A randomized Phase III trial commenced in Japan in March 2013. Post-operative adjuvant chemotherapy with etoposide plus cisplatin is the current standard treatment for resected pulmonary high-grade neuroendocrine carcinoma including small cell lung cancer and large cell neuroendocrine carcinoma. The purpose of this study is to confirm the superiority of irinotecan plus cisplatin in terms of overall survival over etoposide plus cisplatin as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary high-grade neuroendocrine carcinoma patients. A total of 220 patients will be accrued from 54 Japanese institutions within 6 years. The primary endpoint is overall survival and the secondary endpoints are relapse-free survival, proportion of treatment completion, adverse events, serious adverse events and second malignancy. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000010298 [http://www.umin.ac.jp/ctr/index.htm].

Key words: lung neoplasms – high-grade neuroendocrine carcinoma – adjuvant chemotherapy – Phase III

INTRODUCTION

Lung cancer has been the leading cause of cancer-related deaths in Japan since 1988. High-grade neuroendocrine carcinoma (HGNEC) including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) accounts for ~15% of all lung cancers (1,2).

LCNEC was first proposed by Travis et al. (3), who added LCNEC as the fourth category of pulmonary neuroendocrine tumors, which had originally been classified into three categories, typical carcinoid, atypical carcinoid and SCLC. Although it has been classified into a non-small cell lung cancer (NSCLC) by the WHO classification, LCNEC has neuroendocrine features and an aggressive clinical course that are common with SCLC and both are recognized as HGNEC. LCNEC is typically diagnosed post-operatively using surgical specimens and rarely diagnosed pre-operatively with biopsy specimens because of the difficulties associated with its diagnosis from a small amount of specimens. Furthermore, a differential diagnosis between LCNEC...
and SCLC is known to be challenging in some cases even with surgical specimens.

A previous study reported that the prognosis of patients with surgery alone for SCLC and LCNEC was poor; the 5-year survival was shown to be 35.7% for SCLC and 40.3% for LCNEC (4). However, several retrospective studies have described the favorable outcomes of clinical Stage I SCLC patients who underwent surgery followed by adjuvant chemotherapy (5). Based on these reports, surgery plus adjuvant chemotherapy is regarded as a standard therapy for clinical Stage I SCLC. Reports on LCNEC are very limited because it is still a new entity. However, post-operative chemotherapy has also been added as a standard therapy in practice for LCNEC because its prognosis after surgery alone is poor.

The Japan Clinical Oncology Group study, JCOG9101, which is a Phase II trial to evaluate the feasibility of etoposide and cisplatin (EP) for completely resected pathological Stage I–IIIA SCLC patients, demonstrated the sufficient feasibility of the EP regimen (6). The survival of each stage was better than that of pathological Stage I–III patients who were administered cyclophosphamide, doxorubicin and vincristine (CAV) in another prospective study (7). Thus, EP has been considered acceptable as a current standard post-operative adjuvant chemotherapy regimen for SCLC.

The only report of a prospective study on adjuvant chemotherapy in pathological Stage I–IV LCNEC revealed the favorable outcomes of EP (8). One retrospective review of adjuvant chemotherapy for LCNEC compared two major categories of regimens; one for a SCLC regimen, a combination of platinum and etoposide, and the other for NSCLC regimens, a combination of platinum and gemcitabine, taxanes or vinorelbine. The findings of this review showed that SCLC regimens significantly prolonged survival (median survival time 42 months versus 11 months, \( P < 0.0001 \)) (9). Therefore, the EP regimen is regarded as a standard post-operative adjuvant therapy regimen for LCNEC in Japan.

JCOG9511, a Phase III trial comparing irinotecan plus cisplatin (IP) with EP in SCLC patients with extended disease (ED-SCLC), showed that survival was significantly longer in the IP arm than in the EP arm (12.8 months versus 9.4 months, \( P = 0.002 \) by the log-rank test) (10). However, all three randomized controlled trials conducted afterwards to confirm the superiority of IP failed to demonstrate a difference in survival between the two arms (11–13). On the other hand, a recent meta-analysis has suggested that overall survival may be superior with irinotecan plus platinum than with etoposide plus platinum (14). Therefore, IP is regarded as one of the standard treatment options for ED-SCLC patients and is also expected to be a promising regimen in adjuvant chemotherapy for completely resected HGNEC patients. Kenmotsu et al. (15) conducted a multicenter Phase II pilot study to evaluate the feasibility of IP in post-operative adjuvant chemotherapy for HGNEC patients, and showed that the proportion of completion of treatment and toxicities were acceptable.

Based on these backgrounds, we have commenced a multicenter randomized controlled trial to confirm the superiority of IP in terms of overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

The JCOG Protocol Review Committee approved this study protocol in February 2013 and patient enrollment began in March 2013. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution.

**PROTOCOL DIGEST OF THE JCOG1205/1206**

**OBJECTIVES**

The purpose of this study is to confirm the superiority of IP in overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

**STUDY SETTING**

A multi-institutional two-arm open label randomized Phase III study.

**ENDPOINTS**

The primary endpoint is overall survival (OS) in all randomized patients. OS is defined as days from randomization to death from any cause, and it is censored at the last day when the patient is alive. The secondary endpoints are relapse-free survival (RFS), proportion of treatment completion, adverse events, serious adverse events and second malignancy. RFS is defined as days from randomization to relapse or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of relapse.

**ELIGIBILITY CRITERIA**

**INCLUSION CRITERIA**

1. Pathologically proven high-grade neuroendocrine carcinoma (small cell carcinoma including combined small cell carcinoma, or large cell neuroendocrine carcinoma including combined large cell neuroendocrine carcinoma)
2. Pathological Stage I–IIIA based on the seventh UICC-TNM classification (16).
3. Pathologically proven R0, R1 (is) or R1 (cy+) based on the seventh edition of the General Rule for Clinical and Pathological Record of Lung Cancer by the Japan Lung Cancer Society (17)
4. Aged 20–74-years-old
5. ECOG performance status of 0 or 1
6. Lobectomy or more extended surgery was performed
7. ND 2a-1 or more extended lymph node dissection was performed
8. Within 28–56 days after surgery
9. No distant metastasis including brain metastasis
10. No prior chemotherapy or radiotherapy for any cancers
TREATMENT METHODS

Patients in the EP arm receive four courses of post-operative EP (etoposide, 100 mg/m²/day, Day 1–3; cisplatin 80 mg/m²/day, Day 1) repeated every 3 weeks. Patients in the IP arm receive four courses of post-operative IP (irinotecan, 60 mg/m²/day, Day 1, 8, 15; cisplatin, 60 mg/m²/day, Day 1) repeated every 4 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 or more and 100 000/mm³ or more, respectively. The administration of irinotecan is skipped on Day 8 and/or 15 when at least one of the following occurs; a leukocyte count <2000/mm³, platelet count <100 000/mm³, diarrhea Grade 1 or higher or a fever of 37.5°C or higher. The dose of etoposide and irinotecan in the subsequent cycles is reduced by 20 mg/m² and 10 mg/m² from the planned dose, respectively, when the leukocyte count is <1000 mg/m², platelet count is <20 000/mm³ and/or Grade 3 non-hematologic toxicities (excluding hyponatremia and weight loss) develop. The dose of cisplatin is reduced by 20 mg/m² in the EP arm and 10 mg/m² in the IP arm when patients have serum creatinine >1.5 mg/dl, but not exceeding 2.0 mg/dl, Grade 2–3 peripheral motor or sensory neuropathy, myalgia, arthralgia or other Grade 3 non-hematologic toxicities (excluding hyponatremia and weight loss). The protocol treatment is terminated when serum creatinine exceeds 2.0 mg/dl or patients develop Grade 4 non-hematologic toxicities (other than hyperglycemia, hypernatremia, hyponatremia, hyperkalemia and hypokalemia). After completion of the protocol treatment, patients are observed without anti-cancer treatment until recurrence is detected.

FOLLOW-UP

All randomized patients are followed-up for at least 5 years after patient accrual is completed while analysis of the primary endpoint is conducted 3 years after accrual completion.

Chest X-rays are performed every 6 months for the first 5 years and every year afterwards. Tumor markers (CEA, NSE and ProGRP), enhanced computed tomography of the thorax and enhanced computed tomography or ultrasound of the upper abdomen are evaluated every 6 months for the first 3 years and every year from the fourth to the fifth year.

STUDY DESIGN AND STATISTICAL ANALYSIS

This randomized trial is designed to confirm the superiority of IP in terms of overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

We assumed the 3-year survival with post-operative EP to be 70% and expected a 10% increase in the 3-year survival with post-operative IP. According to Schoenfeld and Richter’s method (18), the sample size was calculated as 104 patients per arm with a one-sided alpha level of 5%, a power of 70%, an expected accrual period of 6 years and a follow-up period of 3 years. Eighty-eight events in total are expected. The total sample size was set at 220 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, taking multiplicity into account using the Lan–DeMets method with the O’Brien and Fleming type alpha spending function (19). The first interim analysis will be conducted after half of the planned number of patients is enrolled and the second interim analysis after the planned patient accrual and their protocol treatment is completed. 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 IP arm is demonstrated with a one-sided P value of the stratified log-rank test below an adjusted alpha level, the study will be terminated.

EXCLUSION CRITERIA

(1) Synchronous or metachronous (within 5 years) malignancy, 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) Pregnant or lactating women or women of childbearing potential
(5) Severe mental disease
(6) Serious post-operative complications
(7) Patients receiving systemic steroid medication
(8) Poorly controlled diabetes mellitus or receiving the routine administration of insulin
(9) Poorly controlled hypertension
(10) Unstable angina within 3 weeks, or with a history of myocardial infarction within 6 months
(11) Positive serum HBs antigen or HCV antibody
(12) Positive serum HIV antibody
(13) Interstitial pneumonia, pulmonary fibrosis or severe emphysema

RANDOMIZATION

After confirming the eligibility criteria, registration is made by telephone, fax or a web-based system to the JCOG Data Center. Patients are randomized to either arm A (EP) or arm B (IP) by the minimization method balancing the arms with institution, sex (male versus female), pathological stage (Stage I versus Stage II–IIIA) and pathological type (SCLC versus LCNEC).
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.

**UMIN Registration Number**

This trial has been registered at the UMIN Clinical Trials Registry as UMIN000010298 [http://www.umin.ac.jp/ctr/index.htm].

**PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)**

Asahikawa Medical Center, National Hospital Organization Hokkaido Cancer Center, KKR Sapporo Medical Center, Miyagi Cancer Center, National Hospital Organization Sendai Medical Center, Tohoku University Hospital, 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, Chiba University Graduate School of Medicine, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, National Center for Global Health and Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University Hospital, Yokohama City University Medical Center, Kanagawa Cancer Center, Yokohama Municipal Citizen’s Hospital, Niigata Cancer Center Hospital, Kanazawa University School of Medicine, Gifu Municipal Hospital, Shizuoka Cancer Center, Nagoya University School of Medicine, Aichi Cancer Center Hospital, National Hospital Organization Nagoya Medical Center, Aichi Cancer Center Aichi Hospital, Kyoto University Hospital, Osaka City University Hospital, Kinki University Faculty of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Disease, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka City General Hospital, Kobe City Medical Center General Hospital, Hyogo Cancer Center, Kurashiki Central Hospital, Okayama University Hospital, National Hospital Organization Kure Medical Center Chugoku Cancer Center, Hiroshima University Hospital, National Hospital Organization Yamaguchi-Ube Medical Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, School of Medicine Fukuoka University, Nagasaki University Hospital, Kumamoto University Medical School, Kumamoto Chuo Hospital, Kumamoto Regional Medical Center Hospital and National Hospital Organization Okinawa Hospital

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**Conflict of interest statement**

None declared.

**References**