Molecular Epidemiologic Study in Non–small-cell Lung Cancer

Disclosure

The authors have stated that they have no conflicts of interest.

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Original Study

Clinicopathological Features in Young Patients Treated for Small-Cell Lung Cancer: Significance of Immunohistological and Molecular Analyses

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Abstract

The validity of the diagnosis in young patients who had been diagnosed as having small-cell lung cancer (SCLC) has not been adequately described. We reevaluated the clinical data of 8 young patients. Genetic rearrangements of nuclear protein of the testis (*NUT*) were revealed in 2 patients. Caution is needed when diagnosing SCLC, especially in young patients.

Background: Small-cell lung cancer in young patients is very rare and has not been adequately described. In addition, malignancies associated with genetic rearrangements of nuclear protein of the testis (*NUT*) have been reported in young patients. **Patients and Methods:** We reviewed the clinical records of patients younger than 40 years of age who had been diagnosed as having SCLC and had been treated for this condition. We also examined *NUT* rearrangements using immunohistochemistry (IHC) staining and fluorescence in situ hybridization (FISH) analysis. **Results:** We evaluated the diagnoses and treatment outcomes of 8 young patients among 747 SCLC patients. Based on further analyses using IHC staining and FISH, *NUT* rearrangements were found in 2 of these cases. The range of the overall survival period was 3.6 to 49.7 months. The 2 patients with *NUT* rearrangements survived for less than 12 months. **Conclusion:** *NUT* rearrangements were identified in 2 patients who had been previously diagnosed as having SCLC. Further attention regarding the diagnosis of SCLC in young patients is needed.

Clinical Lung Cancer, Vol. 15, No. 3, 244-7
Keywords: Chemotherapy, FISH, IHC, *NUT* midline carcinoma, *NUT* rearrangements

Introduction

The median age at the time of the diagnosis of lung cancer is 71 years according to the Surveillance, Epidemiology and End Results Cancer Statistics. Lung cancer in patients younger than the age of 40 years is rare and comprises approximately 2.7% of all lung cancers.[1] Various reports have discussed the prognosis of lung cancer in young patients. Some studies have shown that young patients have a better prognosis,[2,3] and others have reported no survival differences between young and old patients.[1,4]

Small-cell lung cancer (SCLC) is an undifferentiated neoplasm composed of primitive-appearing small cells, and rapid progression and extensive metastases are typically observed at the time of presentation. Some previous articles have reported the incidence of SCLC in young patients.[1,4-8] SCLC patients account for 0% to 5% of lung cancer patients younger than 40 years of age.[1,4] However, the treatment outcomes have not been reported and the results of the pathological examinations have not been validated in young SCLC patients.

Recently, carcinomas with nuclear protein of the testis (*NUT*) rearrangements have been included in the differential diagnosis of SCLC because of their morphological similarities. *NUT* midline carcinoma (NMC) often arises from midline structures, such as the mediastinum and the upper aerodigestive tract, in young people. NMC is a rare and aggressive carcinoma that is characterized by chromosomal rearrangement at the *NUT* gene.[9] NMC is a lethal

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Submitted: Mar 23, 2013; Revised: May 16, 2013; Accepted: Jun 18, 2013; Epub: Dec 14, 2013

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1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2013.06.012

disease despite intensive therapies[10,11] and must be considered in differential diagnoses of poorly differentiated squamous cell carcinoma, undifferentiated carcinoma, and other small round cell tumors.[12] SCLC with *NUT* rearrangements has not been previously reported.

The objective of the present study was to reevaluate the validity of the diagnosis of SCLC in young patients before the era of immunohistochemistry (IHC) staining and molecular analyses, including the evaluation of *NUT* rearrangements. We also evaluated the clinical response to treatment and the outcome of SCLC in young patients.

Patients and Methods

Patients

Small-cell lung cancer patients who were 40 years old or younger and who had been treated with chemotherapy at the National Cancer Center Hospital in Tokyo, Japan, between 1993 and 2010 were retrospectively identified.

Data Collection and Evaluation of Tumor Response

The following clinical data were collected from the medical records: patient characteristics, treatment regimens, and treatment outcomes. The tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1. We evaluated the best overall response. When the disease status was stably maintained for more than 8 weeks, the patient was considered to have stable disease.

Immunohistochemical and Molecular Analyses

For IHC staining, 4-μm thick sections from a paraffin block were routinely deparaffinized. The detailed antigen retrieval methods and antibody dilutions used for each primary antibody are listed in Table 1. We used an automated stainer (DAKO, Carpinteria, CA) for the primary antibody incubation, according to the vendor's protocol. ChemMateEnVision (DAKO) detection methods were used.

To assess the presence of *NUT* rearrangements, we used break-apart *NUT* probes (RP11-412E10 for *NUT* centromere and RP11-1H8 for *NUT* telomere; Chromosome Science Lab, Inc, Sapporo, Japan) according to the manufacturer's instructions. At least 50 nonoverlapping tumor cells were examined, and cases with more than 20% of the cells showing split-apart signals were considered to be positive for *NUT* rearrangements.

Survival Definition

Overall survival was defined as the period between the start of the first treatment and death from any cause or the last follow-up examination.

Results

Patient Characteristics

A retrospective review of 747 patients who had been diagnosed as having SCLC was conducted. Although 9 patients younger than the age of 40 years were originally diagnosed as having SCLC and were treated accordingly, the tumor in 1 patient did not exhibit the typical morphological features of SCLC according to the presently used pathological criteria. Thus, we excluded this patient and ultimately retrieved clinical data for 8 patients (1.1%) younger than the age of 40 years. The patients were between the ages of 18 and 40 and consisted of 4 men and 4 women; 5 of the patients were current smokers. Three patients had limited disease SCLC (LD-SCLC), and 5 patients had extended disease SCLC.

Histological Profiles

Among the 8 cases, 4 cases were reevaluated using hematoxylin and eosin (H & E) and IHC staining. The other 4 cases were reviewed based on pathological reports obtained from the primary hospital. Based on the standard pathological criteria used for the diagnosis of SCLC,[13] 4 patients had received accurate diagnoses of SCLC (patients 1-4). However, the 4 other patients might not have actually had SCLC, because these patients exhibited atypical morphological features for SCLC (patients 5-8). The clinical information and the IHC results for all patients are listed in Table 2. *NUT* rearrangements were observed in 2 patients (Patients 7 and 8). One patient (patient 7) had positive *NUT* IHC and fluorescence in situ hybridization findings in addition to exhibiting the typical morphological features of SCLC (Fig. 1).

Clinical Response and Outcome

Overall, 4 of the 8 patients responded to first-line treatment (4 partial response, 2 stable disease, 1 progressive disease, and 1 not evaluated). All 3 LD-SCLC patients had partial responses to chemoradiotherapy. Of the 2 NMC patients, 1 NMC patient (patient 7) had progressive disease after 2 cycles of cisplatin-based chemotherapy. Another NMC patient (patient 8) had a partial response to 2 cycles of cisplatin-based chemotherapy. The overall survival periods of the patients ranged from 3.6 to 49.7 months. The patients with *NUT* rearrangements survived for less than 12 months.

Discussion

In our study, we used immunohistological and molecular analyses to reevaluate the treatment outcomes and the validity of the diagnoses in young patients who had been diagnosed as having SCLC. Based on our reevaluation of 8 patients, we could identify only

Table 1 Antibodies Used for the Immunohistochemical Analysis

Antibody	Source	Clone	Pretreatment	Dilution
TTF-1	DAKO	8G7G3/1	Citrate buffer	1/100
CD56	Novocastra	1B6	Citrate buffer	1/200
CD99	SIGNET	013	Citrate buffer	1/50
Synaptophysin	DAKO	27G12	TRS9 (98°C, 40 min)	1/100
Chromogranin A	DAKO	—	Citrate buffer	1/500
NUT	Cell Signaling	C52B1	TRS9 (98°C, 40 min)	1/45

Table 2 Patient Characteristics and Histological Profiles

Patient	Sex	Age	PS	Stage	ProGRP	IHC Results	CD99	Initial Treatment	Response	OS, Months
1	F	18	0	LD	657	+	–	Chemoradiotherapy	PR	49.7
2	M	40	1	LD	ND	+	–	Chemoradiotherapy	PR	19.7
3	M	39	1	ED	11,040	ND	ND	Chemotherapy alone	SD	12.3
4	F	34	1	ED	12,010	+	ND	Chemotherapy alone	SD	43.1
5	M	39	1	LD	ND	ND	ND	Chemoradiotherapy	PR	18.8
6	F	21	1	ED	ND	–	ND	Chemotherapy alone	NE	6.0
7	M	24	1	ED	38	+[a]	–	Chemotherapy alone	PD	7.2
8	F	29	1	ED	28	–	–	Chemotherapy alone	PR	3.6

Abbreviations: ED = extended disease; F = female; IHC results = immunohistochemistry results for neuroendocrine antigens; LD = limited disease; M = male; ND = no available data; NE = not evaluated; OS = overall survival; ProGRP = progastrin-releasing peptide; PS = performance status.
[a]CD56 was positive in only part of the tumor.

4 patients who had received accurate diagnoses of SCLC. Evaluations based only on morphological features were likely to have resulted in misdiagnosis; 2 of the patients were ultimately diagnosed as having NMC. Thus, special attention to the possible presence of NMC mimicking SCLC is needed for the differential diagnosis of SCLC in patients younger than 40 years.

Most SCLCs exhibit a typical morphology and their diagnosis is thus straightforward, with IHC staining being unnecessary.[13] However, in problematic cases, such as in young patients, nonsmokers, and tumors that are difficult to distinguish from other malignancies, a diagnosis of SCLC should be very carefully performed using immunohistochemical and molecular diagnostic techniques. Of note, our additional analyses revealed the presence of NMCs in 2 of the patients who had originally been diagnosed as having SCLC and had been treated accordingly. Thus, for the accurate diagnosis of SCLC, especially in young patients, not only light microscopy examinations but also immunohistochemical and molecular analyses should be performed.

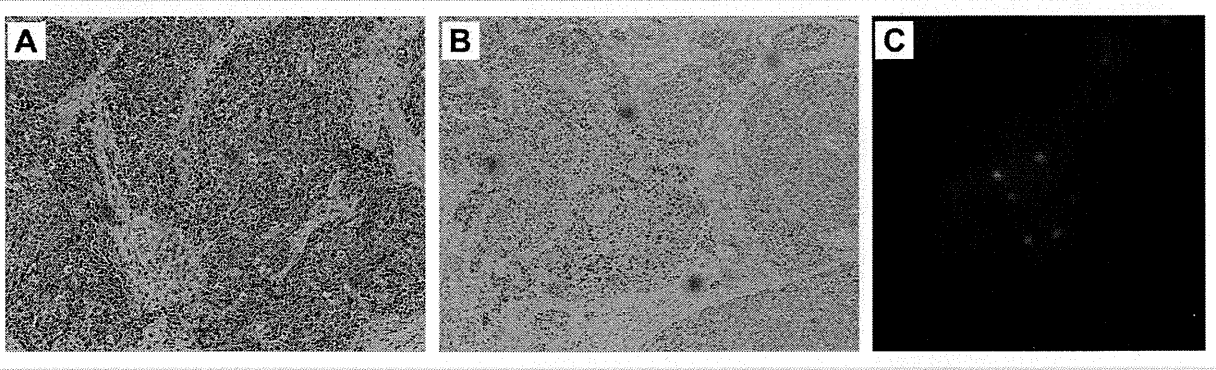
Approximately 60 cases of NMC have been reported to date.[14] In two-thirds of these reported NMC cases, *NUT* on chromosome 15q14 is fused to *BRD4* on chromosome 19p13.1, forming *NUT-BRD4*. In approximately one-third of the cases, the partner gene is *BRD3* or an uncharacterized gene (*NUT-BRD3* and *NUT* variants).[10,15] The histological differential diagnosis of NMC includes poorly differentiated squamous cell carcinoma, undifferentiated carcinoma, and other small blue round cell tumors, such as primitive neuroectodermal tumor.[12] In our study, the H & E results in 2 patients with NUT rearrangements showed features that were consistent with combined small-cell and squamous cell carcinoma in 1 patient (patient 7) and with small-cell carcinoma in another patient (patient 8). Previous reports and review articles have suggested that negative neuroendocrine antigen results are helpful for the diagnosis of NMC[12]; however, patient 7 exhibited not only a neuroendocrine morphology, but also immunopositivity for CD56. Although CD56 is not a complete marker for neuroendocrine differentiation, NMC with positive neuroendocrine markers has not been previously reported; thus, this is the first case report to describe such a lesion. These results indicate that young patients should not be diagnosed as having SCLC based only on a neuroendocrine morphology and a neuroendocrine phenotype without performing an analysis to detect *NUT* rearrangements.

Concerning the treatment of NMC, most previously reported patients received combination multidrug chemotherapy, such as platinum-based regimens[16,17] and lymphoma regimens[16]; however, most of these patients died within 1 year.[10,15] No drugs that contribute to a long survival period have been found. As for new agents, the domain inhibitor for *BRD4* and histone deacetylase inhibitors have been studied and reported in some journals.[18-20] Although these agents are still in development, the use of these agents for the treatment of NMC is anticipated. The accumulation of numerous NMC cases is important, and the development of more effective treatments for patient with NMC is needed.

Conclusion

Malignancies in young patients should be carefully diagnosed using IHC and molecular diagnostic techniques. Moreover, the possibility of NMC should be considered, especially in young

Figure 1 Histologic Features. (A) Dense Sheets of Small Cells With Granular Nuclear Chromatin are Visible on Hematoxylin and Eosin Staining in Patient 7. (B) Immunohistochemistry and (C) Fluorescence in Situ Hybridization Findings Were Positive for *NUT*



patients thought to have SCLC in which atypical histological features are observed using H & E and IHC staining.

Clinical Practice Points

- Most SCLC cases can be diagnosed using H & E staining.
- However, in problematic cases, such as young patients, nonsmokers, and tumors that are difficult to distinguish from other malignancies, the diagnosis of SCLC should be very carefully performed.
- In our study, genetic rearrangement of *NUT* was revealed in 2 patients.
- We suggest that a diagnosis of SCLC should be very carefully performed using immunohistochemical and molecular diagnostic techniques, especially in young patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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Lung Cancer

A Phase II Study of Amrubicin as a Third-Line or Fourth-Line Chemotherapy for Patients With Non-Small Cell Lung Cancer: Hokkaido Lung Cancer Clinical Study Group Trial (HOT) 0901

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Amrubicin • Chemotherapy • Fourth line • Non-small cell lung cancer • Third line

ABSTRACT

Amrubicin, a third-generation synthetic anthracycline agent, has favorable clinical activity and acceptable toxicity for the treatment of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer. We conducted this study to evaluate the efficacy and safety of amrubicin for advanced NSCLC patients as a third- or fourth-line therapy. Eligible patients had recurrent or refractory advanced NSCLC after second- or third-line therapy. Patients received amrubicin, 35 mg/m^2 i.v. on days 1–3 every 3 weeks. The primary endpoint was the disease control rate (DCR). Secondary endpoints were the overall survival (OS) time, progression-free survival (PFS) time, response rate, and toxicity profile. Of the 41 patients enrolled, 26 received amrubicin as a third-line and 15 received it as a fourth-line therapy. The median number of treatment cycles was two (range, 1–9). Objective responses were complete response ($n = 0$), partial response ($n = 4$), stable disease ($n = 21$), progressive disease ($n = 15$), and not evaluable ($n = 1$), resulting in a DCR of 61.0% (95% confidence interval, 46.0%–75.9%). The overall response rate was 9.8% (95% confidence interval, 0.6%–18.8%). The median PFS interval was 3.0 months, median OS time was 12.6 months, and 1-year survival rate was 53.7%. Grade 3 or 4 hematological toxicities were neutropenia (68%), anemia (12%), thrombocytopenia (12%), and febrile neutropenia (17%). Nonhematological toxicities were mild and reversible. No treatment-related deaths were observed. Amrubicin showed significant clinical activity with manageable toxicities as a third- or fourth-line therapy for patients with advanced NSCLC. This study provides relevant data for routine practice and future prospective trials evaluating third- or fourth-line treatment strategies for patients with advanced NSCLC. ***The Oncologist*** 2013;18:439–445

Implications for Practice: There is a paucity of prospective studies that specifically address the role of cytotoxic agents as a third-line therapy for non-small cell lung cancer (NSCLC) patients. Amrubicin showed significant clinical activity with manageable toxicities as a third- or fourth-line therapy for advanced NSCLC. Amrubicin could be a better candidate in these settings for routine practice.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide [1]. First-line therapies, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutations, as well as platinum-based chemotherapy in conjunction with third-generation antitumor agents significantly improve survival outcomes and quality of life in patients with advanced non-small cell lung cancer (NSCLC) [2–5]. Despite these favorable outcomes, most patients receiving first-line therapy experience disease progression and require salvage therapy. Second-line therapy also has beneficial effects on survival and quality of life outcomes [2, 6, 7].

Docetaxel, pemetrexed, gefitinib, and erlotinib are considered standard second-line therapies based on several randomized controlled trials [6–9]. Because of the improved efficacy of first-line, second-line, and maintenance therapy

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for NSCLC, a high proportion of patients (26%–38%) receive third-line therapy [10, 11]. Thus, there is an urgent need for new third-line therapy options. To date, there is a paucity of studies that address the role of third-line therapy, and they are primarily retrospective analyses [12–14].

Amrubicin, a completely synthetic 9-amino-anthracycline, is a potent inhibitor of DNA topoisomerase II [15]. A phase II study of amrubicin in both NSCLC and SCLC patients demonstrated promising results and tolerable toxicity [16, 17]. The clinical significance of amrubicin has recently focused on the treatment of recurring lung cancer. A phase I and a pharmacokinetic study of amrubicin in previously treated NSCLC and SCLC patients recommend an amrubicin dose of 35 mg/m^2 per day on three consecutive days every 3 weeks [18]. Amrubicin is a promising third-line therapy agent because it has a different mechanism of action from those of other available anticancer agents.

Currently, there is no prospective study that specifically addresses the role of third-line therapy for NSCLC patients. We therefore conducted a multicenter prospective phase II trial of amrubicin (35 mg/m^2) to confirm the efficacy and safety of the drug in NSCLC patients as a third- or fourth-line therapy.

Patients and Methods

Patient Eligibility

Eligible patients met the following criteria: histologic or cytologic confirmation of NSCLC, recurrent or refractory disease after two or three previous treatment regimens, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2, age ≤75 years, adequate bone marrow function (leukocyte count ≥3,000/mm^3, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin content ≥9.0 g/dL), adequate function of other organs (total bilirubin concentration ≤1.5 mg/dL, aspartate transaminase and alanine transaminase levels ≤2.0× the upper limit of normal, and creatinine clearance ≥50 mL/minute), P_aO_2 ≥60 Torr or S_pO_2 ≥95%, left ventricular ejection fraction ≥60% on echocardiography, and a life expectancy ≥3 months.

Patients with previous amrubicin therapy, exceeding the critical dosage in prior anthracycline drug therapy, using corticosteroid or immunosuppressive drugs, with an active infectious disease with serious medical complications (active peptic ulcer, heart disease, diabetes mellitus, or cerebrovascular disease), with radiographic signs of interstitial pneumonia or pulmonary fibrosis, with third-space fluid collection requiring drainage, who were lactating or pregnant, with symptomatic brain metastasis, or with active concomitant malignancy were deemed ineligible.

This study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines [19]. The protocol was approved by the institutional review boards of all participating institutions, and all patients provided written informed consent before treatment.

Treatment Plan

Amrubicin was dissolved in 20 mL physiological saline and was administered i.v. for >5 minutes at a dose of 35 mg/m^2·per day on days 1–3 every 3 weeks. All patients received at least two cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue treatment.

Subsequent cycles of treatment were withheld until the following criteria were satisfied: the leukocyte count was ≥3,000/mm^3, the neutrophil count was ≥1,500/mm^3, the platelet count was ≥100,000/mm^3, total bilirubin was ≤2.0 mg/dL, there was no infection, the ECOG PS score was ≤2, and the grade of any nonhematologic toxicity was ≤2. If these criteria were not satisfied within 36 days after the onset of the last treatment, the patient was removed from the study. The dose of amrubicin was reduced to 30 mg/m^2 per day for cases of leukopenia or neutropenia of grade 4 persisting for >4 days, thrombocytopenia of grade 4 or requiring platelet transfusion, febrile neutropenia, or nonhematologic toxicity of grade ≥3 (except for anorexia, nausea, or alopecia) during the previous course. If these toxicities occurred after reduction of the amrubicin dose to 30 mg/m^2 per day, the dose was further reduced to 25 mg/m^2 per day. A third reduction was not permitted, and the protocol treatment was terminated. Use of prophylactic antibiotics was not permitted.

Evaluation

Baseline assessment included a physical examination; CBC with differential, hepatic, and renal function tests; urinalysis; 12-lead electrocardiogram; echocardiogram; and chest radiography. Visible and palpable tumors were measured during the baseline assessment using chest radiography, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans (when clinically indicated). During the study, medical history and physical examination results, vital signs, ECOG PS scores, CBCs, and blood chemistries were monitored weekly. Tumor responses were assessed using chest radiography, CT, or MRI (when clinically indicated) at every cycle until disease progression. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.0 [20]. A response of >4 weeks duration was considered a complete response (CR) or a partial response (PR) and a response of >6 weeks from the initiation of chemotherapy was considered stable disease (SD). Clinical response data were confirmed by central review.

Toxicities were assessed according to the National Cancer Institute-Common Toxicity Criteria, version 3.0.

The progression-free survival (PFS) was defined as the time from the date of enrollment to the date of documented progression or death from any cause and was censored at the date of the last follow-up visit for surviving patients who had not progressed. The overall survival (OS) time was defined as the time from the date of enrollment to the date of death or last follow-up. Data for patients without any events were censored on the last date with a nonevent status.

Statistical Analysis

The primary endpoint was the disease control rate (DCR), defined as the proportion of patients whose best response was a CR, a PR, or SD among all per-protocol patients. Sample size was determined according to the one-arm binomial design devised by the Southwestern Oncology Group. Assuming that a DCR of 50% in eligible patients indicates potential usefulness, whereas a DCR of 30% is the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.20$, the estimated accrual number was 37 patients. Allowing for a patient ineligibility rate of 10%, we planned on enrolling 40 patients in the study. Secondary endpoints were the OS, PFS, objective response rate (ORR), and

toxicity profiles. Survival curves were estimated using the Kaplan–Meier method. Statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC).

This study is registered with the University Hospital Medical Information Network (UMIN), number UMIN C000002306.

Results

Patient Characteristics

From August 2009 to May 2011, 41 patients were enrolled from 10 participating institutions. Patient characteristics are summarized in Table 1. The median age was 66 years (range, 43–74 years), 70.7% of patients were male, and most patients (97.6%) had a good ECOG PS score of 0–1. Histologic analysis revealed that 30 patients (73.2%) had adenocarcinoma and eight patients (19.5%) had squamous cell carcinoma. Seven patients (17.1%) were positive and 26 patients (63.4%) were negative for the *EGFR* mutation. Twenty-six patients (63.4%) received amrubicin as a third-line therapy and 15 patients (36.6%) received the drug as a fourth-line therapy.

Seven patients (17.1%) received thoracic surgery and nine patients (22.0%) received thoracic radiotherapy. Table 2 shows the content of prior therapeutic regimens. All patients had received a platinum-containing doublet regimen as a first- or second-line therapy. The regimens used in first-line therapy were as follows: platinum-containing doublets in 38 patients (92.7%), a single agent in two patients (4.9%), and gefitinib in one patient (2.4%). The regimens used in second-line therapy were as follows: a single agent in 21 patients (51.2%), platinum-containing doublets in 13 patients (31.7%), nonplatinum doublets in four patients (9.8%), and gefitinib in three patients (7.3%). The regimens used in third-line therapy were as follows: platinum-containing doublets in six patients (14.6%), a single agent in six patients (14.6%), and nonplatinum doublets in three patients (7.3%). Of the seven patients harboring *EGFR* mutations, three had not received EGFR TKIs before enrollment into this study because of patient refusal or later confirmation of the *EGFR* mutation.

Treatment Administered

The median number of treatment cycles was two (range, 1–9 cycles). In all, 30 (73.2%) patients completed at least two cycles of treatment and 109 treatment cycles in total were delivered overall. The mean relative dose intensity of amrubicin was 91.1%. A reduction in the amrubicin dose was necessary, according to the study protocol, in eight cycles (7.3% of the total cycles). All patients received the first cycle of amrubicin in an inpatient setting to check the safety of administration, and most patients received further cycles of amrubicin in an outpatient setting. Subsequent treatment delay was observed in 29 of 109 cycles (26.6%). The primary reasons for dose reduction were grade 4 neutropenia (four of all cycles), febrile neutropenia (three of all cycles), and grade 3 headache (one of all cycles). Treatment was discontinued in 11 patients after the first cycle and in 10 patients after the second cycle; reasons for discontinuation included progressive disease (24 patients), toxicity (six patients), completing the scheduled treatment (four patients), patient refusal (two patients), and physician decision (two patients). Following the protocol treatment, 23 (56%) patients eventually received subsequent therapy: nine (22%) received a single agent, nine (22%) received EGFR TKIs, three (7%) received platinum-containing doublets, and two (5%) received nonplatinum doublets.

Table 1. Patient characteristics

Characteristic	*n* of patients
Enrolled patients	41
Age, yrs	
Median	66
Range	43–74
Gender	
Male	29
Female	12
ECOG performance status score	
0	16
1	24
2	1
Histological type	
Adenocarcinoma	30
Squamous cell carcinoma	8
Large cell carcinoma	2
Other (not specified)	1
EGFR mutation status	
Positive	7
Negative	26
Unknown	8
n of prior treatment regimens	
2	26
3	15

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Response and Survival

Among the 41 assessable patients, there were four PRs and no case of CR, for an overall response rate of 9.8% (95% confidence interval [CI], 0.6%–18.8%) (Table 3). Twenty-one patients (51.2%) had SD, yielding an overall DCR of 61.0% (95% CI, 46.0%–75.9%). Fifteen patients had progressive disease as their best response and the response of one patient could not be confirmed as a result of receipt of subsequent chemotherapy before response evaluation. The lower end of the 95% CI was thus higher than the threshold DCR of 30%, and the primary endpoint was met. We found no significant difference in the ORR or DCR among gender, age, tumor histology, *EGFR* mutation status, or treatment line, except for the DCR and *EGFR* mutation status—the DCR was 100% in seven patients with an *EGFR* mutation, 46.2% in 26 patients with wild-type *EGFR*, and 85.7% in seven patients with an unknown *EGFR* status ($p = .012$).

Of the 41 patients, 13 were alive as of May 2012 (>1 year after the last patient was enrolled). With a median follow-up time of 12.6 months, the median PFS and median survival time (MST) for all enrolled patients were 3.0 months (95% CI, 2.0–4.1 months) and 12.6 months (95% CI, 6.8–19.3 months), respectively (Figs. 1 and 2). The 1-year survival rate was 53.7% (95% CI, 38.4%–68.9%).

Table 2. Characteristics of prior first-line, second-line, and third-line therapies

Characteristic	First-line therapy	Second-line therapy	Third-line therapy
Total	41	41	15
Treatment regimen			
Doublet	38	17	9
Platinum-based doublets	38	13	6
Paclitaxel based	15	5	2
Gemcitabine based	9	1	1
Vinorelbine based	5	0	0
Docetaxel based	4	2	0
Pemetrexed based	3	4	2
Other	2	1	1
Nonplatinum doublets	0	4	3
Single agent	2	21	6
Docetaxel	2	15	2
Pemetrexed	0	6	2
Vinorelbine	0	0	2
Gefitinib	1	3	0

Table 3. Overall response rate for patients treated with amrubicin as determined by central review

Response	*n* of patients	%	95% CI
Complete response	0	0	
Partial response	4	9.8	
Stable disease	21	51.2	
Progressive disease	15	36.6	
Not evaluable	1	2.4	
Overall response rate	4	9.8	0.6%–18.8%
Disease control rate	25	61.0	46.0%–75.9%

Abbreviation: CI, confidence interval.

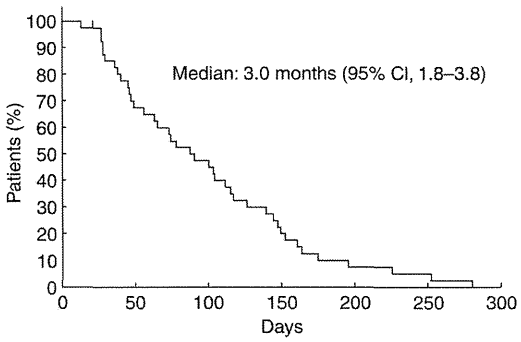

Figure 1. Kaplan–Meier analysis of progression-free survival for all 41 treated patients.
Abbreviation: CI, confidence interval.

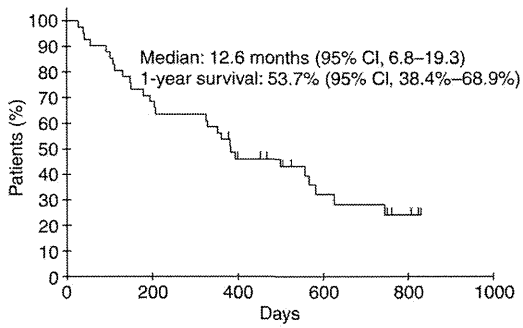

Figure 2. Kaplan–Meier analysis of overall survival for all 41 treated patients.
Abbreviation: CI, confidence interval.

Toxicity

All 41 treated patients were assessed for toxicity. Table 4 summarizes the hematological and nonhematological toxicities. With regard to hematological toxicities, 68% of patients experienced grade 3 or 4 neutropenia and 17% developed febrile neutropenia. Nineteen patients (46%) were treated with G-CSF for 1–11 days during the first treatment cycle because of neutropenia. Although no serious hematologic events were observed, grade 3 or 4 thrombocytopenia was observed in five patients (12%; one received a platelet transfusion) and anemia was observed in five patients (12%; two received a packed RBC transfusion). The most common nonhematologic toxicities of grade 3 or 4 were anorexia (12%), infection (10%), nausea or vomiting (10%), diarrhea (2%), stomatitis (2%), and pneumonitis (2%). Most nonhematologic toxicities were mild and reversible. Neither cardiac toxicity nor treatment-related deaths were observed in this study.

Discussion

This is the first prospective phase II study designed to evaluate the efficacy and safety of a cytotoxic agent as a third- or

Table 4. Toxicity for all cycles

	Grade				Grade ≥3	
Toxicity	**1**	**2**	**3**	**4**	***n***	**%**
Hematologic						
Leukopenia	7	5	17	5	22	53.7
Neutropenia	4	5	8	20	28	68.3
Anemia	23	6	4	1	5	12.2
Thrombocytopenia	6	3	4	1	5	12.2
Febrile neutropenia	0	0	7	0	7	17.1
Nonhematologic						
Nausea/vomiting	15	4	4	0	4	9.8
Anorexia	10	5	5	0	5	12.2
Diarrhea	2	0	1	0	1	2.4
Stomatitis	0	0	1	0	1	2.4
Pneumonitis	1	2	1	0	1	2.4
Infection	0	1	4	0	4	9.8
Fever	0	1	0	0	0	0
Fatigue	1	1	0	0	0	0
Liver dysfunction	7	0	0	0	0	0

fourth-line chemotherapy for patients with advanced NSCLC. Our study demonstrated the efficacy of amrubicin as shown by the ORR of 9.8%, DCR of 61.0%, median PFS of 3.0 months, median OS of 12.6 months, and 1-year survival rate of 53.7% in 41 patients. Although common, hematological toxicities were manageable and nonhematological toxicities were mild and reversible. Previous phase III trials for second- or third-line therapy of NSCLC patients have reported ORRs of 7.6%–9.1%, median OS of 6.7–8.3 months, and 1-year survival rates of 29.7%–34% [6–9, 21]. Amrubicin is a potent inhibitor of topoisomerase II, with a different mechanism of action from those of the currently available active cytotoxic agents for advanced NSCLC [15].

Several studies have evaluated the efficacy and safety of amrubicin for patients with advanced NSCLC. With regard to the dose of amrubicin, favorable results with tolerable toxicity were demonstrated with 45 mg/m^2 per day on three consecutive days every 3 weeks for first-line therapy [17, 22], 40 mg/m^2 for second-line therapy (West Japan Thoracic Oncology Group [WJTOG]0401 trial) [23], 35 mg/m^2 for primarily second-line therapy and for a small number of patients treated with third-line therapy [24], and 35 mg/m^2 or 40 mg/m^2 for third or subsequent lines of therapy [25]. Based upon these results, we conducted a prospective phase II trial of amrubicin at a dose of 35 mg/m^2 in NSCLC patients as a third- or fourth-line therapy.

The incidence of febrile neutropenia was certainly high in this study (17%, seven of 41 patients). Five patients developed febrile neutropenia in the first cycle, one patient developed this toxicity in the second cycle, and one patient developed this toxicity in the fourth cycle. A previous phase II study of amrubicin at 40 mg/m^2 for the second-line therapy of NSCLC patients (the WJTOG0401 trial) reported that 29.5% of the patients developed febrile neutropenia [23]. Thus, the possible reasons for the higher incidence of febrile neutropenia in our study are as follows: the 35-mg/m^2 dose of amrubicin might be formidable in the third- or fourth-line setting and neither the prophylactic use of G-CSF nor the prophylactic use of antibiotics was allowed. In addition, an adverse event of particular concern related to amrubicin administration is cardiac toxicity, the incidence of which was 3.2% in previous trials [17, 22]. For safety reasons, this study allowed the enrollment of only patients with a left ventricular ejection fraction of 60% as determined by echocardiography. No cardiac toxicity was observed in our trial, and there were no treatment-related deaths in this study.

The number of patients who need third-line therapy is increasing, and third-line therapy represents a clinical problem for advanced NSCLC treatment. However, there is no standard definition for third-line therapy because the population of patients who could be grouped as potential candidates is heterogeneous [13] and clinical trial information regarding this population is sparse. Retrospective analyses from three institutions reported that 20.3%, 28.2%, and 38.4% of patients received third-line chemotherapy in clinical practice [11, 14, 26]. Those analyses showed that the ORR was 5.6%–17.0%, the DCR was 34.4%–44.4%, the median PFS was 2.4 months, and the median OS was 5.8–12.0 months. Patients who received third-line therapy benefited over those who did not.

In the second-line or later settings, the MST is not associated with the ORR, but is associated with the DCR [27]. Because amrubicin has a different mechanism of action from those of other anticancer agents and is associated with a high DCR with tolerable toxicity [15, 17], we conducted the present study in which the DCR was chosen as the primary endpoint. Based on a DCR of 33%–56% in previous phase III trials of second- and third-line therapy of NSCLC patients [7, 8, 28, 29] and the third- and fourth-line settings of this study, we assumed that a DCR of 50% was a desirable target and that a DCR of 30% was irrelevant. The lower end of the 95% CI in the present study was higher than the threshold DCR of 30%, and the primary endpoint was met. Single-agent chemotherapy and

EGFR TKI therapy had advantages over doublet chemotherapy in prolonging PFS and decreasing toxicity when used in third-line therapy [26]. In a BR.21 trial, erlotinib demonstrated survival benefits when administered as a second- or third-line therapy, compared with placebo (OS, 6.7 months vs. 4.7 months, respectively) [7]. That landmark trial included 49% of patients receiving third-line therapy; thus, treatment with erlotinib is recommended as a third-line therapy for patients with a PS of 0–3 who have not received prior EGFR TKIs. These data are not sufficient to make a recommendation for or against using a cytotoxic agent as a third-line therapy. However, there is no prospective trial of cytotoxic agents in that setting, which encouraged us to conduct the present study.

Similar to any phase II study, this analysis has several limitations. All patients enrolled in this study had an ECOG PS of 0–1, except for one patient with PS score of 2. Thus, these patients may not be representative of the population of patients with NSCLC who receive third- or fourth-line therapy in clinical practice. Additionally, seven (17%) patients harboring an *EGFR* mutation had an excellent prognosis (median OS, 16.7 months; range, 10.8–27.2 months). The survival outcome might have been influenced by the good health condition of these patients or by the indolent nature of the patients' disease. Therefore, further evaluation is warranted to implement this regimen into daily clinical practice as a third- or fourth-line therapy.

Conclusion

In conclusion, amrubicin is a promising agent associated with effective disease control and manageable toxicity as a third- or fourth-line treatment for patients with advanced NSCLC. This study provides relevant data for routine practice and future prospective trials evaluating third- or fourth-line treatment strategies for patients with advanced NSCLC.

Acknowledgments

This study is registered with University Hospital Medical Information Network Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm; identification number, UMIN C000002306).

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Disclosures

The author indicated no financial relationships.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(2)116–121
doi:10.1093/jjco/hyt195
Advance Access Publication 13 December 2013

Original Articles

A Feasibility Study of Carboplatin Plus Irinotecan Treatment for Elderly Patients with Extensive Disease Small-cell Lung Cancer

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Received September 2, 2013; accepted November 17, 2013

Objective: The role of platinum agents plus irinotecan has been unclear for elderly patients with extensive disease small-cell lung cancer. We conducted a feasibility study to evaluate the safety and efficacy of carboplatin plus irinotecan in preparation for a planned Phase III study.
Methods: Based on another Phase I study, carboplatin area under the curve of four Day 1 plus irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks for four courses was administered. Patients aged ≥70 years with a performance status of 0–2 were eligible. The primary endpoint was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. If the feasibility was ≥60% in the first 10 patients, this endpoint would be considered to be met.
Results: Eleven patients were registered. The median age was 77 years, and nine patients had a performance status of 1. Ten patients completed four courses of treatment, and neither dose omission nor modification was required. The feasibility was 91% (10/11) and the relative dose intensity was 76.9%. Because neutropenia was frequently prolonged, the next course was delayed in 53% of all courses. Other toxicities were generally mild, and the only Grade 4 toxicity was hyponatremia. The overall response rate was 90% (9/10), and the progression-free survival and the overall survival were 5.1 and 10.9 months, respectively.
Conclusions: This regimen appears to be feasible and effective. Based on these results, a Phase II/III trial comparing carboplatin plus etoposide with carboplatin plus irinotecan for elderly patients with extensive disease small-cell lung cancer is being planned by the Japan Clinical Oncology Group.

Key words: chemo-respiratory tract – chemo-Phase I–III – clinical trials – lung medicine

INTRODUCTION

Approximately 30–40% of patients with small-cell lung cancer (SCLC) are ≥70 years old, and the proportion of elderly SCLC patients is continuously increasing in Japan (1–3). However, as elderly patients have been frequently excluded from clinical trials, no standard chemotherapeutic regimen has been established for this patient population. Moreover, standard chemotherapeutic regimens for non-elderly SCLC patients are not always suitable for older patients due to their vulnerable organ function and/or co-morbidities. Therefore, the establishment of a chemotherapeutic regimen that is well balanced between safety and efficacy for this population should be pursued.

The Japan Clinical Oncology Group (JCOG) 9702 study compared carboplatin plus etoposide (CE) versus split-dose cisplatin plus etoposide (SPE) in elderly and poor-risk patients with extensive disease (ED)-SCLC (4). Based on the results of this study, the JCOG concluded that the SPE regimen should remain as the standard treatment for elderly and poor-risk patients with ED-SCLC, the CE regimen being an alternative. However, because the CE regimen does not require hydration and can be administered in an outpatient setting, elderly patients with ED-SCLC in Japan more commonly receive this regimen.

In contrast, the Phase III JCOG 9511 study has shown that irinotecan plus cisplatin (IP) is more effective than etoposide plus cisplatin (EP) for treating non-elderly patients with ED-SCLC (5). However, elderly patients (age $\geq$71 years) were excluded from this trial. When considering the treatment plan for elderly patients with ED-SCLC, the 1-day bolus administration of this cisplatin-based regimen would be difficult because hydration is required. Until now, the carboplatin plus irinotecan (CI) regimen has been repeatedly reported. Although several studies included patients 70 years of age or older, few studies were especially designed for the elderly. Therefore, it would be meaningful to consider a CI regimen for the elderly. Two randomized trials have compared CI with CE for ED-SCLC patients. Although Schmittel et al. (6) did not show a significant survival benefit in the CI arm, survival was marginally better and fewer hematological toxicities were observed. In contrast, Hermes et al. (7) reported a significant survival advantage of CI over CE. Although these trials were not specifically designed for elderly patients and the doses used differed from Japanese standard doses, we believed it was worthwhile to investigate the efficacy of CI in elderly patients with ED-SCLC. Furthermore, a recent meta-analysis of camptothecins compared with etoposide in combination with platinum in ED-SCLC showed a survival benefit associated with camptothecins plus platinum (excluding nogitecan) over etoposide plus platinum in a subgroup analysis (8). Thus, a Phase III trial comparing CE with CI in elderly patients with ED-SCLC is being warranted in the JCOG Lung Cancer Study Group (LCSG).

In our previous study (9), we reported the 4-weekly schedule of CI regimen using prophylactic granulocyte colony-stimulating factor (G-CSF) support in elderly patients with SCLC. However, this study was not a Phase I study and had a heterogeneous patient population. In addition, because not only chemotherapy-naïve but also pretreated patients were included and the treatment drug dose was changed according to the patient's characteristics, the recommended dose could not be decided in the study. Recently, prophylactic use of G-CSF has not been preferred in clinical practice in Japan because more expensive cost and prolonged hospital stays are required. For the reason given above, we cannot apply the previous data to plan the Phase III study and we think that optimal schedule and dose of CI for elderly patients with SCLC have not been established. On the other hand, Thoracic Oncology Research Group (TORG) decided a recommended dose of 3-weekly schedule of CI regimen for elderly patients with limited disease (LD)-SCLC in a Phase I study (unpublished data). Because thoracic radiotherapy was sequentially administered after four courses of chemotherapy in this Phase I study, it might be justified that the recommended dose of CI for LD-SCLC could be used in elderly patients with ED-SCLC based on these data. Furthermore, because members of JCOG and TORG were much different, JCOG-LCSG recommended a further feasibility study by only JCOG members for elderly patients with ED-SCLC. Therefore, we conducted a feasibility study to evaluate the safety and efficacy of CI in elderly patients with ED-SCLC in preparation for a future JCOG Phase III study designed to compare CE with CI in this patient population. This study is registered with the UMIN Clinical Trials Registry as trial 000003208.

PATIENTS AND METHODS

Patient Selection

Patients with the following inclusion criteria were enrolled: age $\geq$70 years; cytologically or histologically confirmed SCLC; ED stage (defined as at least one of the following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion and pericardial effusion); no prior chest radiotherapy or chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; no other co-existing malignancy and adequate hematologic, hepatic and renal organ function (leukocyte count $\geq$4000/mm^3, absolute neutrophil count [ANC] $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3, hemoglobin level $\geq$9.0 g/dl, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels $\leq 2\times$ upper limit of normal range, total bilirubin $\leq$1.5 mg/dl, creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min and $PaO_2 \geq$ 60 mmHg). The additional criteria were: no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, no diarrhea and provision of written informed consent. The exclusion criteria included brain metastases requiring radiotherapy, superior vena cava syndrome requiring radiotherapy and serious medical or psychiatric illness. Patients with interstitial pneumonitis detected by chest computed tomography (CT) scan were excluded. All the patients had chest X-ray, CT scan of the chest and abdomen, CT scan or magnetic resonance imaging of the brain and isotope bone scanning or positron emission tomography within 28 days before registration.

Treatment Plan

Based on our previous feasibility study using CI for elderly patients with SCLC (9), the TORG conducted a Phase I study of the CI regimen and sequential thoracic radiotherapy for elderly patients with LD-SCLC. In that study, the recommended dose was carboplatin area under the curve (AUC) of four Day 1 and irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks (unpublished data). Although the TORG study

included only elderly patients with LD-SCLC, we elected to use the recommended dose from this study in the current study of elderly patients with ED-SCLC. Thus, all the patients were assigned to carboplatin AUC 4 intravenously (IV) on Day 1 plus irinotecan 50 mg/m^2 IV on Days 1 and 8 every 21 days. Irinotecan on Day 8 was withdrawn if leukocyte counts were $<3000/mm^3$, platelet counts were $<100\,000/mm^3$ or if diarrhea Grade ≥ 1 occurred. Treatment was repeated for up to four cycles. Subsequent cycles were permitted only if the ANC was $\geq 1500/mm^3$, the leukocyte count was $\geq 3000/mm^3$, the platelet count was $\geq 100\,000/mm^3$, serum creatinine was ≤ 1.57 mg/dl, AST/ALT levels were $\leq 2.5\times$ upper limit of normal range, PS was 0–2, neither infection nor fever was present and treatment-related non-hematologic toxicities (excluding alopecia) had resolved to Grade ≤ 2 after Day 21. A treatment delay of ≤ 2 weeks was permitted. Use of G-CSFs was recommended in accordance with their package inserts or clinical recommendations. If G-CSF therapy was administered, the criteria for the next cycle had to be satisfied both after Day 21 and ≥ 2 days after discontinuation of G-CSF. Antiemetic prophylaxis with 5-HT_3 antagonists plus dexamethasone was routinely administered. Dose modifications were allowed only once if Grade 4 leukopenia or neutropenia lasting ≥ 4 days, Grade 4 thrombocytopenia or Grade 3 non-hematological toxicities, except for nausea/vomiting, constipation, hyponatremia and creatinine, occurred. When dose modification was needed, the next treatment course was started with carboplatin AUC 4 on Day 1 plus irinotecan 40 mg/m^2 on Days 1 and 8 every 21 days.

The protocol treatment was terminated if any of the following occurred: disease progression, a treatment delay ≥ 2 weeks, need for dose modification two times, Grade 2–4 pneumonitis and Grade 4 non-hematological toxicities. Because this was a feasibility study, post-protocol treatments were left to the discretion of the treating physicians.

Study Design

This trial was designed as a multicenter prospective feasibility study. The study protocol was approved by the institutional review board at each institution prior to study initiation. The primary objective was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. Patients showing disease progression prior to receiving three courses of chemotherapy were excluded from the feasibility evaluation. In addition, even if irinotecan was not administered on Day 8 due to toxicity, the chemotherapy course was judged as being complete. In the JCOG9702 (4), the percentages of patients who have received three and four courses of CE regimen were 69 and 63%, respectively. In this study, we considered that the completion rate of three or more courses of chemotherapy was a more appropriate endpoint than that of four courses because CI regimen might be more toxic than the CE regimen. Therefore, we concluded that the study treatment was feasible when the completion rate of three or more courses of chemotherapy was $\geq 60\%$. Ten patients were initially registered into this study. If the feasibility (completion rate) was $>60\%$, the study would be considered to have yielded positive results and to be finished. If the completion rate was 30 to $<60\%$, we planned to enroll 10 more patients to confirm whether the low rate was due to the treatment regimen or to chance. If the feasibility remained at $<60\%$ in a total of 20 patients, the study would be considered to have yielded negative results. The secondary objectives were toxicity status, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.0. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have a stable disease (SD) if it was confirmed and sustained for 6 weeks or longer.

The relative dose intensity (RDI) of irinotecan was calculated by dividing the actual received dose of the agent among all chemotherapy courses (mg/m^2/week) by the total projected dose of the four treatment courses (mg/m^2/week).When chemotherapy was completed without any delays or skipping of agents, the RDI was 100%.

Table 1. Patient characteristics

Median age, years (range)	77.5 (70–82)
Gender	
Male/female	10/0
ECOG PS 0/1	1/9
TNM classification	
T 4/3/2/1	4/2/1/3
N 0/1/2/3	1/1/2/6
M 0/1	1/9
Brinkman index	
Median (range)	1110 (840–3000)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

RESULTS

Patient Characteristics

From March 2010 through March 2011, 11 patients were registered in three institutions. One patient withdrew consent after Day1 of the first course. Because this patient did not experience acute toxicities and the reason seemed to be related to other personal problems, we thought one more additional patient to the previously scheduled 10 patients were appropriate for this study. The median age was 77 (range, 70–82) years and nine patients had a PS of 1, all of whom were male (Table 1). The median Brinkman Index was 1110 (range,

840–3000). A patient with M0 had a contralateral hilar lymph node metastasis.

Drug Delivery and Dose Intensity

Except for the one patient who withdrew consent, all the patients completed four courses of treatment and no omission of irinotecan on Day 8 occurred (Table 2). Furthermore, no patients required dose modifications. Because the completion rate was 91% (10/11), the primary endpoint of a ≥60% completion rate was met. The RDI of irinotecan was 76.9%. The median course delays between the first and second courses, second and third courses and third and fourth courses were 8.5 (range, 2–11) days, 5.5 (range, 0–10) days and 6.5 (range, 0–17) days, respectively. Of a total of 30 courses, the reasons for chemotherapy delay of ≥4 days were leukopenia or neutropenia in 15 patients (50%) and thrombocytopenia and leukopenia in one patient (3%). Delays caused by bed scheduling at participating institutions occurred in six cases (20%).

Toxicities

Toxicity profiles are shown in Table 3. Both hematological and non-hematological toxicities were generally mild. The only Grade 4 toxicity was hyponatremia in one patient. Grade 3 ANC, hemoglobin and thrombocytopenia occurred in six (60%), one (10%) and two (20%) patients, respectively. G-CSF was administered to three patients. No treatment-related deaths occurred during the study.

One patient suffered from pneumonia during his first course of chemotherapy. He received antibiotic therapy for 7 days and fully recovered. He did not experience infection in subsequent protocol treatment cycles.

Another patient suffered from Grade 4 hyponatremia (117 mEq/l) during his first course of chemotherapy. He did not have any history of renal dysfunction and was considered to have syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a paraneoplastic syndrome. Appropriate intravenous crystalloid infusion facilitated full recovery, and he was able to continue chemotherapy. Severe hyponatremia was not observed in his subsequent protocol treatment cycles.

Efficacy

Nine patients achieved PR and one patient experienced SD, yielding an ORR of 90%. The median PFS was 5.1 months (95% confidence interval [CI]: 3.9–5.8; Fig. 1), and the median OS was 10.9 months (95% CI: 7.6–16.8; Fig. 2).

Second-Line Therapy

A total of 9 patients received second-line chemotherapy. The most commonly administered agent was amrubicin ($n = 7$). Other regimens included nogitecan ($n = 1$) and CI ($n = 1$). Palliative chest radiotherapy was administered to one patient. Only one patient did not receive second-line chemotherapy, due to poor PS.

Table 2. Additional days required in each course and the reasons for delays

Patient no.	Courses 1 and 2	Courses 2 and 3	Courses 3 and 4
1	+7[a]	+10[a]	+11[a]
3	+8[a]	+4[a]	+8[a]
4	+7[b]	+7[b]	+6[b]
5	+11[b]	+7[b]	0[d]
6	+11[a]	+4[a]	+7[a]
7	+8[c]	+9[b]	+2[d]
8	+9[a]	0[d]	+13[a]
9	+2[d]	0[d]	0[d]
10	+11[a]	+2[d]	+1[d]
11	+11[a]	+8[a]	+17[a]
Median delays (range)	8.5 (2–11)	5.5 (0–10)	6.5 (0–17)

Relative dose intensity = 76.9%.
[a]Leukocytopenia.
[b]No available bed.
[c]Leukocytopenia/thrombocytopenia.
[d]No delay or delay within 2 days.

Table 3. Toxicity (worst of any course)

	Grade		
	2	3	4
Hematological			
Leukopenia	3	3	0
Neutropenia	2	6	0
Anemia	5	1	0
Thrombocytopenia	2	2	0
Non-hematological			
High AST/ALT	1	0	0
Creatinine	0	0	0
Nausea	2	0	0
Vomiting	0	0	0
Diarrhea	3	0	0
Constipation	1	0	0
Pneumonitis	0	0	0
Bleeding	0	0	0
Infection	0	1	0
Hyponatremia	0	0	1
Peripheral neuropathy	1	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

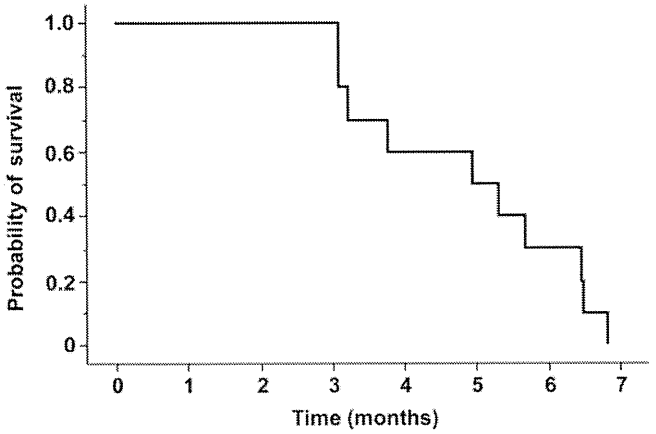

Figure 1. Progression-free survival. Median: 5.1 months (95% confidence interval [CI]: 3.9–5.8).

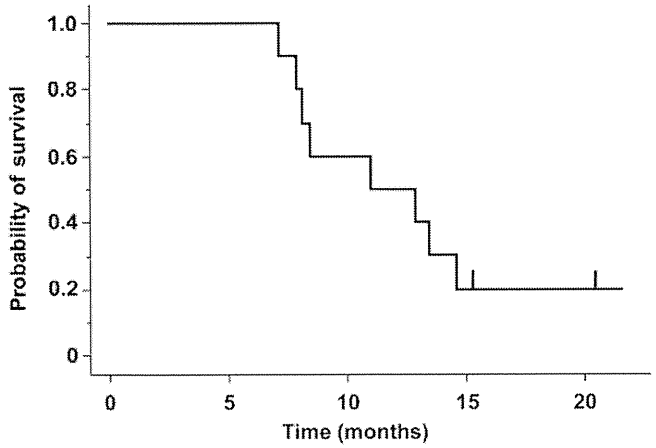

Figure 2. Overall survival. Median: 10.9 months (95% CI: 7.6–16.8).

DISCUSSION

Standard treatment for elderly patients with ED-SCLC has been controversial until now. Moreover, no global treatment consensus for these elderly patients has yet been reached. Because the median age of lung cancer patients is increasing in Japan, the need to formulate a strategy for treating this population is urgent. Some trials have shown that irinotecan might be a key drug for SCLC, particularly among Asian individuals (5,9); therefore, we conducted this feasibility study of CI in elderly SCLC patients. In this study, except for one patient who withdrew consent for chemotherapy, all other patients completed four courses of protocol treatment and the primary endpoint was met, with a feasibility of 91% (10/11). The toxicities were tolerable in this study. In general, Grade 4 hematologic toxicities are commonly experienced in association with chemotherapy for SCLC, even in patients with a good PS and adequate organ function (4–9). Only one patient in the present study experienced Grade 4 hyponatremia, and no Grade 4 hematologic toxicities were observed. The low frequency of diarrhea is particularly interesting. While the JCOG 9511 study comparing IP with EP (5) showed that the frequency of diarrhea associated with the IP regimen was relatively high (16%), no Grade 3 or 4 diarrhea was observed in the present study. Although the reason for this low frequency of diarrhea remains unclear, the low dose of irinotecan used (50 mg/m^2, Days 1 and 8) might have been a contributing factor.

While no CRs were observed, the 90% (9/10) response rate was satisfactory. Moreover, both OS and PFS were slightly longer than those observed in both treatment arms of JCOG 9702, which had almost the identical eligibility criteria (4). These data suggest that the CI regimen might improve outcomes of elderly patients with ED-SCLC. Two possible reasons may explain the promising efficacy observed in this trial. First, amrubicin was administered to 70% of patients as second-line chemotherapy. This agent was not administered at the time of the JCOG 9702 study. Because some investigators reported that second-line amrubicin was effective in relapsed SCLC (10–13), the use of this agent might have positively impacted on survival in this study. Secondly, all of the patients PS of 0–1, even though the eligibility criteria also allowed a PS of 2. In contrast, 26% of patients in the JCOG9702 study had a PS of 2–3 (4). Therefore, patient selection may have also contributed to the prolonged survival and reduced toxicities observed in this study.

This study has several limitations. First, we could have conducted more dose escalation due to the mild toxicity. However, chemotherapy delays occurred frequently, primarily due to neutropenia. Because dose escalation could have potentially caused more severe myelosuppression or delays of chemotherapy administration, we believe that it would have been difficult to escalate the dose in this trial. Secondly, our regimen included relatively low doses compared with the regimens used in non-elderly patients. Administration of irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks yields a dose intensity of 33 mg/m^2/week. In contrast, the dose intensity of irinotecan (60 mg/m^2, Days 1, 8 and 15, every 4 weeks) was 45 mg/m^2/week in JCOG9511. However, the omission of Day 15 irinotecan occurred in 50% of the courses in JCOG9511 (5). As no omission of Day 8 irinotecan occurred in the present study and course delays only occurred occasionally, the actual difference in dose intensity between the present trial and JCOG9511 may be relatively small. Thirdly, this feasibility study had a small sample size. Further investigation with a larger number of patients is warranted to verify the current results. Fourthly, this trial was not designed based upon an appropriate statistical method. However, if this study was done as a Phase II study using a Simon Minimax design, ~30–40 patients were required. At the time of study initiation, we felt that CI regimen became a promising experimental arm for a future Phase III trial based on our previous study. In addition, many JCOG members hesitated to perform a time-consuming Phase II trial of CI regimen. Therefore, we evaluated the feasibility of this regimen using a small sample size of 10 patients. If a marginal result for feasibility was obtained in the first 10 patients, additional 10 patients were required to avoid a negative result by chance.

In conclusion, treatment with CI in elderly ED-SCLC patients is feasible and appears to provide less toxicities and more efficacy than other regimens. Based on the current study, a Phase II/III trial comparing CE with CI in elderly patients with ED-SCLC is being scheduled by the JCOG LCSG.

Funding

This research was supported in part by National Cancer Center Research and Development Fund (23-A-18).

Conflict of interest statement

None declared.

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Int J Clin Oncol (2014) 19:63–67
DOI 10.1007/s10147-012-0509-2

ORIGINAL ARTICLE

Comparison of chemotherapeutic efficacy between LCNEC diagnosed using large specimens and possible LCNEC diagnosed using small biopsy specimens

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Received: 11 July 2012 / Accepted: 3 December 2012 / Published online: 19 December 2012

Abstract
Background It is often difficult to diagnose large cell neuroendocrine carcinomas (LCNEC) of the lung using small biopsy specimens. Some recent studies attempted to diagnose LCNEC using biopsy specimens; in 2011, the International Association for the Study of Lung Cancer pathological panels suggested possible LCNEC as a diagnosis for LCNEC by using biopsy specimens. Here, we compared the chemotherapeutic efficacy in possible LCNEC and LCNEC diagnosed using surgically resected specimens.
Methods We retrospectively reviewed patients who received platinum-based chemotherapy as first-line chemotherapy at our institution during September 2002–September 2011. Further, we compared the clinical characteristics, chemotherapeutic responses, and survival outcomes of patients diagnosed as having "LCNEC definite" with those diagnosed as having "possible LCNEC."
Results We selected 34 patients of whom 10 were diagnosed with LCNEC using surgically resected specimens and 24 patients with possible LCNEC were diagnosed using small biopsy specimens. In both groups, almost all patients were men and were smokers. Small-cell carcinoma-based chemotherapy, such as platinum plus irinotecan or platinum plus etoposide, was used for treating 60 % LCNEC patients (6/10) and 67 % possible LCNEC patients. In the LCNEC and possible LCNEC groups, respectively, the response rate was 70 and 54 % ($p = 0.39$), median progression-free survival was 2.9 and 4.4 months ($p = 0.20$), and median survival time was 12.8 and 9.1 months ($p = 0.50$).
Conclusion No statistically significant differences were found in chemotherapeutic responses and survival outcomes between the 2 groups, which suggests that chemotherapeutic efficacy is similar in both possible LCNEC and LCNEC.

Keywords LCNEC · Possible LCNEC · Small cell carcinoma · Chemotherapy · Biopsy

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Introduction

In the 2004 edition of the World Health Organization (WHO) classification, large cell neuroendocrine carcinoma (LCNEC) of the lung was defined using detailed criteria for each subtype of neuroendocrine tumor; LCNEC was subcategorized as a variant of large cell carcinoma. The histological findings of LCNEC are large tumor cells with a low nuclear/cytoplasm ratio, prominent nucleoli, a high

mitotic rate (11 or more mitotic figures in 10 high-power fields), a high degree of necrosis, and neuroendocrine (NE) morphologic features, such as rosette formation, organoid nesting, and palisading. Immunohistochemical positive staining for at least 1 NE marker, such as neural cell adhesion molecule (NCAM), chromogranin A, and synaptophysin, is also required [1].

LCNEC is a rare tumor accounting for approximately 3 % of all resected pulmonary malignancies [2–4]. Most previous reports have found that LCNEC predicted poorer survival than expected for stage-matched non-small-cell lung carcinoma (NSCLC) [2–4]. The malignant behavior and poor prognosis of LCNEC have been reported to be similar to those of small-cell lung carcinoma (SCLC) [5, 6]. However, these reports were limited to surgically resected specimens, because it is difficult to fully meet the histological criteria required to diagnose LCNEC using small biopsy specimens. One of the serious problems with LCNEC is that there are few studies evaluating the clinical features and prognosis of advanced cases, since diagnosis of advanced LCNEC using a small specimen is often difficult. There is no established therapeutic strategy for LCNEC, particularly for advanced cases.

Recently, Igawa et al. [7] attempted to diagnose advanced LCNEC using biopsy specimens, and reported that the pathological findings of LCNEC on biopsy specimens were defined NSCLC with some NE morphology and 1 or more positive NE markers with a high Ki-67/MIB 1 labeling index. Shimada et al. [8] also reported similar results. In 2011, Travis and colleagues suggested use of the term "possible LCNEC" for NSCLC with NE morphology and positive NE markers (NCAM, chromogranin A, and/or synaptophysin), excluding definite adenocarcinoma and squamous cell carcinoma, in a small biopsy specimen [9]. To evaluate the diagnosis of possible LCNEC, we compared the efficacy of chemotherapy in LCNEC and possible LCNEC in this study.

Patients and methods

Patients

From September 2002 to September 2011, we selected patients consecutively whose pathological diagnoses were LCNEC or possible LCNEC who received platinum-based chemotherapy as first-line chemotherapy from patient records at Shizuoka Cancer Center. We excluded patients who received concurrent chemo-radiotherapy. LCNEC and possible LCNEC were diagnosed using either primary or metastatic lesions. The sampling method was not defined, i.e., whether it was by biopsy or surgery. LCNEC was diagnosed according to the 2004 WHO criteria, using samples obtained by surgically resection. The diagnosis of possible LCNEC was made when LCNEC was highly suspected, but it was difficult to fulfill the conventional WHO criteria. All cases had confirmed positivity of 1 or more immunohistochemical NE markers (NCAM, chromogranin A, and synaptophysin) and showed a high MIB 1 labeling index (more than 40 %).

Evaluation

Chemotherapeutic response was accessed according to the Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST guideline (version 1.1) [10]. To define disease progression or relapse, patients were evaluated by physical examination, chest radiography, and computed tomography (CT) of the chest and abdomen. In some patients, we used positron emission tomography (PET)–CT, magnetic resonance imaging (MRI), or bone scintigraphy to detect the extent of disease progression. Their clinical disease staging was reassessed according to the latest Union for International Cancer Control (UICC) staging criteria (7th edition) [11].

Progression-free survival (PFS) was scored as an event of documented disease recurrence or death measured from the start of first-line chemotherapy to the date of an event or the last follow-up. Overall survival (OS) was measured from the start of first-line chemotherapy to the date of death or the last follow-up.

Statistical analysis

All categorical variables and objective response rates were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Distributions of PFS and OS were estimated using the Kaplan–Meier method, and the LCNEC and possible LCNEC groups were compared using the log-rank test. All p values were 2 sided, and values <0.05 were considered statistically significant. All analyses were performed using JMP 9 software (SAS Institute, Cary, NC, USA). This study was approved by the institutional review board.

Results

A total of 34 patients were eligible for this retrospective study, including 10 LCNEC patients diagnosed using surgically resected specimens. The resection sites for diagnosis of LCNEC were the lung ($n = 6$), brain metastasis ($n = 3$), and bone metastasis ($n = 1$). All 24 possible LCNEC patients were diagnosed using small biopsy specimens, and the biopsy sites were transbronchial biopsy ($n = 18$), CT-guided needle biopsy ($n = 4$), surgical