Table IV. *Adverse events of stage 2 in this phase II study.*

		Grade		Any grade	
	Toxicity*	3/4 (n)	(%)	(n)	(%)
Hematological	Leukopenia	4/0	13.8	26	89.7
	Neutropenia	8/6	48.2	28	96.6
	Thrombocytopenia	5/7	41.4	27	93.1
	Anemia	14/3	58.6	29	100.0
Hepatic	AST	2/0	6.9	15	48.2
	ALT	0/0	0	17	58.6
	T-bilirubin	0/0	0	7	24.1
Gastrointestinal	Anorexia	0/0	0	26	89.7
	Nausea	0/0	0	25	86.2
	Vomiting	0/0	0	15	51.7
	Constipation	0/0	0	20	69.0
	Diarrhoea	0/0	0	10	34.5
	Hiccup	0/0	0	11	37.9
Systemic	Fatigue	1/0	3.4	21	72.4
	Body weight loss	1/0	3.4	12	41.4
Fever and other	Fever	0/0	0	5	17.2
	Alopecia	0/0	0	21	72.4

Severity of each event was evaluated according to CTCAE version 3.0.

and did not influence on study continuation. Similar incidence of such as increase was reported for irinotecan (4). Since the total treatment of completed cycles for both stages 1 and 2 was expected to be 4, high tolerability was estimated. The response rate to Tp combination with CDDP in this study was very much improved compared with the 39% response to Tp mono therapy (21). On the other hand, no difference in the toxic profile was observed, suggesting that the contribution of CDDP was solely for efficacy. The toxicity difference between two schedules is considered as the influence on renal function disorder caused by CDDP as observed in the regimen of CDDP day 1 schedule (7).

The response rate of this combination was equally matched to that of irinotecan in combination with CDDP, but superior in median survival time and 1-year survival rate. Furthermore, this regimen had a better profile for incidence and grade of diarrhea than that of irinotecan.

The median survival times and 1-year survival rate in this study were similar to those obtained in Japanese patients with irinotecan regimen. Noda *et al.* showed survival benefit for CDDP plus irinotecan in comparison with PE (4). However, two similar trials (22, 23) did not show any benefit of irinotecan in combination with CDDP over PE. The sample size or ethnic effect has been considered as the reason for this difference (22). Taking these studies together, irinotecan is an active drug for SCLC in some populations and settings. Superior results of Topo I inhibitor and CDDP regimens in Asian individual, Japanese, and Korean, have been reported (24-26).

The clinical efficacy of Topo I inhibitor plus CDDP is summarized in Table V. The response rates, median survival times and survival rates of patients treated with Tp plus CDDP and irinotecan plus CDDP regimens are better than the combination of etoposide plus CDDP. Since it is known that the efficacies of etoposide and CDDP combination in Japan and North America/Europe are similar, there may be difference in response to the CDDP combination with Topo I inhibitor or with Topo II inhibitor in Japanese patients. Recently, an ethnic effect for response to chemotherapy, such as the gefitinib study, has been revealed (27). These results suggest the possibility of an ethnic effect in non-small cell lung cancer therapy, and study of such as effect may lead to a novel therapy against ED-SCLC. Tp, when compared with irinotecan, has a lower rate of associated diarrhea. Therefore, Tp combined with CDDP therapy resulted in a higher response rate and survival time from this study. It is possible that this combination therapy regimen of Tp for previously untreated ED-SCLC patients may be as useful as irinotecan combination with CDDP therapy.

Conclusion

The combination of Topo I inhibitor, Tp on 5 consecutive days and CDDP on day 5 with G-CSF support is a safe and active regimen for therapy-naive Japanese patients with ED-SCLC. This regimen appeared to be well-tolerated in this patient population. Future clinical trials should elucidate the role of Tp in first-line treatment of ED-SCLC.

Acknowledgements

This study was supported by an unrestricted grant from Nippon Kayaku Co., Ltd., Tokyo, Japan.

References

1 Adjei AA, Marks RS and Bonner JA: Current guidelines for the management of small cell lung cancer. Mayo Clin Proc *74*: 809-816, 1999.

2 Pujol JL, Carestia L and Daures JP: Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen *versus* a regimen without this alkylating agent. Br J Cancer *83(1)*: 8-15, 2000.

3 Sundstrom S, Bremnes RM, Kaasa S, Aasebo Ulf, Hatlevoll R, Dahle R, Boye B, Wang M, Vigander T, Vilsvik J, Skovlund E, Hannisdal E and Aamdal S: Cisplatin and etoposide regimen Is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol *20(24)*: 4665-4672, 2002.

4 Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S and Saijo N: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med *346(2)*: 85-91, 2002.

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.

Received July 13, 2011
Revised August 18, 2011
Accepted August 19, 2011

Lung Cancer 74 (2011) 80–84

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

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

Naoyuki Nogami[a], Katsuyuki Hotta[b,*], Shoichi Kuyama[c], Katsuyuki Kiura[b], Nagio Takigawa[b], Kenichi Chikamori[d], Takuo Shibayama[e], Daizo Kishino[d], Shinobu Hosokawa[f], Akihiko Tamaoki[g], Shingo Harita[c], Masahiro Tabata[b], Hiroshi Ueoka[d], Tetsu Shinkai[a], Mitsune Tanimoto[b]

[a] Department of Respiratory Medicine, NHO Shikoku Cancer Center, Matsuyama, Japan
[b] Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Kitaku, Okayama 700-8558, Japan
[c] Department of Medicine, Chugoku Central Hospital, Fukuyama, Japan
[d] Department of Respiratory Medicine, NHO Yamaguchi-Ube Medical Center, Ube, Japan
[e] Department of Medicine, NHO Minami-Okayama Medical Center, Okayama, Japan
[f] Department of Respiratory Medicine, Okayama Red Cross Hospital, Okayama, Japan
[g] Department of Respiratory Medicine, Okayama Institute of Health and Prevention, Okayama, Japan

ARTICLE INFO

Article history:
Received 20 October 2010
Accepted 23 January 2011

Keywords:
Lung cancer
Topotecan
Amrubicin
Chemo-naive
Sensitive relapse
Refractory relapse

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

* Corresponding author at: Tel.: +81 86 235 7227; fax: +81 86 232 8226.
E-mail address: khotta@md.okayama-u.ac.jp (K. Hotta).

0169-5002/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2011.01.018

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	23	74	12	43
(95% CI)		(55–88)		(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.

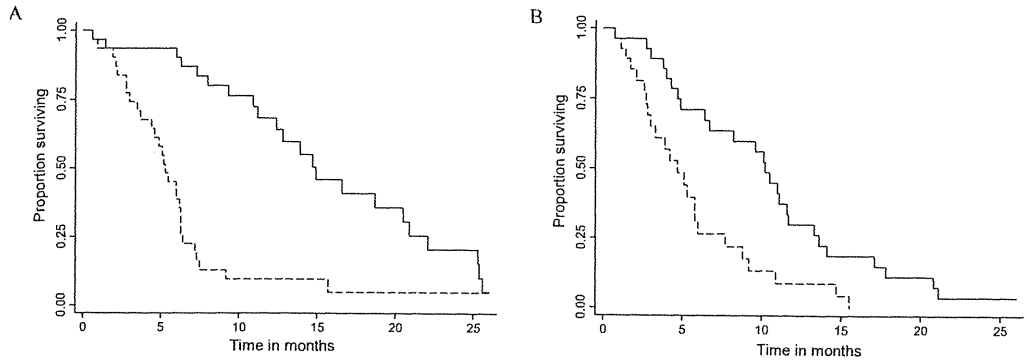

Fig. 1. Overall (solid) and progression-free (dotted) survival curves. (A) Chemotherapy-naïve patients and (B) relapsed patients.

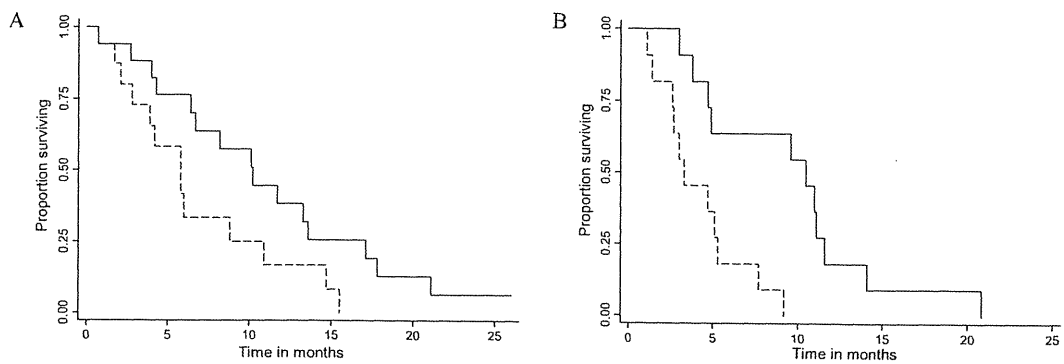

Fig. 2. Overall (solid) and progression-free (dotted) survival curves. (A) Sensitive-relapsed patients and (B) refractory-relapsed patients.

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.

Funding

None.

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.

Acknowledgments

We thank the Okayama Lung Cancer Study Group members for their dedication and cooperation throughout the course of this work. The authors are also deeply grateful for all of the participants who made this study possible.

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.

British Journal of Cancer (2011) 105, 1267–1272

www.bjcancer.com

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

Y Fujisaka*[,1,9], T Sugiyama[2], H Saito[3], S Nagase[4], S Kudoh[5], M Endo[6], H Sakai[7], Y Ohashi[8] and N Saijo[9]

[1]Respiratory Medicine, Osaka Medical College Hospital, Osaka, Japan; [2]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Iwate, Japan; [3]Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Aichi, Japan; [4]Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan; [5]Department of Respiratory Medicine, Osaka City University Hospital, Osaka, Japan; [6]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [7]Department of Thoracic Oncology, Saitama Cancer Center, Saitama, Japan; [8]Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan; [9]Department of Medical Oncology, Kinki University Faculty of Medicine, 377-2, Ohno-higashi, Osakasayama, Osaka 589-8511, Japan

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.

British Journal of Cancer (2011) **105,** 1267–1272. doi:10.1038/bjc.2011.395 www.bjcancer.com
Published online 29 September 2011

Keywords: chemotherapy-induced anaemia; erythropoietin; survival

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.

*Correspondence: Dr Y Fujisaka; E-mail: fujisaka_y@dotd.med.kindai.ac.jp
Received 23 May 2011; revised 5 September 2011; accepted 8 September 2011; published online 29 September 2011

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.

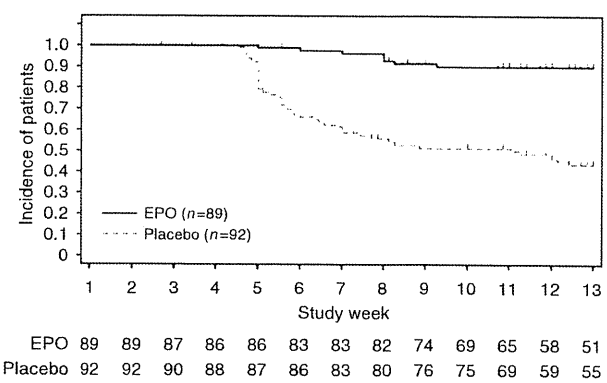

Figure 1 Time to RBC transfusion or haemoglobin level $<8.0\,g\,dl^{-1}$.

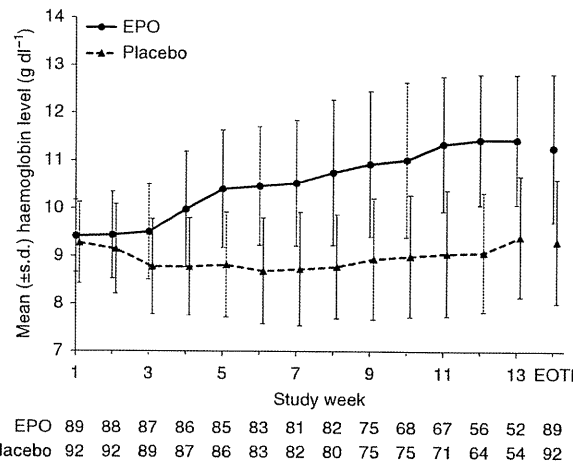

Figure 2 Change in haemoglobin level by treatment group. Abbreviation: EOTP = end of treatment period.

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.

ACKNOWLEDGEMENTS

This study was supported by Chugai Pharmaceutical Co., Ltd, Tokyo, Japan. We thank Yutaka Ariyoshi of the Aichi Cancer Center Aichi Hospital, a remunerated consultant of Chugai Pharmaceutical Co., Ltd, for providing advice on this manuscript. The following institutions participated in this study: Osaka Medical College Hospital, Iwate Medical University School of Medicine, Aichi Cancer Center Aichi Hospital, Tokyo Medical

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

Jpn J Clin Oncol 2011;41(10)1155
doi:10.1093/jjco/hyr127

Editorial

Preface for JCOG Review Series

Nagahiro Saijo

Kinki University School of Medicine

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.

British Journal of Cancer (2011) 105, 1131–1136

www.bjcancer.com

Phase I study of irinotecan and gefitinib in patients with gefitinib treatment failure for non-small cell lung cancer

A Horiike[1], K Kudo[1], E Miyauchi[1], F Ohyanagi[1], K Kasahara[2], T Horai[1] and M Nishio*[,1]

[1]*Thoracic Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ward, Tokyo 135-8550, Japan;* [2]*Department of Respiratory Medicine, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan*

BACKGROUND: Currently, no effective treatments exist for non-small cell lung cancer (NSCLC) after failure of gefitinib therapy. Pre-clinical studies have demonstrated that gefitinib-resistant NSCLC cells are more sensitive to irinotecan than parental cells, and that combined administration of irinotecan and gefitinib has a synergistic additive effect. We conducted a phase I study to evaluate the combination of irinotecan and gefitinib as a therapeutic option for NSCLC patients with progressive disease (PD) after initial gefitinib treatment.

METHODS: Eligibility criteria included histologically confirmed NSCLC, age range of 20–74 years, refractory to or relapsed after gefitinib treatment, one or more previous chemotherapy regimens, Eastern Cooperative Oncology Group performance status 0–2, adequate organ function, and informed consent. Patients were treated with irinotecan on days 1 and 15, and treated daily with gefitinib from day 2 every 4 weeks. The treatment was continued until disease progression. The gefitinib dose was fixed at 250 mg. Irinotecan dosing started at 50 mg m^{-2} and was escalated in patients by 25 mg m^{-2} increments up to a maximum dose of 150 mg m^{-2}.

RESULTS: Twenty-seven patients were enrolled: male/female = 14/13; median age = 60 (45–75); histology, adenocarcinoma/non-adenocarcinoma = 25/2; performance status 0–1/2 = 19/8; previous response to gefitinib, partial response/stable disease/PD = 21/2/4. Dose-limiting toxicities were observed in 2 patients at level 3. Maximum tolerated dose was not determined, and the full dose of irinotecan could be combined with the full dose of gefitinib. The disease control rate (DCR) and response rate (RR) were 69.2 and 26.9%, respectively. For 12 patients at level 5 (the recommended phase II dose), the DCR and RR were 75.0% and 41.7%, respectively. The median treatment cycles were 4; median time to treatment failure, 57 days (95% confidence interval (CI), 32–82 days); median overall survival, 244 days (95% CI, 185–303 days); and 1-year survival rate, 32.6%.

CONCLUSION: The combination of irinotecan and gefitinib was well tolerated and potentially beneficial for NSCLC patients failing initial gefitinib monotherapy.

British Journal of Cancer (2011) **105,** 1131–1136. doi:10.1038/bjc.2011.375 www.bjcancer.com
Published online 13 September 2011

Keywords: gefitinib; resistance; irinotecan; non-small cell lung cancer

The epidermal growth factor receptor (EGFR) is a well-established target for anticancer therapy because it is expressed or over-expressed in a variety of tumours, including non-small cell lung cancer (NSCLC) (Rusch *et al*, 1993). Gefitinib is an EGFR tyrosine kinase inhibitor (TKI), and the first targeted drug developed and approved for NSCLC (Fukuoka *et al*, 2003; Kris *et al*, 2003). Various large phase III studies have been performed on unselected previously treated NSCLC patients. In a study performed by Kim *et al* (2008), gefitinib monotherapy resulted in survival that was non-inferior to that for docetaxel monotherapy, whereas in a study performed by Maruyama *et al* (2008), gefitinib monotherapy did not result in non-inferior survival (Kim *et al*, 2008; Maruyama *et al*, 2008). Gefitinib therapy elicits extraordinary responses in patients who are women, patients who have never smoked, patients with adenocarcinomas, patients of Asian origin, and patients with an EGFR mutation (Lynch *et al*, 2004; Paez *et al*, 2004; Thatcher *et al*, 2005; Park and Goto, 2006).

Recently, phase III studies in patients with these clinical backgrounds or molecular mutations demonstrated that gefitinib monotherapy improved progression-free survival (PFS) as compared with platinum-doublet chemotherapy (Mok *et al*, 2009a; Maemondo *et al*, 2010; Mitsudomi *et al*, 2010). Therefore, gefitinib monotherapy has become a standard therapy for the treatment of advanced NSCLC. Unfortunately, even patients who show an initial response to gefitinib may eventually develop an acquired resistance to gefitinib. This happens, almost without exception, after varying periods of time. Two major mechanistic explanations have thus far been identified for acquired gefitinib resistance in NSCLC patients with an EGFR mutation. These include a second site EGFR mutation (T790M) and *MET* amplification (Kobayashi *et al*, 2005; Kwak *et al*, 2005; Pao *et al*, 2005; Engelman *et al*, 2007b).

Irinotecan (CPT-11) is a water-soluble derivative of camptothecin that inhibits DNA topoisomerase I (Kawato *et al*, 1991). In a phase III study comparing therapy with vindesine (VDS) + CDDP to therapy with CPT-11 alone or to therapy with

*Correspondence: Dr M Nishio; E-mail: mnishio@jfcr.or.jp
Received 11 April 2011; revised 1 August 2011; accepted 19 August 2011; published online 13 September 2011

CPT-11 + cisplatin (CDDP), no significant difference was observed between the overall survival (OS) achieved with CPT-11 + CDDP and with VDS + CDDP, and between the OS achieved with CPT-11 alone and with VDS + CDDP. In subgroup analyses, OSs of CPT-11 + CDDP- and CPT-11-treated patients were superior to VDS + CDDP-treated patients with stage IV disease (Negoro *et al*, 2003). Based on this result, CPT-11 is thought to be a key drug for NSCLC treatment.

Preclinical studies have shown that the combination of CPT-11 and gefitinib has a synergistic beneficial effect in various tumour cell lines (Koizumi *et al*, 2004; Stewart *et al*, 2004; Shimoyama *et al*, 2006). Concerning NSCLC, the combination of CPT-11 and gefitinib is synergistic in EGFR wild-type cell line, mutant cell line, and gefitinib-resistant cell line. Furthermore, gefitinib-resistant NSCLC cells are more sensitive to CPT-11 than parental cells are, and sequential administration of CPT-11 and gefitinib has more remarkable beneficial effects than concurrent administration of both (Shimoyama *et al*, 2006). Based on this evidence, we conducted a phase I study to evaluate the combination of CPT-11 and gefitinib as a therapeutic option for NSCLC patients with progressive disease (PD) previously treated with gefitinib alone.

METHODS

Study design

This phase I study was conducted in patients with advanced NSCLC previously treated with gefitinib. The primary objective of this study was to determine the maximum tolerated dose (MTD) of CPT-11 that could be administered in combination with gefitinib. Secondary objectives included determination of dose-limiting toxicities (DLTs) and a dosing recommendation for a phase II trial involving administration of CPT-11 plus gefitinib. Study treatment was provided until disease progression or unacceptable toxicities occurred.

Treatment schedule

The patients were treated with CPT-11 on days 1 and 15. Gefitinib was administered daily from day 2 until day 28 in cycle 1 and from day 1 until day 28 after cycle 2. This treatment cycle was repeated every 4 weeks. The treatment was continued until disease progression. CPT-11 diluted in 250 ml of 5% glucose was administered intravenously over 90 min. Prophylactic antiemetic therapy, consisting of granisetron ($40\,mg\,kg^{-1}$) and dexamethasone (8 mg per body weight), was routinely prescribed.

Treatment modification

CPT-11 was not administered if any of the following toxicities were noted on day 1 or 15: leucocytes $<3000\,mm^{-3}$, platelets $<100\,000\,mm^{-3}$, serum creatinine $>1.5\,mg\,dl^{-1}$, total bilirubin $>1.5\,mg\,dl^{-1}$, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal, grade 1 or higher infection, and grade 2 or higher diarrhoea. Gefitinib was not administered when grade 3 or higher rash or unacceptable toxicity occurred.

Dose escalation

The gefitinib dose was fixed at 250 mg per body weight. The following dose levels of CPT-11 were administered: level 1, $50\,mg\,m^{-2}$; level 2, $75\,mg\,m^{-2}$; level 3, $100\,mg\,m^{-2}$; level 4, $125\,mg\,m^{-2}$; and level 5, $150\,mg\,m^{-2}$. The dosing of CPT-11 was escalated in different patients at $25\,mg\,m^{-2}$ increments with an upper limit of $150\,mg\,m^{-2}$, which is the recommended biweekly single agent dose of CPT-11 in Japan. The MTD of CPT-11 was defined as the dose at which at least two of three or three of six patients developed DLT during the first cycle of treatment. Intrapatient dose escalation was not permitted. If MTD was not reached on level 5, level 5 was defined as the recommended dose for this study. Six to nine additional patients were treated at the recommended phase II dosing to confirm tolerability and response of this combination therapy.

Eligibility criteria

The eligibility criteria for enrolment in this study were as follows: histologically confirmed NSCLC, age range of 20–74 years, progression of disease even after gefitinib treatment, one or more previous chemotherapy regimens, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy of at least 3 months, adequate organ function (leucocyte count $\geqslant 4000\,mm^{-3}$, haemoglobin level $\geqslant 9.0\,g\,dl^{-1}$, platelet count $\geqslant 100\,000\,mm^{-3}$, serum creatinine level $\leqslant 1.5\,mg\,dl^{-1}$, total bilirubin level $\leqslant 1.5\,mg\,dl^{-1}$, AST and ALT levels $\leqslant 3$ times the upper limit of the normal range, and arterial partial pressure of oxygen [PaO_2] $\geqslant 60.0$ torr). Patients were excluded from the trial for any of the following reasons: uncontrolled malignant pleural or pericardial effusion, a concomitant serious illness contraindicating chemotherapy, history of pneumonitis during previous gefitinib therapy, pregnancy, or breast feeding. All patients provided written informed consent. The study protocol was approved by the institutional ethics committee of each of the participating institutions.

Assessment

Toxicities were monitored, graded, and recorded according to the National Cancer Institute Common Toxicity Criteria version 2.0. DLT was defined as follows: grade 4 haematologic toxicities excluding neutropenia, grade 4 neutropenia lasting 4 days or longer, grade 3 or greater febrile neutropenia, and grade 3 or greater non-haematological toxicity excluding nausea, vomiting, and general fatigue. Efficacy was assessed by a physician on the basis of antitumour effect, according to the RECIST version 1.0. The response was confirmed for at least 4 weeks (for a complete or partial response (PR)) or 6 weeks (for stable disease (SD)) after it was first documented. Survival distribution was estimated by the Kaplan–Meier method.

RESULTS

Patient characteristics

From December 2003 to March 2008, 27 patients were enroled in this study. Patient characteristics are summarised in Table 1. The median age of patients entering this study was 60 years. The median performance status was 1. Approximately half of the patients were male, and adenocarcinoma was of a major histologic type. Twelve patients (44.4%) were non-smokers. Before entering this study, all eligible patients had received various chemotherapies. Approximately 50% of the patients had received three chemotherapy regimens. Importantly, all studied patients had received gefitinib, and most patients had received gefitinib as a second-line therapy. Previous gefitinib therapy resulted in 21 patients (77.8%) with PR, 2 patients (7.4%) with SD, and 4 patients (14.8%) with PD. Five patients had acquired resistance to initial gefitinib treatment according to the criteria proposed by Jackman *et al* (2010). One patient had been administered level 2 doses; 2 patients, level 3 doses; and 2 patients, level 5 doses. All five patients achieved PR with initial gefitinib treatment. Three patients developed PD within 1 month of initial gefitinib treatment; these patients might have had primary resistance to initial gefitinib treatment. Two of these patients had been administered level 1 doses, and 1 patient had been administered level 2 doses.

Table 1 Patient characteristics

Characteristics	Number of patients
Patients	27
Gender	
Male	14
Female	13
Age (years)	
Mean	60
Range	45–75
Performance status	
0	2
1	17
2	8
Smoking status	
Current	7
Former	8
Never	12
Histology	
Adenocarcinoma	25
Squamous cell carcinoma	1
Large cell carcinoma	1
EGFR mutation status	
Positive	4
Negative	6
Unknown	17
Number of previous chemotherapy regimens	
2	3
3	15
4	8
5	1
Previous gefitinib response	
PR	21
SD	2
PD	4

Abbreviations: EGFR = epidermal growth factor receptor; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2 Dose-limiting toxicities

Level	CPT-11 (mg m^{-2})	Gefitinib (mg per body weight)	Number of patients		Type of DLT (number of patients)
			Evaluable	DLT	
Level 1	50	250	3	0	
Level 2	75	250	3	0	
Level 3	100	250	6	2	Diarrhoea (2)
Level 4	125	250	3	0	
Level 5	150	250	3	0	

Abbreviations: CPT-11 = irinotecan; DLT = dose-limiting toxicity.

Dosing information is listed in Table 2. In this study, a total of 87 cycles of therapy were given. The number of treatment cycles administered per patient ranged from 1 to 10 (median, 4 cycles).

Safety

Toxicities were evaluated in 27 patients. The DLTs were observed in only 2 patients at level 3 dosing. We defined level 5 as the recommended dose for this study. We added 9 patients at level 5 to confirm tolerability and the response of this combination therapy. Toxicities are summarised in Table 3. The major haematologic toxicities included neutropenia and leucopoenia with dose-dependent occurrence. However, only 2 grade 4 cases of neutropenia were noted at level 5. No patients experienced febrile neutropenia. The major non-hematologic toxicities were nausea, vomiting, and diarrhoea. There was no grade 3 or 4 non-haematologic toxicity except diarrhoea. Grade 3 diarrhoea was observed in 4 patients. No patients experienced pneumonitis. There were no treatment-related deaths.

Efficacy

Twenty-six patients (96.3%) were analysed for response to therapy; 7 patients had PR, 11 patients had SD, and 8 patients had PD (Table 4). The disease control rate (DCR) and response rate (RR) were 69.2% and 26.9%, respectively. From the 12 patients who received level 5 doses (recommended phase II dose), 5 patients achieved PR, 4 patients had SD, and 3 patients had PD. The DCR and RR at level 5 were 75.0% and 41.7%, respectively. From the five patients with acquired resistance to initial gefitinib treatment, one patient achieved PR, two patients had SD, and two patients had PD. From the three patients with primary resistance to initial gefitinib treatment, one patient had SD and two patients had PD. The median time to treatment failure was 57 days (95% confidence interval (CI), 32–82 days); median PFS, 70 days (95% CI, 38–102 days); median OS, 244 days (95% CI, 185–303 days); and 1-year survival rate, 32.6%.

EGFR mutation analysis

EGFR mutations were analysed in 10 of 27 patients by direct sequencing of paraffin-embedded tumour samples extracted before initiation of gefitinib therapy. The EGFR mutations were detected in 4 of 10 patients. In-frame deletions within exon 19 were detected in three patients, and a mutation of L858R was detected within exon 21 in one patient. In the patients with EGFR mutation, two patients had PR, one patient had SD, and one patient had PD. In the other six patients with wild-type EGFR, one patient had PR, one patient had SD, three patients had PD, and one patient was not evaluable. The data are summarised in Table 5. The patients did not undergo re-biopsy after initial gefitinib treatment.

DISCUSSION

Our study showed that combining CPT-11 and gefitinib is feasible without adverse toxicity. The MTD was not determined, and full dose CPT-11 and gefitinib could be combined. Diarrhoea was one of the major non-hematologic toxicities present in the study. Diarrhoea occurred in 22 patients (81.5%), but grade 3 diarrhoea was observed in only 4 patients (15%). Diarrhoea is a major common toxicity of both drugs. Frequency of grade 3 diarrhoea was 21% in a phase II study of CPT-11 monotherapy (Fukuoka *et al*, 1992), and 0–1% in phase II studies of gefitinib monotherapy (Fukuoka *et al*, 2003; Kris *et al*, 2003). Based on these studies, the frequency of diarrhoea was not increased upon CPT-11 and gefitinib combined dosing.

The effect of combination therapy with gefitinib and cytotoxic chemotherapy has already been evaluated for previously untreated advanced NSCLCs. Additionally, two randomised phase III studies evaluated the addition of gefitinib to standard platinum-doublet chemotherapy and found no significant improvement in OS (Giaccone *et al*, 2004; Herbst *et al*, 2004). However, recently, a randomised phase II study showed that sequential administration of EGFR-TKI, following chemotherapy, led to a significant improvement in PFS versus administration of chemotherapy alone

Table 3 Toxicities in (a) first cycle; (b) all cycles

(a)

	Level 1 (*N* = 3)				Level 2 (*N* = 3)				Level 3 (*N* = 6)				Level 4 (*N* = 3)				Level 5 (*N* = 12)			
NCI-CTC grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Leucocytes	0	0	0	0	0	0	0	0	1	3	0	0	2	0	0	0	4	3	2	0
Neutrophils	0	0	0	0	0	0	0	0	3	0	1	0	1	0	0	0	2	3	3	1
Haemoglobin	3	0	0	0	1	1	0	0	3	1	0	0	2	0	0	0	5	2	1	0
Platelets	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
General fatigue	0	0	0	0	0	1	0	0	3	0	0	0	1	0	0	0	3	1	0	0
Rash	3	0	0	0	3	0	0	0	4	0	0	0	1	0	0	0	4	1	0	0
Nausea/vomiting	1	0	0	0	1	1	0	0	4	0	0	0	2	1	0	0	8	4	0	0
Diarrhoea	1	1	0	0	2	0	0	0	2	0	2	0	1	2	0	0	6	3	2	0
Stomatitis	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	3	0	0
AST, ALT	1	0	0	0	2	0	0	0	1	2	0	0	1	0	0	0	5	2	0	0
Total bilirubin	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	3	1	0	0
Creatinine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0

(b)

	Level 1–4 (*N* = 15)					Level 5 (*N* = 12)					Total (*N* = 27)
NCI-CTC grade	**1**	**2**	**3**	**4**	**3–4(%)**	**1**	**2**	**3**	**4**	**3–4(%)**	**3–4(%)**
Leucocytes	3	3	1	0	7	2	5	3	0	25	15
Neutrophils	2	2	3	0	20	2	1	5	2	58	37
Haemoglobin	9	5	0	0	0	7	3	1	0	8	4
Platelets	0	0	0	0	0	2	0	0	0	0	0
General fatigue	4	1	0	0	0	3	1	0	0	0	0
Rash	9	0	0	0	0	4	1	0	0	0	0
Nausea/Vomiting	8	2	0	0	0	8	4	0	0	0	0
Diarrhoea	5	4	2	0	13	5	4	2	0	17	15
Stomatitis	4	0	0	0	0	1	3	0	0	0	0
AST, ALT	5	2	0	0	0	5	2	0	0	0	0
Total bilirubin	2	0	0	0	0	4	2	0	0	0	0
Creatinine	0	0	0	0	0	4	0	0	0	0	0

Abbreviations: N = number of patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 4 Response

	Level 1 (*N* = 3)	Level 2 (*N* = 3)	Level 3 (*N* = 6)	Level 4 (*N* = 3)	Level 5 (*N* = 12)	Total (*N* = 27)
PR	0	0	0	2	5	7
SD	2	1	4	0	4	11
PD	1	2	2	0	3	8
NE	0	0	0	1	0	1

Abbreviations: N = number of patients; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Table 5 Biomarker analysis and clinical outcome

Patient number	Gender	Age	Histology	Previous gefitinib response	EGFR mutation status	Response to CPT-11 and gefitinib
L1-2	Male	54	Squamous	PD	Wild	PD
L2-3	Female	55	Adeno	PD	Wild	PD
L3-5	Female	75	Adeno	PR	Wild	SD
L4-2	Female	57	Adeno	PR	Wild	NE
L5-1	Female	58	Adeno	PR	L858R	SD
L5-2	Male	63	Adeno	PR	Wild	PR
L5-3	Male	75	Adeno	PD	Wild	PD
L5-4	Male	64	Adeno	PR	Deletion	PR
L5-9	Female	64	Adeno	PR	Deletion	PR
L5-12	Female	48	Adeno	PR	Deletion	PD

Abbreviations: CPT-11 = irinotecan; EGFR = epidermal growth factor receptor; Squamous = squamous cell carcinoma; Adeno = adenocarcinoma; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; Wild = wild-type; L858R = L858R within exon 21; Deletion = in-frame deletions within exon 19.

in unselected, previously untreated patients with advanced NSCLC (Mok *et al*, 2009b).

The DCR and RR were 69.2% and 26.9%, respectively, in all patients in our trial, and 75.0% and 41.7% at level 5, respectively. These DCR and RR were very encouraging, especially as patients were resistant to gefitinib. In the two published Japanese phase II studies of CPT-11, in which CPT-11 was administered to previously treated NSCLC patients, RRs were 0% and 13.6%, respectively (Nakai *et al*, 1991; Negoro *et al*, 1991). The efficacy of CPT-11 for treating patients with an EGFR mutation is not known; therefore, it is possible that CPT-11 is effective for patients with an EGFR mutation. However, we hypothesised that CPT-11 and gefitinib would have a synergistic and beneficial effect clinically. To explain this synergistic effect, three biological mechanisms should be considered.

The first mechanism involves data reported in a study by Ohtsuka *et al* (2010). Resistance to EGFR-TKI is associated with the downregulation of ABCG2 expression. Additionally, EGFR-TKI-resistant cell lines with concomitant downregulation of ABCG2 expression have high sensitivity to a topoisomerase I inhibitor alone or in combination with EGFR-TKI when compared with cell lines with normal ABCG2 expression. Second, gefitinib-resistant cells have a high sensitivity to SN-38, a metabolite of the camptothecin derivative CPT-11. In our original data, the half maximal inhibitory concentration values for SN-38 were significantly lower in gefitinib-resistant cells than in gefitinib-sensitive parental cells. We observed an increase in topoisomerase I mRNA expression in gefitinib-resistant cells (unpublished data). Third, the combination of topotecan and gefitinib has been reported to have a synergistic effect in a topotecan-resistant cell line (Yang *et al*, 2005); topotecan is a topoisomerase I inhibitor. Collectively, these data suggest that overall sensitivity to CPT-11 should increase in our patients. Therefore, CPT-11 and gefitinib should have a synergistic beneficial effect in NSCLC patients with acquired resistance to gefitinib.

The mechanistic reasons behind the resistance to EGFR TKI are different, probably involving T790M secondary mutation and *MET* amplification. Recently, some irreversible EGFR-TKIs and MET inhibitors have shown antitumour activity in patients resistant to gefitinib or erlotinib in pre-clinical studies (Kwak *et al*, 2005; Gendreau *et al*, 2007; Engelman *et al*, 2007a; Li *et al*, 2008; Tang *et al*, 2008). At least three irreversible EGFR-TKIs (neratinib (HKI-272), XL647, and PF-00299804) were used in phase II studies of NSCLC patients with acquired resistance to gefitinib or erlotinib (Rizvi *et al*, 2008; Janne *et al*, 2009; Sequist *et al*, 2010). The RRs were 3.4% (EGFR mutant) and 0% (EGFR wild-type) in neratinib, 4.3% in XL647, and 7.0% in PF-00299804. The RRs of our combination of gefitinib and CPT-11 were similar to those for irreversible EGFR-TKIs treatment. Therefore, we think that this combination can be used as a treatment option for patients failing gefitinib monotherapy.

In conclusion, the combination of CPT-11 and gefitinib was well tolerated and potentially therapeutic for NSCLC patients no longer responding to gefitinib monotherapy. Larger phase II studies are required to evaluate the efficacy of this combination therapy for NSCLC patients with PD no longer responding to gefitinib treatment.

REFERENCES

Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, Zhao F, Vincent PW, Naumov GN, Bradner JE, Althaus IW, Gandhi L, Shapiro GI, Nelson JM, Heymach JV, Meyerson M, Wong KK, Janne PA (2007a) PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res* **67:** 11924–11932

Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Janne PA (2007b) MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **316:** 1039–1043

Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* **10:** 16–20

Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP, Baselga J (2003) Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol* **21:** 2237–2246

Gendreau SB, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, Bentzien F, Cancilla B, Lutman J, Chu F, Jackman L, Shi Y, Yu P, Wang J, Aftab DT, Jaeger CT, Meyer SM, De Costa A, Engell K, Chen J, Martini JF, Joly AH (2007) Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. *Clin Cancer Res* **13:** 3713–3723

Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH (2004) Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. *J Clin Oncol* **22:** 777–784

Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH (2004) Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. *J Clin Oncol* **22:** 785–794

Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Janne PA, Lynch T, Johnson BE, Miller VA (2010) Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol* **28:** 357–360

Janne PA, Reckamp K, Koczywas M, Engelman JA, Camidge DR, Rajan A, Khuri F, Liang JQ, O'Connell J, Giaccone G (2009) Efficacy and safety of PF-00299804 (PF299) in patients (pt) with advanced NSCLC after failure of at least one prior chemotherapy regimen and prior treatment with erlotinib (E): a two-arm, phase II trial. *Proc Am Soc Clin Onc* **27**(Suppl): abstract 8063

Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K (1991) Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res* **51:** 4187–4191

Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, Li LY, Watkins CL, Sellers MV, Lowe ES, Sun Y, Liao ML, Osterlind K, Reck M, Armour AA, Shepherd FA, Lippman SM, Douillard JY (2008) Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* **372:** 1809–1818

Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B (2005) EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* **352:** 786–792

Koizumi F, Kanzawa F, Ueda Y, Koh Y, Tsukiyama S, Taguchi F, Tamura T, Saijo N, Nishio K (2004) Synergistic interaction between the EGFR tyrosine kinase inhibitor gefitinib ("Iressa") and the DNA topoisomerase I inhibitor CPT-11 (irinotecan) in human colorectal cancer cells. *Int J Cancer* **108:** 464–472

Kris MG, Natale RB, Herbst RS, Lynch Jr TJ, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ, Kay AC (2003) Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* **290:** 2149–2158

Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW, Harris PL, Driscoll DR, Fidias P, Lynch TJ, Rabindran SK, McGinnis JP, Wissner A, Sharma SV, Isselbacher KJ, Settleman J, Haber DA (2005) Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. *Proc Natl Acad Sci USA* **102:** 7665–7670