoposide plus cisplatin (EP) arm (12.8 months versus 9.4 months, \( P = 0.002 \) by the log-rank test) (4). Although three randomized controlled trials conducted after the JCOG9511 study failed to reproduce the superiority of IP (5–7), a meta-analysis suggested that IP may be superior to EP in terms of overall survival with less hematological toxicities (8). Therefore, the introduction of irinotecan in the treatment of elderly patients with ED-SCLC is expected to produce promising results.

Misumi et al. (9) conducted a feasibility study of carboplatin plus irinotecan (CI) for elderly ED-SCLC patients at six institutions in Japan to determine the optimal dose. Four courses of carboplatin (AUC = 4 mg/ml × min, Day 1) and irinotecan (50 mg/m²/day, Days 1 and 8) repeated every 3 weeks was chosen as the study regimen based on the previously reported Phase I study for LD-SCLC (10). Ten patients were enrolled and all of them completed the planned three courses without dose reductions. Responses were observed in 9 out of 10 patients. Although no Grade 4 adverse events occurred, prolonged hematological toxicities were observed. Therefore, further dose escalations were judged to be infeasible, and carboplatin (AUC = 4 mg/ml × min, Day 1) and irinotecan (50 mg/m²/day, Days 1 and 8) repeated every 3 weeks was determined to be the optimal regimen for elderly patients.

Two randomized Phase III trials that compared CE versus CI for ED-SCLC including both elderly and non-elderly patients were conducted in Europe. Although Schmittel et al. (11) reported no significant differences in overall survival between CE and CI (9.0 months versus 10.0 months, \( P = 0.06 \)), Hermes et al. (12) demonstrated that CI was superior to CE (7.1 months versus 8.5 months, \( P = 0.02 \)). Grade 3 or 4 hematological toxicities were similar between the arms or milder in CI, whereas diarrhea was more frequent in CI in both studies.

Based on these backgrounds, we commenced a multicenter randomized Phase II/III trial to confirm the superiority of CI in terms of overall survival over CE for elderly ED-SCLC patients (Fig. 1).

The JCOG Protocol Review Committee approved this study protocol in November 2013 and patient enrollment began in December 2013. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000012605 (http://www.umin.ac.jp/ctr/index.htm).

**Protocol digest of the JCOG1201**

**Objectives**
The purpose of this study is to confirm the superiority of CI in terms of overall survival (OS) over CE in elderly patients with ED-SCLC in Phase II/III design.

**Study setting**
A multi-institutional two-arm open label randomized Phase II/III study.

**Endpoints**
The primary endpoint and secondary endpoint in the Phase II part is the response rate in the CI arm and adverse events, respectively. The primary endpoint in the Phase III part is OS in all randomized patients. OS is defined as days from randomization to death from any cause, and is censored at the last day when the patient is alive. The secondary endpoints in the Phase III part are progression-free survival (PFS), response rate, adverse events, serious adverse events and the symptom score. PFS is defined as days from randomization to progression or death from any cause, and is censored at the last day when the patient is alive without any evidence of progression.

**Eligibility criteria**

1. **Inclusion criteria**

   **Histologically or cytologically confirmed SCLC.**

   **Extensive disease diagnosed with enhanced chest CT, enhanced cranial CT or MRI, enhanced upper abdominal CT or ultrasound, bone scintigraphy or FDG-PET.**

   **No serious tumor-related complications such as superior vena cava syndrome, massive or uncontrollable pleural or cardiac effusion, or symptomatic brain metastasis.**

   **Aged 71 years or older.**

   **ECOG performance status of 0–2.**

   **With measurable lesions.**

   **No prior surgery, radiotherapy or chemotherapy for SCLC.**

   **No prior thoracic radiotherapy or chemotherapy for any other cancers.**

   **Adequate organ functions.**

   **No diarrhea or intestinal obstruction.**

   **Written informed consent.**

   **Histologically or cytologically confirmed SCLC.**

   **Extensive disease diagnosed with enhanced chest CT, enhanced cranial CT or MRI, enhanced upper abdominal CT or ultrasound, bone scintigraphy or FDG-PET.**

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   **No diarrhea or intestinal obstruction.**

   **Written informed consent.**

![Figure 1. Schema of the study. PS, performance status; AUC, area under the curve.](http://www.umin.ac.jp/ctr/index.htm)
Exclusion criteria
1. Synchronous or metachronous (within 5 years) malignancies, except for carcinoma in situ or mucosal tumors curatively treated with local therapy.
2. Active infection requiring systemic therapy.
3. Body temperature 38°C.
4. Severe mental disease.
5. Patients receiving systemic steroid medication.
6. Poorly controlled diabetes mellitus or receiving the routine administration of insulin.
7. Poorly controlled hypertension.
8. Unstable angina within 3 weeks or a history of myocardial infarction within 6 months.
9. Interstitial pneumonia, pulmonary fibrosis or severe emphysema.

Randomization
After confirming the eligibility criteria, registration is made by a web-based system to the JCOG Data Center. Patients are randomized to either the CE arm or CI arm by the minimization method balancing the arms with the institution, ECOG performance status (0 versus 1 versus 2), and sex (male versus female).

Treatment methods
Patients in the CE arm receive four courses of CE (carboplatin, AUC 5, Day 1; etoposide, 80 mg/m²/day, Day 1–3) repeated every 3 weeks. Patients in the CI arm receive four courses of CI (carboplatin, AUC 4, Day 1; irinotecan, 50 mg/m²/day, Day 1, 8) repeated every 3 weeks. When the leukocyte count is decreased to <3000/mm³ or the platelet count to <100 000/mm³ on the planned first day of both arms, the start of chemotherapy is delayed until the counts recover to ≥3000/mm³ and ≥100 000/mm³, respectively. The administration of irinotecan is skipped on Day 8 when at least one of the following occurs; a leukocyte count <3000/mm³, platelet count <100 000/mm³, diarrhea Grade 1 or higher, or a fever of ≥38°C. The dose of etoposide and irinotecan in the subsequent cycles is reduced by 20 and 10 mg/m² from the planned dose, respectively, when the leukocyte count is <1000 mg/m², platelet count is <25 000/mm³ and/or Grade 3 non-hematologic toxicities (excluding nausea, vomiting, hyponatremia, anorexia and increased creatinine levels) develop. The dose of carboplatin is reduced to AUC 4 in the CE arm when patients have a leukocyte count <1000 mg/m³, platelet count <25 000/mm³ and/or Grade 3 non-hematologic toxicities (excluding nausea, vomiting, hyponatremia, anorexia and increased creatinine levels). The dose of carboplatin in the CI arm is not modified. The protocol treatment is terminated when patients exhibit Grade 4 non-hematologic toxicities. After completion of the protocol treatment, patients are observed without anti-cancer treatment including prophylactic cranial irradiation until recurrence is detected. Crossover is allowed in both arms after the termination of the protocol treatment or at the time of progression.

Follow-up
All randomized patients are followed-up for at least 1.5 years after patient accrual is completed. Enhanced chest CT and tests for tumor markers (CEA,NSE and ProGRP) are performed during the second and fourth courses to evaluate responses. Enhanced computed tomography of the upper abdomen and enhanced computed tomography or enhanced MRI of the brain are also performed during the second and fourth courses when patients have lesions in the examined regions at baseline. Bone scintigraphy or fluorodeoxyglucose-positron emission tomography is performed when progression is suspected. Chest X-rays, complete blood counts and chemistries are performed every month for the first year, every 3 months for the second year, and every 6 months afterwards.

Study design and statistical analysis
This randomized Phase II/III trial is designed to confirm the superiority of CI in terms of overall survival over CE for elderly ED-SCLC patients. The Phase II part is incorporated to confirm if CI has adequate efficacy to proceed to the Phase III part because there have been few studies to support the efficacy of CI for elderly ED-SCLC patients.

In the Phase II part, the planned sample size is 48 patients in the CI arm, which was calculated based on an expected response rate of 65% and a threshold of 45%, with a one-sided alpha of 0.1 and a beta of 0.1.

In the Phase III part, we assumed the median survival time with CE to be 11.0 months, and expected a 3.5-month increase in the median survival time with CI based on the result of JCOG9511. According to Schoenfeld and Richter’s method (13), the sample size was calculated as 183 patients per arm with a one-sided alpha level of 5%, a power of 80%, an accrual period of 5 years, a follow-up period of 1.5 years, and 324 expected events in total. The total sample size was set at 370 patients to account for patients lost to follow-up. All statistical analyses will be conducted at the JCOG Data Center.

Interim analysis and monitoring
We plan to conduct two interim analyses. The first interim analysis will be conducted as the analysis of Phase II part to determine whether to proceed to the Phase III part after the pre-planned accrual of the Phase II part, the first 48 patients in CI arm, is completed. The second interim analysis with a comparison between the arms will be conducted after half of the planned number of patients in the Phase III part is enrolled. The Lan–DeMets method with the O’Brien and Fleming type alpha spending function will be used to adjust multiplicity of the second interim analysis and the primary analysis (14).

The Data and Safety Monitoring Committee (DSMC) of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. If the superiority of the CI arm is demonstrated in the second interim analysis with a one-sided P value of the stratified log-rank test below an adjusted alpha level, the study will be terminated.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

Participating institutions (from North to South)
Ashihikawa Medical Center, National Hospital Organization Hokkaido Cancer Center, KKR Sapporo Medical Center, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital and Cancer Center, Tochigi Cancer Center, National Nishigunma Hospital, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, National Center for Global Health and Medicine (NCGM), Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University Hospital, Kanagawa Cancer Center, Yokohama Municipal Citizen’s Hospital, Niigata Cancer Center Hospital, Gifu Municipal Hospital,
Funding
This study is supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-18 and 26-A-4).

Conflict of interest statement
None declared.

References