Table V. *Comparison of clinical trials of Topo-I-inhibitor and CDDP in untreated extensive disease of small-cell lung cancer.*

Authors	Current study	Kudoh (15)	Noda (14)		Heigener (13)		Eckardt (14)		Lara (20)	
Examined arm	Topotecan + CDDP	Irinotecan + CDDP	Irinotecan + CDDP	ETP + CDDP	Topotecan + CDDP	ETP + CDDP	Po-Topotecan + CDDP	ETP + CDDP	Irinotecan +CDDP	ETP + CDDP
Response rate (%)	82.8	86 ED: 35 pts	84.4	67.5	55.5	45.5	63	69	60	57
Median overall survival time (months)	17.5	13.0	12.8	9.4	10.3	9.4	9.2	9.4	9.9	9.1
1-year survival rate (%)	79.3	21.7/2-year survival	58.4	37.7	39.7	36.1	31	31	41	34
Nationality	Japanese	Japanese	Japanese		European		European		America	

ETP: Etoposide, ED: extensive-disease.

5 Kollmannsberger C, Mross K, Jakob A, Kanz L and Bokemeyer C: Topotecan a novel topoisomerase I inhibitor: Pharmacology and clinical experience. Oncology *56*: 1-12, 1999.

6 Kaufmann SH, Peereboom D, Buckwalter CA, Svingen PA, Grochow LB, Donehower RC and Rowinsky EK: Cytotoxic effects of topotecan combined with various anticancer agents in human cancer cell line. J Nati Cancer Inst *88(11)*: 734- 741, 1996.

7 Rowinsky EK, Kaufmann SH, Baker SD, Grochow LB, Chen TL, Peereboom D, Bowling MK, Sartorius SE, Ettinger DS, Arlene E and Donehower C: Sequences of topotecan and cisplatin: phase I, pharmacologic, and *in vitro* studies to examine sequence dependence. J Clin Oncol *14*: 3074-3084, 1996.

8 Huinink WB, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, Broom C, Scarabelli C, Davidson N, Spanczynski M, Bolis G, Malmstrom H, Coleman R, Fields SC and Heron J-F: Topotecan *versus* paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol *15*: 2183-2193, 1997.

9 Long III HJ, Bundy BN, Grendys EC, Benba JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA and Fiorica J: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group Study. J Clin Oncol *23*: 4626-4633, 2005.

10 Ardizzoni A, Manegold C, Debruyne C, Gaafar R, Buchholz E, Smit EF, Lianes P, Velde Gt, Bosquee L, Legrand C, Neumaier C, King K and Giaccone G: European Organization for Research and Treatment of Cancer (EORTC) 08957 Phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. Clinical Cancer Research *9*: 143-150, 2003.

11 Miller AA, Hargis JB, Lilenbaum RC, Field SZ, Rosner GL and Schilsky RL: Phase I study of topotecan and cisplatin in patients with advanced solid tumors: A cancer and leukemia group B study. J Clin Oncol *12*: 2743-2750,1994.

12 Sorenson M, Jensen PB, Herrstedt J, Hirsch FR and Hansen HH. A dose escalating study of topotecan preceding cisplatin in previously untreated patients with small- cell lung cancer. Ann Oncol *11*: 829-835, 2000.

13 Heigener DF, Freitag L, Eschbach C, Huber RH, Fink T, Hummler S, Banik N and Wolf M: Topotecan/cisplatin (TP) compared to cisplatin/etoposide (PE) for patients with extensive disease-small cell lung cancer (ED-SCLC): Final results of a randomized phase III trial. J Clin Oncol ASCO Ann Meet Proc *26*: 7513, 2008.

14 Eckardt JR, Pawel J, Papai Z, Tomova A, Tzekova V, Crofts TE, Brannon S, Wissel P and Ross G: Open-Label, Multicenter, Randomized, phase III study comparing oral topotecan/cisplatin *versus* etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive disease small cell lung cancer. J Clin Oncol *24*: 2044-2051, 2006.

15 Kudoh S, Fujiwara Y, Takeda Y, Ymamoto H, Kinoshita A, Ariyoshi Y, Furuse K and Fukuoka M: Phase II study of irinotecan combination with cisplatin in patients with previously untreated small-cell lung cancer. J Clin Oncol *16*: 1068-1074, 1998.

16 Ichinose Y, Seto T, Nishiwaki Y, Kiura K, Sakai H, Yokoyama A, Segawa Y, Ando M and Watanabe K: Phase I study of Topotecan and Cisplatin in patients with small cell lung cancer. Jpn J Clin Oncol *41(2)*: 197-203, 2011.

17 Homepage/Web site [Edited 9 Aug 2006]. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events Version 3.0. [cited 2006 Aug. 9]. Available at; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

18 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Geyther SG: New guidelines to evaluate the response to treatment in solid tumor (RECIST Guidelines). J Natl Cancer Inst *92*: 205-216, 2000.

19 Miller AA, Lilenbaum RC, Lynch TJ, Rosner GL, Ratain MJ, Green MR and Schilsky RL: Treatment-related fatal sepsis from topotecan/cisplatin and topotecan/paclitaxel. J Clin Oncol *4(6)*: 1964-1965, 1996.

20 Rowinsky EK, and Verweij J: Review of Phase I Clinical study with topotecan. Sem Oncol *24*: S20-3-S20-10, 1997.

21 Schiller JH, Kim KM, Hutson P, DeVore R, Glick J, Stewart J, and Johnson D: Phase II study of topotecan in patients with extensive- stage small- cell carcinoma of the lung: An eastern cooperative oncology group trial. J Clin Oncol *14*: 2345-2352, 1996.

22 Lara PN Jr. Natale R, Crowley J, Lenz HL, Redman MW, Carleton JE, Jett J, Langer CJ, Kuebler P, Dakhil SR, Chansky K and Gandara DR: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive stage small cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol *27*: 2530-2535, 2009.

23 Hanna N, Bunn Jr. PA, Langer C, Einhorn L, Guthrie T Jr., Beck T, Ansari R, Ellis P, Byene M, Morrison M, Hariharan S, Wang B and Sandler A: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive stage disease small cell lung Cancer. J Clin Oncol *24*: 2038-2043, 2006.

24 Han JY, Lee DH, Lee SY, Park CG, Kim HY, Kim EA, Yoon SM, Lee HGi and Lee JS: A phase II study of dose-intensified weekly concomitant administration of cisplatin and irinotecan in chemo-naive patients with extensive disease small cell lung cancer. Med Oncol *22*: 281-290, 2005.

25 Lee JE, Park HS, Jung SS, Kim JO and Kim SY: Phase II study of 3-week schedule of irinotecan combined with cisplatin in previously untreated extensive stage small cell lung cancer. Oncology *73*: 76-80, 2007.

26 Bas SH, Ryoo HM, Do YR, Song HS, Kwon KY, Kim MK, Lee KH, Hyun MS, Lee WS, Hur InK, Baek JH and Park KU: A Phase II study of biweekly irinotecan and cisplatin for patients with extensive stage disease small cell lung cancer. Lung Cancer *59*: 76-80, 2008.

27 Thatcher N, Chang A, Parikh P, Pereira JR, Ciuleanu T, Pawel JV, Thongprasert S, Tan EH, Pemberton K, Archer V and Carroll K: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomized, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet *366*: 1527-1537, 2005.

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A phase II study of amrubicin and topotecan combination therapy in patients with relapsed or extensive-disease small-cell lung cancer: Okayama Lung Cancer Study Group Trial 0401

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ABSTRACT

Backgrounds: Chemotherapy is a mainstay in the treatment of extensive-disease small-cell lung cancer (ED-SCLC), although the survival benefit remains modest. We conducted a phase II trial of amrubicin (a topoisomerase II inhibitor) and topotecan (a topoisomerase I inhibitor) in chemotherapy-naïve and relapsed SCLC patients.
Methods: Amrubicin (35 mg/m^2) and topotecan (0.75 mg/m^2) were administered on days 3–5 and 1–5, respectively. The objective response rate (ORR) was set as the primary endpoint, which was assessed separately in chemotherapy-naïve and relapsed cases.
Results: Fifty-nine patients were enrolled (chemotherapy-naïve 31, relapsed 28). The ORRs were 74% and 43% in the chemotherapy-naïve and relapsed cases, respectively. Survival data were also promising, with a median progression-free survival time and median survival time of 5.3 and 14.9 months and 4.7 and 10.2 months in the chemotherapy-naïve and relapsed cases, respectively. Even refractory-relapsed cases responded to the treatment favorably (27% ORR). The primary toxicity was myelosuppression with grades 3 or 4 neutropenia in 97% of the patients, which led to grades 3 or 4 febrile neutropenia in 41% of the patients and two toxic deaths.
Conclusion: This phase II study showed the favorable efficacy and moderate safety profiles of a topotecan and amrubicin two-drug combination especially in relapsed patients with ED-SCLC.

1. Introduction

The standard regimen for patients with extensive disease small-cell lung cancer (ED-SCLC) has been cisplatin (CDDP)-based chemotherapy. Combination therapy with etoposide (ETP) and CDDP or irinotecan and CDDP has been very effective in previously untreated patients with ED-SCLC [1,2]. However, the long-term survival rate is low; early relapse occurs in the majority of responders, and salvage chemotherapy for SCLC yields disappointing results [3]. The survival of patients with ED-SCLC enrolled in phase III trials has not improved significantly over the last two decades, clearly suggesting the need for the further development of novel, more effective agents or combination regimens [4].

Recently, several novel agents have been developed with unique mechanisms of action and have shown promise in the treatment of SCLC [5]. One of them, amrubicin, is an entirely synthetic anthracycline that inhibits DNA topoisomerase II activity. With an overall response rate (ORR) of 78.8% and median survival time (MST) of 11.0 months, amrubicin has demonstrated antitumor activity against previously untreated SCLC [6]. Another novel agent, topotecan, is a semi-synthetic water-soluble analog of camptothecin that inhibits DNA topoisomerase I activity. It, too, has shown favorable antitumor activity against SCLC with an ORR of 39% and MST of 9.0 months [7]. Previously, we conducted a phase I trial to determine the safety and efficacy of a two-drug combination chemotherapeutic regimen

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of amrubicin and topotecan in patients with untreated or relapsed ED-SCLC [8].

Based on the results of the phase I trial, we conducted a phase II trial of amrubicin and topotecan in patients with untreated or relapsed ED-SCLC to determine the ORR primarily. Secondary objectives were to investigate toxicity, progression-free survival (PFS), and overall survival.

2. Materials and methods

2.1. Eligibility criteria

Patients were recruited based on the following eligibility criteria: pathologically proven SCLC; chemotherapy-naïve ED-SCLC defined as distant metastasis, contralateral hilar lymph node metastasis or malignant pleural effusion [9], or relapsed disease (one prior regimen allowed); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3; age ≤75 years; presence of measurable lesions; no chemotherapy within 4 weeks before entry in the study; adequate hematological [white blood cell (WBC) count ≥3000/μL, neutrophil count ≥1500/μL, hemoglobin level ≥8.5 g/dL, platelet count ≥10×10^4/μL], renal (serum creatinine level ≤1.5 mg/dL), and hepatic (total bilirubin level ≤1.5 mg/dL, serum transaminases ≤2.5 × upper limit of normal range) function; and adequate pulmonary reserves [arterial oxygen pressure (PaO_2) ≥60 Torr]. Relapsed cases included those with sensitive relapse (an interval of at least 90 days after the completion of first-line chemotherapy) and chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse within 90 days after the completion of first-line chemotherapy). Patients with symptomatic brain metastasis, double cancer, massive effusion requiring drainage, or severe comorbidities (*e.g.*, uncontrolled diabetes, heart disease, infectious disease, or pulmonary fibrosis) were ineligible. Pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiography, electrocardiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan. Staging was conducted according to the tumor, node, metastasis system [10]. Positron emission tomography (PET)/CT was also used for staging in some cases.

All patients gave written consent, and the protocol was approved by the institutional review board of each participating institute and performed in accordance with the amended 2000 version of the World Medical Association's Declaration of Helsinki.

2.2. Treatment scheme

The doses and schedules of both agents were based on phase I trial results [8]. Topotecan was diluted in 100 mL of physiological saline and administered intravenously as a 1-h infusion at a dose of 0.75 mg/m^2 on days 1 through 5. After completing the topotecan infusion, amrubicin was diluted in 20 mL of physiological saline and administered intravenously as a 5-min bolus injection at a dose of 35 mg/m^2 on days 3 through 5. Each patient was pre-medicated with intravenous dexamethasone and granisetron.

The treatment was repeated every 4 weeks for up to four cycles unless disease progression or unacceptable toxicity was observed, or the patient refused further treatment. Initiation of the next cycle of chemotherapy was delayed until the WBC and platelet count recovered to ≥3000/μL and ≥10×10^4/μL, respectively, and non-hematologic toxicities resolved to ≤grade 1. If hematological toxicity of grade 4 lasting more than 4 days or non-hematological toxicity ≥grade 3 was observed in a prior cycle, the amrubicin dose was reduced each cycle by 5 mg/m^2. The protocol treatment was stopped if patients developed the same toxicities after the second dose reduction. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was observed, use of granulocyte colony-stimulating factor (G-CSF) was permitted.

2.3. Assessment of antitumor activity and toxicity

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines were applied to evaluate responses. Patients were evaluated for SCLC, with tumor assessments at baseline every two cycles, and at the end of treatment. The best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence. Complete and partial responses were confirmed by two observations no <4 weeks apart. A determination of stable disease required disease stabilization for at least 6 weeks. In this study, we also defined the disease control rate (DCR) as the proportion of patients with complete and partial responses and stable disease [11]. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Patients were monitored closely for signs of cardiotoxicity during the study, and an electrocardiogram was required at the start of treatment.

2.4. Statistical analysis

The primary endpoint of this study was the overall response rate (ORR), and secondary end points were PFS, overall survival, and the toxicity profile. The efficacy of topotecan and amrubicin combination therapy was assessed separately for chemotherapy-naïve and relapsed patients. For chemo-naïve cases, assuming that a 90% ORR in eligible patients would indicate potential usefulness, whereas a 70% ORR would constitute the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.10$, the estimated accrual was 25 patients. For relapsed cases, assuming that a 30% ORR would indicate potential usefulness, whereas a 10% ORR would constitute the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.10$, the estimated accrual was also 25 patients. This regimen was to be rejected when <12 and <2 of the first 16 cases had an ORR at the interim analysis, for the chemotherapy-naïve and salvage cases, respectively. With an assumed 10% dropout rate, the number of patients needed was 28 each. Overall survival was defined as the interval between the date of enrollment in this study and death or the last follow-up visit. PFS was defined as the interval between the date of enrollment and the date of the first observation of disease progression or death from any cause. The survival distribution was estimated using the Kaplan–Meier method. All statistical analyses were conducted with STATA/SE version 10.0 software (College Station, TX).

3. Results

3.1. Patient characteristics and treatment delivery

A total of 59 consecutive patients with 31 chemotherapy-naïve and 28 relapsed ED-SCLC were enrolled from eight institutions. Their demographics are shown in Table 1. All patients were assessable for efficacy and safety. The median number of treatment cycles was four (range 1–7 cycles) and three (range 1–8 cycles) in the chemotherapy-naïve and relapsed cases, respectively. Among patients who received only three or less cycles of treatment, the most common reason for treatment cessation, was disease progression (15 of the 29 patients). At the time of analysis, 29 of 31 (94%) chemotherapy-naïve and 24 of 28 (86%) relapsed patients developed disease progression. Of these, 26 chemotherapy-naïve and 11 relapsed patients received salvage chemotherapies: platinum-based doublet ($n = 19$), non-platinum-based doublet ($n = 5$), and monotherapy ($n = 2$) in the chemotherapy-naïve patients, and

Table 1
Demographics of the patients ($n=59$).

	Chemo-naïve ($n=31$)	Relapsed ($n=28$)
Age, median (range), years	67 (52–75)	69 (54–73)
Gender (M/F)	28/3	24/4
ECOG PS (0/1/2)	3/26/2	11/15/2
Smoking history (current/former/never)	11/15/2	16/12/3
Prior irinotecan use	–	7
Prior etoposide use	–	21
Type of treatment setting		
Sensitive relapse	–	17
Refractory relapse	–	11

Sensitive relapse (at ≥90 days after completion of first-line chemotherapy). Chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse within 90 days after completing first-line chemotherapy). *Abbreviations*: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2
Objective response and survival.

	Chemo-naïve ($n=31$)		Relapsed ($n=28$)	
	No.	%	No.	%
Response				
Complete response	1	3	0	0
Partial response	22	71	12	43
Stable disease	6	19	11	39
Progressive disease	2	6	4	14
Not assessable	–	–	1[a]	3
Overall response rate (95% CI)	23	74 (55–88)	12	43 (24–63)
Disease control rate	29	94	23	82
Survival				
Median PFS (months)	5.3		4.7	
Median OS (months)	14.9		10.2	
1-yr OS (95% CI; %)	68.4 (47.8–82.3)		29.9 (14.3–47.4)	

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval.
[a] Early death.

platinum-based doublet ($n=4$), non-platinum doublet ($n=1$), and monotherapy ($n=6$) in the relapsed patients.

3.2. Response

Due to early febrile neutropenia-related death (day 20, cycle 1), one patient received no formal response assessment. The planned interim analysis revealed this regimen had potent activity (13 and 6 responders) and the committee decided to continue further patient accrual in the chemotherapy-naïve and salvage settings, respectively. The ORR of chemotherapy-naïve patients was 74% (95% confidence interval (CI) 55–88%). This did not satisfy the initial setting of the lower limit of interest (70%), and thus the primary endpoint was not met for this population. By contrast, 43% of relapsed patients responded to the study treatment (95% CI 24–63%), which clearly met the lower limit of interest (10%).

In 28 relapsed patients, the ORR and DCR were 53% and 82%, respectively, for the sensitive-relapsed cases, and 27% and 82%, respectively, for the refractory-relapsed cases (Table 3).

3.3. Survival

All the patients were assessable for the survival analysis. At the time of this analysis (January 2010), 11 patients were still alive, and median follow-up time was 43.2 months ranging from 4.3 to 75.9 months. The median PFS time was 5.3 months for the chemotherapy-naïve cases and 4.7 months for relapsed cases (Table 2 and Fig. 1). The overall median survival time (MST) was 14.9 and 10.2 months for the chemotherapy-naïve and relapsed cases, respectively. When relapsed cases were classified by the type of relapse pattern, the median progression-free survival was 5.8 months in patients with sensitive relapse and 3.3 months in patients with refractory relapse. The overall median survival time was 10.2 and 10.5 months in sensitive and refractory relapse, respectively (Fig. 2).

3.4. Safety

Adverse events of grade 3 or worse are listed in Table 4. Myelosuppression was the primary adverse event. Grades 3 and 4 neutropenia, thrombocytopenia, and anemia were observed in 97%, 51%, and 42% of the patients, respectively. Median duration of neutropenia was five days. G-CSF was administered in 50 patients (85%), whereas 14 patients received blood transfusion. Grade 3 or worse non-hematological toxicities including anthracycline-

Table 3
Subset analysis of efficacy stratified by the type of relapse.

	Sensitive relapse ($n=17$)		Refractory relapse ($n=11$)	
	No.	%	No.	%
Response				
Complete response	0	0	0	0
Partial response	9	53	3	27
Stable disease	5	29	6	55
Progressive disease	2	12	2	18
Not assessable	1[a]	6	–	–
Overall response rate	9	53	3	27
Disease control rate	14	82	9	82
Survival				
Median PFS (months)	5.8		3.3	
Median OS (months)	10.2		10.5	
1-yr OS (95% CI; %)	38.2 (15.9–60.5)		18.2 (2.9–44.2)	

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval.
[a] Early death.

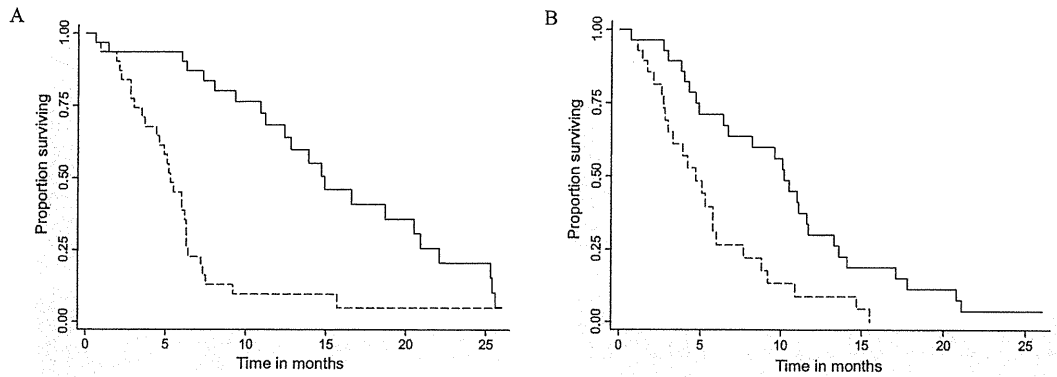

Fig. 1. Overall (solid) and progression-free (dotted) survival curves. (A) Chemotherapy-naïve patients and (B) relapsed patients.

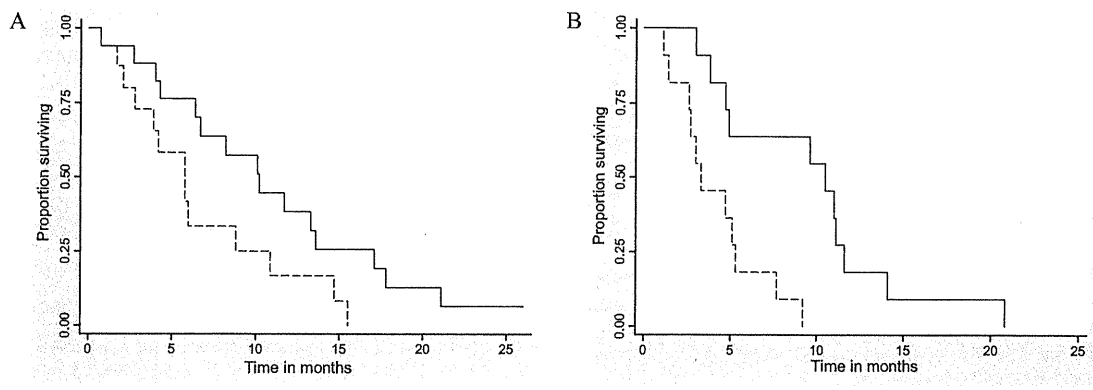

Fig. 2. Overall (solid) and progression-free (dotted) survival curves. (A) Sensitive-relapsed patients and (B) refractory-relapsed patients.

related cardiac toxicities were relatively mild, except for febrile neutropenia, which resulted in two treatment-related deaths (chemo-naïve setting and refractory relapsed setting in one each).

4. Discussion

In this relatively small study, the combination of amrubicin and topotecan yielded an ORR of 74% and 43% in the chemotherapy-naïve and relapsed cases, respectively. The survival data were also promising with a median PFS time and MST of 5.3 and 14.9 months and 4.7 and 10.2 months in the chemotherapy-naïve and relapsed cases, respectively. Even refractory-relapsed cases responded to this treatment (27% ORR). The major observed toxicity was myelosuppression. Grades 3 and 4 neutropenia occurred in 97% of the patients, resulting in grades 3 and 4 febrile neutropenia in 41% of the patients.

Table 4
Adverse events (grade 3 or worse).

	Grade 3	Grade 4	≥Grade 3 (%)
Hematologic			
Neutropenia	10	47	97
Thrombocytopenia	15	15	51
Anemia	21	4	42
Non-hematologic			
Fatigue	2	3	9
Febrile neutropenia	20	4	41
Nausea/vomiting	2	1	5
Diarrhea	0	1	2
Pneumonitis	1	1	3
Ileus	0	1	2

In a first-line setting, platinum plus irinotecan or etoposide is considered a standard treatment for ED-SCLC and approved in Japan. These regimens produce an ORR of 68–84%, a median PFS of 4.8–6.9 months, and a MST of 9.4–12.8 months [1]. Combination therapy consisting of cisplatin plus topotecan or cisplatin plus amrubicin has also been evaluated and has similar effects (56–88% ORR, 7.0-month median PFS, and 10.3–13.6 month-MST) [12,13]. In this study, combination therapy of topotecan and amrubicin produced less favorable efficacy than we initially expected although it yielded a nearly identical efficacy with a 74% ORR, 5.3-month median PFS, and 14.9 month-MST.

With regard to relapsed patients, Inoue et al. conducted a randomized phase II trial of amrubicin versus topotecan for relapsed SCLC patients and reported an ORR of 38% and 13% in amrubicin monotherapy and topotecan monotherapy, respectively [14]. The respective median PFS times and MSTs were 3.5 and 8.1 months (amrubicin monotherapy) and 2.2 and 8.4 months (topotecan monotherapy). Based on our *post hoc* sub-analysis stratifying relapse type, the efficacy of the amrubicin and topotecan combination therapy seemed more favorable especially in the refractory-relapsed cases when compared simply with each single therapy (27% vs. 0–17% ORR, 82% vs. 18–68% DCR, 3.3 vs. 1.5–2.6-month median PFS, and 10.5 vs. 5.3–5.4-month MST) [14]. Another trial also showed somewhat lower response rate of amrubicin monotherapy for refractory cases [15]. This might suggest some synergistic effects of the two drugs despite the need for further investigations.

As for the toxicity profiles, neutropenia in our combination therapy was mainly moderate, which parallels that in our prior phase I trial [8]. The occurrence of neutropenia in 83–93% of the patients undergoing amrubicin monotherapy [14,16,17] and 87% of the patients undergoing topotecan monotherapy

[14] seemed also similar to our findings. Furthermore, as in monotherapy, non-hematological toxicities other than febrile neutropenia of the amrubicin and topotecan combination therapy were generally tolerable. However, thrombocytopenia, anemia, febrile neutropenia and two toxic deaths seemed more severe in the combination therapy than the monotherapy [6,14,15], suggesting the need for cautious administration of the doublet therapy.

We have several limitations. Since this was an exploratory phase II single-arm trial, some selection bias is possible, and a simple comparison between our results and historical clinical data would be unwarranted and inconclusive. A prospective comparative study is clearly required. Also, this study design mixes up 3 populations of patients (untreated, relapsed-sensitive, and relapsed-refractory). Since only 59 patients enrolled, interpretation of the results is limited by the 3 small subsets of patients. The two populations of relapsed patients should have been stratified prospectively. Furthermore, we accrued PS3 patients as well as PS 0–2 patients in this study according to the previous clinical trial designs [18,19]. However, to date, this inclusion criterion has been unusual in most clinical trials, and the great majority of patients accrued in this study had indeed an excellent PS (0 or 1 in 93%). Thus, the efficacy and safety for PS 2–3 pts would still remain unclear.

5. Conclusions

In conclusion, this phase II study showed the favorable efficacy and moderate safety profiles of a topotecan and amrubicin two-drug combination especially in relapsed patients with ED-SCLC, while this regimen was less effective in the first-line setting and not worth while further being evaluated.

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Contributors

KH, KK, and HU were involved in the conception and design of the study. NN, KH, SK, KK, NT, KC, TS, DK, SH, AT, SH, and MT were involved in the provision of study material, patients, and data acquisition. KH, KK and NT were involved in data analysis and interpretation. All authors were involved in writing the report and approved the final version.

Conflict of interest

None declared.

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References

[1] Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85–91.
[2] Hanna N, Bunn Jr PA, Langer C, Einhorn L, Guthrie Jr T, Beck T, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038–43.
[3] Krug LM, Kris MG, Rosenzweig K, Travis WD. Small cell lung cancer. In: De 301 Vita Jr VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 8th 302 ed. Philadelphia: Lippincott-Raven; 2008. p. 946–71.
[4] Oze I, Hotta K, Kiura K, Ochi N, Takigawa N, Fujiwara Y, et al. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. PLoS One 2009;4:e7835.
[5] Ettinger DS. New drugs for chemotherapy-naive patients with extensive-disease small cell lung cancer. Semin Oncol 2001;28:27–9.
[6] Yana T, Negoro S, Takada Y, Yokota S, Fukuoka M, The West Japan Lung Cancer Group. Phase II study of amrubicin (SM-5887), a 9-amino-anthracycline, in previously untreated patients with extensive stage small-cell lung cancer (ES-SCLC): a West Japan Lung Cancer Group Trial. Proc Am Soc Clin Oncol 1998;17:450c [abstr 1734].
[7] Schiller JH, Kim K, Hutson P, DeVore R, Glick J, Stewart J, et al. Phase II study of topotecan in patients with extensive-stage small-cell carcinoma of the lung: an Eastern Cooperative Oncology Group Trial. J Clin Oncol 1996;14:2345–52.
[8] Shibayama T, Hotta K, Takigawa N, Tada A, Ueoka H, Harita S, et al. A phase I and pharmacological study of amrubicin and topotecan in patients of small-cell lung cancer with relapsed or extensive-disease small-cell lung cancer. Lung Cancer 2006;53:189–95.
[9] Stahel R, Aisner J, Ginsberg R, et al. Staging and prognostic factors in small cell lung cancer. Lung Cancer 1989;5:119.
[10] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710–7.
[11] Hotta K, Fujiwara Y, Kiura K, Tabata M, Takigawa N, Ueoka H, et al. Relationship between response rate and survival in over 50,000 patients of advanced non-small-cell lung cancer treated with systemic chemotherapy. J Thorac Oncol 2007;2:402–7.
[12] Heigener DF, Freitag L, Eschbach C, Huber RM, Fink T, Hummler S, et al. Topotecan/cisplatin (TP) compared to cisplatin/etoposide (PE) for patients with extensive disease-small cell lung cancer (ED-SCLC): final results of a randomised phase III trial. J Clin Oncol 2008;26 [May 20 suppl.; abstr 7513].
[13] Ohe Y, Negoro S, Matsui K, Nakagawa K, Sugiura T, Takada Y, et al. Phase I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 2005;16:430–6.
[14] Inoue A, Sugawara S, Yamazaki K, Maemondo M, Suzuki T, Gomi K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 2008;26:5401–6.
[15] Ettinger DS, Jotte R, Lorigan P, Gupta V, Garbo L, Alemany C, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. J Clin Oncol 2010;28:2598–603.
[16] Okamoto I, Hamada A, Matsunaga Y, Sasaki J, Fujii S, Uramoto H, et al. Phase I and pharmacokinetic study of amrubicin, a synthetic 9-aminoanthracycline, in patients with refractory or relapsed lung cancer. Cancer Chemother Pharmacol 2006;57:282–8.
[17] Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of tefractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol 2006;24:5448–53.
[18] Souhami RL, Spiro SG, Rudd RM, Ruiz de Elvira MC, James LE, Gower NH, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 1997;89:577–80.
[19] Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial Medical Research Council Lung Cancer Working Party. Lancet 1996;348:563–6.

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Randomised, phase III trial of epoetin-β to treat chemotherapy-induced anaemia according to the EU regulation

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BACKGROUND: Erythropoietin-stimulating agents (ESAs) effectively decrease the transfusion requirements of patients with chemotherapy-induced anaemia (CIA). Recent studies indicate that ESAs increase mortality and accelerate tumour progression. The studies also identify a 1.6-fold increased risk of venous thromboembolism. The ESA labelling was thus revised in Europe and the United States in 2008. This is the first randomised, phase III trial evaluating the efficacy and safety of epoetin-β (EPO), an ESA, dosed in accordance with the revised labelling, which specifies that ESAs should be administered to CIA patients with a haemoglobin level of $\leqslant 10\,g\,dl^{-1}$ and that a sustained haemoglobin level of $>12\,g\,dl^{-1}$ should be avoided.

METHODS: A total of 186 CIA patients ($8.0\,g\,dl^{-1} \leqslant$ haemoglobin $\leqslant 10.0\,g\,dl^{-1}$) with lung or gynaecological cancer were randomised to receive EPO 36 000 IU or placebo weekly for 12 weeks.

RESULTS: The proportion of patients receiving transfusions or with haemoglobin $<8.0\,g\,dl^{-1}$ between week 5 and the end of the treatment period as the primary end point was significantly lower in the EPO group ($n=89$) than in the placebo group ($n=92$; 10.0% *vs* 56.4%, $P<0.001$). The proportion receiving transfusions was significantly lower in the EPO group (4.5% *vs* 19.6%, $P=0.002$). Changes in quality of life were not different. No significant differences in adverse events – for example, the incidence of thromboembolic events was 1.1% for each group – or the 1-year overall survival were observed between groups.

CONCLUSION: Weekly EPO administered according to the revised labelling approved by the European Medicines Agency is effective and well tolerated for CIA treatment. Further investigations are needed on the effect of ESAs on mortality.

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Anaemia is a common adverse event in cancer patients receiving chemotherapy, particularly in patients with lung and gynaecological cancers (Ludwig *et al*, 2004; Ohe *et al*, 2007; Katsumata *et al*, 2009). Several of the symptoms associated with anaemia, such as fatigue, syncope, palpitations and dyspnoea, reduce patient activity and have a profound effect on the quality of life (QOL) (Bokemeyer *et al*, 2007). Red blood cell (RBC) transfusion is one of the available treatments for anaemia. However, RBC transfusion is associated with a risk of volume overload, infection of unknown virus and transfusion reactions. And in Japan, blood transfusion therapy is problematic because of an increasing demand for blood products and a scarcity of blood supply arising from the declining birth rate and ageing population.

In Europe and the United States, erythropoiesis-stimulating agents (ESAs) have been used since 1993 for the treatment of chemotherapy-induced anaemia (CIA). The ESAs increase haemoglobin levels and reduce the need for RBC transfusion (Littlewood *et al*, 2001; Österborg *et al*, 2002). Since 2003, several studies have suggested that ESAs are associated with increased mortality and/or tumour progression in cancer patients when administered with a target haemoglobin level of $>12\,g\,dl^{-1}$ (Hedenus *et al*, 2003; Henke *et al*, 2003; Leyland-Jones *et al*, 2005; Overgaard *et al*, 2007; Wright *et al*, 2007; Smith *et al*, 2008; Thomas *et al*, 2008). Accordingly, the risks of ESAs have been investigated by regulatory authorities (Juneja *et al*, 2008) and, in response to these investigations, the labelling of ESAs in Europe and the United States was revised in 2008. A recent meta-analysis of ESAs has suggested that the increase in mortality in ESA-treated cancer patients undergoing chemotherapy is less pronounced than in those patients undergoing other anticancer treatments such as radiotherapy or no anticancer treatment (Bohlius *et al*, 2009a, b). Similarly, another meta-analysis indicated that when used within current European Organisation for Research and Treatment of Cancer (EORTC) treatment guidelines, the ESA epoetin-β (EPO) had no negative impact on survival and tumour progression (Aapro *et al*, 2008a). However, the risks of ESAs have also been shown to be independent of haemoglobin levels and dosing (Bennett *et al*, 2008; Bohlius *et al*, 2009a, b), and these meta-analyses were not able to verify that the risks of ESAs were completely eradicated by adherence to the new labelling.

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The purposes of this study were to evaluate the efficacy and safety of EPO for the treatment of CIA with a dosing strategy according to the current labelling approved by the European Medicines Agency (EMA) (inclusion haemoglobin level criteria $\leqslant 10\,g\,dl^{-1}$, ceiling haemoglobin level $= 12\,g\,dl^{-1}$). We previously conducted a dose-finding study of once-weekly EPO in CIA patients with malignant lymphoma or lung cancer, and recommended a weekly dose of 36 000 IU based on our results (Morishima *et al*, 2006).

PATIENTS AND METHODS

Patient eligibility

Inclusion criteria were as follows: (1) lung or gynaecological cancer; (2) receiving platinum-based chemotherapy and expected to receive at least two additional cycles of chemotherapy; (3) CIA ($8.0\,g\,dl^{-1} \leqslant$ haemoglobin level $\leqslant 10.0\,g\,dl^{-1}$); (4) age between 20 and 79 years; (5) Eastern Cooperative Oncology Group performance status (PS) of 0–2; and (6) adequate hepatic and renal function.

Exclusion criteria included: (1) iron-deficiency anaemia (serum transferrin saturation (TSAT) $<15\%$ or mean corpuscular volume (MCV) $<80\,\mu m^3$); (2) ESA therapy within 8 weeks or RBC transfusion within 4 weeks before the study; (3) surgery scheduled during the study period; (4) previous radiation therapy to the pelvis; (5) documented haemorrhagic lesions; (6) history of myocardial, pulmonary or cerebral infarction; (7) uncontrolled hypertension; (8) history of hypersensitivity to ESA; (9) serious drug allergy; and (10) tumour in the central nervous system.

Study design and treatment

This multicentre, randomised, double-blind, placebo-controlled, phase III study was conducted at 37 sites in Japan. The protocol was approved by the institutional review board of the respective hospitals, and written informed consent was obtained from all patients who participated in the study. Patients were randomised 1 : 1 to receive EPO 36 000 IU or placebo subcutaneously once a week for up to 12 weeks. Epoetin-β and placebo were supplied by Chugai Pharmaceutical Co., Ltd (Tokyo, Japan). Participants in the study and investigators (outcome assessors) were blinded toward treatment allocation. Randomisation was conducted by a contract research organisation (CRO) that was independent from the investigators. The randomisation was carried out by a central registration system and was stratified by tumour type, PS, haemoglobin level and institution using a dynamic balancing method. The randomisation table was kept sealed and stored until a database lock by the CRO. Analysis methods were determined before the database lock.

If the haemoglobin level increased to $>12.0\,g\,dl^{-1}$ at any time during the study, administration was discontinued until the haemoglobin level decreased to $\leqslant 11.0\,g\,dl^{-1}$, and was then restarted at two-thirds of the previous dose (24 000 IU). If the planned cycle of chemotherapy was completed or discontinued, treatment was withheld at 6 weeks after day 1 of the final chemotherapy cycle. A daily dose of 100–200 mg elemental iron was administrated if TSAT fell to $<15\%$ or MCV fell to $<80\,\mu m^3$. The RBC transfusion was allowed at the discretion of the investigator during the study.

Evaluation of efficacy and safety

The primary end point of this study was the proportion of patients receiving RBC transfusion or with a haemoglobin level $<8.0\,g\,dl^{-1}$ between week 5 and the end of the treatment period (EOTP). The secondary end points were the proportion of patients receiving RBC transfusion between week 5 and the EOTP, change in haemoglobin level and QOL from baseline to the EOTP. QOL was evaluated using the Japanese Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire (Yoshimura *et al*, 2004). In this study, the FACT-An total fatigue subscale, which consists of 13 fatigue-related questions, was the principal means of analysis. The FACT-An total fatigue subscale scores (FSS) range from 0 to 52, with higher scores indicating less fatigue.

Safety end points included adverse events, tumour progression and death (during the treatment phase and 1-year follow-up period). Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria, ver. 3, translated by the Japan Clinical Oncology Group. The presence of neutralising antibodies to EPO was assessed at baseline and the EOTP.

Statistical analysis

The sample size of 160 patients (including an anticipated withdrawal rate of 40%, mainly because of completing or discontinuing the planned cycle of chemotherapy) was calculated to yield 80% power to significantly detect a 25% reduction (from 45 to 20%) in the primary end point, the proportion of patients receiving RBC transfusion or with a haemoglobin level $<8.0\,g\,dl^{-1}$ between week 5 and the EOTP. Statistical testing was conducted using a two-sided significance level of $P = 0.05$. The study was not powered for QOL as a secondary efficacy end point. Patients who received at least one dose of the study drug comprised the safety population. For efficacy analysis, ineligible patients were excluded from the safety population, resulting in the full analysis set (FAS) population. The proportion of patients receiving RBC transfusion or with a haemoglobin level $<8.0\,g\,dl^{-1}$ was estimated by the Kaplan–Meier method. The requirement for RBC transfusion was compared using the χ^2 method. Changes in the haemoglobin level and FSS between groups were compared using Student's *t*-test.

RESULTS

Demographics and baseline characteristics

A total of 186 patients were enroled in the study between June and December 2008, and 181 (89 EPO and 92 placebo) of these were eligible for efficacy evaluation (the FAS population). Five patients were excluded because of discontinuation before the first dosing for the following reasons: withdrawal of patient consent ($n = 2$), chemotherapy regimen cancelled ($n = 1$), patient eligibility criteria violation ($n = 1$) and a positive result in the skin test to EPO ($n = 1$). In all, 51 (57%) patients in the EPO group and 55 (60%) in the placebo group completed 12 weeks of the study. Elemental iron was administrated in 40 patients (45%) in the EPO group and 32 (35%) in the placebo group. The demographics and baseline characteristics of the FAS population were well balanced (Table 1). The range of haemoglobin levels at screening was $8.0–10.0\,g\,dl^{-1}$, whereas those at baseline (1–17 days after the screening) ranged from 7.2 to $11.4\,g\,dl^{-1}$. The main chemotherapeutic regimen for both lung and gynaecological cancer was carboplatin-paclitaxel therapy.

Transfusion-related and haemoglobin end points

The proportion of patients receiving RBC transfusion or with a haemoglobin level $<8.0\,g\,dl^{-1}$ between week 5 and the EOTP was significantly lower in the EPO group than the placebo group (10.0%; 95% confidence intervals (CIs) in the EPO group, 3.4–16.6 *vs* 56.4%; 95% CI in the placebo group, 45.4–67.4%, $P<0.001$; Figure 1). Fewer patients received RBC transfusions between week 5 and the EOTP in the EPO group (4 of 89 patients, 4.5%) than in the placebo group (18 of 92 patients, 19.6%, $P = 0.002$). The range of pretransfusion haemoglobin levels at the time of the first transfusion was $5.3–8.1\,g\,dl^{-1}$.

Table 1 Characteristics of full analysis population

	EPO ($n=89$)	Placebo ($n=92$)
Sex		
Male	47	40
Female	42	52
Age (years), median (min–max)	67 (40–79)	63.5 (44–79)
Weight (kg), median (min–max)	53.5 (35–102)	52.8 (37.4–78.1)
Tumour		
Small cell lung cancer	20 (22.5)	22 (23.9)
Non-small cell lung cancer	40 (44.9)	38 (41.3)
Ovarian cancer	19 (21.3)	19 (20.7)
Other	10 (11.2)	13 (14.1)
ECOG performance status		
0	42 (47.2)	41 (44.6)
1	45 (50.6)	50 (54.3)
2	2 (2.2)	1 (1.1)
Haemoglobin ($g\,dl^{-1}$), median (min–max)	9.4 (8.1–11.4)	9.3 (7.2–11.4)
Transferrin saturation (%), median (min–max)	25.1 (5.4–97.6)	24.1 (6.4–99.4)
Serum endogenous erythropoietin ($mIU\,ml^{-1}$), median (min–max)	43 (7.78–577)	43.6 (10.5–320)

Abbreviations: EPO = epoetin-β; ECOG = Eastern Cooperative Oncology Group.

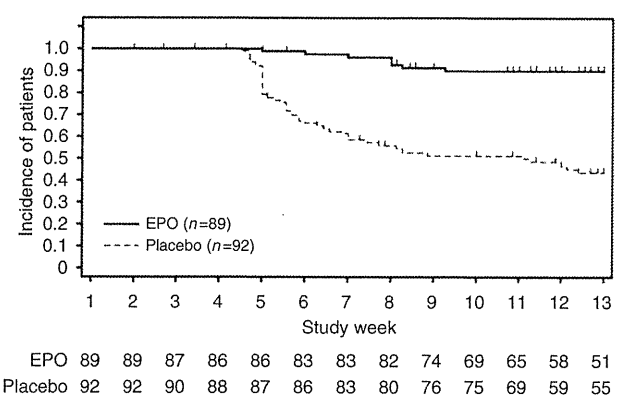

Figure 1 Time to RBC transfusion or haemoglobin level $<8.0\,g\,dl^{-1}$.

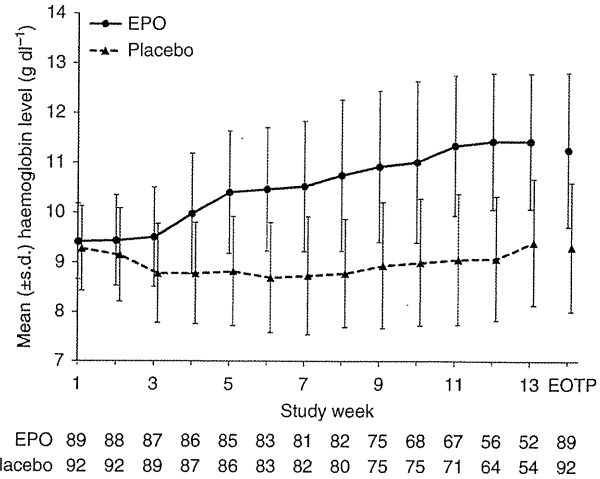

Figure 2 Change in haemoglobin level by treatment group. Abbreviation: EOTP = end of treatment period.

Table 2 Incidence of adverse events

	EPO ($n=89$)		Placebo ($n=92$)	
	No. of patients	%	No. of patients	%
Adverse events	88	98.9	92	100.0
Common adverse events				
Neutropenia	82	92.1	74	80.4
Leucopenia	81	91.0	77	83.7
Thrombocytopenia	61	68.5	55	59.8
Lymphocytopenia	44	49.4	52	56.5
Anorexia	43	48.3	50	54.3
Nausea	43	48.3	46	50.0
Adverse drug reactions	37	41.6	28	30.4
Common adverse drug reactions				
Constipation	6	6.7	2	2.2
Increased blood pressure	5	5.6	3	3.3
Diarrhoea	5	5.6	1	1.1

Abbreviation: EPO = epoetin-β.

The mean change in haemoglobin level from baseline to the EOTP in the EPO group ($1.9\,g\,dl^{-1}$) was significantly higher than that in the placebo group ($0.0\,g\,dl^{-1}$, $P<0.001$). Figure 2 shows the mean changes in haemoglobin levels throughout the study in both groups. The mean nadir haemoglobin level between week 5 and the EOTP was $9.7\,g\,dl^{-1}$ in the EPO group and $7.9\,g\,dl^{-1}$ in the placebo group ($P<0.001$).

The percentage of patients with a haemoglobin level $>12.0\,g\,dl^{-1}$ after dosing, and whose administration was halted, was 50% in the EPO group and 2% in the placebo group.

QOL

Overall compliance in terms of the percentage of patients who completed the FACT-An questionnaire was 98.3% (178 of 181) at baseline and 93.9% (170 of 181) at the end of the study. The mean baseline FSS was 35 points in the EPO group and 33 points in the placebo group. The mean changes in FSS from baseline to the EOTP in the EPO group were higher than in the placebo group, but these changes did not achieve statistical significance (0.30 *vs* −0.99, $P=0.387$).

Safety

A total of 181 patients received study treatment and were included in the safety analysis. The overall incidence of adverse events was similar between the two groups (99% EPO and 100% placebo). There were 120 adverse events (in 37 patients) related to the study drug (adverse drug reactions) in the EPO group and 78 (in 28 patients) in the placebo group. Of these adverse drug reactions, constipation (6.7%), increased blood pressure (5.6%) and diarrhoea (5.6%) were reported by at least 5% of patients in the EPO group (Table 2). In all, 8 patients (14 events) in the EPO group and 17 patients (21 events) in the placebo group experienced serious adverse events. Of these, 5 events (acute respiratory distress syndrome, pneumonia, pulmonary embolism, neutropenia and thrombocytopenia) were considered to be related to EPO. As a thromboembolic event, one pulmonary embolism was observed in the EPO group. It was not associated with higher haemoglobin

level (the haemoglobin level at the onset was 9.4 g dl^{-1}). In the placebo group, haemorrhagic cerebral infarction (asymptomatic; no treatment was required) occurred in one patient. The proportion of patients who experienced tumour progression during the treatment period was similar in both groups (27.0% in the EPO group and 26.1% in the placebo group). No neutralising antibodies to EPO were detected.

Survival

One patient in the EPO group died during the active study period. Follow-up survival data for all 181 patients who received the study drug were gathered through December 2009, at which time the median follow-up period was 54 weeks after the first dose of study drug. The 1-year overall survivals were 58.7% (95% CI, 48.4–69.1%) and 63.4% (95% CI, 53.4–73.3%) in the EPO and placebo groups, respectively ($P=0.560$, by the log-rank test), and the hazard ratio (HR) was 1.15 (95% CI, 0.72–1.85).

DISCUSSION

Erythropoietin-stimulating agents, one of the treatment options for anaemia, raise haemoglobin levels, reduce the proportion of patients requiring transfusions and improve QOL (Littlewood *et al*, 2001; Österborg *et al*, 2002; Boogaerts *et al*, 2003; Iconomou *et al*, 2003). However, recent meta-analyses on QOL have shown that ESAs induce a statistically significant but not clinically meaningful improvement of fatigue as measured with FACT-Fatigue (Tonelli *et al*, 2009; Minton *et al*, 2010). The ESAs have been approved for the treatment of CIA, and are widely used in the United States and Europe. The EPO is approved and marketed in Europe but not in the United States.

In recent years, however, several randomised clinical trials using ESAs (Hedenus *et al*, 2003; Henke *et al*, 2003; Leyland-Jones *et al*, 2005; Overgaard *et al*, 2007; Wright *et al*, 2007; Smith *et al*, 2008; Thomas *et al*, 2008) and meta-analyses (Bennett *et al*, 2008; Bohlius *et al*, 2009a, b) have raised concerns about the negative impact on overall survival and tumour progression. Such safety issues regarding the use of ESAs in cancer patients have been discussed by regulatory authorities in the United States and Europe for several years (Juneja *et al*, 2008). To minimise the risks, both regulatory authorities have revised the labelling for ESAs and restricted their use in cancer patients. One of the restrictions in the United States is not to administer ESAs to patients with potentially curable cancers. Based on the decisions made by the EMA, the current labelling information specifies that ESAs should be administered to cancer patients with CIA whose haemoglobin level is $\leqslant 10$ g dl^{-1} and that a sustained haemoglobin level of >12 g dl^{-1} should be avoided. The present study was the first to evaluate the efficacy and safety of ESAs when dosed in accordance with the current labelling approved by the EMA in a randomised, double-blind, placebo-controlled manner. The inclusion criterion with regard to haemoglobin level was 8.0–10.0 g dl^{-1}, and the median baseline haemoglobin level was 9.4 g dl^{-1} in the EPO group and 9.3 g dl^{-1} in the placebo group. If the haemoglobin level increased to >12.0 g dl^{-1} during the study period, the study drug was discontinued until the haemoglobin level decreased to $\leqslant 11.0$ g dl^{-1}.

The results of this study demonstrated that once-weekly EPO administration significantly reduced the proportion of patients requiring RBC transfusions or having a haemoglobin level <8.0 g dl^{-1} after 4 weeks of treatment (10.0% *vs* 56.4%, $P<0.001$) and also reduced the proportion of patients requiring RBC transfusions (4.5% *vs* 19.6%, $P=0.002$); however, the dosing strategy in this study was conservative compared with those of previous studies (Boogaerts *et al*, 2003; Iconomou *et al*, 2003; Fujisaka *et al*, 2006; Morishima *et al*, 2006; Nakagawa *et al*, 2007; Aapro *et al*, 2008a, b; Suzuki *et al*, 2008; Bohlius *et al*, 2009a, b; Tsuboi *et al*, 2009). The relatively low percentage of patients receiving transfusions in both groups reflects the fact that most physicians hesitate to prescribe transfusions, preferring to monitor the situation until anaemia symptoms become remarkable. The pretransfusion haemoglobin levels at the time of the first transfusion in the current study were in the range of 5.3–8.1 g dl^{-1}.

EPO was well tolerated in this study. The incidence and types of adverse events were similar between the EPO and placebo groups. Previous meta-analyses have indicated that the use of ESAs leads to an increased risk of thromboembolic events (relative risk (RR) 1.67; 95% CI, 1.35–2.06 (Bohlius *et al*, 2006) and RR 1.57; 95% CI, 1.31–1.87 (Bennett *et al*, 2008)). In the current study, one pulmonary embolism was observed during treatment with EPO, but no death due to thromboembolic events was reported.

The results of the latest Cochrane meta-analysis using individual patient data from 53 ESA trials were recently published in the *Lancet* (Bohlius *et al*, 2009a, b). In this report, subgroup analysis of data from chemotherapy-treated patients (10 441 patients in 38 trials) indicated that the increase in mortality associated with ESAs was less pronounced in this population (HR for death during the active study periods = 1.10; 95% CI, 0.98–1.24, $P=0.12$; HR for overall survival = 1.04; 95% CI, 0.97–1.11, $P=0.263$) than in patients undergoing other anticancer treatments such as radiotherapy, radiochemotherapy or no anticancer treatment (HR 1.33–1.53). However, none of the studies included in the Cochrane meta-analysis used ESAs in accordance with the revised labelling indications (baseline haemoglobin levels, target and ceiling and so on). Although the current study was not designed and not powered to show that EPO did not increase mortality in this dosing scheme and that EPO was safe, the number of patients who died during the study period was one in the EPO group and none in the placebo group. The 1-year overall survival in the EPO group was 58.7% (95% CI 48.4–69.1%) and that in the placebo group was 63.4% (95% CI 53.4–73.3%; log-rank, $P=0.560$). There have been considerable debates as to the mechanism by which ESAs increase the risk for mortality (Fandrey and Dicato, 2009). One possible explanation is that aggressive dosing with ESAs to achieve higher target haemoglobin levels (not recommended in the revised labelling information) can cause adverse effects. The FDA has requested that a prospective randomised controlled trial of the use of ESAs be carried out, assessing their safety at haemoglobin levels of <12 g dl^{-1}. Such a trial is currently ongoing in patients with non-small cell lung cancer undergoing chemotherapy.

In conclusion, the findings from this study provide new evidence that ESAs are effective and well tolerated when used within the revised labelling indications by the EMA, with the limitation that we did not formally search for thromboembolic events. However, it is important that ESAs be used in accordance with the labelled indications. In addition, the risk of thromboembolic events and possible negative effects on survival should be carefully weighed against the benefits of ESA treatment in patients with CIA, taking into account the patients' comorbidities and the conditions under which they are treated. Further investigations are needed on the effect of ESAs on mortality.

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University, Osaka City University Hospital, Shizuoka Cancer Center, Saitama Cancer Center, Okayama University Hospital, Kinki University Hospital, Nagoya Daini Red Cross Hospital, Aichi Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Kyushu University Hospital, National Cancer Center Hospital, Tochigi Cancer Center, Hyogo Cancer Center, National Kyushu Cancer Center, Gihu Municipal Hospital, Tohoku University Hospital, Niigata University Medical & Dental Hospital, Sapporo Medical University Hospital, Niigata Cancer Center Hospital, Kanazawa University Hospital, Hokkaido University Hospital, Fujita Health University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, National Hospital Organization Nagoya Medical Center, Nippon Medical School Hospital, Nagoya University Hospital, Kurashiki Central Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Yokohama Municipal Citizen's Hospital, National Cancer Center Hospital East, Tsukuba University Hospital, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Hokkaido Cancer Center and Kurume University Hospital.

REFERENCES

Aapro M, Leonard RC, Barnadas A, Marangolo M, Untch M, Malamos N, Mayordomo J, Reichert D, Pedrini JL, Ukarma L, Scherhag A, Burger HU (2008a) Effect of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy: results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) study. *J Cin Oncol* **26:** 592–598

Aapro M, Scherhag A, Burger HU (2008b) Effect of treatment with epoetin-beta on survival, tumour progression and thromboembolic events in patients with cancer: an updated meta-analysis of 12 randomised controlled studies including 2301 patients. *Br J Cancer* **99:** 14–22

Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, Barnato SE, Elverman KM, Courtney DM, McKoy JM, Edwards BJ, Tigue CC, Raisch DW, Yarnold PR, Dorr DA, Kuzel TM, Tallman MS, Trifilio SM, West DP, Lai SY, Henke M (2008) Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* **299:** 914–924

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke M, Weingart O, Kluge S, Piper M, Rades D, Steensma DP, Djulbegovic B, Fey MF, Ray-Coquard I, Machtay M, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A (2009a) Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomized trials. *Lancet* **373:** 1532–1542

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke M, Weingart O, Kluge S, Piper M, Rades D, Steensma DP, Djulbegovic B, Fey MF, Ray-Coquard I, Machtay M, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A (2009b) Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomized trials. *Erratum in Lancet* **374:** 28

Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B, Bennett CL, Langensiepen S, Hyde C, Engert A (2006) Recombinant human erythropoietins and cancer patients: up-dated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* **98:** 708–714

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, Repetto L, Soubeyran P (2007) EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* **43:** 258–270

Boogaerts M, Coiffier B, Kainz C, the Epoetin β QOL Working Group (2003) Impact of epoetin β on quality of life in patients with malignant disease. *Br J Cancer* **88:** 988–995

Fandrey J, Dicato M (2009) Examining the involvement of erythropoiesis-stimulating agents in tumor proliferation (erythropoietin receptors, receptor binding, signal transduction), angiogenesis, and venous thromboembolic events. *Oncologist* **14**(Suppl 1)**:** 34–42. Review

Fujisaka Y, Tamura T, Ohe Y, Kunitoh H, Sekine I, Yamamoto N, Nokihara H, Horiike A, Kodama T, Saijo N (2006) Pharmacokinetics and pharmacodynamics of weekly epoetin beta in lung cancer patients. *Jpn J Clin Oncol* **36:** 477–482

Hedenus M, Adriansson M, Miguel JS, Kramer MHH, Schipperus MR, Juvonen E, Taylor K, Belch A, Altés A, Martinelli G, Watson D, Matcham J, Rossi G, Littlewood TJ, on behalf of the Darbepoetin Alfa 20000161 Study Group (2003) Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol* **122:** 394–403

Henke M, Laszig R, Rübe C, Schäfer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H (2003) Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* **362:** 1255–1260

Iconomou G, Koutras A, Rigopoulos A, Vagenakis AG, Kalofonos HP (2003) Effect of recombinant human erythropoietin on quality of life in cancer patients receiving chemotherapy: results of a randomized, controlled trial. *J Pain Symptom Manage* **25:** 512–518

Juneja V, Keegan P, Gootenberg JE, Rothmann MD, Shen YL, Lee KY, Weiss KD, Pazdur R (2008) Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. *Clin Cancer Res* **14:** 3242–3247

Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K, for the Japanese Gynecologic Oncology Group (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* **374:** 1331–1338

Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E (2005) Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* **23:** 5960–5972

Littlewood TJ, Bajetta E, Nortier JWR, Vercammen E, Rapoport B, for the Epoetin Alfa Study Group (2001) Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* **19:** 2865–2874

Ludwig H, Belle SV, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascón P, Kosmidis P, Krzakowski M, Nortier J, Olmi P, Schneider M, Schrijvers D (2004) The European Cancer Anaemia Survey (ECAS): a large multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer* **40:** 2293–2306

Minton O, Richardson A, Sharpe M, Hotopf M, Stone P (2010) Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev*: CD006704

Morishima Y, Ogura M, Yoneda S, Sakai H, Tobinai K, Nishiwaki Y, Minami H, Hotta T, Ezaki K, Ohe Y, Yokoyama A, Tsuboi M, Mori K, Watanabe K, Ohashi Y, Hirashima K, Saijo N, Japan Erythropoietin Study Group (2006) Once-weekly epoetin-beta improves hemoglobin levels in cancer patients with chemotherapy-induced anemia: a randomized, double-blind, dose-finding study. *Jpn J Cin Oncol* **36:** 655–661

Nakagawa K, Ozaki T, Satoh T, Miyazaki M, Akashi Y, Terashima M, Fujisaka Y, Tamura T, Fukuoka M, Saijo N (2007) Epoetin beta subcutaneous administration to lung cancer patients with anemia; results of pharmacokinetics/pharmacodynamics study. *Jpn J LungCancer* **47:** 313–322

Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y, Fukuoka M, for the FACS Cooperative Group (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and ciaplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* **18:** 317–323

Österborg A, Brandberg Y, Molostova V, Iosava G, Abdulkadyrov K, Hedenus M, Messinger D, for the Epoetin Beta Hematology Study Group

(2002) Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. *J Clin Oncol* **20:** 2486–2494

Overgaard J, Hoff C, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, Johansen J, Andersen L, Evensen J (2007) Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC) – the Danish Head and Neck Cancer Group DAHANCA 10 randomized trial. *Eur J Cancer* 5(Suppl): 7

Smith Jr RE, Aapro MS, Ludwig H, Pintér T, Šmakal M, Ciuleanu TE, Chen L, Lillie T, Glaspy JA (2008) Darbepoetin alfa for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Oncol* **26:** 1040–1050

Suzuki Y, Tokuda Y, Fujiwara Y, Minami H, Ohashi Y, Saijo N (2008) Weekly epoetin beta maintains hemoglobin levels and improves quality of life in patients with non-myeloid malignancies receiving chemotherapy. *Jpn J Cin Oncol* **38:** 214–221

Thomas G, Ali S, Hoebers FJP, Darcy KM, Rodgers WH, Patel M, Abulafia O, Lucci III JA, Begg AC (2008) Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dl with erythropoietin vs above 10.0 g/dl without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* **108:** 317–325

Tonelli M, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Lloyd A, Wiebe N, Klarenbach S (2009) Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* **180:** E62–E71

Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N (2009) Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: results of a multicenter, phase III, randomized, double-blind, placebo-controlled study. *Jpn J Clin Oncol* **39:** 163–168

Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, Szechtman B, Roa W, Mulroy L, Rudinskas L, Gagnon B, Okawara GS, Levine MN (2007) Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* **25:** 1027–1032

Yoshimura A, Kobayashi K, Fumimoto H, Fujiki Y, Eremenco S, Kudoh S (2004) Cross-cultural validation of the Japanese Functional Assessment of Cancer Therapy-Anemia (FACT-An). *J Nippon Med Sch* **71:** 314–322

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Editorial

Preface for JCOG Review Series

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JCOG (Japan Clinical Oncology Group) was started in 1990 and is the only governmental clinical trial group in Japan. The ultimate purpose of JCOG is to establish gold standard therapies for each tumor type based on scientifically and ethically scheduled investigator-initiated clinical trials. JCOG is composed of various committees for auditing and management, a data center and clinical study groups. The steering committee meeting is held four times a year and decides the missions, principles and policies of JCOG, the exchange of JCOG members and the approval of practical protocols for clinical trials. JCOG has 15 study groups and about 170 member institutions and hospitals. The number of nominated institutions is limited to keep high quality of JCOG. Inactive institutions have been replaced with other institutions by the steering committee. The number of patients accrued for each clinical trial is influenced by the number of active protocols in each trial group. Some groups are very active, while others have not yet completed any trials. JCOG conducts only investigator-initiated trials and so far has not been involved in any IND (Investigational New Drug) trials. Because JCOG does not receive any funding from pharmaceutical companies, the data are not biased by conflicts of interest. Since 1978, JCOG has conducted 216 clinical trials, the majority of which were Phase III trials. The results have been presented at regional and international scientific meetings and have been reported in mainly English language journals as original articles. Some have been published in journals with high impact factors, such as the *New England Journal of Medicine*, the *Journal of the National Cancer Institute*, and the *Journal of Clinical Oncology*.

In addition to the evaluation of new anticancer drugs, radiation therapy and new surgical procedures have also been tested in randomized controlled trials. Extremely important data have been published by surgical groups. Some clinical trials have produced positive results, but others did not achieve their primary endpoints. In addition, the accrual of patients was sometimes so poor that the clinical trial had to be interrupted. In a few studies, an independent data monitoring committee suggested that patient accrual be stopped because of the high incidence of severe toxicity arising from treatment and unexpected negative or inverse results. Recently, the publication of such data has become extremely difficult because of the rapid increase in articles that are being submitted to popular journals. The editors of such journals have suggested that the rejection rate should be as high as 80–90% and that 'Me too-type' articles with no significant data and single-arm Phase II studies of standard therapy should be rejected because the cost of publication is becoming too high and too many articles are waiting for publication. As a result of this situation, data concerning negative results or interrupted clinical trials are often difficult to publish. Nevertheless, such information is very important to young active investigators who are developing new protocols for clinical trials. JCOG has a policy that the outcome of a clinical trial should be published in English once it has been approved by the protocol review committee. The *Japanese Journal of Clinical Oncology* has agreed to publish review articles for each clinical trial group, enabling 'hidden data' to become available. Consequently, the chairman of each group in JCOG has been asked to write a review article on their study group.

In each review, the author has included all the clinical trials within their group that have been approved by the protocol review committee of JCOG. Readers should be able to recognize the development/refinement of each study group and understand the reasons for negative results and low patient accruals as well as the unexpected early termination of studies. Readers will also be able to understand the success rate of clinical trials. To complete each clinical trial, numerous specialists must join and collaborate with one other. Therefore, clinical trials with negative results and with low accruals should be avoided as much as possible. This series will provide important information regarding the writing of proper clinical protocols for clinical trials.

The first review is written by Dr Takashi Onda, Gynecologic Oncology Division of National Cancer Center, on behalf of the chairman of the gynecological group. The group has published four articles reporting the results of the JCOG9412, 0206, 0602 and 0505 trials in the *Int J Gynecol Cancer*, *Gynecol Oncol*, *Jpn J Clin Oncol* and *Jpn J Clin Oncol*, respectively. Additionally, JCOG0102 and 0503 are introduced in the review article.

Small-cell lung carcinoma with long-term survival: A case report

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Abstract. Small-cell lung carcinoma is the most aggressive among lung cancer subtypes, has a poor prognosis and is highly associated with smoking. We present a case of small-cell lung carcinoma in a patient who had never smoked and has survived for 14 years without achieving a complete remission since the first relapse. His long-term survival may be ascribed to the slow growth of the cancer cells, limited metastasis and favorable responses to the treatments he has received. During these 14 years, only two lymph node metastases and a single metastasis to the brain developed. His small-cell lung carcinoma has been well controlled each time by the various treatments he has received, including chemotherapy, radiotherapy and surgery. Pathologically, the tumor was a typical small-cell lung carcinoma with extensive necrosis. Results showed the mitotic rate and the cell proliferation markers to be greater than those in the intermediate-grade atypical carcinoid, but relatively low. Thus, we conclude that this case belongs to an overlap between intermediate- and high-grade neuroendocrine tumors.

Introduction

The 2004 World Health Organization (WHO) classification proposed four subtypes of pulmonary neuroendocrine (NE) tumors: low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC) and two high-grade tumors, large cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC) (1). SCLC is a highly aggressive cancer and results in mortality in 2-4 months without treatment. Most patients respond to primary therapy, but survival remains poor and median survival times are reported to be approximately 24 months in limited disease and 12 months in extensive disease (2,3). In this study, we present a case of SCLC in a never smoker who has survived for 14 years without achieving a complete remission following the initial relapse.

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Key words: small-cell lung carcinoma, pulmonary neuroendocrine tumors, atypical carcinoid, The 2004 WHO Classification, long-term survival

Case report

In November 1996, a 44-year-old male, with no history of smoking, presented at the Osaka Medical Center for Cancer and Cardiovascular Diseases with an abnormal hilar shadow in the left lung, complaining of cough and dyspnea. A computerized tomography (CT) scan revealed a 4.5x3.0 cm hilar mass in the left lung (Fig. 1A). The patient was cytologically diagnosed with SCLC by bronchoscopic examination (Fig. 1B). Metastatic workup demonstrated that he had limited disease, cT2aN2M0 stage IIIA (the 7th edition of the TNM system for lung cancer). The values of serum neuron-specific enolase and carcinoembryonic antigen were within normal limits and the pro-gastrin-releasing-peptide (ProGRP) was not measured at the time. The patient received four cycles of chemotherapy consisting of cisplatin (CDDP) and etoposide, with concurrent thoracic radiation of 44 Gy at 2.2 Gy/fraction daily. The treatment resulted in a complete response. Prophylactic cranial irradiation was not performed since there was no evidence to recommend it at the time (4).

The patient remained asymptomatic and no sign of disease recurrence was detected until December 1998, when right mandibular lymphadenopathy was evidenced. By that time, the level of ProGRP had gradually been elevating from 25 pg/ml in October 1997 to 76 pg/ml in August 1998 and 133 pg/ml in December 1998 (normal range 0-45 pg/ml). Aspiration needle cytology of the lymph node revealed metastasis of SCLC, leading to the diagnosis of recurrence of SCLC as the cancer cells obtained from the lymph node revealed almost the same morphological features as the primary lung tumor cells. Since imaging studies showed no recurrence with the exception of the lesion, and the WBC count was ~3,000/μl, the patient was administered palliative radiotherapy with a total dose of 70 Gy without chemotherapy. The lymphadenopathy disappeared and the level of ProGRP decreased to 14.1 pg/ml. Two years later, in April 2000, the right axillary lymph node was found to be enlarged and cytology revealed metastasis of SCLC. Palliative radiotherapy with a total dose of 60 Gy was administered to the lesion. The lymph node swelling did not disappear completely, but the level of ProGRP decreased from 154 to 44 pg/ml. Although the level of ProGRP was slowly

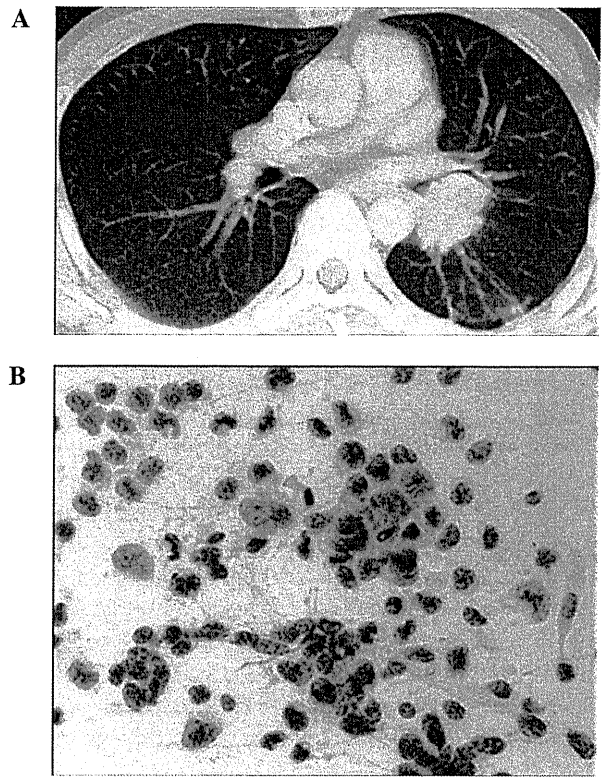

Figure 1. (A) A CT image in November 1996 revealed a 4.5x3.0-cm hilar mass in the left lung. (B) Cytology of the material obtained bronchoscopically from the primary lung tumor revealed SCLC.

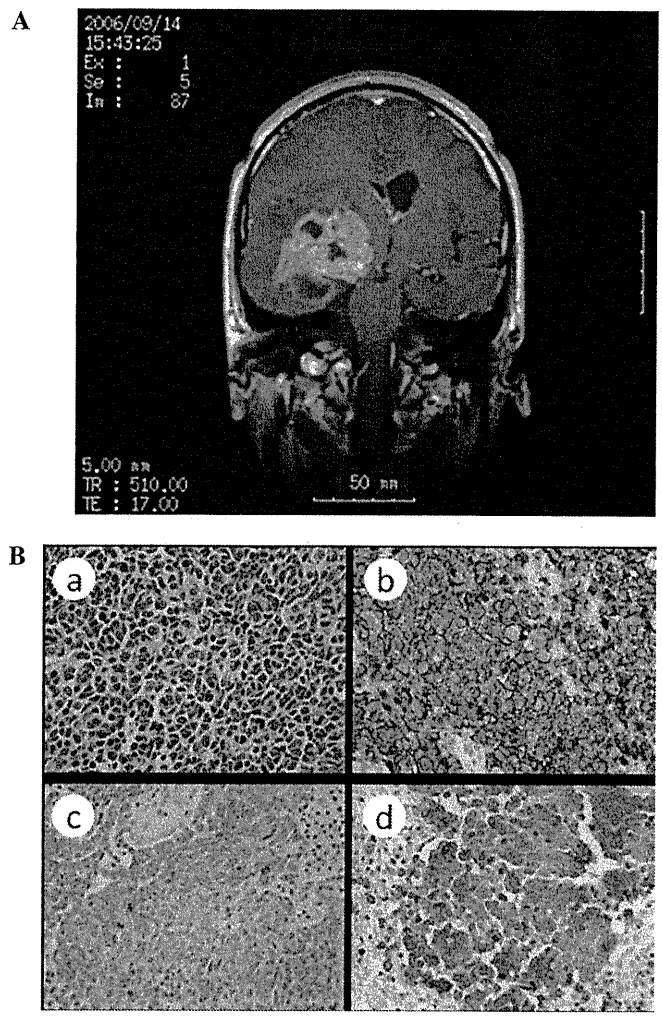

Figure 2. (A) Brain MRI in September 2006 showed a huge mass in the right temporal lobe. (B) Hematoxylin and eosin (H&E) and immunohistological staining of the specimen from the resected brain tumor. The tumor cells were positive for CD56, chromogranin and synaptophysin, indicating the neuroendocrine origin of the tumor. a, H&E stain; b, CD56 stain; c, chromogranin stain; d, synaptophysin stain. Original magnification, x200.

elevated to 150 pg/ml in November 2002, the patient observed no further symptoms and subsequently stopped consultation with the hospital.

The patient presented at the Osaka Medical Center for Cancer and Cardiovascular Diseases again in September 2006. Neurological examinations at admission indicated cerebral abnormality: left upper 1/4 homonymous hemianopsia and dysrhythmia on the electroencephalogram. The level of ProGRP was markedly elevated (2,860 pg/ml). Magnetic resonance imaging (MRI) of the brain revealed a huge mass in the right temporal lobe (Fig. 2A). The brain tumor was completely excised and histopathological examination determined it to be a metastasis of SCLC. The tumor was cytologically identical to the primary lung cancer, showing extensive necrosis, a high nuclear-to-cytoplasmic ratio and fine nuclear chromatin. The mitotic rate was 14 mitoses per 10 high-power fields (HPF) in this resected specimen. The Ki-67 labeling index was 25%. Immunohistochemical stains were positive for NE markers, including chromogranin A, synaptophysin and CD56 (Fig. 2B). The primary hilar tumor in the left lung and the right axillary lymph node revealed an increased uptake of fludeoxyglucose in positron emission tomography (PET) scanning. The patient received whole brain radiation therapy (WBRT) (30 Gy in 10 fractions), followed by systemic chemotherapy with CDDP and irinotecan hydrochloride (CPT11). Although the doses of CDDP and CPT11 were reduced to 50 and 50 mg/m^2, respectively, ProGRP levels decreased notably to 90.7 pg/ml, following chemotherapy.

From September 2007, the level of ProGRP was again gradually elevated. Recurrence of brain metastasis was detected on the MRI in November 2008 and the patient underwent intensity-modulated radiotherapy (IMRT) for the brain tumor. Following IMRT, the patient was administered chemotherapy with CDDP and CPT11. However, compliance to the chemotherapy was poor due to hematological toxicity. In September 2009, the patient was admitted for obstructive pneumonia in the left lower lobe with high fever, and treated successfully with antibiotics. The level of ProGRP elevated to 724 pg/ml and distinct progression of the primary hilar tumor in the left lung was again detected by CT. The patient refused to complete systemic chemotherapy and was followed up for 1 year. In November 2010, CT and PET detected distinct progression of the primary lung tumor resulting in atelectasis of the left lower lobe and right axillary lymphadenopathy. The level of ProGRP was elevated to 1,640 pg/ml. Chemotherapy with amrubicin was administered in December 2010.

At present, the clinical course of the patient has continued for 14 years following the initial diagnosis of SCLC and 4 years following the diagnosis of brain metastasis. The brain remains relapse-free at present. The patient is currently

continuing treatment with amrubicin for SCLC and his performance remains positive.

Discussion

NE tumors represent approximately 20% of all primary lung neoplasms (5). NE tumors of the lung are separated into four subgroups: low-grade TC, intermediate-grade AC and two high-grade malignancies, LCNEC and SCLC, according to WHO in 2004 (1). SCLC is the most common NE tumor (20% of total lung cancers), followed by LCNEC (3%), TC (2%) and AC (0.2%) (6). The tumors differ morphologically, immunohistochemically and structurally. The WHO classification defines SCLC as a NE tumor with greater than 10 mitoses/10 HPF and small-cell cytologic features. TC is considered a NE tumor with carcinoid morphology, fewer than 2 mitoses/10 HPF and lacking in necrosis, while AC is defined as a NE tumor with carcinoid morphology showing 2-10 mitoses/10 HPF or necrosis (1). The grade of malignancy of each NE subtype is correlated with clinicopathological behavior and prognosis of the disease. TC and AC are relatively slow-growing tumors and generally exhibit a favorable outcome, while LCNEC and SCLC are very aggressive with a dismal prognosis (5,6).

The accurate differential diagnosis of carcinoids from SCLC is critical in the selection of the appropriate treatment. Usually, SCLC is rarely mistaken for carcinoids, with the exception of small biopsy materials. There are also certain differences in the clinical background and profiles according to the subgroup of NE tumors. Unlike carcinoids, SCLC is markedly associated with a history of smoking (7,8). Carcinoids tend to occur in younger patients (mean age 45-50 years), whereas the high-grade NE tumors affect older patients (mean age 65 years). The former are capable of distant metastases in less than 20% of cases (most commonly to liver and bones), and SCLC tends to metastasize to the brain, liver, adrenal glands and bone with higher frequency (5,6). Due to the low response rates for chemo- and radiotherapy, surgical resection is primarily used in the treatment of carcinoids, whereas the standard treatment for limited-stage SCLC includes combined chemoradiotherapy due to high sensitivity.

This case was initially diagnosed as SCLC in 1996 by cytological sampling obtained using bronchoscopy. The initial chemoradiotherapy resulted in a complete response. Ten years later, a metastatic brain tumor was excised. Although the clinical course was not typical for SCLC, the histopathological features of the resected tumor confirmed the diagnosis of SCLC due to the morphology of the tumor cells, the positive staining with neuroendocrine markers and the 14 mitoses/10 HPF with extensive necrosis (according to the WHO classification in 2004). The Ki-67 proliferative index has recently been considered to be useful in distinguishing between the various subtypes of NE tumors, particularly in small biopsy and cytology specimens. The Ki-67 proliferation rate of TC is less than 2% and AC is less than 20% (typical rate ~10%), while the two high-grade NE tumors are higher than 20% (typical rate for SCLC is 60-100%) (6,9,10). The Ki-67 index of this case was 25%.

The clinical manifestations of this case, such as slow-growing tumors, limited metastatic potential and a favorable prognosis, with an over 14-year survival, support the diagnosis of AC, while the morphological, immunohistochemical and structural features of the tumors are typical of SCLC. We believe that this case fits the diagnostic criteria of SCLC according to the WHO classification, but it is a borderline case between AC and SCLC. Asamura *et al* reported that 5-year survival rates for TC, AC, LCNEC and SCLC in Japanese surgical cases of NE tumors were 96.2, 77.8, 40.3 and 35.7%, respectively (8). An analysis of Japanese lung cancer patients registered in 2002 revealed that SCLC accounted for 9.2% of new lung cancer cases in Japan, and 5-year survival rates were 17.2% for stage IIIA, 12.4% for stage IIIB, 3.8% for stage IV and 14.7% overall (11).

The prognosis is particularly dismal in SCLC patients with brain metastasis. In the practice guidelines recently published in the Journal of Neurooncology, the authors recommend surgical resection followed by WBRT for newly-diagnosed single brain metastases, which improves outcomes when compared to WBRT alone. However, these authors indicate that the recommendation does not apply to relatively radiosensitive tumors such as SCLC (12). By contrast, Jesien-Lewandowicz *et al* assert that patients with solitary brain metastasis from SCLC should be treated radically, in particular those at younger ages with a small primary tumor in the lung, good performance status and lack of systemic dissemination (13). Four case reports describe excellent long-term survival following resection of a solitary metastatic brain tumor of SCLC and adjuvant WBRT (13-16). In the present case, surgical resection followed by WBRT and chemotherapy was successful. Imai *et al* suggest that a subtype of slow-growing SCLC, which shows different biological properties, should be distinguished from the common type SCLC (16). Although unusual, patients with this subtype of NE tumor may potentially achieve longer survival than those with typical SCLC, and should be treated with local and multimodality treatment on a case-by-case basis.

In conclusion, we present a case report of a SCLC patient who has survived for 14 years following initial diagnosis with persistent disease, in spite of repetitive multimodality therapies. This case suggests the existence of borderline cases between intermediate- and high-grade NE tumors, and that long-term survival may be expected with suitable treatments. A method should be established to select SCLC patients with a favorable prognosis, such as this case, and to find optimal therapeutic approaches for such patients.

References

1. Beasley MB, Brambilla E and Travis WD: The 2004 World Health Organization classification of lung tumors. Semin Roentgenol 40: 90-97, 2005.
2. Jackman DM and Johnson BE: Small-cell lung cancer. Lancet 366: 1385-1396, 2005.
3. El Maalouf G, Rodier JM, Faivre S and Raymond E: Could we expect to improve survival in small cell lung cancer? Lung Cancer 57 (Suppl 2): 30-34, 2007.
4. Auperin A, Arriagada R, Pignon JP, *et al*: Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic cranial irradiation overview collaborative group. N Engl J Med 341: 476-484, 1999.
5. Gustafsson BI, Kidd M, Chan A, Malfertheiner MV and Modlin IM: Bronchopulmonary neuroendocrine tumors. Cancer 113: 5-21, 2008.

6. Rekhtman N: Neuroendocrine tumors of the lung: an update. Arch Pathol Lab Med 134: 1628-1638, 2010.
7. Ou SH, Ziogas A and Zell JA: Prognostic factors for survival in extensive stage small cell lung cancer (ed-sclc): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. J Thorac Oncol 4: 37-43, 2009.
8. Asamura H, Kameya T, Matsuno Y, *et al*: Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 24: 70-76, 2006.
9. Aslan DL, Gulbahce HE, Pambuccian SE, Manivel JC and Jessurun J: Ki-67 immunoreactivity in the differential diagnosis of pulmonary neuroendocrine neoplasms in specimens with extensive crush artifact. Am J Clin Pathol 123: 874-878, 2005.
10. Pelosi G, Rodriguez J, Viale G and Rosai J: Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. Am J Surg Pathol 29: 179-187, 2005.
11. Sawabata N, Asamura H, Goya T, Mori M, Nakanishi Y, Eguchi K, Koshiishi Y, Okumura M, Miyaoka E and Fujii Y: Japanese lung cancer registry study: first prospective enrollment of a large number of surgical and nonsurgical cases in 2002. J Thorac Oncol 5: 1369-1375, 2010.
12. Gaspar LE, Mehta MP, Patchell RA, *et al*: The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96: 17-32, 2010.
13. Jesien-Lewandowicz E, Spych M, Fijuth J and Kordek R: Solitary brain metastasis of an occult and stable small-cell lung cancer in a schizophrenic patient: a 3-year control. Lung Cancer 69: 245-248, 2010.
14. Abratt RP, de Groot M and Willcox PA: Resection of a solitary brain metastasis in a patient with small cell lung cancer – long-term survival. Eur J Cancer 31A: 419, 1995.
15. Harrison ML and Goldstein D: Prolonged survival in a patient with an occult primary small-cell lung cancer and a solitary brain metastasis at diagnosis. Intern Med J 32: 621-622, 2002.
16. Imai R, Hayakawa K, Sakurai H, Nakayama Y, Mitsuhashi N and Niibe H: Small cell lung cancer with a brain metastasis controlled for 5 years: a case report. Jpn J Clin Oncol 31: 116-118, 2001.

The Risk of Cytotoxic Chemotherapy-Related Exacerbation of Interstitial Lung Disease with Lung Cancer

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Introduction: It is unknown what type of interstitial lung disease (ILD) has high risk for chemotherapy-related exacerbation of ILD. We investigated the risk of exacerbation of ILD for patients with lung cancer with ILD.

Methods: One hundred nine patients with lung cancer with ILD treated with cytotoxic chemotherapy at Shizuoka Cancer Center between August 2002 and April 2010 were retrospectively reviewed.

Results: On pretreatment computed tomography (CT) of the chest, 69 patients (63%) were identified with usual interstitial pneumonia (UIP) pattern, and 40 patients (37%) had non-UIP pattern. Patients with UIP pattern developed cytotoxic chemotherapy-related exacerbation of ILD more frequently than those with non-UIP pattern (30 versus 8%, $p = 0.005$). The incidence of grade 5 pulmonary toxicities was 9% in patients with UIP pattern, compared with 3% in those with non-UIP pattern. Multivariate analyses demonstrated that age (<70 years) and CT pattern (UIP) were significant independent risk factors for cytotoxic chemotherapy-related exacerbation of ILD. In small cell lung cancer, overall survival (OS) from the start of first-line chemotherapy was significantly shorter in UIP pattern than non-UIP pattern (median OS: 9 versus 16 months, $p = 0.0475$), whereas there was no significant difference in patients with non-small cell lung cancer (median OS: 12 versus 9 months, $p = 0.2529$).

Conclusions: Our results indicated that the incidence of exacerbation of ILD was significantly higher in patients with lung cancer with UIP pattern on CT findings than in those with non-UIP pattern. Therefore, great care is required when administering cytotoxic chemotherapy agents for patients with lung cancer with UIP pattern.

Key Words: Lung cancer, Interstitial lung disease, Usual interstitial pneumonia, Cytotoxic chemotherapy, Exacerbation.

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Interstitial lung disease (ILD) is called diffuse parenchymal lung disease and is a diverse group of pulmonary disorders classified together because of similar clinical, radiological, physiological, or pathological features.[1] Preexisting ILD or idiopathic interstitial pneumonias (IIPs) are considered to be a risk factor for drug-related ILD.[2] A prospective large cohort study for gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has shown that preexisting ILD is not only a strong risk factor for gefitinib-related ILD but also a strong risk factor for cytotoxic chemotherapy-related ILD.[3] Cytotoxic chemotherapy agents, such as gemcitabine, docetaxel, and amrubicin, have been reported to develop severe ILD associated with cytotoxic chemotherapy.[4–6] Chemotherapy-related ILD is not common but is a potentially fatal complication of treatment for lung cancer.

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia of unknown cause limited to the lungs and associated with poor prognosis.[7,8] The American Thoracic Society (ATS) and European Respiratory Society (ERS) have defined IPF as clinical conditions characterized by progressive dyspnea and chronic cough, restrictive lung disease, and the histopathologic pattern of usual interstitial pneumonia (UIP).[7] In addition, in patients with IPF, the incidence of lung cancer is reported to be higher than in patients without IPF.[9–13]

In clinical practice, patients with lung cancer with ILD have been carefully treated with cytotoxic chemotherapy. Nevertheless, it is unknown what kind of chemotherapeutic agents are optimal for patients with lung cancer with ILD. In addition, it is also unknown what type of ILD has high risk for exacerbation of ILD.

To assess the risk of cytotoxic chemotherapy-related ILD, we retrospectively analyzed pretreatment computed tomography (CT) and investigated the clinical course of patients with lung cancer with ILD.

METHODS

The medical records of patients with lung cancer with ILD treated with cytotoxic chemotherapy at the Shizuoka Cancer Center between August 2002 and April 2010 were retrospectively reviewed. In this study, pretreatment CT of the chest was evaluated by one radiologist (M.E.) and two pulmonologists (H.K. and T.N.), who had no knowledge of

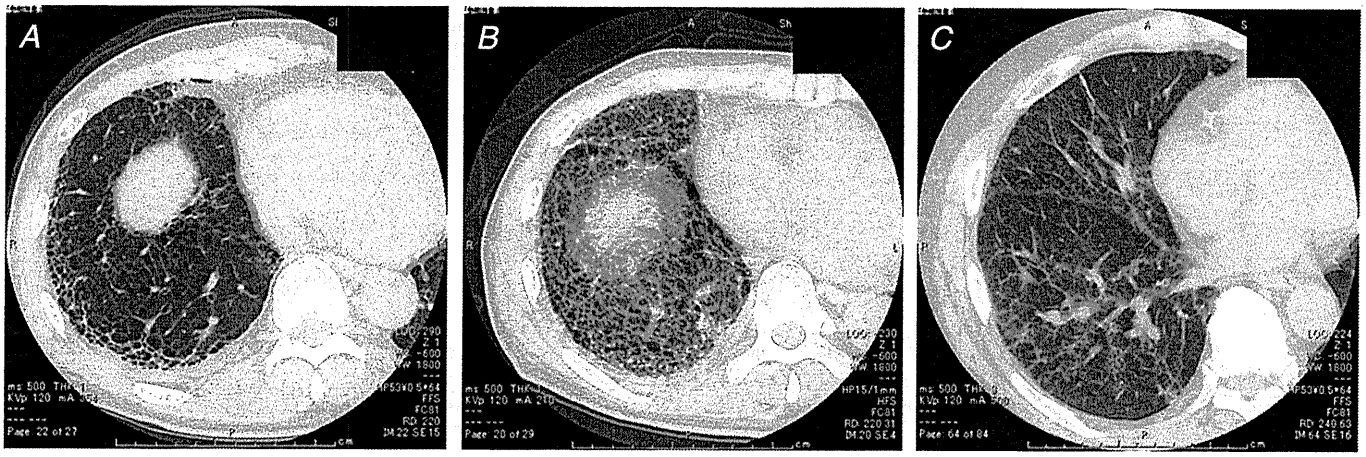

FIGURE 1. High-resolution computed tomography (HRCT) image of the chest. *A*, Pretreatment HRCT image of the chest showing subpleural distribution, honeycombing, traction bronchiectasis, and architectural distortion (UIP pattern). *B*, HRCT image of the chest showing ground-glass abnormality superimposed on pretreatment interstitial shadow (chemotherapy-related exacerbation of ILD). *C*, Pretreatment HRCT image of the chest showing patchy ground-glass opacity with reticulation, traction bronchiectasis, and architectural distortion (non-UIP pattern). UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

the patient's outcome. The chest CT examinations were performed using multidetector-row CT machine at the end of suspended inspiration. CT images were reconstructed to 5-mm slice thickness, and thin section chest CT with 1 mm reconstruction thickness was also performed for evaluating primary tumor and ILD. ILD was diagnosed when the criteria of ground-glass opacity, consolidation, or reticular shadow in both lung fields were met. On the basis of CT characteristics, we classified the patients with ILD into two groups: UIP pattern and non-UIP pattern. Diagnosis of UIP pattern was based on CT features as defined by the International Consensus Statement of the ATS and ERS, showing subpleural distribution, honeycombing, traction bronchiectasis, and architectural distortion (Figure 1*A*).[7,14] All other cases, whose CT of the chest revealed ILD excluding the UIP pattern, were diagnosed as non-UIP pattern (Figure 1*C*).

Chemotherapy-related exacerbation of ILD was diagnosed on the basis of CT findings (bilateral ground-glass abnormality with or without focal consolidation, superimposed on pretreatment interstitial shadow) (Figure 1*B*).[15] Patients with apparent pulmonary infection, pulmonary embolism, or heart failure were excluded. Chemotherapy-related exacerbation of ILD was evaluated based on pneumonitis/pulmonary infiltrates by National Cancer Institute Common Terminology Criteria version 3.0—grade 3: symptomatic, interfering with activities of daily living, and oxygen indicated; grade 4: life-threatening; and grade 5: death. The patients who developed exacerbation of ILD within 1 year after thoracic radiotherapy and who received epidermal growth factor receptor tyrosine kinase inhibitor in the clinical course were excluded from chemotherapy-related exacerbation of ILD. To assess the incidence of exacerbation of ILD by treatment regimen, the duration between last administration of cytotoxic chemotherapy and the onset of exacerbation of ILD was defined as 4 weeks or less.

Univariate and multivariate analyses were performed to identify risk factors for the exacerbation of ILD associated with cytotoxic chemotherapy. All categorical variables were analyzed by the χ^2 test or Fisher's exact test, as appropriate. Multivariate analyses were performed using a logistic regression procedure to assess the relationship between various factors and exacerbation of ILD. Clinical evaluation of overall survival (OS) after the start of first-line chemotherapy was conducted by the Kaplan-Meier method to assess the time to death. The log-rank test was used to compare cumulative survival in each group. All p values were reported as two-sided, and values less than 0.05 were considered statistically significant. This study was approved by the institutional review board.

RESULTS

Patient Characteristics

One hundred nine patients were diagnosed with lung cancer with ILD and treated with cytotoxic chemotherapy. The characteristics of the patients are shown in Table 1. The median age was 69 years (range: 54–84 years), and almost all patients were smokers and men with good performance status. Histologically, adenocarcinoma, squamous cell carcinoma, and small cell lung cancer (SCLC) were observed in 33, 30, and 30%, respectively. Others included large cell carcinoma and undifferentiated non-small cell cancer. Stages III and IV were observed in 40 and 53%, respectively, and recurrence after surgical resection occurred in 7%. In SCLC, limited and extensive diseases were observed in 33 and 67%, respectively. On the basis of pretreatment CT of the chest, 69 patients (63%) were identified with UIP pattern, and 40 patients (37%) had non-UIP pattern. Although there were some imbalances between the two groups in terms of stage IV