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Clinical Studies

A randomised trial of intrapericardial bleomycin for malignant pericardial effusion with lung cancer (JCOG9811)

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Safety and efficacy of intrapericardial (ipc) instillation of bleomycin (BLM) following pericardial drainage in patients with malignant pericardial effusion (MPE) remain unclear. Patients with pathologically documented lung cancer, who had undergone pericardial drainage for MPE within 72 h of enrolment, were randomised to either arm A (observation alone after drainage) or arm B (ipc BLM at 15 mg, followed by additional ipc BLM 10 mg every 48 h). The drainage tube was removed when daily drainage was 20 ml or less. The primary end point was survival with MPE control (effusion failure-free survival, EFFS) at 2 months. Eighty patients were enrolled, and 79 were eligible. Effusion failure-free survival at 2 months was 29% in arm A and 46% in arm B (one-sided $P = 0.086$ by Fisher's exact test). Arm B tended to favour EFFS, with a hazard ratio of 0.64 (95% confidence interval: 0.40–1.03, one-sided $P = 0.030$ by log-rank test). No significant differences in the acute toxicities or complications were observed. The median survival was 79 days and 119 days in arm A and arm B, respectively. This medium-sized trial failed to show statistical significance in the primary end point. Although ipc BLM appeared safe and effective in the management of MPE, the therapeutic advantage seems modest.
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Malignant pericardial effusion (MPE) is a grave complication of malignant tumours. The frequency of pericardial involvement by malignancy has been estimated to be 10–21% at autopsy (Theologides, 1978; Klatt and Heitz, 1990).

Malignant pericardial effusions are often asymptomatic and detected incidentally by echocardiography or computed tomography. Symptomatic cases, however, often manifest cardiac tamponade, which can rapidly lead to cardiovascular collapse and death, unless promptly treated (Press and Livingston, 1987).

Lung cancer is the most frequent cause of MPE, and other common primary sites include breast cancer, oesophageal cancer, lymphoma and leukaemia (Abraham *et al*, 1990; Wilkes *et al*, 1995; Yonemori *et al*, 2007). The prognosis of MPE in lung cancer patients is particularly poor, with a reported median survival of 3 months or less (Okamoto *et al*, 1993; Gornik *et al*, 2005).

Although prompt diagnosis and pericardial drainage result in good palliation of symptoms, drainage alone is often inadequate to prevent re-accumulation of the fluid after the drainage tube is removed (Shepherd, 1997). There are numerous reports of pericardial sclerosis for MPE by the instillation of various agents, such as tetracycline/doxycycline (Shepherd *et al*, 1987; Maher *et al*, 1996), a streptococcal preparation (Imamura *et al*, 1991), bleomycin (BLM) (Vaitkus *et al*, 1994; Liu *et al*, 1996; Maruyama *et al*, 2007), thiotepa (Colleoni *et al*, 1998; Martinoni *et al*, 2004), cisplatin/carboplatin (Moriya *et al*, 2000; Tomkowski *et al*, 2004), 5-fluorouracil (Lerner-Tung *et al*, 1997), anthracyclines (Kawashima *et al*, 1999), vinblastine (Primrose *et al*, 1983), mitoxyantrone (Norum *et al*, 1998), mitomycin C (Kaira *et al*, 2005) and ^{32}P-colloid (Dempke and Firusian, 1999), after drainage. Platinum agents are actually not 'classic' sclerosants to induce inflammatory adhesion of the pericardial sac; they were apparently used as local chemotherapy. Whereas each study reports favourable outcomes in terms of MPE control and prevention of re-accumulation, almost all were performed as phase II trials, and no definite conclusions could be drawn (Press and Livingston, 1987; Vaitkus *et al*, 1994).

In one of the very few randomised trials conducted to date, Liu *et al* (1996) reported that BLM is the preferred agent for sclerosis, because of the lower morbidity associated with it. However, to the best of our knowledge, the efficacy and safety of pericardial sclerosis itself has never been evaluated by a prospective randomised trial.

This trial was aimed at evaluating the safety and efficacy of pericardial sclerosis induced by intrapericardial (ipc) BLM

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instillation, as compared with pericardial drainage alone, in lung cancer patients with MPE.

PATIENTS AND METHODS

Patient eligibility criteria

Patients with pathologically documented lung cancer, who had undergone pericardial drainage for clinical MPE (moderate to large accumulation of fluid), were eligible for study entry. Indications for the drainage were clinically determined; cases after emergent drainage and those after elective one were both included. Patient registration should be done within 72 h of drainage. The eligibility criteria were as follows: 75 years of age or less, expected life prognosis of 6 weeks or more with control of the MPE and minimum organ functions (leukocyte count $\geqslant$ 3000 per mm^3, platelet count $\geqslant$ 75 000 per mm^3, haemoglobin $\geqslant$ 9.0 g dl^{-1} and no renal or hepatic failure; however, laboratory abnormalities related to cardiac tamponade were allowed). Patients with chemotherapy-naive small cell cancer were excluded. Other exclusion criteria included apparently non-malignant effusion (e.g., purulent effusion), recurrent MPE, myocardial infarction or unstable angina within the previous 3 months, constrictive pericarditis, active interstitial pneumonia, severe infection and disseminated intravascular coagulation. Those with an unstable clinical condition attributable to other severe complications, such as superior vena cava syndrome, central airway obstruction or uncontrollable massive pleural effusion, were also excluded.

Patient eligibility was confirmed by the Japan Clinical Oncology Group Data Center before patient registration. The study protocol was approved by the institutional review boards at each participating centre and all the patients provided written informed consent.

Treatment plan

The study protocol did not limit the method used for the pericardial drainage. Both percutaneous tube pericardiostomy (non-surgical method), in which a drainage catheter is inserted using the Seldinger technique, and subxiphoid pericardiostomy (surgical method), in which a drainage tube is placed surgically, were allowed; each participating institution, however, basically adhered to one method, which they used in routine practice. The drainage method used was recorded on the case report form.

After registration with telephone or facsimile, the patients were randomly assigned to one of the two treatment arms with block randomisation stratified by the institution. In arm A, no additional intervention was performed and the patient was observed clinically after the pericardial drainage. In arm B, 15 mg of BLM dissolved in 20 ml of normal saline was instilled through the drainage catheter into the pericardial space immediately after the patient registration. The catheter was then clamped and reopened after 2 h, allowing resumption of the drainage. Additional doses of BLM at 10 mg were instilled similarly every 48 h, unless the criteria for tube removal, as described below, were met.

The drainage tube was removed, in both arm A and arm B, when the drainage volume per 24 h was 20 ml or less. If the criterion was met during the 24 h preceding randomisation in a patient allocated to arm A, the tube was immediately removed.

Patient evaluation and follow-up

Primary control of the MPE was considered to be achieved when the drainage tube could be successfully removed within 7 days of randomisation. When the criterion for tube removal, that is 20 ml per 24 h, could not be met by 7 days, the case was judged to show primary failure of the protocol therapy: treatment after off-protocol was not limited by the study protocol. When the drainage tube had to be removed because of obstruction, but re-drainage was clinically unnecessary, it was judged to have been successfully removed with primary control of MPE.

Monitoring for recurrence of the MPE in those who showed primary control was conducted by echocardiography at 1, 2, 4, 6 and 12 months. When the estimated fluid volume in the recurrent effusion exceeded 100 ml, the case was labelled as showing MPE re-accumulation and recurrence. Re-drainage was performed as clinically indicated.

The adverse effects of the therapy were evaluated according to the Japan Clinical Oncology Group Toxicity Criteria (Tobinai *et al*, 1993), modified from the National Cancer Institute Common Toxicity Criteria version 1.

The primary end point of the study was effusion failure-free survival (EFFS) rate at 2 months; EFFS was patient survival without MPE recurrence as defined above, in patients showing primary control. It was calculated as the period from the date of pericardial drainage to the date of MPE recurrence or the patient's death. For those patients with primary failure, MPE recurrence was considered to have occurred at the date of drainage, with an EFFS of zero. Effusion failure-free survival was judged regardless of the other disease status.

The secondary end points included the primary MPE control rate, time to drainage tube removal, EFFS, treatment-related morbidity, proportion of late pericardial or cardiac complication, overall survival (OS) and symptom scores.

Study-specific four-item symptom scores were completed by patients at the time of randomisation (i.e., after pericardial drainage) and at 1 month after the enrolment. The scores were to be interviewed by the health professionals other than the attending physicians. The items consisted of cough, pain, anorexia and shortness of breath. The scoring was conducted as follows: as not at all present (0), a little (1), moderate (2) and very much (3). The score for each item and the sum of the total score for all the four items were compared between the baseline and the follow-up assessments, and judged to be improved (lower scores in the follow-up assessments), stable (no change of scores) or worsened (higher scores, or the patient could not fill out the questionnaire, in the follow-up assessments).

Statistical considerations

From the historical data, the EFFS rate at 2 months in arm A was assumed to be 30% and that in arm B was presumed to be 60%. The study was designed to provide 80% power with 5% one-sided α. The required sample size was calculated as 80 patients, 40 in each arm, for comparing independent proportions.

The OS, time to tube removal and EFFS of both arms were calculated by the Kaplan–Meier method and compared by log-rank tests. The primary MPE control rate, symptom scores, complication rates and EFFS at each of the follow-up points were compared using Fisher's exact test. All analyses were performed with the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics and treatment delivery

From August 1999 to January 2006, 80 patients from 14 institutions were enrolled and randomised, 42 to arm A and 38 to arm B. One patient in arm B was found to be ineligible because of late registry, 2 weeks after the pericardial drainage. All 80 patients were analysed for their characteristics and chemotherapy morbidity, and the 79 eligible patients were analysed for efficacy and survival.

Table 1 lists the characteristics of the patients, which were generally well balanced between the arms, except for the effusion cytology: there were numerically more patients with

Table 1 Patient characteristics

Arm	A (drainage alone)	B (ipc BLM)
N	42	38
Gender		
Male	27	24
Female	15	14
Median age (range)	60.5 (39–75)	60 (42–73)
Histology		
Small cell	3	2
Non-small cell	39	36
Prior chemotherapy		
Yes	29	24
No	13	14
Prior thoracic radiotherapy		
Yes	11	9
No	31	29
Drainage methods		
Surgical	19	17
Others	23	21
Median drainage volume in ml (range)	550 (250–1750)	600 (130–1930)
Effusion cytology		
Negative	6	11
Indeterminate	1	0
Positive	33	25
Not examined	2	2

ipc BLM = intrapericardial bleomycin instillation.

cytology-positive effusions in arm A. Cytology of the effusion was positive in 58 cases out of the 76 examined (76%).

In arm B, all 38 patients received at least one ipc BLM instillation and a total of 74 administrations: seven patients received four administrations (total BLM dose: 45 mg), five received three administrations (total BLM: 35 mg), five received two administrations (total BLM: 25 mg) and the remaining 21 received a single administration (total BLM: 15 mg). There was no apparent relationship between total dose and efficacy end points such as EFFS, except that those required four administrations had a worse primary control of the MPE.

A total of 24 patients (14 in arm A and 10 in arm B) received systemic chemotherapy after drainage tube removal. Nine patients (five in arm A and four in arm B) received gefitinib. Cytotoxic chemotherapy was administered to 21 patients (11 in arm A and 10 in arm B).

Morbidity and early deaths

Table 2 summarises the morbidity of the protocol therapy. Although 30 (38%) of the patients experienced some pain, no significant difference in the incidence and severity of pain was observed between the arms. Bleeding and infections were rare and generally controllable. Two patients in arm B developed transient fever of moderate degree (38–38.7°C). One case with constrictive pericarditis at 4 months and another with late cardiac dysfunction at 12 months after the registry, both reported to be grade 2, were observed in arm B.

As anticipated, there were as many as nine early deaths within 30 days of randomisation; five in arm A and four in arm B. Although the death was ascribed to disease progression in the majority, two patients in arm A died of massive bleeding during surgical attempts at re-drainage for recurrent MPE, possibly due to

Table 2 Morbidity of the protocol therapy

Arm	A (drainage alone)	B (ipc BLM)
N	42	38
Pain		
None	25	25
Medication not required	4	4
Controlled with non-opioid analgesics	9	7
Controlled with opioid analgesics	4	2
Uncontrollable	0	0
Infection		
None	39	35
Controllable	3	3
Uncontrollable	0	0
Bleeding		
None	42	36
Controllable	0	1
Severe	0	1
Late complications		
None	42	36
Pulmonary	0	0
Cardiac function	0	1 (grade 2)
Constrictive pericarditis	0	1 (grade 2)

ipc BLM = intrapericardial bleomycin instillation.

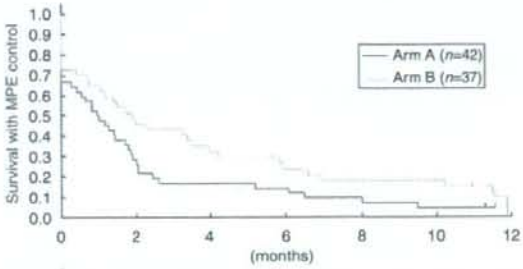

Figure 1 Effusion failure-free survival (EFFS). The median EFFS was 30 days in arm A and 57 days in arm B, with a hazard ratio of 0.64 (95% confidence interval: 0.40–1.03), with arm B significantly favouring this parameter (one-sided $P = 0.030$ by log-rank test).

crack formation in the ventricular wall upon dissection of the adherent pericardium. Another patient in arm B died suddenly on day 12 of the protocol without a clear cause.

Efficacy end points

Primary control of the MPE with successful tube removal within 7 days of randomisation was achieved in 28 of the 42 cases (67%) in arm A and 27 of the 37 eligible cases (73%) in arm B, the difference between the two groups not being statistically significant. The median time to tube removal was 7 days in each arm. Arm B favoured EFFS (Figure 1), with a hazard ratio of 0.64 (95% confidence interval: 0.40–1.03, and one-sided $P = 0.030$ by log-rank test).

The EFFS at 1, 2, 4, 6 and 12 months was 50, 29, 17, 14 and 5%, respectively, for arm A, and 65, 46, 32, 24 and 10%, respectively, for arm B. Although arm B also favoured the primary end point, EFFS at 2 months (46 *vs* 29%), the difference between the two

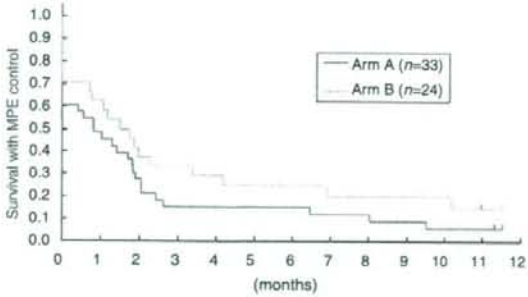

Figure 2 Effusion failure-free survival (EFFS) in effusion cytology-positive patients. In the effusion cytology-positive patient subset, arm B favoured EFFS. The hazard ratio was 0.69 (95% confidence interval: 0.39–1.21).

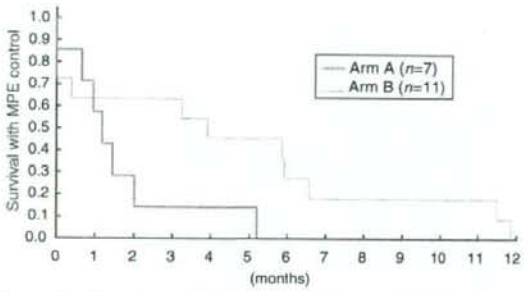

Figure 3 Effusion failure-free survival (EFFS) in effusion cytology-negative or -indeterminate patients. In the effusion cytology-negative or -indeterminate patient subset, arm B favoured EFFS. The hazard ratio was 0.39 (95% confidence interval: 0.12–1.21).

groups was not statistically significant (one-sided $P = 0.086$ by Fisher's exact test).

The median OS was not significantly different between the two arms: 79 days in arm A and 119 days in arm B. The OS rates at 6 months were 27 and 31% in arm A and arm B, respectively.

Subgroup analysis

As more patients in arm A had cytology-positive effusion, which has been reported to be associated with a poor prognosis (Gornik *et al*, 2005), subset analysis was performed according to the effusion cytology status (Figures 2 and 3). In both cytology-positive patients (Figure 2) and cytology-negative or -indeterminate patients (Figure 3), arm B favoured EFFS.

Thirty-six patients had undergone surgical (subxiphoid pericardiostomy) and 43 had undergone non-surgical (percutaneous tube pericardiostomy) drainage before randomisation. Patients with surgical drainage tended to have a longer EFFS (Figure 4). The effect of ipc BLM was observed irrespective of the drainage method employed; arm B tended to favour EFFS both in patients with surgical drainage (hazard ratio 0.62, 95% confidence interval: 0.30–1.29) and in those with non-surgical drainage (hazard ratio 0.56, 95% confidence interval: 0.29–1.05).

Symptom palliation

The baseline symptom scores were taken for all of the 79 eligible patients, at enrolment (after drainage). At the 1-month follow-up,

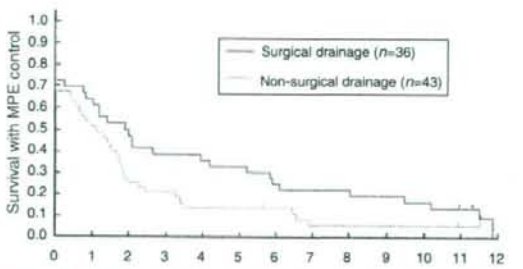

Figure 4 Effusion failure-free survival (EFFS) and drainage method. Patients with surgical drainage tended to have longer EFFS (median EFFS: 2.0 *vs* 1.1 month).

Table 3 Symptom palliation

Arm	A (drainage alone)	B (ipc BLM)
N eligible	42	37
% of those with improved or stable scores[a]		
Cough	60%	57%
Pain	50%	62%
Anorexia	55%	62%
Dyspnoea	62%	46%
Total	55%	51%

ipc BLM = intrapericardial bleomycin instillation. [a]The scores at 1 month were compared with those at enrolment.

approximately half of the patients (55% in arm A and 51% in arm B) had stable or improved overall scores. There were no significant differences between the arms for any of the symptom scores (Table 3).

DISCUSSION

Malignant pericardial effusion is a potentially life-threatening complication of malignancy that usually manifests itself at an advanced or terminal stage of the disease. It brings great agony to the patient once it becomes symptomatic, with dyspnoea, orthopnoea, chest pain and cough. Although the prognosis of the patients with MPE is very poor, especially in those with chemotherapy-resistant tumours such as non-small-cell lung cancer (Press and Livingston, 1987; Okamoto *et al*, 1993; Gornik *et al*, 2005; Yonemori *et al*, 2007), optimal management is very important for palliation.

Pericardial sclerosis following drainage has been widely performed. However, data are available mainly from phase II trials or case series. In fact, historical comparison has failed to demonstrate the efficacy of pericardial sclerosis over drainage alone (Okamoto *et al*, 1993; Vaitkus *et al*, 1994). It has also been suggested that sclerosis may be effective in preventing re-accumulation of MPE after percutaneous tube pericardiostomy, but not after subxiphoid pericardiotomy, because the surgical intervention alone was considered to be sufficient to prevent recurrent MPE (Press and Livingston, 1987; Park *et al*, 1991; McDonald *et al*, 2003).

In addition, there are some potential morbidities associated with pericardial sclerosis; most of the agents used as sclerosants produce unpleasant adverse effects, such as fever and pain (Liu *et al*, 1996). There is also concern about the complications of the procedure, both in the short term, such as bleeding and infection,

and in the long term, such as constrictive pericarditis, as the inflammatory response causes adhesion of the visceral and parietal pericardium (Shepherd, 1997).

We undertook a randomised trial to evaluate the efficacy of pericardial sclerosis following drainage as compared with drainage alone. We chose BLM as the sclerosant agent for ipc instillation, because of its low toxicity as compared with doxycycline, reported from an earlier randomised trial (Liu *et al*, 1996). We included only patients with non-small-cell lung cancer or chemotherapy-treated small cell cancer to minimise the influence of systemic chemotherapy after the protocol study (Vaitkus *et al*, 1994). We randomised the patients after the pericardial drainage, as we judged that obtaining informed consent before it, that is when the patients suffer from symptoms of MPE, would be very difficult. Therefore, we did not specify the indication for drainage and enrolled cases after both emergent and elective drainage. We thus focused on the prevention of MPE recurrence. We could not find any comparable phase III trial on this participant, and no such trial is registered in ClinicalTrial gov.

We found that ipc BLM instillation seemed to be effective at preventing the recurrence of MPE. However, the benefit in the primary end point, that is, EFFS at 2 months, was not significantly different, which is a major drawback to make a definitive conclusion. The therapeutic benefit, which could not be demonstrated with our modestly sample-sized trial, therefore, might be only a modest one. On the other hand, the benefit of ipc BLM seemed to be unrelated to the drainage method. As expected, the OS was poor in both arms and not significantly different.

Our study has several limitations. One is that without significant survival prolongation and difference of symptom scores, modest improvement of the EFFS might not represent true patient benefit. We believe, however, that conductance of our trial itself would be fully justified; given the severe symptoms of uncontrolled MPE and the inconvenience of the drainage tube, survival without MPE would be a worthwhile treatment goal.

The second limitation was that we limited the participants to lung cancer patients, which makes it difficult to evaluate late complications due to short OS. In patients with more chemotherapy-sensitive tumours such as breast cancer or lymphoma, many more patients may be expected to live for up to at least 1 year longer. There would be greater concern about late pericardial or cardiac complications, which we did observe in two of our own cases. Even for lung cancer patients, advances in systemic therapy may be expected to improve the outcome of those with even far-advanced disease in the future, which would evidently modify the risk/benefit of ipc BLM.

The third limitation of our study was that we did not control for the method of primary pericardial drainage, and each institution chose it in accordance with its daily practice. We do not believe that our results were much biased by the drainage methods, as each participating institution basically adhered to one method of its choice, and the ipc BLM arm tended to favour EFFS in both subgroups with surgical and non-surgical drainage. However, control for the drainage method or indication (emergent *vs* elective) for drainage might be necessary in future trials, as they might well affect the patient outcomes. In fact, we did observe that, although not a randomised comparison and thus it should be interpreted with caution, patients who underwent surgical drainage tended to have a better MPE control.

Recently, less invasive techniques for surgical treatment of MPE have been described, such as percutaneous balloon pericardiotomy (Ziskind *et al*, 1993; Wang *et al*, 2002), which create a pleuro-pericardial communication and allow fluid drainage into pleural space. It was reported to be effective and safe, and may potentially obviate the need for surgical intervention. However, it has yet to be compared with other drainage methods and its role has not been established. No patient underwent this procedure in our study.

One ancillary finding of our study was that two patients died of major bleeding during surgical attempts at re-drainage for recurrent MPE. Although it has rarely been reported in the literature, partial adhesions could have led to injury to the cardiac wall during the surgical procedure.

In this trial, we evaluated the safety and efficacy of pericardial sclerosis with a 'classic' sclerosant agent of BLM. Future trial designs would include one to compare BLM with another agent with a different mode of action, such as intrapericardial instillation of a platinum compound as 'local chemotherapy'.

In conclusion, we found that pericardial sclerosis with ipc BLM after drainage appears to be safe and effective, overall, in the management of MPE in patients with lung cancer and should be a valid therapeutic option in these patients. We could not, however, demonstrate a statistical significance in the primary end point with the modest sample size of 80. The therapeutic advantage might not be large enough, and more trials are warranted.

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Conflict of interest

The authors have no conflicts of interest to declare.

Registered in www.clinicaltrials.gov, ClinicalTrials.gov number, NCT00132613 and in UMIN-CTR[www.umin.ac.jp/ctr/], identification number, C000000030.

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Appendix

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Study participants: The following institutions and investigators participated in the trial:

National Hospital Organization Dohoku Hospital (Yuka Fujita and Satoru Fujiuchi), Tochigi Cancer Center (Kiyoshi Mori and Yukari Kamiyama), National Cancer Center Hospital East (Kaoru Kubota, Yutaka Nishiwaki and Nagahiro Saijo), National Cancer Center Hospital (Noboru Yamamoto, Tomohide Tamura and Hideo Kunitoh), International Medical Center (Koichiro Kudo and Yuichiro Takeda), Cancer Institute Hospital (Takeshi Horai and Makoto Nishio), Kanagawa Cancer Center (Kazumasa Noda and Fumihiro Oshita), Yokohama Municipal Citizen's Hospital (Koshiro Watanabe and Hiroaki Okamoto), Niigata Cancer Center Hospital (Akira Yokoyama and Yuko Tsukada), Gifu City Hospital (Yoshiyuki Sawa and Takashi Ishiguro), Aichi Cancer Center Hospital (Toyoaki Hida), National Hospital Organization Nagoya Medical Center (Hideo Saka), Kinki University Hospital (Kazuhiko Nakagawa and Isamu Okamoto) and Kyushu University Hospital (Yoichi Nakanishi and Koichi Takayama).

Phase I/II Pharmacokinetic and Pharmacogenomic Study of *UGT1A1* Polymorphism in Elderly Patients With Advanced Non–Small Cell Lung Cancer Treated With Irinotecan

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This phase II study investigated the recommended dose (RD) of irinotecan (CPT-11) by dose escalation in elderly (≥70 years) chemotherapy-naive Japanese patients with advanced non–small cell lung cancer. *UGT1A1*28* and **6* polymorphisms and pharmacokinetics were also investigated. Thirty-seven patients received the RD, 100 mg/m^2 of intravenous CPT-11, on days 1 and 8 of each 3-week cycle in phase II. The overall response rate was 8.1%. The median survival time was 441 days, and time to progression was 132 days. A significant correlation was observed between the incidence of grade 3/4 neutropenia and area under the time-concentration curve (AUC) values of SN-38. A reduction in AUC ratios ($AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$) and a rise in incidence of grade 3/4 neutropenia were observed with increase in polymorphism. The regimen was well tolerated and provided good disease control and promising survival effects. An analysis of the influence of *UGT1A1*28* and **6* polymorphisms provides useful information for the prediction of CPT-11-related hematological toxicity.

Lung cancer is the most common fatal cancer in Japan and in Western countries.[1] The majority of cases of advanced non–small cell lung cancer (NSCLC) are found among patients aged >65 years, and the number of such cases is predicted to rise with increases in the numbers of the elderly.[2,3]

Chemotherapy has been shown to yield better results than best supportive care in NSCLC patients in terms of survival and quality of life.[4] Platinum-based regimens containing a third-generation agent, including irinotecan (CPT-11), taxanes, gemcitabine (GEM), and vinorelbine (VNR), have been the mainstream treatment for patients with NSCLC.[5] However, these regimens have been associated with high toxicity while providing no survival benefit in elderly patients. Several prospective randomized trials have investigated optimal chemotherapy in patients aged ≥70 years with advanced NSCLC.[6–9] The regimens investigated have included VNR monotherapy,[6] GEM plus VNR vs. VNR alone,[7] VNR vs. GEM vs. VNR plus GEM,[8] and docetaxel (DOC) vs. VNR.[9] The results of the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) led to the recommendation that VNR monotherapy be used as first-line therapy in elderly patients with advanced NSCLC.[6] On the basis of these studies, and given that GEM is less active than VNR, many researchers now recommend VNR monotherapy.

CPT-11 is a semi-synthetic camptothecin derivative with topoisomerase I–inhibiting activity.[10–12] CPT-11, a prodrug, is converted to its active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin), by carboxylesterase, which is 100- to 1,000-fold more cytotoxic than CPT-11. Further hepatic metabolism by uridine diphospho-glucuronosyl-transferases (UGTs) converts SN-38 to its inactive metabolite, SN-38 glucuronide (SN-38G).[10–12]

Phase III clinical studies on CPT-11 conducted in NSCLC patients have included a comparison we made of CPT-11

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monotherapy, a cisplatin-plus-vindesine group (VDS-P), and a cisplatin-plus-CPT-11 (IP) group.[13] The response rate in the CPT-11 monotherapy group in a subset of elderly patients (aged 70–75 years) in that study was 40.0%, similar to that in the VDS-P group (43.5%). Moreover, the response rate was higher in the IP group (60.9%) than in those undergoing either of the other two regimens. Interestingly, survival time was better in the CPT-11 monotherapy group (44.3 weeks) than in the VDS-P group (35.7 weeks). As for adverse events in this subset of elderly patients, although the incidence of diarrhea tended to be higher in the CPT-11 monotherapy group, leukopenia, neutropenia, nausea/vomiting, and anorexia were all mild. Because these findings suggested that CPT-11 monotherapy might be a useful regimen in elderly patients with NSCLC, the regimen was investigated in this prospective study.

Severe CPT-11-associated diarrhea and myelosuppression have been reported as dose-limiting toxicities (DLTs).[14,15] These effects correlate significantly with the area under the time-concentration curve (AUC) values of CPT-11 and its active metabolite SN-38 and glucuronized SN-38.[14,15] Among UGT isoforms, *UGT1A1* is believed to be responsible for SN-38 glucuronidation and is also thought to be involved in the large inter-individual variations seen in SN-38 pharmacokinetics.[16] Several studies have reported a correlation between the adverse effects of CPT-11 and the presence of *UGT1A1* polymorphisms including *UGT1A1*28* and *UGT1A1*6*.[17–19] Ethnic differences have also been reported in the distribution of these polymorphisms, with higher incidences of *UGT1A1*6* occurring in Asians (including Japanese) than in Caucasians.[20–22] This suggests that *UGT1A1* polymorphism is an important determining factor in the efficacy and toxicity of CPT-11 and that pharmacogenetics-guided dosing of CPT-11 may help to individualize the dose of CPT-11 and moderate its toxicity in cancer patients.

We performed phase I and II studies involving CPT-11 monotherapy on days 1 and 8 of a 3-week cycle in elderly patients with NSCLC to determine the DLT, maximum-tolerated dose (MTD), and recommended dose (RD) and to investigate the antitumor effect and safety of the RD. Further, a prospective analysis of *UGT1A1* mutations was performed, and we investigated the relationship between the presence of these polymorphisms and the occurrence of adverse events. We also analyzed the variation in the pharmacokinetics of CPT-11 and its metabolites in elderly patients.

RESULTS

Patient characteristics

Between April 2003 and March 2006, 46 patients with stage IIIB/IV NSCLC were enrolled. In the overall study population, 76% of the patients (35 of 46) had stage IV disease, and 69.5% (32 of 46) had adenocarcinoma. Twelve patients were enrolled and treated in phase I. Six patients were treated at dose level 1 (60 mg/m^2), three patients at dose level 2 (80 mg/m^2), and three patients at dose level 3 (100 mg/m^2). DLT of persistent grade 2 leukopenia was observed in one patient at dose level 1, and an additional three patients were enrolled at this dose level. No further DLTs were observed in these patients or in patients receiving 80 or 100 mg/m^2. Therefore the MTD was not reached in this study, and the RD was set at 100 mg/m^2, in accordance with the study protocol described in "Methods."

In phase II, 34 additional patients were treated at 100 mg/m^2, making a total of 37 patients treated with the RD. **Table 1** shows the selected baseline demographics and disease characteristics of the patients treated with the RD. There were 25 men and 12 women, with a median age of 76 years (range: 71–88).

The median number of treatment cycles in phase II was 4.0 (range: 1–18); 37.8% of patients (14 of 37) received five or more cycles, and the percentage of patients with 6-month or longer treatment was ~22%. The relative dose intensity was 90.0%. Twenty-five of the 37 patients went on to second-line therapy comprising gefitinib (in 7 patients, 28%), different regimens of CPT-11 (7 patients, 28%), carboplatin/paclitaxel (4 patients, 16%), DOC (3 patients, 12%), GEM (3 patients, 12%), and S-1/cisplatin (1 patient, 4%).

Response and survival

All 37 patients (including 3 patients in phase I) who received the RD were evaluated to determine the overall response rate. The overall response rate was 8.1% (complete response (CR): 0, partial response (PR): 3; 3/37, 95% confidence interval: 1.7–21.9), and the disease control rate was 21.6% (8/37, 95% confidence interval: 9.8–38.2). The median survival time (MST) was 441 days after a median follow-up of 440 days, and the 1-year survival rate was 56.8% (**Figure 1**). The median time to progression (TTP) was 132 days.

Toxicity

In phase I, persistent grade 2 leukopenia was observed in one patient who received treatment at level 1, and the second cycle could not be started until day 30. This adverse event was therefore regarded as a DLT. Adverse events that occurred in phase II are summarized in **Table 2**. The most frequently observed hematological toxicity (grade 3/4) was neutropenia (27.0%).

Table 1 Demographics of patients treated with irinotecan 100 mg/m^2

Characteristic	No. of patients (N = 37)	%
Sex		
Male	25	68
Female	12	32
Age (years)		
Median	76.0	
Range	71–88	
Performance status		
0	11	30
1	26	70
Histology		
Adenocarcinoma	25	68
Other	12	32
Stage		
IIIB	10	27
IV	27	73

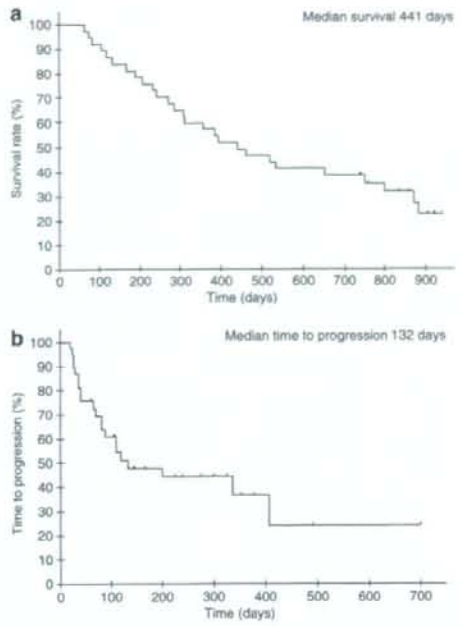

Figure 1 Elderly patients with advanced NSCLC treated with irinotecan. (**a**) Kaplan–Meier overall survival curve and (**b**) time-to-progression curve.

Table 2 Summary of adverse events in phase II (all courses)

	CPT-11 dose: 100 mg/m² (*N* = 37)	
Adverse event, patients	**Any event**	**Grade 3/4 (%)**
Leukopenia	26	9 (24.3)
Neutropenia	28	10 (27)
Anemia	27	4 (10.8)
Thrombocytopenia	1	1 (2.7)
Febrile neutropenia	0	0 (0)
Diarrhea	28	3 (8.1)
Nausea	23	4 (10.8)
Vomiting	13	0 (0)
Anorexia	31	9 (24.3)
Fatigue	14	1 (2.7)

Adverse events were assessed using National Cancer Institute Common Toxicity Criteria.

Frequently observed nonhematological toxicities (grade 3/4) included nausea (10.8%), anorexia (24.3%), and diarrhea (8.1%). Grade 4 toxicity (neutropenia) occurred in one patient who received treatment at level 3. Treatment-related death occurred in one patient, due to interstitial pneumonia.

Relationship of *UGT1A1*6* and **28* polymorphisms to pharmacokinetics and toxicity of CPT-11

The analysis of *UGT1A1* genotypes was performed in the 36 patients who had provided informed consent, and their

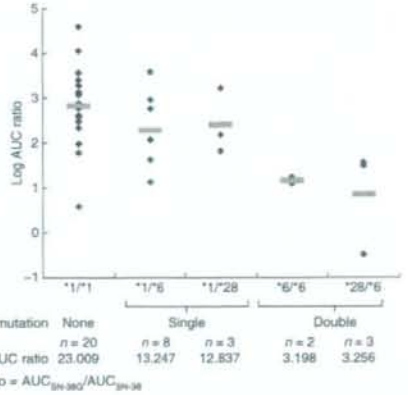

Figure 2 Comparison of area under the time-concentration curve (AUC) ratios by type of polymorphism in 36 patients treated with 100 mg/m² of irinotecan. The pharmacokinetic profile of irinotecan was affected to similar extents by **28* heterozygous and **6* heterozygous mutations, and by **6* homozygous and **6/*28* heterozygous mutations. The lines indicate geometric mean and the *y*-axis represents the log scale.

Table 3 Relationships between polymorphisms and adverse events and pharmacokinetic profile by type of *UGT1A1* polymorphism

	*UGT1A1*28 or UGT1A1*6* mutation			
	No mutation (*n* = 20)	**Single (*n* = 11)**	**Double (*n* = 5)**	***P***
Adverse events (no. of patient (%))				
Leukopenia grade 3 or 4				
First cycle	0 (0%)	3 (27%)	2 (40%)	0.006[a]
All cycles	3 (15%)	3 (27%)	3 (60%)	0.046[a]
Neutropenia grade 3 or 4				
First cycle	1 (5%)	2 (18%)	2 (40%)	0.039[a]
All cycles	3 (15%)	3 (27%)	4 (80%)	0.008[a]
AUC ratio[b]	23.009	12.949	3.233	0.001[c]

Adverse events were assessed using National Cancer Institute Common Toxicity Criteria.

[a]Jonckheere–Terpstra test; [b]AUC ratio = $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$; [c]Cochran–Armitage test.

polymorphisms are categorized and listed in **Figure 2**. Double mutations of *UGT1A1*28* and **6* (**6/*6* and **28/*6*) were detected in 5 of 36 patients (14%), and single mutations of *UGT1A1*28* or **6* were found in 11 of 36 patients (31%). No mutation was detected in 20 of 36 patients (55.6%). No *UGT1A1*28/*28* was found in homozygous patients.

Pharmacokinetic analyses were performed in the first cycle of treatment at a dosage of 100 mg/m², and the $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$ ratios of the *UGT1A1*28* and **6* polymorphisms were compared (**Figure 2**). The $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$ was 23.009 in the wild-type group. In the single-mutation group, the AUC ratios were 12.837 and 13.247 in **28* heterozygous and **6* heterozygous patients, respectively. In the double-mutation group, the ratios were 3.198 and 3.256 in **6* homozygous and **6/*28* heterozygous patients, respectively.

Table 4 Relationship between adverse events and pharmacokinetic profile during the first cycle of irinotecan treatment

Adverse event	Pharmacokinetic parameter	Spearman's rank correlation ρ (*P* value)
Leukopenia	CPT-11 AUC_{0-inf}	0.463 (<0.001)
	CPT-11 C_{max}	0.384 (0.001)
	SN-38 AUC_{0-inf}	0.542 (<0.001)
	SN-38 C_{max}	0.513 (<0.001)
Neutropenia	CPT-11 AUC_{0-inf}	0.449 (<0.001)
	CPT-11 C_{max}	0.314 (0.017)
	SN-38 AUC_{0-inf}	0.587 (<0.001)
	SN-38 C_{max}	0.59 (<0.001)

AUC, area under the time-concentration curve; C_{max}, peak plasma concentration; CPT-11, irinotecan.

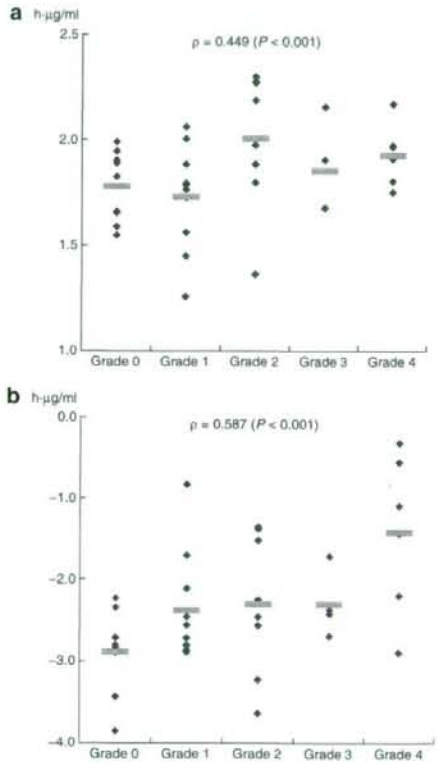

Figure 3 Correlation between neutropenia and pharmacokinetic profile: (**a**) CPT-11 AUC_{0-inf} and (**b**) SN-38 AUC_{0-inf}. The lines indicate geometric mean and the *y*-axis represents the log scale. AUC, area under the time-concentration curve.

The AUC_{SN-38G}/AUC_{SN-38} ratio was highest in the wild-type group, lower in the single-mutation group, and least in the double-mutation group. Although the number of patients was insufficient to establish statistical significance, the AUC_{SN-38G}/AUC_{SN-38} ratios of **6* heterozygous patients were nearly equivalent to those of **28* heterozygous patients, and those of **6* homozygous patients were nearly equivalent to those of **6/*28* heterozygous patients.

The association of *UGT1A1*28* and **6* polymorphisms with grade 3/4 hematological toxicity or AUC ratio was investigated during the first cycle of therapy. Significant correlations were observed between *UGT1A1*28* and **6* polymorphisms and AUC ratio ($P = 0.001$) and between *UGT1A1*28* and **6* polymorphisms and grade 3/4 hematological toxicity (**Table 3**). When the same association was examined through all cycles, a similar correlation between the incidence of grade 3/4 hematotoxicity and polymorphisms was observed (**Table 3**).

The relationship between adverse events and pharmacokinetic profile was further analyzed (**Table 4**). All five parameters correlated well with the frequency of grade 3/4 leukopenia and neutropenia ($P < 0.001$). The correlation between neutropenia and pharmacokinetic profile (CPT-11 AUC_{0-inf} and SN-38 AUC_{0-inf}) is shown in **Figure 3**. Both of these parameters correlated with neutropenia (CPT-11 AUC_{0-inf}: $\rho = 0.449$ ($P < 0.001$), SN-38 AUC_{0-inf}: $\rho = 0.587$ ($P < 0.001$)). The pharmacokinetic parameters of SN-38 appeared to correlate more significantly than those of CPT-11.

DISCUSSION

In this study, CPT-11 was administered on days 1 and 8 every 3 weeks in elderly patients (aged ≥70 years) with NSCLC, and the DLT, MTD, and RD were determined. The efficacy and safety of this regimen were investigated at the RD. In addition, the results were compared prospectively with the results of pharmacokinetic analysis and exploratory analysis of *UGT1A1* gene polymorphisms.

The results showed low antitumor effect for CPT-11 (response rate, 8.1%). The disease control rate was 21.6%. However, the TTP in this study was 132 days. This was longer than that observed in the phase III study we conducted.[13] Although the incidences of grade 3 or higher leukopenia, neutropenia, and anorexia were >20%, other adverse events occurred less frequently, and tolerability was acceptable. Also, the median number of treatment courses was four, and 22% of the patients were able to undergo prolonged treatment (more than eight courses). Almost all the doses of CPT-11 were administered as planned (dose intensity, 90%), and 25 patients were able to proceed to second-line therapy. As a result, an MST of 441 days was achieved. Because the MST was longer than predicted at the start of this study, the median follow-up time was also longer (440 days). These findings suggest that the regimen tested in this study is feasible and appropriate in elderly patients.

The high tolerability of this regimen contrasts with the results of a phase III comparative study of DOC monotherapy vs. VNR monotherapy in elderly patients (West Japan Thoracic Oncology Group Trial 9904)[9] conducted in Japan at around the same time. The response rate of 8.1% in our study was lower than that achieved with DOC monotherapy (22.7% in the West Japan Thoracic Oncology Group study). However, the survival time (14.3 months) was better in our study than that reported

in the West Japan Thoracic Oncology Group study. Moreover, the incidences of grade 3/4 neutropenia and leukopenia were 83 and 58%, respectively, with DOC,[9] which were higher than those in this study. These results indicate that this CPT-11 regimen should be considered as an option for first-line therapy in elderly patients with NSCLC.

To the best of our knowledge, this is the first prospective study with NSCLC patients that has explored the association between *UGT1A1* polymorphisms and the clinical effects of CPT-11 treatment. The $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$ ratios were 23.009 in the wild-type group, 12.837 and 13.247 in the single-mutation group, and 3.198 and 3.256 in the double-mutation group, with the AUC ratio decreasing from wild-type to single-mutation to double-mutation groups. Furthermore, the individual AUC ratios in **6* heterozygous patients were similar to those in **28* heterozygous patients, and those in **6* homozygous patients were similar to those in **6/*28* heterozygous patients, although the number of patients in this study was too small to establish statistical significance.

Among the adverse events occurring during the first course of treatment, a correlation was observed between the incidence of grade 3/4 leukopenia or neutropenia and the AUC and peak plasma concentration of SN-38, as has been reported previously in relation to serious adverse reactions.[17–19] The results also showed that the incidence of grade 3/4 leukopenia and neutropenia was lowest in the wild-type group, higher in the single-mutation group, and highest in the double-mutation group of *UGT1A1*. We consider our classification of polymorphisms of *UGT1A1* as single-mutation and double-mutation appropriate.

The 100 mg/m^2 dose of intravenous CPT-11 on days 1 and 8 every 3 weeks was well tolerated in this prospective phase II study. These results suggest that this CPT-11 regimen should be considered as one of the options for first-line therapy in elderly patients with NSCLC. A phase III study has been scheduled to clarify the effect of *UGT1A1* mutations on response to CPT-11 therapy.

METHODS

Eligibility criteria. Chemotherapy- and radiotherapy-naive patients with histologically or cytologically proven stage IIIB/IV NSCLC were enrolled. Other eligibility criteria included age ≥70 years; measurable and assessable disease; Eastern Cooperative Oncology Group performance status of 0–1; an expected survival duration of ≥12 weeks; adequate bone marrow function (leukocyte count 4,000–12,000/mm^3; hemoglobin concentration ≥9.5 g/dl; platelet count ≥100,000/mm^3); serum creatinine at or below the institutional upper limits of normal level; total bilirubin level ≤1.5 mg/dl; and aspartate aminotransferase and alanine aminotransferase levels ≤100 IU. Laboratory tests were performed within 7 days of enrollment in the study. Exclusion criteria included the presence of symptomatic brain metastasis or apparent dementia; active concomitant malignancy; massive pleural effusion or ascites; active infection; severe heart disease or elevated electrocardiogram abnormality; uncontrolled diabetes mellitus; ileus; pulmonary fibrosis; diarrhea; or bleeding tendency. Written informed consent was obtained from all the participants. Institutional Review Board approval was obtained for the study protocol at each institution.

Treatment schedule. CPT-11 was administered intravenously over 1.5 h on days 1 and 8 of each 3-week cycle. In the phase I study, the starting dose, 60 mg/m^2 (level 1), was increased in 20-mg/m^2 increments to 100 mg/m^2 (level 3). The dosage of 100 mg/m^2 was used as the upper limit because this is the approved dosage for NSCLC in Japan. Dose escalation was carried out on the basis of toxicities encountered during cycle 1 of therapy. A cohort of at least three patients was treated at each dose level. If none of the first three patients experienced DLTs, the dose was escalated to the next level. If one of the three patients experienced DLTs, additional patients were enrolled at the same dose level to a total of at least six patients. The MTD was defined as the dose level below the one at which at least 33% of the patients experienced DLTs, defined as febrile neutropenia (neutrophil count <1,000/mm^3 and fever ≥38.5 °C), grade 4 neutropenia lasting >4 days, grade 3 or 4 leukopenia or anemia, grade 3 or 4 thrombocytopenia, or nonhematological toxicity (except electrolyte abnormality, nausea, anorexia, fatigue, or alopecia). A delay in the second CPT-11 administration of >7 days during the first cycle or >4 weeks between cycles was also categorized as a DLT. The RD was defined as the dose level below the MTD. If the MTD was not achieved at 100 mg/m^2, then 100 mg/m^2 was considered to be the RD because this is the dose that is used in clinical practice for nonelderly NSCLC patients.

Evaluation. In the phase II study, the efficacy and toxicity of CPT-11 monotherapy were evaluated at the RD. Tumor size was assessed by computed tomography at intervals of ≥6 weeks. Tumor response was categorized as CR, PR, stable disease, or progressive disease according to Response Evaluation Criteria in Solid Tumors.[23] Response rate was defined as CR plus PR. Disease control rate was defined as CR plus PR plus stable disease, including "shown no progression for 6 months." In order to be assigned a status of PR, the change in tumor size had to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. As for stable disease, it had to be confirmed by an assessment performed at least once after study enrollment but not earlier than 6 weeks. All tumor assessments were carried out by an investigator, and subsequently reviewed by the external response review committee. Toxicity was graded in accordance with the National Cancer Institute Common Toxicity Criteria, version 2 (ref. 24).

Pharmacokinetic assay. Venous blood for pharmacokinetic analysis was collected in sodium-heparinized and -evacuated tubes on day 1 of cycle 1, before CPT-11 infusion, at the end of infusion, and at 1, 2, 4, 7, and 24 h after infusion. The concentrations of unchanged CPT-11, SN-38, and SN-38G in plasma were determined using high-performance liquid chromatography,[25] and the $AUC_{0\text{-}inf}$ and peak plasma concentration were calculated using WinNonlin Version 4.1 (Pharsight, Mountain View, CA). The AUC ratio of SN-38G to SN-38 ($AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$) was calculated as a surrogate marker for *UGT1A1* activity involved in SN-38 glucuronidation.

UGT1A1 genotyping assay. *UGT1A1* polymorphisms were categorized into three groups: wild-type (**1/*1*), homozygous (**28/*28*, **6/*6*, **28/*6*), and heterozygous (**1/*28*, **1/*6*). Ando *et al.*[26] have reported that serious adverse events are associated with double-heterozygous (**28/*6*) as well as homozygous (**28/*28*, **6/*6*) polymorphisms. Sai *et al.*[27] also showed that the $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$ ratio in patients with **28/*6* was similar to that in patients with **28/*28* and significantly lower than that in patients in the wild-type group.[22] On the basis of these two reports, we defined patients with *UGT1A1*28/*6*—along with those having the homozygous genotype of *UGT1A1*28/*28* or *UGT1A1*6/*6*—as the double-mutation group. Patients with the heterozygous genotype of either *UGT1A1*28* or *UGT1A1*6* were defined as the single-mutation group. Patients with no *UGT1A1*28* or *UGT1A1*6* mutations were defined as the no-mutation group.

Genomic DNA was extracted from the peripheral blood mononuclear cells of the 3 patients who received the RD in phase I and from 33 patients in phase II. One patient did not consent to analysis of *UGT1A1* genotype. For genotyping of *UGT1A1*6* polymorphism, products were amplified by direct PCR sequencing using the primer 5′-AAGTAGGAGAGGGCGAACC-3′ as described in ref. 26. Genotyping for the *UGT1A1*28* polymorphism was performed by subjecting amplified products to gel electrophoresis and determining the product size by migration rate, depending on the number of bases.

Statistical analysis. In the phase II study, the primary end point was the response rate. Secondary end points included survival time and 1-year survival rate. For achieving the ±15% confidence interval under an expected response rate of 25%, a total sample size of 33 patients was calculated as being required for the study.

The 95% confidence interval for treatment response was estimated according to *F*-distribution. Overall survival and cumulative TTP were determined using the Kaplan–Meier method. Overall survival time was calculated from the first day of therapy until the death of the patient or the last day that the patient was known to be alive. TTP was defined as the period from the first day of treatment to the date of (i) first evidence of any toxicity requiring discontinuation of protocol therapy, (ii) progressive disease, or (iii) death.

The Cochran-Armitage trend test was used for analyzing the trend of grade 3/4 adverse events across polymorphism types. Spearman's rank correlation test was used to assess the relationship between the grade of hematological toxicity and the pharmacokinetic profile in the first cycle. In this assessment, the grade according to the National Cancer Institute Common Toxicity Criteria was used as the continuous variable. The association between pharmacokinetic profiles and the type of polymorphism was assessed using the Jonckheere–Terpstra test. All analyses were performed using the SAS software, version 8.2 (SAS Institute, Cary, NC).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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EXPERT REVIEWS

Gefitinib for the treatment of non-small-cell lung cancer

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Gefitinib is an orally bioavailable, EGF receptor tyrosine kinase inhibitor and was the first targeted drug to be approved for non-small-cell lung cancer (NSCLC). Identification of objective tumor regressions with gefitinib in NSCLC patients has resulted in intense, worldwide clinical and basic research directed toward finding the optimal use of gefitinib in NSCLC. A recent large international Phase III study (IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere [INTEREST]) comparing gefitinib and docetaxel in unselected pretreated patients showed equivalent survival with better tolerability and quality of life. In addition, a Phase III study (WJTOG0203) evaluating gefitinib as sequential therapy after platinum-doublet chemotherapy showed the improved progression-free survival time. Furthermore, a large-scale randomized study (IRESSA Pan-Asia study [IPASS]) comparing gefitinib monotherapy with carboplatin/paclitaxel for previously untreated patients with adenocarcinoma who were never- or light-smokers showed an improved progression-free survival time in the gefitinib arm. A smaller Phase III study of pretreated Japanese patients (V-15-32) also demonstrated no difference in overall survival compared with docetaxel, with a statistically greater overall response rate. Somatic mutations in the *EGFR* gene, the target of gefitinib, were associated with dramatic and durable regressions in patients with NSCLC. Currently, investigators are trying to determine the optimal approach to select patients for treatment with gefitinib. This article aims to briefly summarize the profile of gefitinib, *EGFR* mutations, landmark trials with gefitinib and, also, ongoing trials that may herald an era of individualized therapy in at least some NSCLC patients.

KEYWORDS: EGF receptor • *EGFR* gene mutation • gefitinib • non-small-cell lung cancer • tyrosine kinase inhibitor

Lung cancer is the most common cause of cancer deaths worldwide. Lung cancer is divided into two morphological types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC is a distinct clinicopathological entity with a highly aggressive clinical course and neuroendocrine properties. Patients with SCLC are generally more sensitive to a variety of cytotoxic drugs and radiation therapy compared with NSCLC patients. NSCLC, which is less sensitive to chemotherapeutic agents, accounts for over 80% of all lung cancers and NSCLC can be further subdivided by histological type into adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma and others. Adenocarcinoma is the predominant histological subtype and is increasing among patients with lung cancer. Among adenocarcinoma bronchioloalveolar carcinoma is a well-differentiated subtype originating in the peripheral lung that spreads through the airways.

Currently, platinum-based combination chemotherapy regimens, including several active new chemotherapeutic agents, comprise the standard option for patients with advanced NSCLC and good performance status. However, various combinations of drugs have similar efficacy, producing objective response rates of 30–40%, a median survival time of 8–10 months and 1-year survival rates of 30–40% [1–3]. These results remain unsatisfactory and new modalities of treatment are urgently awaited. Recently, novel molecular-targeted strategies that block cancer progression pathways have been suggested as a more cancer cell-specific treatment to control cancer and are considered an exciting therapeutic approach for treating NSCLC [4]. The development of agents that target the EGF receptor (EGFR) signal transduction pathways have provided a class of novel targeted therapeutic agents with improved side-effect profiles compared with conventional chemotherapeutic agents. EGFR is a promising target for anticancer therapy because it is expressed in a variety of tumors, including NSCLC [5]. Furthermore, high levels of EGFR expression have been associated with a poor prognosis in lung cancer patients in several studies.

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EGFR-targeted cancer therapies are being developed currently, and gefitinib (IRESSA®; AstraZeneca, Wilmington, DE, USA) is an orally active, selective EGFR tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells.

Overview of the market

Lung cancer frequently presents at an advanced and biologically aggressive stage, resulting in poor prognosis. Surgery, chemotherapy and radiation have been generally unsatisfactory, especially in the treatment of advanced disease, and new strategies based on better understanding of the biology are clearly needed to improve the treatment efficacy of this fatal disease. The development of agents that target EGFR signal transduction pathways have provided a class of novel targeted therapeutic agents. Different approaches to inhibiting EGFR have resulted in a number of EGFR-targeted agents in clinical development, including small-molecule EGFR TKIs and monoclonal antibodies. The role of cetuximab (Erbitux®), a monoclonal antibody directed at the extracellular domain of the EGFR, and of gefitinib and erlotinib (Tarceva®; OSI Pharmaceuticals, NY, USA), oral, low-molecular-weight ATP-competitive inhibitors of the EGFR's tyrosine kinase domain is under investigation. Anti-EGFR monoclonal antibodies have demonstrated activity in the therapy of advanced colorectal carcinoma [6] and in a variety of epithelial tumor types, including head and neck cancer and NSCLC. A large Phase III study has found that targeted therapy with cetuximab, combined with platinum-based chemotherapy, improves survival outcome as a first-line treatment for patients with advanced NSCLC (overall survival [OS]: 11.3 months vs 10.1 months; $p = 0.044$) [7]. Erlotinib is another TKI with slightly different pharmacologic characteristics from gefitinib. Similar to gefitinib, erlotinib is a potent inhibitor of EGFR autophosphorylation, with a concentration that inhibits 50% in the nanomolar range *in vitro*. Erlotinib is the only EGFR TKI approved based on demonstrating improved survival versus placebo, which was observed in patients with advanced NSCLC who had been treated previously with chemotherapy. The randomized study (BR.21 study) brought erlotinib to registration by the US FDA on November 19, 2004, for the treatment of second- and third-line advanced NSCLC [8]. Other EGFR TKIs are currently under investigation in Phase I/II trials, many of which have differing selectivities for the various members of the human EGFR family. In the near future, gefitinib and erlotinib may face competition from EGFR-specific TKIs, such as EKB-569 (Wyeth, Maidenhead, UK) and CL-387785 (Calbiochem, CA, USA), and EGFR-family TKIs, such as BIBW-2992 (Boehringer Ingelheim, Berkshire, UK), HKI-272 (Wyeth), PKI-166 (Novartis), GW-572016 (GlaxoSmithKline, NC, USA), CI-1033 (Pfizer, MI, USA) and PF-00299804 (Pfizer). The VEGF pathway forms another target for cancer treatment, because the growth of solid tumor is angiogenesis dependent. VEGF and EGF exert their biological effects directly or indirectly on tumor growth and metastasis/invasion, as well as on tumor angiogenesis. The biological effects by VEGF and EGF are mediated through activation of their specific downstream signaling, but both factors also share common downstream signaling pathways. There is, thus, the potential for improved therapeutic efficacy by the combination of both EGF/EGFR-targeting and VEGF/VEGF receptor-targeting drugs, although they have a different side-effect profile. It may also face competition later on from multitargeted TKIs, such as ZD6474 (AstraZeneca), AEE-788 (Novartis) and XL647 (Exelixis Inc., San Francisco, CA, USA). Karaman *et al.* have reported small-molecule kinase interaction maps, which provide a useful graphic overview of how compounds interact with the kinome [9].

Gefitinib: an EGFR TKI

Gefitinib is the first molecularly targeted agent to be registered for advanced NSCLC. In Phase II clinical trials, the selective and orally active EGFR TKI gefitinib produced objective tumor responses and symptom improvement in patients with NSCLC who had previously received chemotherapy (response rates of 12–18% and symptom improvement rates of 40–44% in IRESSA Dose Evaluation in Advanced Lung Cancer [IDEAL]-1 and -2) [10,11]. Partial clinical responses to gefitinib have been observed most frequently in women, never-smokers and patients with adenocarcinomas. The IRESSA Survival Evaluation in Lung Cancer (ISEL) study also showed a survival benefit for gefitinib over placebo in Asian patients and never-smokers [12]. Thus, gefitinib clinical trials have shown that higher response rates and longer survival are associated with specific patient characteristics. Using conventional doublet chemotherapy simultaneously with gefitinib or erlotinib in unselected first-line patients does not increase survival [13–16], but the results of a recent Phase III study showed that gefitinib improves progression-free survival (PFS) as sequential therapy after platinum-doublet chemotherapy [17]. The Phase III IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere (INTEREST) and V-15-32 studies comparing gefitinib and docetaxel in unselected pretreated patients showed no difference in OS, suggesting that gefitinib and docetaxel were equally effective as the second-line therapy [18,19]. In addition, the Phase III IRESSA Pan-Asia study (IPASS) comparing gefitinib monotherapy with carboplatin/paclitaxel showed an improved PFS time in the gefitinib arm [20]. On the other hand, molecular studies have revealed that EGFR-activating mutations and high *EGFR* gene copy number are frequently found in patients who have the best outcomes with EGFR TKIs [21–27]. Currently, investigators are trying to determine the optimal approach to selecting patients for treatment with EGFR TKIs. Gefitinib is the first class of oral targeted therapies to produce such responses in advanced NSCLC and the most studied agent in clinical trials.

Chemistry

Gefitinib, 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline (ZD1839, IRESSA; Figure 1), is an orally active, low-molecular-weight (447 kDa) quinazolin derivative

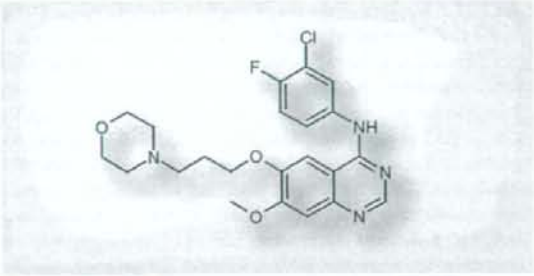

Figure 1. Gefitinib.

with a molecular formula $C_{22}H_{24}ClFN_4O_3$ that specifically inhibits the activation of EGFR tyrosine kinase through competitive binding of the ATP-binding domain of the receptor.

It is readily soluble at pH1 and highly insoluble above pH7. Gefitinib is very stable at room temperature with a proven shelf-life of 36 months [28].

Pharmacodynamics

Gefitinib selectively inhibits the activation of EGFR tyrosine kinase through competitive binding of the ATP-binding domain of the receptor. Selectivity was demonstrated versus HER2 and the VEGF tyrosine kinases, kinase insert domain receptor and Flt-1, with at least a 100-fold difference in IC_{50} for EGFR compared with other tyrosine kinases. Similarly, gefitinib did not inhibit the activity of the serine threonine kinases raf, MEK-1 and ERK-2 (MAPK) [29]. In the Phase I trials, the maximum tolerated dosage was 700 mg/day, although dosages as low as 150 mg/day provided plasma concentrations sufficient for pharmacological activity, evidence of targeted biological effect and anti-tumor activity [30–33]. An analysis of pharmacodynamics marker levels in the skin also provided evidence that sufficient gefitinib was reaching the skin and inhibiting EGFR signaling at 150 mg/day [34]. Additionally, objective tumor responses observed across a dosage range of 150–1000 mg/day indicated that these dosages resulted in target inhibition in tumors. Two large Phase II trials (IDEAL-1 and -2) evaluated 250- and 500-mg/day dosages of gefitinib in patients with advanced NSCLC. As predicted from the Phase I trials, dosages of more than 250 mg/day provided no additional efficacy benefit, whereas adverse effects increased in a dose-dependent manner. Consequently, the recommended dose of gefitinib in NSCLC is 250 mg/day [10,11]. Pharmacodynamic studies indicate that gefitinib blocks cell cycle progression in the G_1 phase by upregulating $p27^{Kip1}$, a cell cycle inhibitor, and downregulating c-fos, a transcriptional activator that is prominent in EGFR-mediated signaling [35]. Elevated levels of $p27^{Kip1}$ block cell cycle progression in the G_1 phase of growth. This sustains the hypophosphorylated state of the *Rb* gene product, which is necessary to keep cells from progressing in the cell cycle [36]. The inhibition of tumor growth seen with gefitinib is also accompanied by decreases in VEGF, basic FGF and TGF-α, all potent inducers of tumor angiogenesis [37]. Thus, gefitinib may also inhibit tumor growth by interfering with angiogenesis. These observations suggest that by inhibiting the EGFR tyrosine kinase, gefitinib treatment alters expression levels of key molecules in tumor cells that are important for stimulating proliferation, cell cycle progression, tumor angiogenesis, metastasis and inhibition of apoptosis. Gefitinib treatment can also cause apoptosis to occur *in vitro*, the frequency of which correlates with the cell line sensitivity to the drug and provides a link with the tumor shrinkage reported clinically [38].

Pharmacokinetics & metabolism

The pharmacokinetic profile revealed that gefitinib is orally bioavailable and suitable for once-daily dosing in cancer patients. In healthy volunteer studies, gefitinib was absorbed moderately slowly, reaching C_{max} 3–7 h after administration. The elimination half-life of 28 h suggests that once-daily oral administration is appropriate [34]. In the initial Phase I studies of gefitinib, sequential skin biopsies were performed prior to and after 4 weeks of therapy [34]. The skin was selected as the target tissue due to its easy access and the established role of the EGFR in renewal of the dermis. Inhibition of EGFR phosphorylation and EGFR-dependent downstream processes was detected at dosages of 150 mg/day, well below the maximal tolerable dosage (MTD) of 700 mg/day. In a clinical study (BCIRG 103), gefitinib (250 mg) was administered orally to breast cancer patients for at least 14 days [39]. Gefitinib concentrations in each tumor sample (mean: 7.5 µg/g) were substantially higher (mean: 42-fold) than the corresponding plasma sample (mean: 0.18 µg/ml). Haura *et al.* conducted a pilot Phase II study of a 28-day preoperative course of gefitinib 250 mg orally, followed by surgical resection for patients with stage IA to selected IIIA NSCLC [40]. Tumor penetration of gefitinib was assessed in surgically resected tumor samples along with plasma assessment on day 28. Day 28 plasma concentrations of gefitinib averaged 531 ± 344 nM (range: 65–1211 nM) while tumor concentrations of gefitinib averaged 33,108 ± 44,312 nM (range: 74–134,669 nM). These results also demonstrate that NSCLC tumor penetration of gefitinib is high, as its tumor concentrations were much higher than concentrations found in plasma.

Gefitinib is metabolized extensively by expressed cytochrome P450 (CYP)3A4, producing a similar range of metabolites to liver microsomes, while CYP3A5 produced a range of metabolites, similar to CYP3A4 but to a much lower degree [41,42]. By contrast, CYP2D6 catalyzed rapid and extensive metabolism of gefitinib to desmethyl-gefitinib (M523595). While formation of M523595 was CYP2D6 mediated, the overall metabolism of gefitinib was dependent primarily on CYP3A4. Quantitatively, the most important routes of gefitinib metabolism were mediated primarily by CYP3A4, while CYP3A5 and CYP2D6 were minor contributors. The wide variability in CYP3A4 activity in human liver is probably a significant factor in the interindividual variability observed in gefitinib pharmacokinetics. Gefitinib has interactions with CYP3A4 inducers, or CYP3A4 enzyme inhibitors or substrate of CYP2D6 (gefitinib inhibits CYP2D6 activity) or H2 blockers. Pharmacokinetic studies have shown that the bioavailability of gefitinib is unaffected by food intake to any clinically significant extent [43].

Clinical efficacy

Several challenges were encountered in designing the clinical trials of gefitinib, because this agent was expected to be cytostatic rather than cytotoxic. These challenges included a scarcity of precedents, the way in which 'biological activity' was defined, the integration of outcomes across multiple tumor types in Phase I trials, the relationship between biological activity and clinical outcome, and unknown pharamakokinetic and pharmacodynamic relationships. Initially, clinical trials of gefitinib were performed principally in unselected patient populations with NSCLC. However, recent results indicate that different patients derive different degrees of clinical benefit from treatment with gefitinib. The identification of the patients who are most likely to derive clinical benefit from gefitinib is of paramount importance.

Phase I

As biologically targeted agents are expected to provide clinical benefits that are not predicted by surrogate end points of toxicity to normal replicating tissue, new Phase I trials have been designed to determine the optimum biological dose for use in further studies. Initial Phase I trials performed in healthy volunteers showed that oral administration of gefitinib given once on day 1 (50, 100, 250 or 500 mg) or daily for 14 days (100 mg/day) was feasible [44]. Four multicenter Phase I trials then evaluated the safety profile of gefitinib (50–1000 mg/day) in more than 250 patients with a wide range of solid tumors that were known to express EGFR, although baseline EGFR expression levels were not determined [30–32,45]. Adverse events (AEs) occurred at dosages of 50 mg/day, with the most commonly reported AEs being mild-to-moderate acne-like rash, diarrhea, nausea, anorexia, vomiting and asthenia. The frequency of AEs, such as skin rash and diarrhea, increased with dose, and the MTD was identified as 700 mg/day. Clinical benefit was not dose-related, whereas the most common AEs (skin rash and acne) increased with gefitinib dose. In addition, pharmacokinetic studies indicated that plasma levels of gefitinib over this dose range were sufficient for effective EGFR inhibition. Although the lowest dose at which objective tumor responses were observed was 150 mg/day, there was potential for individuals receiving this dose to have subtherapeutic exposure as a result of interpatient variability in pharmacokinetics. Accordingly, the slightly higher dosage of 250 mg/day was chosen. The second dosage chosen was 500 mg/day, which was the highest dosage that was well tolerated by most patients on a daily dosing schedule. Both dosages were significantly lower than the MTD, unlike conventional dosage selection for chemotherapy agents, which would use the MTD.

Phase II

Large-scale dose-evaluation study

Two large, dose-randomized, double-blind, parallel-group, multicenter Phase II trials (IDEAL-1 and -2) independently evaluated the activity of gefitinib 250 and 500 mg/day in 425 patients with advanced NSCLC [10,11]. These trials allowed a more detailed evaluation of the doses selected from the Phase I trials and included symptom improvement as an additional end point. In IDEAL-1, conducted mainly in Europe and Japan, patients with one or two prior chemotherapy regimens, including a platinum compound, were randomly assigned to receive gefitinib at 250 or 500 mg/day. Response rate approached 20% and was similar in both arms, and symptom improvement was 40%, which was higher in patients who had an objective response. Adverse effects were, in general, well tolerated, but were more severe with the 500-mg dose. In IDEAL-2, the study was performed in 30 centers in the USA. In total, 221 patients were randomly assigned to receive either gefitinib 250 or 500 mg daily. A total of 126 patients (58%) had three or more regimens in the past and 65% had histology of adenocarcinoma. Symptoms of NSCLC improved in 43% of patients receiving gefitinib 250 mg and in 35% of those receiving 500 mg. There was no significant difference in response rate or survival between the two doses. There was a good correlation between clinical response and symptomatic improvement. However, the gefitinib 500-mg dose was more toxic as it induced more acne-like rash and diarrhea. In conclusion, gefitinib was well tolerated at 250 mg/day and it induced anti-tumor activity in approximately 10% of patients. These results are impressive compared with chemotherapy, which induces far more adverse effects and, probably, even a lower level of activity.

Gefitinib as first-line treatment

In East Asia, Phase II trials of gefitinib as first-line therapy have demonstrated good response rates of 30% compared with those in patients of non-East Asian origin (<10%) [46–51]. In a prospective Phase II trial of chemotherapy-naive patients with advanced NSCLC conducted in Japan, 40 patients treated with first-line gefitinib were evaluated for response. Partial response was seen in 12 (30%) patients [47]. Response to gefitinib in studies of non-Asian patients have been shown to be much lower than in studies of Asian patients. In a study in the USA, response rate among 70 patients with advanced NSCLC and poor performance status (2 or 3) was 4% [50]. In Germany, response rate among 58 patients with inoperable advanced NSCLC and good performance status (0–2) was 5% [49]. Results from IRESSA in NSCLC versus Vinorelbine Investigation in the Elderly (INVITE) reported no statistical difference between gefitinib and chemotherapy first-line for median PFS rates (2.7 vs 2.9 months, respectively) or overall response rates (3.1 vs 5.1%, respectively) [52,53]. Iressa NSCLC Trial Evaluating Poor Performance Patients (INSTEP) reported a response rate of 6% and a trend toward improved efficacy end points with gefitinib first-line compared with placebo, with similar improvements in quality of life and symptoms in Western patients with poor performance status [54]. See Table 1 for a detailed list.

Gefitinib therapy in selected patients

Table 2 lists several reports on gefitinib sensitivity in selected patients [55–66]. In 2004, several investigators reported that somatic mutations in the gene for the EGFR [21–23], the targets

Table 1. Phase II studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Gefitinib in the second- and third-line treatment of advanced NSCLC							
Fukuoka *et al.* (IDEAL-1)	Gefitinib 250 mg daily	103	18.4	2.7	7.6*	Randomized Phase II trial conducted mainly in Europe and Japan	[10]
	Gefitinib 500 mg daily	105	19.0	2.8	8.0		
Kris *et al.* (IDEAL-2)	Gefitinib 250 mg daily	102	12.0	NA	7.0**	Randomized Phase II trial conducted in the USA	[11]
	Gefitinib 500 mg daily	114	9.0		6.0		
Gefitinib in the first-line treatment of patients with NSCLC							
Goss *et al.* (INSTEP)	Gefitinib	100	6.0			Randomized Phase II trial in patients with poor performance status; modest benefit seen with gefitinib	[54]
	Placebo	101	1.0				
Crino *et al.* (INVITE)	Gefitinib	97	3.1	2.7		Randomized Phase II trial in elderly patients; similar efficacy observed	[52]
	Vinorelbine	99	5.1	2.9			
Niho *et al.*	Gefitinib 250 mg	40	30.0	NA	13.9		[47]
Lin *et al.*	Gefitinib 250 mg	53	32.1	3.2	9.4		[46]
Suzuki *et al.*	Gefitinib 250 mg	34	26.5		14.1		[48]
Reck *et al.*	Gefitinib 250 mg	58	5.0	1.6	6.7		[49]
Spigel *et al.*	Gefitinib 250 mg	70	4.0	3.7	6.3	Patients with poor performance status	[50]
Swinson *et al.*	Gefitinib 250 mg	41	10.0	1	2.7	Patients unsuitable for chemotherapy	[51]
Gefitinib compared with docetaxel in the second-line treatment of advanced NSCLC							
Cufer *et al.* (SIGN)	Gefitinib 250 mg	68	13.2	3.0	7.5***	Open label,randomized Phase II study; fewer drug-related side effects with gefitinib	[114]
	Docetaxel 75 mg/m²	73	13.7	3.4	7.1		

*p = NS.
**p = 0.40.
***p = 0.88.
HR: Hazard ratio; IDEAL: IRESSA Dose Evaluation in Advanced Lung Cancer; INVITE: Iressa in NSCLC versus Vinorelbine Investigation in the Elderly; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; PFS: Progression-free survival.

of gefitinib, were associated with dramatic and durable regressions with gefitinib in patients with NSCLC. To confirm the encouraging but retrospective results of early studies, multiple groups undertook prospective Phase II trials of gefitinib in patients found to have an *EGFR* mutation on screening. To date, at least nine studies have been reported [55–63]. Collectively, these showed that nearly 80% of patients whose tumors had either exon 19 deletions or L858R mutations had radiographic responses to gefitinib, although responses varied between different trials. The combined analysis of seven prospective trials conducted in Japan, which examined the efficacy and safety of gefitinib monotherapy for NSCLC with *EGFR* mutations, has been reported. In this study, Morita *et al.* updated OS and PFS data for the combined survival analysis and examined prognostic factors for OS and PFS (I-CAMP study) [67]. A total of 148 patients were combined from the seven trials and median OS and PFS of 24.3 months and 9.7 months weer reported, respectively. The combined response rate was 76.4%, and only 6% of the patients had progressive disease. They concluded that gefitinib produces significant anti-tumor activity and prolonged survival in this selected NSCLC population. A prospective Phase II study has also demonstrated that gene copy number assessed by fluorescent *in situ* hybridization (FISH) [25] may predict clinical outcome in TKI-treated NSCLC patients. In advanced bronchioloalveolar carcinoma, a distinct subtype of adenocarcinoma, gefitinib was clinically active in both chemotherapy-naive and pretreated patients [65,66].

Phase III

Gefitinib in combination with chemotherapy

The IRESSA NSCLC Trial Assessing Combination Treatment (INTACT)-1 and -2 studies were large randomized studies of two dosages of gefitinib (250 or 500 mg/day), or placebo, in combination with two different chemotherapy regimens [13,14]. INTACT-1 used cisplatin and gemcitabine (cisplatin 80 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8 every

Table 2. Phase II studies of gefitinib in selected patients.

Author	Selection	Patients (n)	Response rate (%)	TTP/PFS (months)	MST (months)	1-year survival (%)	Ref.
EGFR selected							
Inoue *et al.*	Mutation	16	75	9.7	NR	NR	[55]
Sutani *et al.*	Mutation	27	78	9.4	15.4	NR	[56]
Asahina *et al.*	Mutation	16	75	8.9	NR	88	[57]
Sunaga *et al.*	Mutation	19	84	13	NR	NR	[58]
Yoshida *et al.*	Mutation	21	90	7.7	NR	NR	[59]
Tamura *et al.*	Mutation	28	75	11.5	NR	79	[60]
Sugio *et al.*	Mutation	16	50	8.8	15.4	NR	[61]
Sequist *et al.* (iTARGET)	Mutation*	31	55	9.2	17.5	73	[62]
Yang *et al.*	Mutation†	43	84	8.9	24		[63]
	Mutation‡	12	16	2.1	6.7		
Cappuzzo *et al.* (ONCOBELL)	FISH	42	48	6.4	NR	64	[25]
Never-smokers							
Lee *et al.*		72	55	5.5	19.7	76	[64]
Cappuzzo *et al.*	Never smoker or FISH)	42	48	6.4	NR	64	[25]
Bronchioloalveolar carcinoma							
West *et al.*		101	17	4	13	51	[65]
Cadranel *et al.*		88	13	2.9	13.3	55	[66]

*EGFR mutations were primarily exon 19 deletions (53%) and L858R (26%), although 21% of mutation-positive cases had less-common subtypes, including exon 20 insertions, T790M/L858R, G719A and L861Q.
†Del 19 or L858R.
‡Other mutations.
EGFR: EGF receptor; MST: Median survival time; NR: Not reported; PFS: Progression-free survival time; TTP: Time to progression.

3 weeks), whereas INTACT-2 used carboplatin and paclitaxel (carboplatin given at AUC of 6 and paclitaxel at 225 mg/m^2 in 3-h infusions every 3 weeks). Chemotherapy was administered for up to six cycles and gefitinib or placebo were continued in nonprogressing patients until progression. A total of 1093 and 1037 patients were entered, respectively, in the two studies in less than 1 year of accrual. These two large randomized studies failed to demonstrate a survival increase with the addition of gefitinib to standard chemotherapy in first-line treatment of advanced NSCLC. A subset analysis of patients with adenocarcinoma who received 90 days of chemotherapy or more in the INTACT-2 study demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect. In general, treatment was well tolerated and the toxicity of chemotherapy did not overlap with gefitinib treatment, which made the studies feasible. However, as expected, gefitinib 500 mg was associated with a higher degree of toxicity, as observed in the IDEAL studies, which led to more dose reductions and treatment interruptions. In none of these studies were patients selected based on EGFR expression or any other marker of efficacy, and this lack of patient selection may have caused the lack of positive outcome. In addition, the antagonistic effect of EGFR TKIs may also halt cells in the G_1 phase of their cycle and, therefore, render them insensitive to chemotherapy. Interestingly, however, the time-to-progression curves and survival curves suggest that maintenance EGFR inhibition may be helpful after termination of chemotherapy. These considerations would suggest that sequential therapies are the best approach to this disease for front-line therapy.

The Southwest Oncology Group trial, SWOG0023, was designed to deliver gefitinib after completion of chemoradiotherapy and consolidation chemotherapy, avoiding a potentially negative interaction with chemotherapy. In this randomized, placebo-controlled trial in unresectable stage III NSCLC, gefitinib maintenance therapy failed to show a survival advantage in an unplanned interim analysis; the inferior survival observed in the gefitinib arm raises the possibility of a deleterious effect [68]. The reasons for this result remain unclear. Recently,

Hida *et al.* reported the results of a randomized Phase III trial (WJTOG0203), which evaluated whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in advanced NSCLC (stage IIIb/IV) [17]. In this study, sequential gefitinib following dual platinum-based induction therapy improved PFS (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.57–0.80; $p < 0.001$), with a trend toward improved overall survival ($p = 0.10$). Furthermore, a prespecified subset analysis showed that gefitinib significantly increased overall survival for patients with adenocarcinoma (n = 467; HR: 0.79; 95% CI: 0.65–0.98; $p = 0.03$) and for smokers (n = 410; HR: 0.79; 95% CI: 0.64–0.98; $p = 0.03$). However, gefitinib failed to show a significant survival advantage in patients with nonadenocarcinoma. These results demonstrate a possible clinical benefit for sequential therapy of gefitinib, especially in adenocarcinoma histology. Regarding the maintenance effects, although no benefit with concurrent EGFR TKI was seen in response rate, PFS or OS in the INTACT 2 and Tarceva responses in conjunction with paclitaxel and carboplatin (TRIBUTE) trials, landmark analyses of them favored patients receiving single-agent TKI maintenance therapy after completion of chemotherapy (Table 3) [14,15].

Gefitinib versus best supportive care

In the ISEL study, 1692 patients from 28 countries (not including Japan) were randomized to receive gefitinib 250 mg/day versus placebo [12]. Approximately 20% of the patients included in the study were Asians. Among the subjects, 1129 were assigned to the gefitinib group and 563 to the placebo group. Although the response rate was similar to that observed with erlotinib in BR.21 [8], in the ISEL study, gefitinib failed to prolong survival in comparison with placebo in the overall population. As for the differences in the ISEL and BR.21 patient populations, 90% of the patients in ISEL were chemorefractory, while patients in BR.21 were not required to be refractory to their previous treatment [8,12]. Median survival was 5.6 months for gefitinib and 5.1 months for placebo ($p = 0.08$; HR: 0.89; 95% CI: 0.77–1.02). Among the 812 patients with adenocarcinoma, median survival times were 6.3 and 5.4 months, respectively ($p = 0.09$; HR: 0.84; 0.49–0.92). However, gefitinib prolonged survival in never-smokers (median survival time [MST]: 8.9 vs 6.1 months; $p = 0.012$) as well as in Asian patients (MST: 9.5 vs 5.5 months; $p = 0.01$) in preplanned subset analyses. Based on these results, the FDA limits the indication of gefitinib to cancer patients who are currently benefiting or have previously benefited from gefitinib treatment or are enrolled in clinical trials as of June 2005.

Gefitinib versus chemotherapy in pretreated advanced NSCLC

Recently, the results of two large Phase III studies were reported (INTEREST and V-15-32). The INTEREST trial compared gefitinib with docetaxel as the second- or third-line therapy in 1466 advanced NSCLC patients with prior treatment of platinum-based chemotherapy [18,69]. Noninferiority of gefitinib in OS was demonstrated (MST: 7.6 vs 8.0 months; HR: 1.020; 95% CI: 0.905–1.150). The one point that should be highlighted in this study is that all of the predictors of efficacy identified in the gefitinib versus placebo studies, including adenocarcinoma, women, Asian and never-smoker, disappear in the comparison with the docetaxel group. The results suggest that these clinical characteristics may be efficacy predictors for docetaxel as well as gefitinib. Gefitinib and docetaxel were equally effective as the second-line therapy for advanced NSCLC patients but gefitinib resulted in an improved quality of life and less toxicity compared with docetaxel. Recently, Douillard *et al.* reported that OS was equally improved with both gefitinib or docetaxel treatments in *EGFR* mutation positive patients compared with *EGFR* mutation-negative patients [69]. On the other hand, PFS was longer with gefitinib than docetaxel in mutation-positive patients [69]. In the V-15-32 trial, however, noninferiority of gefitinib was not demonstrated [19]. The V-15-32 trial, almost identical to the INTEREST trial comparing gefitinib with docetaxel, was a comparative study of 489 patients that was conducted in Japan. The response rate in the gefitinib group was approximately twice as high as in the docetaxel group, but it was impossible to demonstrate noninferiority in OS of gefitinib compared with docetaxel. The survival rate at an early stage, such as less than 1 year, and the CI for therapeutic effects indicated that docetaxel was better than gefitinib. While noninferiority in OS between gefitinib and docetaxel was not demonstrated according to predefined criteria, there was no statistically significant difference in survival between the two arms. This discrepancy in survival between the INTEREST and V-15-32 could be attributable to the smaller patient numbers and imbalances in poststudy treatments in the V-15-32 trial (36% in the gefitinib vs 53% in the docetaxel arm had switched over to the opposite treatment after discontinuation of the study treatment). These two studies established the fact that gefitinib is better tolerated than docetaxel with less toxicities and better quality of life. Recently, Lee *et al.* reported the results of randomized Phase III study (Iressa as Second line Therapy in Advanced NSCLC-Korea [ISTANA]) conducted in Korea [70]. They concluded that PFS was longer with gefitinib compared with docetaxel ($p = 0.04$).

Gefitinib versus chemotherapy as first-line therapy in NSCLC

The result of IPASS has been reported [20]. This large-scale randomized study, which compared gefitinib monotherapy with carboplatin/paclitaxel for previously untreated patients with adenocarcinoma who were never- or light-smokers, was started in April 2004. The results showed improved PFS time in the gefitinib arm; however, the HR was constant over time, initially favoring the carboplatin/paclitaxel arm and later favoring the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. Results of this pivotal trial might establish the role of gefitinib as the first-line therapy in selected patients with advanced NSCLC (Table 3).

Randomized trials currently in progress

At present, the West Japan Oncology Group is conducting a multicenter clinical trial (WJTOG3405) that targets progressive/recurrent lung cancer patients with *EGFR* gene mutations