chemotherapy, but the disease remains incurable. Usually a platinum-containing regimen is chosen. For ED SCLC, the MST is less than one year with currently available chemotherapy, and long-term survivors are still rare [4,5].

Furthermore, the prognosis is exceedingly poor for patients who receive second-line therapy after relapse. Response is influenced by the time to progression after cessation of first-line therapy. Patients who relapse less than three months after the completion of first-line therapy are termed refractory; they have response rates that are lower than for those patients who relapse more than three months after therapy, who are termed sensitive. The objective for these patients is palliation and increased quality of life, and therefore salvage therapy should be limited to patients with a good performance status (PS) and without significant comorbidities [3].

A water soluble derivative of camptothecin, irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor, has been synthesised for use in chemotherapy. The chemical structures of irinotecan and its major metabolites found in plasma are shown in Figure 1. Irinotecan is converted by hepatic and peripheral carboxylesterase to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN38). This is subsequently glucuronidated by hepatic uridine diphosphate glucuronosyl transferase-1A1 (UGT 1A1), the enzyme responsible for bilirubin glucuronidation with multi-genetic variants, to SN38-glucuronide (SN38G) [6]. The patient with UGT1A1*28 has an impaired capacity for glucuronidation of SN-38, increased exposure to SN-38, and there is increased clinical toxicity when treated with irinotecan. To measure UGT1A1*28, in August 2005, FDA in the US cleared the Invader Molecular Assay for irinotecan dosing. However, irinotecan activity is not determined by the product of one gene [7]. Irinotecan, SN-38 and SN-38 glucuronide (SN-38G) may be shunted out of the cell via members of the ATP-binding cassette transporters [8]. The metabolism and pharmacogenetics of irinotecan is beyond the scope of this review, but there are some excellent reviews on this subject [9-11].

It should be cautioned that there are drug–drug interactions [12] with irinotecan. Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in patients receiving the CYP3A4 enzyme-inducing anticonvulsants phenyntoin, phenobarbital or carbamazepine [13]. Rifampin, rifabutin and St. John's Wort are also CYP 3A4 inducers [14,15]. St. John's Wort is contraindicated during irinotecan therapy. Ketoconazole, a strong inhibitor of CYP3A4 [16], and contraindicated during irinotecan therapy, should be discontinued in patients at least one week prior to starting irinotecan therapy.

In Japan, 1245 cancer patients received irinotecan as a single agent in Phase I or Phase II trials that were conducted to obtain approval for commercial use from the Ministry of Health, Labour and Welfare. Of the 1245 patients, 55 (4.4%) died from toxicities of irinotecan, mainly myelosuppression and/or diarrhoea [17].

· The onset of diarrhoea can occur early or be delayed beyond 24 h after injection of irinotecan. Early-onset diarrhoea is a cholinergic effect. Anticholinergic drugs, such as atropine, seem to easily reverse this side effect. Late-onset diarrhoea represents the dose-limiting toxicity (DLT) of irinotecan; it can be severe and life-threatening, especially in combination with neutropenia. Late-onset diarrhoea is treated with loperamide, and identification of high-dose loperamide as an effective remedy for this toxic effect greatly facilitated development of irinotecan [18,19]. These studies established the usefulness of high-dose loperamide. Patients should be instructed to take high-dose loperamide at the first onset of any irinotecan-associated late-onset diarrhoea that has occurred at least 12 h after drug administration. This therapy has been widely used for the management of diarrhoea caused by irinotecan.

For the treatment of SCLC, initial irinotecan is usually administered on days 1 and 8 every 3 weeks or on days 1, 8 and 15 every 4 weeks. The dose ranges from 50 to 70 mg/m^2 when administered weekly. As an example of the dose modification of irinotecan, Kudoh et al. [20] used the following dose modification: irinotecan is not given on days 8 or 15 if the leukocyte or platelet counts were < 3000/µl or < 75,000/µl, respectively. It is also withheld if the patient develops diarrhoea of grade 2 (increase of 4 – 6 stools/day, or nocturnal stools) or worse (grade 3: increase of > 6 stools/day or incontinence; grade 4: physiological consequences requiring intensive care). The next course of treatment can only be initiated if the leukocyte count is ≥ 4000/µl, the platelet count is ≥ 10,000/µl, serum creatinine is less than the upper limit of normal, and diarrhoea has been resolved. There is no dose modification for the leukocyte count, platelet count or diarrhoea during the same course. The dose of irinotecan in the next course was reduced by 10 mg/m^2 if the leukocyte count was < 2000/µl, the platelet count was < 50,000/µl, or diarrhoea was grade 3 to 4. This dose modification was applied in most studies with minor variation. For example, in some studies, the delay in the irinotecan doses was applied when the leukocyte count was < 2000/µl [21] instead of 3000/µl.

Another available topoisomerase-I inhibitor, topotecan, has achieved response rates of up to 22% in previously treated patients with SCLC and survival almost double that achieved with other single agents. Compared with cyclophosphamide/doxorubicin/vincristine (CAV), single-agent topotecan achieved a higher response rate, longer survival and statistically significant improvements in dyspnoea, hoarseness, fatigue, anorexia and interference with daily activities [22,23]. The incidence of grade 3 – 4 diarrhoea was extremely low (1%). The clinical comparison of these two topoisomerase-I inhibitors has not been tried. This review focuses mainly on the recent results of irinotecan in the treatment of SCLC in connection with patient safety considerations.
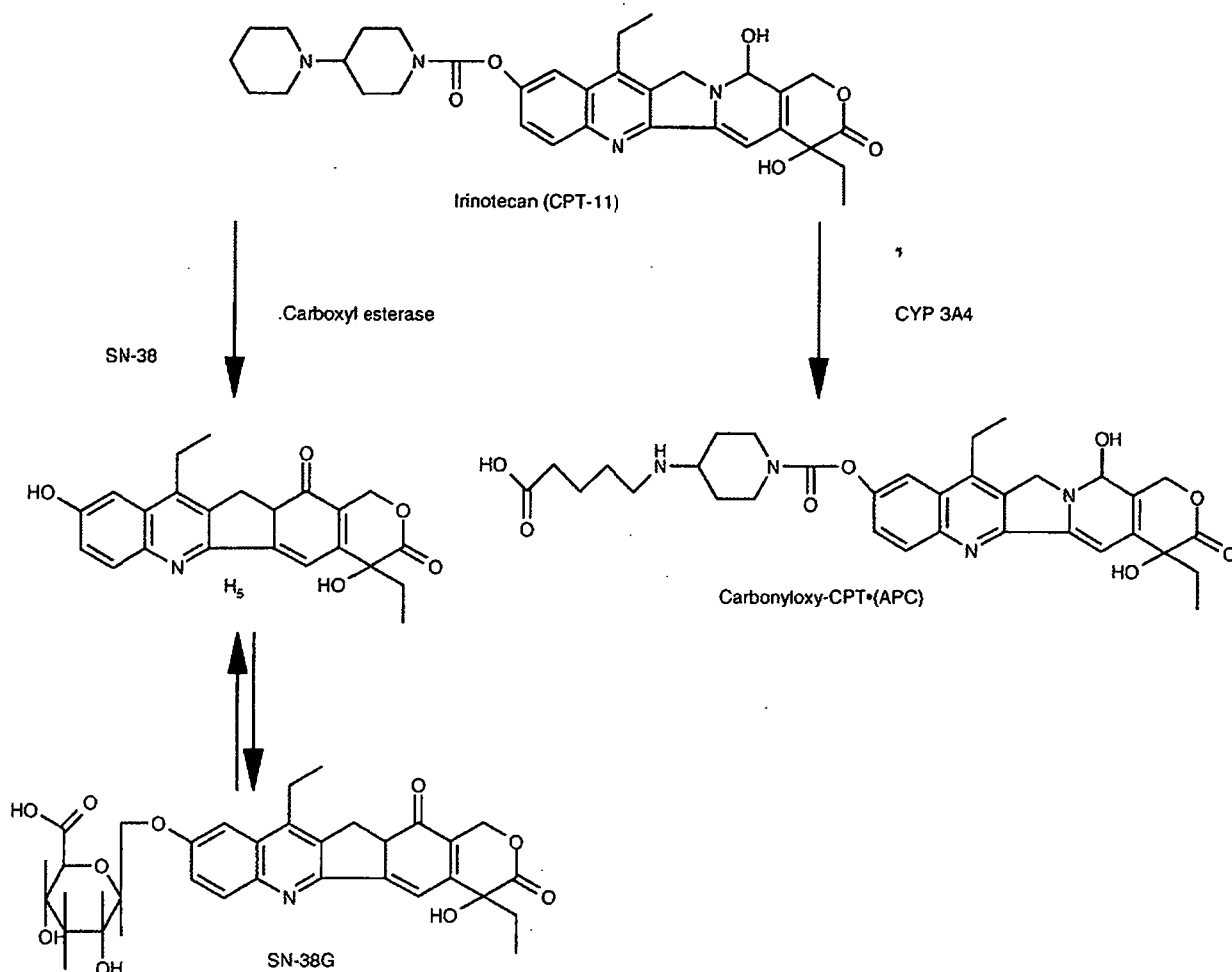

Irinotecan (CPT-11)

.Carboxyl esterase

CYP 3A4

SN-38

H_s

Carbonyloxy-CPT•(APC)

SN-38G

Figure 1. Metabolism of irinotecan. Chemical structures of CPT-11 and its major metabolites.

2. Irinotecan containing regimens as front-line treatment

2.1 Irinotecan plus cisplatin for ED SCLC

Clinically, irinotecan was proved to be effective against SCLC [24]. Negoro *et al.* have demonstrated that 13 (37%) out of 35 patients responded, including 33% of previously treated patients and 50% of chemotherapy-naive patients. In a Phase II trial of irinotecan for previously treated SCLC, the response rate was 47% out of 16 patients [25].

IP was tested in a Phase II trial for patients with previously untreated SCLC [20]. A total of 40 patients (53%) had LD and 35 patients (47%) had ED. Initially, irinotecan 80 mg/m² over 90-minutes infusion was given on days 1, 8 and 15, and cisplatin 60 mg/m² was given every 4 weeks. After 3 of the initial 10 patients experienced severe haematological toxicity, diarrhoea and hepatic toxicity, and one patient died of diarrhoea and neutropenia, the irinotecan dose was reduced to 60 mg/m². The response rate was 84%, with a complete response rate of 29%. The MST was 14.3 months for LD

patients and 13.0 months for ED patients, an encouraging result. Although the survival of LD was not increased significantly, this may be due to the small number of LD SCLC patients accrued. This study prompted a Phase III study of the Japan Clinical Oncology Group (JCOG 9511).

The JCOG conducted a multi-centre, randomised, Phase III study which compared irinotecan plus cisplatin with etoposide plus cisplatin (EP) in patients with ED SCLC (JCOG 9511) (Figure 2) [26]. IP consisted of four 4-week cycles of 60 mg/m² of irinotecan on days 1, 8 and 15, and 60 mg/m² of cisplatin on day 1. The regimen of etoposide and cisplatin consisted of four 3-week cycles of 100 mg/m² of etoposide on days 1, 2 and 3, and 80 mg/m² of cisplatin on day 1. The delivered dose intensity for irinotecan was 80%. The results are listed in Table 1. This study was terminated early because an interim analysis found a statistically significant difference in survival between the two arms. The MST was 12.8 months in the IP arm and 9.4 months in the EP arm (p = 0.002). At two years, the proportion of patients surviving was 19.5% in the IP group and 5.2% in the EP

Table 1. IP versus EP in phase III studies.

	IP	EP	p-value	IP	EP	p-value
	JCOG9511 study [26]			*Hanna's study* [27]		
	(n = 75)	(n = 77)		(n = 210)	(n = 104)	
Irinotecan: delivered dose intensity	80%			90%		
Survival						
Median survival time (months)	12.8	9.4	0.002	9.3	10.2	0.6226
1-year survival (%)	58.4	37.7		35.4	36.7	
2-year survival (%)	19.5	5.2		8.0	7.9	
Haematological						
Neutropenia	65.3	92.2	< 0.001	36.2	86.5	< 0.0001
Anaemia	26.7	29.9	0.72	4.8	11.5	< 0.0268
Thrombocytopenia	5.3	18.2	0.002	4.3	19.2	< 0.0001
Nonhaematological				(n = 216)	(n = 106)	
Diarrhoea	16	0	< 0.001	21.3	0	0.0001
Response				(n = 221)	(n = 110)	
Complete response	2.6	9.1		3.6	2.7	
Partial response	81.8	58.4		44.3	40.9	
Overall response	84.4	67.5	0.02	48.0	43.6	
Stable disease	2.6	20.8		4.1	7.3	
Progressive disease	3.9	11.7		20.0	20.0	
Not evaluable	6.5	0		28.1	29.1	

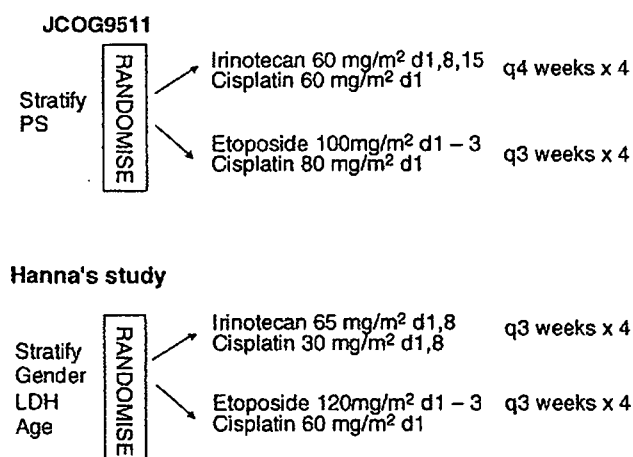EP: Etoposide and cisplatin; IP: Irinotecan and cisplatin.

Figure 2. Two Phase III randomised trials.
LDH: Lactate dehydrogenase.

group. This was the first study to show the superiority of any one regimen over etoposide plus cisplatin for the front-line treatment of ED SCLC, and IP has become one of the standard regimens for ED SCLC in Japan. Severe myelosuppression

was more frequent in the EP group than in the IP group. On the other hand, severe diarrhoea was more frequent in the IP arm than in the EP arm. Despite the dose modifications, major deviations from the protocol resulted in failure to reduce the dose of chemotherapy (in 6 patients); administration of irinotecan despite the presence of grade 1 (increase of < 4 stools/day) or 2 diarrhoea (in 9 patients); continuation of the study treatment despite grade 2 to 3 pulmonary toxicity (in 3 patients); and continuation of the treatment despite grade 3 hepatic toxicity (in 1 patient). There were 3 treatment-related deaths in the IP arm; one patient died of bleeding from a metastatic site in the lung, another patient died of sepsis associated with neutropenia and diarrhoea, and the third patient died of pneumonia associated with neutropenia. These three treatment-related deaths in the IP arm occurred during the first or second cycle of treatment and were attributed to haematological toxicities of the first cycle. This may indicate that severe haematological toxicities, as well as diarrhoea, during the first cycles of chemotherapy should be managed carefully. All cases of grade 1 to 4 diarrhoea occurred during the first and second cycles of the IP arm but early suspension of treatment may have prevented death associated with diarrhoea in all but one patient, which

involved a protocol violation because the patient was given irinotecan on day 8 of the first cycle despite the presence of grade 1 diarrhoea. This suggests that irinotecan should not be administered to patients with any degree of ongoing diarrhoea above their baseline.

Confirmatory studies are underway; currently, there is only one concluded study showing IP superiority, but it had a small sample size. Additionally, pharmacogenomic differences may exist between Japanese and Western populations.

Hanna et al. presented a Phase III trial comparing IP with EP in patients with previously untreated ED SCLC at the ASCO meeting in 2005 (Figure 2, Table 1) [27]. This was designed to confirm the JCOG9511 trial. However, the dose and schedule were modified to increase dose intensity.

The IP arm consisted of cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 on days 1 and 8 every 3 weeks. The EP arm was cisplatin 60 mg/m^2 on day 1, and etoposide 120 mg/m^2 on days 1 – 3 every 3 weeks for 4 cycles, or disease progression, or intolerable toxicity. This was planned to improve tolerability, achieve greater dose intensity and maintain or improve efficacy. The 336 patients were stratified by gender, lactate dehydrogenase level and age, and were randomised in a 2:1 fashion, with 221 treated with IP (median age, 63 years; range, 37 – 82 years; male, 57.5%) and 109 to EP (median age, 62 years; range, 38 – 83 years; male, 57.3%). Baseline characteristics were well balanced across the 2 arms, with a high representation of PS of 0 or 1 (IP, 92.3%; EP, 88.2%). After 30 patients with PS 2 were enrolled, study amendment excluded PS 2 patients. Delivered dose intensity of irinotecan was 39 mg (94%), higher than that of the JCOG9511 trial (80%). In both arms, 65% of patients received 4 or more cycles. Selected grade 3 or 4 toxicities in IP versus EP arm were: diarrhoea (21 versus 0%), neutropenia (35 versus 84%), febrile neutropenia (4 versus 11%). Grade 3 or 4 haematological toxicities were significantly more common with EP than IP. There was a trend towards more febrile neutropenia in the EP arm (10 versus 4%), and significant differences were seen in rates of dehydration (13 versus 3%; p = 0.15), vomiting (13 versus 4%; p = 0.0445), and diarrhoea (21 versus 0%; p < 0.0001). The survival of EP in both trials was similar (MST: 10.2 months in this study and 9.4 months in the JCOG9511 trial). However, the MST of IP was 9.3 months in this trial and 12.8 months in the JCOG9511 trial. Differences in outcome of this study from the JCOG trial may be due to pharmacogenomic or patient characteristic differences, or a change in the dose/schedule of IP. Pharmacogenomic studies among ethnic populations are needed to address this issue. It is likely that IP will prove to be at least as effective as other treatments for patients with ED SCLC.

Other Phase III trials will clarify these issues, including a SWOG S0124-randomised Phase III trial with the dose and schedule of each arm the same as the JCOG9511 trial, and a Phase III study started in June 2002 – (NCT00143455) sponsored by Pfizer. In this second study, IP consists of irinotecan

65 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1. EP consists of etoposide 100 mg/m^2 on days 1 – 3 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. The results of these studies are awaited.

The debate continues regarding the optimal dose of combination chemotherapy as related to improvement of the outcome of SCLC. However, the author can state that too low a dose intensity may lead to poor results. Takigawa et al. used fractionated administration of IP in 15 patients with ED SCLC [28]. Both irinotecan at a dose of 50 mg/m^2 and cisplatin at a dose of 60 mg/m^2 were given on days 1 and 8, and repeated every 4 weeks up to 4 cycles. Although objective response rates were 80%, no complete response (CR) were obtained. The MST was 9.4 months and one-year survival was 40.0%. They stopped enrollment because of no CR and poor survival compared to Kudoh's data [20]. The dose intensity may be low because this regimen had a lower dose of irinotecan (50 mg/m^2) and a two-week rest period.

Han et al. reported a Phase II study of dose-intensified weekly IP in chemo-naive patients with ED SCLC [29]. The initial six patients received cisplatin 50 mg/m^2 followed by irinotecan 90 mg/m^2 on day 1 and 8 of a 21-day cycle (level I), with one treatment death and three febrile neutropenias. The doses of cisplatin and irinotecan were then reduced to 40 mg/m^2 and 80 mg/m^2, respectively (level II). The overall response rate was 97%, with a complete response rate of 26%. The MST was 11.1 months and 1- and 2-year survival rates were 44.1% and 11.8%, respectively. Major grade 3 or 4 toxicities included neutropenia (89%), anaemia (59%) and diarrhoea (27%). There were three treatment-related deaths, occurring in elderly patients aged > 60 years and/or relative poor baseline PS 2 or 3. Although they adopted the oral alkalisation and control of defecation to prevent irinotecan-induced side effects, especially delayed diarrhoea, they are uncertain whether or not this preventive treatment reduced the observed incidence of severe delayed diarrhoea.

2.2 Irinotecan plus carboplatin for ED SCLC

Schmittel et al. studied the DLT and maximum tolerated dose (MTD) of a dose escalation of carboplatin to a fixed dose of irinotecan (IC) in Caucasian patients [30]. They demonstrated that the maximum tolerated dose is irinotecan 50 mg/m^2 administered on day 1, 8 and 15, and carboplatin at an area under the concentration–time curve (AUC) of 5 mg/ml x min, on day 1 of a 4-week cycle. DLT (neutropenia, thrombocytopenia and diarrhoea) was comparable to the results of the Japanese trial at a dose of 60 mg/m^2 of irinotecan and AUC = 5 of carboplatin [31].

Subsequently, Schmittel et al. presented a randomised Phase II trial comparing IC and etoposide plus carboplatin (EC) in ED SCLC [32]. Chemotherapy-naive ED SCLC patients were randomly assigned to receive carboplatin AUC = 5 either in combination with 50 mg/m^2 of irinotecan on days 1, 8 and 15 or with etoposide 140 mg/m^2 on days 1 – 3. In the IC arm, treatment was repeated every four weeks; in the EC arm, every

three weeks. IC improved response rate (10% CR and 61% partial response (PR) in IC, 0% CR and 50% PR in EC) and progression free survival (9 months, p = 0.03) over standard EC (6 months). The MST was 12 months in the IC arm and 10 months in the EC arm, but with no significant difference. Patients with EC had significantly higher incidence of grade 3 to 4 leucopenia, neutropenia and thrombocytopenia. Grade 3 – 4 diarrhoea developed more frequently in the IC arm (11 versus 6%), but with no significant difference. Haematotoxicity was favourable in the IC arm. They extended into a randomised Phase III trial to assess impact on overall survival, and concluded this study showed that even when carboplatin is used instead of cisplatin, the survival of IC and EC was not significantly different, and that myelosuppression was more frequent in EC than IC.

2.3 Irinotecan plus etoposide for ED SCLC

A Phase II study of irinotecan and etoposide (IE) for chemotherapy-naive ED SCLC was recently conducted without platinum by the West Japan Thoracic Oncology Group (WJTOG) [33]. A total of 50 patients were enrolled. This regimen consisted of irinotecan 60 mg/m² on days 1, 8 and 15, and etoposide 80 mg/m² on days 2 – 4. The overall response rate was 66% with a complete response rate of 10%. The MST was 11.5 months and the 1-year survival rate was 43.2%. Grade 3 – 4 neutropenia, thrombocytopenia and diarrhoea were 62.9, 4 and 2%, respectively. There was no treatment-related death. This regimen seems to be equal to the EP regimen. The dose intensity of irinotecan and etoposide achieved with this regimen was not adequate. This may be the reason for the low incidence of diarrhoea (2%). A schedule of irinotecan administered on days 1 and 8 at 3-week intervals may be preferred.

2.4 Triplets including irinotecan for ED SCLC

JCOG9902-DI was a randomised Phase II trial to compare two kinds of three-drug combinations of cisplatin, etoposide and irinotecan (PEI regimens) for the treatment of ED SCLC [34]. A total of 60 patients were randomised to receive either arm A (cisplatin 25 mg/m² on day 1, on weeks 1, 3, 5, 7 and 9 and etoposide 60 mg/m² on days 1 – 3, on weeks 2, 4, 6, 8), or arm B (cisplatin 60 mg/m² on day1, irinotecan 60 mg/m² on days 1, 8, 15 and etoposide 50 mg/m² on days 1 – 3, every week for 4 cycles). Prophylactic G-CSF support was provided in both arms. This study suggested that the PEI combinations in both schedules have significant activity against ED SCLC with acceptable toxicity. The CR rate of 17% and MST of 12.9 months in arm B were much more promising compared with the CR rate of 7% and MST of 8.9 months in arm A. They concluded that arm B should be selected for future Phase III studies. However, because irinotecan administration often needed to be skipped, especially on day 15, they suggested a 3-week schedule in which irinotecan is administered only on days 1 and 8.

Briasoulis et al. showed that irinotecan can be safely combined with cisplatin and etoposide in a convenient and simple schedule of administration over three days [35]. They treated 36 patients with irinotecan on day 1 in combination with fixed doses of cisplatin (20 mg/m²) and etoposide (75 mg/m²), both for 3 consecutive days. Irinotecan dose was escalated from 60 mg/m² by increments of 40 mg/m² in this Phase I trial. The MTD of irinotecan was 140 mg/m² and the recommended optimal dose 120 mg/m². DLTs were febrile neutropenia and grade 3 diarrhoea. This same regimen is being studied with concurrent TRT⁷ in a total dose of 54 Gy in 30 fractions (1.8 Gy once daily) [36].

Thompson et al. reported a Phase II trial of the Minnie Pearl Cancer Research Network at the 2005 ASCO meeting [37]. They added a molecular targeted agent, imatinib (60 mg/day, per os) to chemotherapy of irinotecan (60 mg/m² on days 1, 8 and 15) and carboplatin (AUC = 4) every 4 weeks. Imatinib targets c-kit expression. Grade 3/4 haematological toxicity included: neutropenia (29%/16%), anaemia (13%/1%) and thrombocytopenia (7%/0%). The response rate was 66% with 10% CR. Grade 3 diarrhoea was observed in 21%. There were no treatment-related deaths. The MST was 8.5 months. This suggests that C-kit expression did not correlate with survival and that imatinib offers no efficacy at a cost of increased toxicity when combined with irinotecan and carboplatin in the treatment of ED SCLC.

3. Irinotecan-containing regimens for relapsed or refractory SCLC

Huisman et al. have summarised 21 Phase II studies and 3 randomised trials of second-line chemotherapy in patients with SCLC reported from 1989 to 1999 [38]. They found a cumulative response rate of 21% for multi-drug regimens and 19% for single agents. As yet there is no standard second-line treatment established for patients with SCLC who fail or relapse after front-line treatment.

Irinotecan was combined with various anticancer drugs in doublet or triplet. As doublets, these include cisplatin [39], weekly or every three weeks carboplatin [40,41], etoposide [42], gemcitabine [43,44], ifosfamide [45] and paclitaxel [46]. The responses vary from 10 to 94%, and the MST ranges from 5.8 to 8.9 months. As described earlier on triplet including irinotecan [34,47], a three-drug combination Phase II study of irinotecan, cisplatin and etoposide (PEI regimen) was conducted only for sensitive relapsed SCLC (40 patients) [48]. This Phase II regimen consisted of cisplatin 25 mg/m² weekly for 9 weeks, etoposide 60 mg/m² for 3 days on weeks 1, 3, 5, 7 and 9, and irinotecan 90 mg/m² on weeks 2, 4, 6 and 8 with G-CSF support after day 1 on week 2. The results showed a response rate of 78% (CR rate of 13%) and the MST of 11.8 months. A total of 39 patients (98%) had a good PS of 0 or 1. Grade 3 – 4 neutropenia, thrombocytopenia, and diarrhoea were observed in 73, 33, and 8%, respectively. Nonhaematological toxicities were mild and transient.

Another three-drug combination of cisplatin, ifosfamide and irinotecan with G-CSF was conducted by Fujita et al. [49].

The response rate was 94.4% and the MST was 11.1 months, encouraging result. Because of patient selections, it is difficult to make wholly valid conclusions about the most effective regimen based only on Phase II results. However, three-drug combinations containing irinotecan with G-CSF support may have better survival and feasibility than the doublets. The disadvantage is that triplet regimens require G-CSF support, which may make out-patient treatment difficult.

4. Irinotecan containing regimen for LD SCLC

Two meta-analyses showed that the addition of TRT to chemotherapy in patients with LD SCLC improves survival at two and three years by 5.4% [50,51]. In these meta-analyses, non-platinum-based combination chemotherapies were commonly used, with only a few trials using platinum-based chemotherapy. Cisplatin and etoposide plus TRT is now widely regarded as the standard regimen for LD SCLC, and presents acceptable toxicity [52]. Turrisi *et al.* reported results of once-daily versus twice-daily (b.i.d) TRT with four cycles of cisplatin and etoposide. Results showed that the MST was significantly superior in the b.i.d arm (23 versus 19 months) [53].

Irinotecan showed potent radiosensitising effects in human lung tumour xenografts which were related to the cell cycle [54]. Kubota *et al.* reported a pilot study of concurrent etoposide and cisplatin plus accelerated hyperfractionated TRT followed by irinotecan and cisplatin for LD SCLC (JCOG9903) [21]. Treatment consisted of etoposide 100 mg/m^2 on days 1 - 3, cisplatin 80 mg/m^2 on day 1, and concurrent b.i.d TRT of 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2, days 1, 8, 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles. A total of 31 patients were accrued. Although a pilot study, the MST was 20.2 months and 1-, 2- and 3-year survival rates were 76%, 41%, and 38%, respectively. This encouraging regimen proved safe with acceptable toxicities. A randomised Phase III trial comparing EP with IP following EP plus concurrent TRT for LD SCLC is now underway (JCOG0202).

The WJTOG also conducted a similar regimen [55]. Treatment included cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 - 3 with concurrent TRT (1.5 Gy/b.i.d, a total dose of 45 Gy) followed by 3 cycles irinotecan 60 mg/m^2 on days 1, 8 and 15 and cisplatin 60 mg/m^2. The results of 51 patients were almost identical to JCOG9903; overall response and CR rate was 87.8% and 40.8%, respectively; Grade 4 toxicity included neutropenia (83.7%), anaemia (10.2%), thrombocytopenia (0%), diarrhoea (2%) and infection (2%); the MST was 21.5 months and 2-year survival rate was 45.7%.

A Phase II study of IP induction followed by concurrent b.i.d TRT with EP chemotherapy for LD SCLC was conducted [56] and also showed encouraging results. Treatment consisted of two cycles of cisplatin 40 mg/m^2 and irinotecan 80 mg/m^2 on days 1 and 8 of a 3-week cycle. This was followed by two 3-week cycles of cisplatin 60 mg/m^2 on days 43

and 64, and etoposide 100 mg/m^2 on days 43 - 45 and 64 - 66, with concurrent b.i.d TRT total of 45 Gy beginning on day 43. Thirty-five patients were accrued. The MST was 25 months (but it should be noted that this is a single institution Phase II study).

In these studies, irinotecan was used on an induction or adjuvant setting, and both regimens were encouraging. However, randomised study in which both modalities are compared has not been conducted.

There have been a few trials of concurrent chemoradiotherapy including irinotecan for patients with SCLC as well as NSCLC. Recently, a combined modality treatment of IC and TRT followed by bevacizumab (antiangiogenic anti-VEGF antibody) in the treatment of LD SCLC was conducted in a Phase II trial by the Minnie Pearl Cancer Research Network [57]. Induction therapy consisted of irinotecan 50 mg/m^2 on days 1 and 8, carboplatin AUC = 5 on day1, TRT 1.8 Gy single daily dose to total dose of 61.2 Gy (34 fractions), beginning with the 3rd cycle. Chemotherapy was repeated every three weeks for four cycles. As a maintenance therapy, bevacizumab 10 mg/kg i.v. every 2 weeks was given until disease progression, or a maximun of 10 doses (20 weeks) were administered. The response rate was 81% with 28% CR. This regimen was well tolerated with rare grade 4 toxicity and no treatment-related deaths. One-year progression-free and overall survival were 68% and 71%, respectively. These results suggest that irinotecan can be safely administered with TRT concurrently.

Sohn *et al.* also reported a Phase II study of IP with concurrent TRT in LD SCLC [58]. Chemotherapy of irinotecan 60 mg/m^2 on days 1, 8 and 15 and cisplatin 40 mg/m^2 on days 1 and 8 were repeated every 4 weeks until a maximum of 6 cycles. TRT of 2 Gy/day was commenced on day 1 of the second chemotherapy cycle up to a total of 54 Gy. The results are not concluded at this time.

Langer *et al.* reported a Phase I study of IP and either b.i.d TRT (45 Gy) or once daily RT (70 Gy) to determine if irinotecan can be safely integrated with concurrent TRT and cisplatin in LD SCLC [59]. Acute DLT was defined as grade 4 oesophagitis, pneumonitis, or diarrhoea; grade 4 neutropenic fever; or any attributable grade 5 fatal toxicity ($\leq$ 90 days after RT). Although preliminary, there has been no attributable DLT in the 26 patients that have been enrolled. In combination with cisplatin 60 mg/m^2 every 3 weeks x 4 and either b.i.d TRT or once daily TRT, irinotecan 40 mg/m^2 on days 1 and 8 was safe and feasible. Irinotecan at 50 mg/m^2 on days 1 and 8 every 3 weeks x4 was also feasible in combination with cisplatin and b.i.d TRT. These reports allow us to conclude that irinotecan can be administered with radiotherapy sequentially or concurrently.

5. Expert opinion and conclusion

Irinotecan is effective against SCLC. For the treatment of ED SCLC, IP regimen is at least comparable to EP regimen.

The degree of myelosuppression in the IP regimens was less than that of the EP regimens. However, diarrhoea was more often observed in the IP than the EP regimens, and can lead to severe side effects when the IP regimen is used incautiously. Pharmacogenetic study of irinotecan may prompt one to use the drug in a safer way to avoid severe toxicities. McLeod suggests that at the least, irinotecan 300 – 350 mg/m^2 every 3 weeks should not be given to patients with a known UGT1A1*28 genotype until more definitive guidelines are established [60]. However, the use of UGT1A1*28 genotyping to predict toxicity is controversial and its clinical implications are unclear. Furthermore, whether or not these recommendations are also applicable to patients with SCLC should be

elucidated upon because a lower dose of irinotecan is usually administered weekly for the treatment of SCLC, rather than the every 3 or 4 weeks for colorectal cancers. In the coming decade, we must confront the metabolic and pharmacogenomic differences in various populations for the treatment of cancer. For this, international cooperative studies are warranted and indeed of immense importance.

Considering patient safety, irinotecan can indeed be administered relatively safety in patients with SCLC, provided there is careful monitoring of patients, especially regarding diarrhoea and myelosuppresion. Further studies to avoid severe toxicities are needed to advance the safe use of this otherwise promising drug.

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ORIGINAL REPORT

Predictive Factors for Interstitial Lung Disease, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

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A B S T R A C T

Purpose
Interstitial lung disease (ILD) is a serious adverse effect of gefitinib, but its prevalence and risk factors remain largely unknown. We examined the prevalence of and risk factors for gefitinib-induced ILD associated with practical use of the drug in Japanese with non–small-cell lung cancer (NSCLC).

Patients and Methods
Clinical information was retrospectively assembled for NSCLC patients who started gefitinib treatment at affiliated institutions of the West Japan Thoracic Oncology Group between August 31 and December 31, 2002. Medical records of patients who developed pulmonary infiltrates were reviewed by a central committee of extramural experts for identification of patients with gefitinib-induced ILD. Multivariate logistic or Cox regression analysis was performed to identify independent predictive factors for ILD, antitumor response, and survival.

Results
Seventy cases of and 31 deaths from gefitinib-induced ILD were identified among 1,976 consecutively treated patients at 84 institutions, corresponding to a prevalence of 3.5% and mortality of 1.6%. Gefitinib-induced ILD was significantly associated with male sex, a history of smoking, and coincidence of interstitial pneumonia (odds ratios = 3.10, 4.79, and 2.89, respectively). Predictive factors for response were female sex, no history of smoking, adenocarcinoma histology, metastatic disease, and good performance status (PS), whereas predictive factors for survival were female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, and previous chest surgery.

Conclusion
ILD is a serious adverse effect of gefitinib in the clinical setting that cannot be ignored. However, patient selection based on sex and smoking history can minimize ILD risk and maximize the clinical benefit of gefitinib.

INTRODUCTION

The discovery that signaling by the epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis prompted efforts to target this receptor in anticancer therapy, leading to the development of inhibitors of its tyrosine kinase activity.[1-3] Gefitinib, an orally active inhibitor of the EGFR tyrosine kinase, is a leading agent in the field of EGFR-targeted therapy.[4,5] Two large phase II trials involving previously treated patients with advanced non–small-cell lung cancer (NSCLC) revealed that gefitinib monotherapy was well tolerated and manifested clinically meaningful antitumor activity.[6,7] Objective responses that were both rapid and persistent were apparent at a dose of 250

mg/d in 12% to 18% of patients; the median survival time was 7 to 8 months, with a 1-year survival rate of 27% to 35%, and the most common adverse effects were rash and diarrhea, which were generally mild. Similar response and survival rates were apparent at a dose of 500 mg/d but were accompanied by a higher frequency of adverse events. Higher response rates were apparent in women, Japanese patients, patients with no history of smoking, and patients with adenocarcinoma.[6-8]

Gefitinib was licensed in Japan for the treatment of inoperable or recurrent NSCLC in July 2002. Soon after its introduction, however, life-threatening interstitial lung disease (ILD) attributed to the drug became apparent, despite the absence of severe cases of ILD in the preceding phase I and II

trials, which included a total of 132 Japanese patients.[6,9-11] The publicity associated with this unexpected severe adverse event led to concern among patients and physicians about the risks of taking gefitinib. Although the prevalence of gefitinib-associated ILD in Japan was estimated at approximately 2%, this estimate was based only on case series studies, with no systematic survey allowing direct determination of the prevalence and identification of risk factors for gefitinib-induced ILD having been performed.[12]

In the present study, the West Japan Thoracic Oncology Group (WJTOG) conducted a retrospective survey of 1,976 individuals with NSCLC, representing all the patients who started gefitinib treatment at 84 WJTOG-affiliated institutions between August 31 and December 31, 2002. We examined the prevalence of and risk factors for gefitinib-induced ILD in this Japanese patient population. The therapeutic efficacy of gefitinib was also evaluated to assess risk and benefit in real-life use of gefitinib.

Study Patients

To collect all data of the potential patients with gefitinib-induced ILD, we initially asked 112 affiliated institutions of WJTOG to report the number of NSCLC patients who started gefitinib treatment between August 31 and December 31, 2002 and subsequently developed pulmonary infiltrates. We also asked them to report the total number of patients who started gefitinib treatment during the same period. After confirming the number of potential cases and total patients, we sent case report forms to the respective institutions and asked them to provide demographic and clinical data for the patients. We finally updated the information of all the patients concerning pulmonary infiltrates, antitumor response, and survival status on December 31, 2003, providing an observation period of at least 12 months. This study was approved by the Review Board of the WJTOG.

Confirmation of Gefitinib-Induced ILD

For patients who developed pulmonary infiltrates, in addition to the information collected on case report forms, we obtained detailed clinical data, including chest roentgenograms and computed tomograms taken before and after gefitinib administration; results of examination of bronchoalveolar lavage fluid or lung biopsies when performed at the onset of pulmonary infiltration; laboratory data obtained at the onset of pulmonary infiltration; gefitinib treatment duration before the development of pulmonary infiltrates; and details of treatment for the pulmonary injury. All this information was submitted to a central review committee of extramural experts, comprising at least three thoracic radiologists, one pulmonologist, and one oncologist, for determination of whether each patient indeed developed gefitinib-induced ILD. The committee reviewed all available information including findings of bronchoscopy, clinical course after development of pulmonary infiltrates, and radiologic findings. An infectious etiology was excluded on the basis of extensive microbiologic analysis of blood or other cultures, bronchoalveolar lavage examinations, and titers of antimicrobial antibodies. All experts evaluated the data together to reach unanimous final decisions.

Demographic and Clinical Variables

The following pretreatment demographic and clinical information was obtained from case report forms and evaluated for its relationship to gefitinib-induced ILD: age, sex, smoking status, Eastern Cooperative Oncology Group performance status (PS), coincidental complications, histology, disease stage, body-surface area (BSA), and previous anticancer treatments. Smoking status was classified as no history of smoking (smoking a total of < 100 cigarettes) or a positive history. With regard to coincidental complications, we assessed the presence of pulmonary diseases, diabetes mellitus, and sequelae of previous treatment such as radiation pneumonitis. Disease stage was determined according to the TNM system.[13] Previous anticancer treatment was classified as surgery, radiotherapy, or chemotherapy. We obtained additional information

about the field, dose, and modality of radiotherapy and about the regimen, dose, and number of treatment cycles for chemotherapy. We also collected information about antitumor response and survival after the initiation of gefitinib treatment. We asked the participating institutions to report antitumor response according to the Response Evaluation Criteria in Solid Tumors Group criteria,[14] although it was not confirmed extramurally. Overall survival was calculated from the initiation of gefitinib treatment to the date of death. Patients still alive were censored as of the last known follow-up. Survival data were last updated on December 31, 2003.

Statistical Analysis

Variables were examined for association with ILD development or antitumor response by univariate analysis with the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify predictors of ILD development or antitumor response.[15] Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Prognostic importance of factors was analyzed with the Cox regression model.[16] In multivariate analysis, a forward stepwise procedure was used to select factors for inclusion in the final model with a cutoff value of $P = .2$. For detection of possible synergistic effects of clinical factors, interaction terms of variables selected in the final model were sequentially included and evaluated by the likelihood ratio test. All significance levels were set at $P = .05$. Statistical analyses were performed with SAS version 9 software (SAS Institute, Cary, NC).

Prevalence and Mortality of Gefitinib-Induced ILD

A total of 1,976 patients with NSCLC from 84 (75%) of 112 institutions surveyed were reported as having started gefitinib treatment between August 31 and December 31, 2002 (Fig 1). Among these patients, 102 individuals developed pulmonary infiltrates after treatment initiation and were reported as potential cases of gefitinib-induced ILD. The central review committee evaluated the clinical data of these 102 patients and determined that 70 cases of ILD and 31 deaths were attributable to gefitinib, corresponding to a prevalence of 3.5% (95% CI, 2.8% to 4.5%) and a mortality of 1.6% (95% CI, 1.1% to 2.2%) for gefitinib-induced ILD. All ILD patients had been treated with gefitinib monotherapy, with the exception of one patient who received gefitinib concurrently with cisplatin. None of the ILD patients received radiotherapy simultaneously with gefitinib treatment. The median time from the start of gefitinib treatment to the development of ILD was 31 days (interquartile range, 18 to 50 days), and the median duration of gefitinib treatment before ILD development was 29 days (interquartile range, 18 to 49 days). Among the 70 patients with gefitinib-induced ILD, nine patients (13%) underwent bronchoscopic examination, including six lung biopsies and four bronchoalveolar lavages; all the lung biopsy specimens showed interstitial inflammation and fibrosis, and bronchoalveolar lavage revealed no signs (such as neutrophilia) of infection. Cultures of blood or other specimens were performed for 49 patients with ILD (70%), with no infection detected. After the development of gefitinib-induced ILD, 66 patients (94%) received corticosteroids, and additional antibiotic treatment in 17 of these patients did not increase the proportion of individuals whose ILD improved (18% and 61% with and without antibiotics, respectively).

Risk Factors for Gefitinib-Induced ILD

Of the 1,874 patients who did not develop pulmonary infiltrates, 245 individuals (13.1%) were excluded from further analysis because of insufficient clinical information (Fig 1). We also excluded the 11
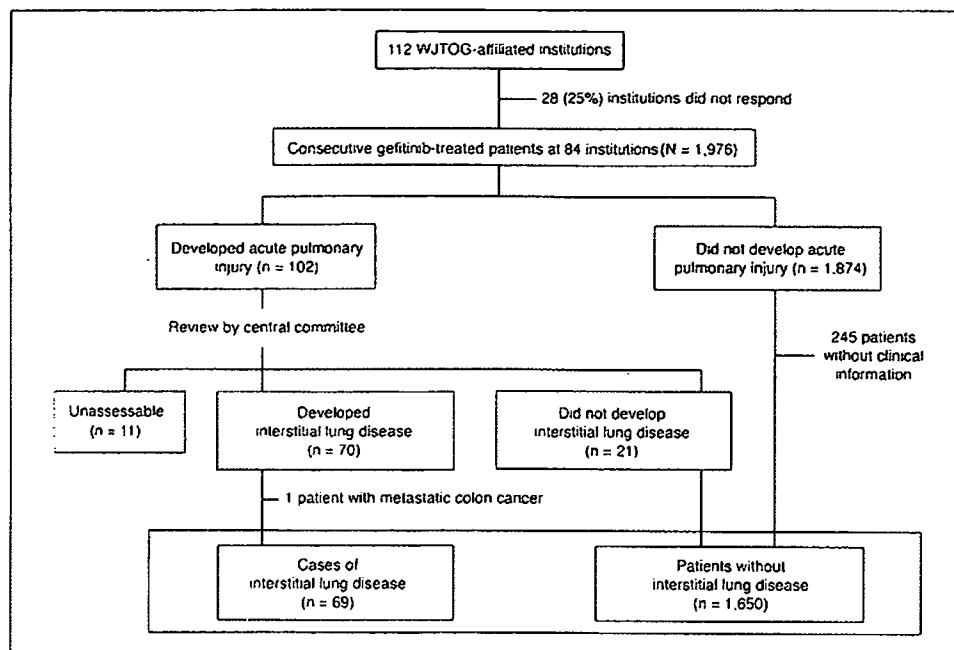
Fig 1. Outline of patient recruitment and classification. WJTOG, West Japan Thoracic Oncology Group.

unassessable patients with pulmonary infiltrates as well as one confirmed patient with gefitinib-induced ILD whose lung tumor proved to be metastatic colon cancer. Therefore, a total of 1,719 patients (69 patients with gefitinib-induced ILD and 1,650 patients without ILD) were subjected to subsequent analyses to identify predictive factors for the development of ILD, antitumor response, and survival. Among these 1,719 patients, 1,599 individuals (93%) received gefitinib as a monotherapy, whereas 71 and 49 individuals received gefitinib simultaneously with chemotherapy or palliative radiation, respectively. Univariate analysis identified male sex, a history of smoking, and the coincidence of interstitial pneumonia as being associated with the development of ILD (Table 1). Multivariate logistic regression analysis revealed sex, smoking status, and coincidence of interstitial pneumonia as independent risk factors for gefitinib-induced ILD; BSA was also selected in a forward stepwise procedure and included in the multivariate analysis to adjust for its potential confounding effect, although it was not significant in the final model (Table 2). A potential interaction between sex and smoking status was not significant ($P = .399$). The adjusted odds ratio for development of ILD was 20.5 (95% CI, 4.9 to 85.7) for males with a history of smoking compared with females with no history of smoking. Among 1,671 patients with known smoking status, the prevalence of ILD ranged from 0.4% in women with no history of smoking to 6.6% in men with a history of smoking (Table 3).

Predictive Factors for Antitumor Response

An antitumor response was observed in 348 of the total of 1,976 patients (including 256 unassessable patients), corresponding to a response rate of 17.6% (95% CI, 16.0% to 19.4%). Univariate analysis revealed that an age of less than 70 years, female sex, no history of smoking, adenocarcinoma histology, metastatic disease, good PS, a history of chest surgery, no history of chest irradiation, the absence of interstitial pneumonia, and a BSA of less than 1.5 m² were associated with an antitumor response (Table 1). Multivariate logistic regression analysis revealed that sex, smoking status, histology, disease stage, and

PS were independently associated with response rate (Table 4). No synergistic effect on antitumor response was apparent between sex and smoking status, sex and histology, or smoking status and histology ($P = .514, .734,$ and $.573$, respectively). The adjusted odds ratio for an antitumor response was 9.2 (95% CI, 5.5 to 15.3) for women with adenocarcinoma and no history of smoking compared with male smokers with a nonadenocarcinoma histology.

Predictive Factors for Survival

We confirmed 1,076 deaths among the study population as of December 31, 2003. Overall, the median survival time and 1-year survival rate were 312 days (interquartile range, 114 to 579 days) and 44.8% (95% CI, 42.3% to 47.2%), respectively. Univariate analysis identified female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, previous chest surgery, no history of chest irradiation, the absence of interstitial pneumonia or diabetes, and a BSA of less than 1.5 m² as being associated with longer survival (Table 1). Cox regression analysis showed that sex, smoking status, histology, disease stage, PS, and previous chest surgery were independent prognostic factors (Table 5). No synergistic effect on survival was observed between sex and smoking status, sex and histology, or smoking status and histology ($P = .490, .785,$ and $.531,$ respectively). Given that previous chemotherapy status is a clinically important factor, we re-examined the survival data separately according to chemotherapy history (Table 6). Survival curves for patients with metastatic disease and a history of chemotherapy (according to independent prognostic factors identified in the Cox regression model) are shown in Figure 2.

We have evaluated clinical data from 1,976 patients with advanced NSCLC who were treated with gefitinib since its licensure in Japan.

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Table 1. Relationship Between Clinical Variables and ILD, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

Variable	ILD				Antitumor Response				Survival		
	Total No. of Patients	Patients With ILD		P	Total No. of Patients	Responders		P	Total No. of Patients	Median Survival (days)	P
		No.	%			No.	%				
Age, years											
< 70	1,047	39	3.7	.446	1,042	230	22.1	.024	1,044	296	.418
≥ 70	672	30	4.5		671	118	17.6		669	333	
Sex											
Female	631	6	1.0	< .001	627	222	35.4	< .001	631	499	< .001
Male	1,088	63	5.8		1,086	126	11.6		1,082	230	
Smoking status											
No smoking history	658	5	0.8	< .001	653	225	34.5	< .001	658	467	< .001
Positive smoking history	1,013	63	6.2		1,012	116	11.5		1,008	227	
Histology											
Adenocarcinoma	1,294	47	3.6	.130	1,288	311	24.2	< .001	1,291	362	< .001
Others	414	22	5.3		414	34	8.2		411	190	
Disease stage											
Metastatic	1,313	59	4.5	.069	1,310	296	22.6	< .001	1,309	280	< .001
Nonmetastatic	406	10	2.5		403	52	12.9		404	435	
Performance status											
0-1	1,161	44	3.8	.664	1,157	274	23.7	< .001	1,157	441	< .001
2	336	14	4.2		336	47	14.0		335	147	
3-4	216	11	5.1		214	26	12.2		216	67	
Previous chest surgery											
Yes	528	15	2.8	.093	527	128	24.3	.008	527	466	< .001
No	1,181	54	4.6		1,177	220	18.7		1,176	253	
Previous thoracic RT											
Yes	472	18	3.8	.767	471	73	15.5	.002	468	263	.005
No	1,235	51	4.1		1,230	273	22.2		1,233	335	
Previous chemotherapy											
Yes	1,356	57	4.2	.440	1,351	275	20.4	.937	1,353	301	.900
No	363	12	3.3		362	73	20.2		360	345	
Coincidence of IP											
Yes	36	5	13.9	.013*	36	1	2.8	.008	35	103	< .001
No	1,683	64	3.8		1,677	347	20.7		1,678	317	
Coincidence of diabetes											
Yes	85	5	5.9	.386*	85	12	14.1	.145	85	190	.002
No	1,634	64	3.9		1,628	336	20.6		1,628	322	
Coincidence of renal failure											
Yes	10	1	10.0	.333*	10	2	20.0	.99*	10	353	.588
No	1,707	67	3.9		1,701	346	20.3		1,701	312	
Body-surface area, m²											
< 1.5	755	30	4.0	.796	751	197	26.2	< .001	755	355	< .001
≥ 1.5	875	37	4.2		874	135	15.5		872	280	

Abbreviations: ILD, interstitial lung disease; RT, radiotherapy; IP, interstitial pneumonia.
*Calculated using Fisher's exact test.

The present study constitutes the first large-scale survey designed to assess the prevalence of and risk factors for gefitinib-induced ILD during practical use of this drug in the Japanese population. The development of ILD subsequent to treatment with conventional cytotoxic chemotherapeutic agents has been recognized for many years, with the use of standard drugs for treatment of NSCLC being associated with ILD at a prevalence of up to 5%.[17,18] Drug-induced ILD in lung cancer patients is difficult to diagnose because of the high prevalence of pre-existing lung disease and respiratory tract infections as well as the progressive malignancy in such individuals. Clinical symptoms of ILD, such as escalating dyspnea, cough, and fever, may be indistinguishable from the symptoms of progressive tumor growth or infection. Computed tomographic features of ILD include pulmonary reticular changes and ground-glass opacity, which are also nonspecific and may not readily indicate a precise etiology.[18] Diagnosis of drug-induced ILD thus relies on rigorous exclusion of all other differential diagnoses, especially those of infection and tumor progression.

In the present study, all suspected cases of ILD were meticulously reviewed at a single study site by extramural experts, including at least three thoracic radiologists, one pulmonologist, and one oncologist, taking into account clinical history, the results of clinical examination, and comparisons of current and previous radiologic findings. Seventy patients with gefitinib-related ILD were thereby confirmed, yielding an overall prevalence of 3.5% and mortality of 1.6%. The prevalence of

Table 2. Risk Factors for Interstitial Lung Disease Identified by Multivariate Logistic Regression Analysis (n = 1,586*)

Variable	Odds Ratio	95% CI	P
Male	3.10	1.15 to 8.36	.025
Positive smoking history	4.79	1.69 to 13.54	.003
Coincidence of IP	2.89	1.06 to 7.84	.038
BSA of < 1.5 m²	1.67	0.98 to 2.83	.059

Abbreviations: IP, interstitial pneumonia; BSA, body-surface area.
*Including 66 patients with gefitinib-induced interstitial lung disease.

Table 4. Predictive Factors for Antitumor Response Identified by Multivariate Logistic Regression Analysis (n = 1,650*)

Variable	Odds Ratio	95% CI	P
Female	2.14	1.53 to 2.98	< .001
No smoking history	2.13	1.53 to 2.96	< .001
Adenocarcinoma	1.97	1.31 to 2.98	.001
Metastatic disease	1.88	1.32 to 2.67	< .001
Performance status†			
2	0.54	0.38 to 0.77	< .001
3-4	0.47	0.30 to 0.76	.001

*Including 338 responders.
†Performance status of 0 to 1 set as reference category

ILD in our study was slightly higher than the prevalence (1.1%) among gefitinib-treated patients in recent phase III trials of standard chemotherapy with or without gefitinib conducted in the United States and Europe.[19,20] In addition, the worldwide prevalence of ILD among 92,750 patients treated with gefitinib was approximately 1%, being approximately 0.3% in a US AstraZeneca Expanded Access Program.[21,22] The reason for the difference in the frequency of gefitinib-related ILD between Japan and Western countries remains unclear. It is possible that a greater awareness of the disease in Japan might lead to more careful and critical examination for ILD or that Japanese may have an increased genetic susceptibility to ILD.[22]

The mechanism of gefitinib-induced ILD has not been fully elucidated. EGFR and transforming growth factor alpha, a member of the EGF family of proteins that binds to and activates the EGFR, are both upregulated early in the response to acute lung injury,[23,24] and EGF family members are implicated in the repair of pulmonary damage.[25,26] In a rodent model of bleomycin-induced pulmonary fibrosis, treatment with gefitinib was shown to augment fibrosis.[27] These findings suggest that inhibition of EGFR signaling by gefitinib impairs the repair of and, thereby, exacerbates pulmonary injury, especially in patients with pulmonary comorbidities. In the present study, we have sought to identify clinical features of NSCLC patients that might increase the risk for development of ILD. Multivariate analysis identified male sex, a history of smoking, and coincidence of interstitial pneumonia as significant risk factors. Thus, the prevalence of gefitinib-induced ILD differed markedly according to sex and smoking status, ranging from 0.4% in females with no history of smoking to 6.6% in male smokers.

This is the first study in which predictive factors for ILD, antitumor response, and survival have been evaluated with the same data set. Multivariate analysis showed that sex, smoking status, tumor histology, disease stage, and PS were independently associated with both antitumor response and survival, mostly consistent with results of previous studies.[6-8] Although not confirmed by multivariate analysis, a smaller BSA might also confer greater efficacy on gefitinib, with further investigation of possible dose dependency being warranted. Female sex and the absence of a history of smoking were both associated with a lower risk for ILD, a higher response rate, and longer survival, suggesting that patient selection on the basis of this favorable profile will not only increase the clinical benefit of treatment with gefitinib but also reduce the risk for development of this life-threatening toxicity. Activating mutations of the EGFR have been identified in a subset of NSCLC patients, and tumors with EGFR mutations are highly sensitive to gefitinib.[28,29] However, these genetic factors have not been confirmed to be predictive of true clinical benefit because they have not yet been found to be associated with survival in NSCLC patients treated with gefitinib.[30] These previous studies showed that EGFR mutations were more frequent in females, individuals with no history of smoking, and patients with adenocarcinoma. We have no data on the frequency of EGFR mutations in the present patient cohort, and further studies to explore the relationship of genetic alterations with ILD risk and treatment efficacy are warranted.

The objective response rate in the present study was 17.6%, which is indicative of an acceptable single-agent activity of gefitinib outside clinical trial settings. Our data showed the median survival time and 1-year survival rate to be 10.0 months and 44%, respectively,

Table 3. Prevalence of ILD, Response Rate, and 1-Year Survival According to Sex and Smoking Status (n = 1,671)

Measure	No Smoking History		Positive Smoking History	
	Female	Male	Female	Male
Prevalence of ILD				
%	0.4	1.8	3.3	6.6
95% CI	0.0 to 1.5	0.4 to 5.3	0.9 to 8.2	5.1 to 8.4
Response rate				
%	38.2	22.1	23.1	9.9
95% CI	33.9 to 42.6	16.0 to 29.2	16.0 to 31.7	8.0 to 12.0
1-year survival				
%	64.6	47.1	50.7	32.1
95% CI	60.2 to 69.0	39.2 to 55.0	41.6 to 59.8	28.9 to 35.3

Abbreviation: ILD, interstitial lung disease.

Table 5. Survival Analysis by the Cox Regression Model (n = 1,643*)

Variable	Hazard Ratio	95% CI	P
Female	0.63	0.53 to 0.75	< .001
No smoking history	0.71	0.60 to 0.84	< .001
Adenocarcinoma	0.69	0.60 to 0.80	< .001
Metastatic disease	1.58	1.35 to 1.84	< .001
Performance status†			
2	2.58	2.23 to 2.99	< .001
3-4	3.71	3.12 to 4.41	< .001
Previous chest surgery	0.70	0.60 to 0.81	< .001

*Including 611 patients censored.
†Performance status of 0 to 1 set as reference category.

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	Chemotherapy Naive			Previously Treated With Chemotherapy		
Variable	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)
Sex						
Female	131	481	64.0	500	502	61.9
Male ·	229	263	36.8	853	217	33.8
Smoking status						
No smoking history	137	433	60.7	521	482	60.1
Positive smoking history	208	263	36.8	800	217	33.8
Histology						
Adenocarcinoma	266	378	51.8	1,025	358	49.2
Other	89	216	29.7	322	189	28.2
Disease stage						
Metastatic	254	299	41.4	1,055	274	40.8
Nonmetastatic	106	433	58.5	298	435	57.0
Performance status						
0-1	225	433	56.6	932	443	57.2
2	65	204	31.2	270	141	18.7
3-4	70	81	26.7	146	63	10.1
Previous chest surgery						
Yes	131	481	63.6	396	462	57.5
No	224	247	36.7	952	262	39.0

Table 6. Median Survival Time and 1-Year Survival According to Clinical Factors

in all patients who received gefitinib after the failure of prior chemotherapy. Given that the present study included many elderly and patients with a poor PS, these survival data do not differ substantially from those obtained with the Japanese cohort of a phase II study (11.8 months and 50%, respectively).[6] These findings suggest that gefitinib treatment in clinical practice may lead to clinical benefit as it did in the clinical trials. Furthermore, the survival data in the present study are similar to those obtained with previously treated patients with a PS of 0 to 2 in a phase III trial of docetaxel (7.5 months and 37%, respectively), which is a standard second-line treatment for NSCLC.[30] These observations emphasize the importance of further comparison of gefitinib with docetaxel as a second-line treatment for NSCLC in ongoing phase III studies. In previous phase III clinical trials, however, gefitinib failed to prolong survival in unselected patients, suggesting
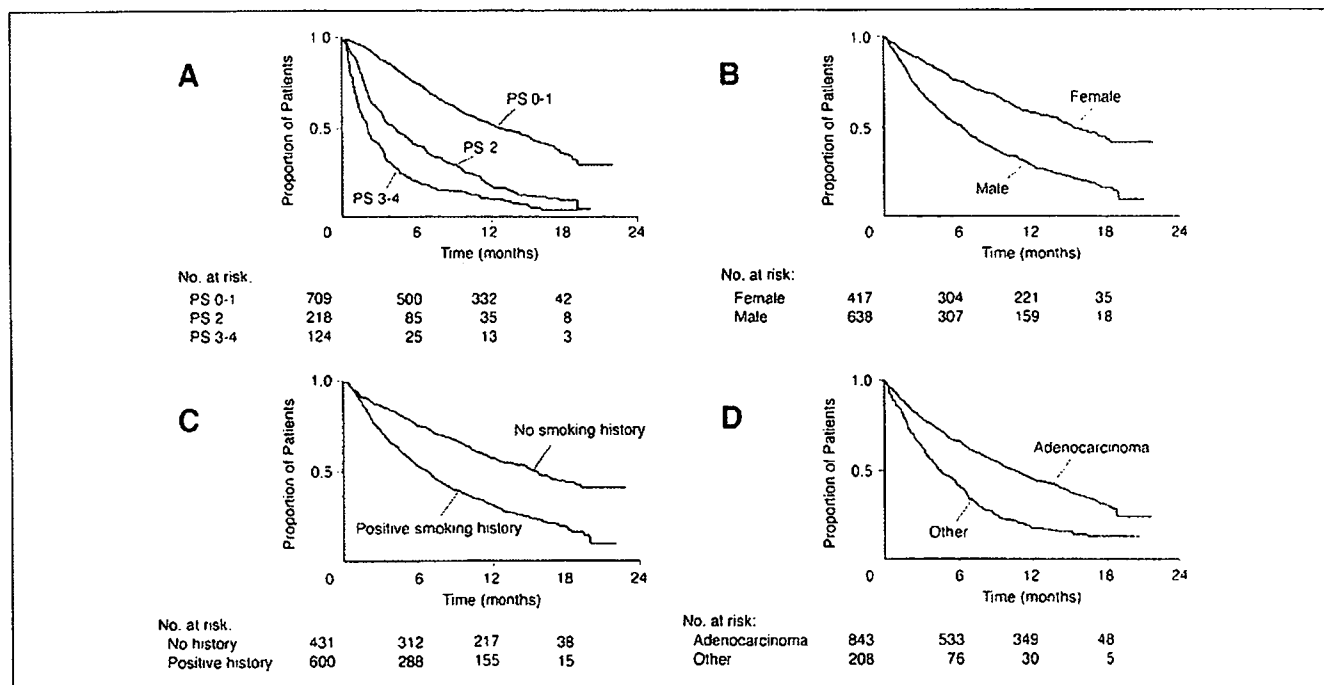

Fig 2. Kaplan-Meier plots of survival for patients with metastatic non-small-cell lung cancer previously treated with chemotherapy classified according to (A) performance status (PS), (B) sex, (C) smoking status, and (D) histology.

the necessity for patient selection on the basis of clinical or genetic factors if true clinical benefit is to be achieved from gefitinib treatment.[19,20,31] Indeed, a randomized phase III trial is now planned in Asian countries to assess the effect of gefitinib on survival in patients selected on the basis of clinical profile.

In conclusion, we have determined the prevalence of gefitinib-related ILD and identified risk factors for this life-threatening adverse event in a large population of Japanese patients with NSCLC treated with this drug. Our data confirmed an acceptable single-agent activity of gefitinib in routine clinical practice. We found that female sex and the absence of a history of smoking, which were known predictive factors for the efficacy of gefitinib, were also associated with a lower risk of gefitinib-induced ILD. Thus, our results indicate that patient selection on the basis of clinical factors can simultaneously minimize the risk of life-threatening ILD and maximize the clinical benefit of gefitinib treatment. They provide both important insight into individual risk-benefit assessment for gefitinib therapy in the practical setting as well as a basis for the planning of future clinical trials to accurately define the scope for gefitinib treatment in NSCLC patients.
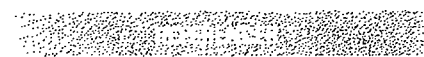
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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

| Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
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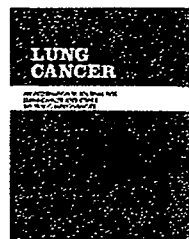
LUNG CANCER

A combination chemotherapy of carboplatin and irinotecan with granulocyte colony-stimulating factor (G-CSF) support in elderly patients with small cell lung cancer[☆]

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Summary

Background: We have previously reported that carboplatin plus etoposide is an effective and relatively non-toxic regimen in elderly patients with small cell lung cancer (SCLC). Recently, the Japan Clinical Oncology Group reported that irinotecan plus cisplatin was more effective than etoposide plus cisplatin in the treatment of non-elderly patients with extensive disease (ED)-SCLC. Therefore, we conducted a prospective feasibility study designed specifically to evaluate the efficacy of carboplatin (day 1) and irinotecan (days 1, 8, 15) with granulocyte colony-stimulating factor (G-CSF) support in elderly SCLC patients.

Methods: Three carboplatin AUC and irinotecan dose levels were used: $4 \, mg/ml \times min$ and $50 \, mg/m^2$, respectively (level 1); $5 \, mg/ml \times min$ and $50 \, mg/m^2$, respectively (level 2), and $5 \, mg/ml \times min$ and $60 \, mg/m^2$, respectively (level 3). Although a phase I trial using this drug combination against non-SCLC performed at our institution found that the recommended dose was level 3, as the current trial included only elderly patients, the starting dose used was level 2. However, if a patient had history of prior chemotherapy, performance status (PS) of 2, or was aged 75 years or more, the dose administered was reduced by 1 level. If a patient had a PS of 0, the dose was increased by 1 level. Cycles were repeated every 4 weeks, and patients aged 70 years or more with a PS of 0—2 were eligible.

Results: Eighteen patients were enrolled, of which nine were given the level 1 dose, seven the level 2 dose, and two the level 3 dose. The patient group had a median age of 75 years, 8 patients had limited disease (LD) versus 10 with ED, 9 had received previous treatment for SCLC versus 9 previously untreated, and 13 had a PS of 0—1 versus 5 with a PS of 2. Seventeen (94%) patients
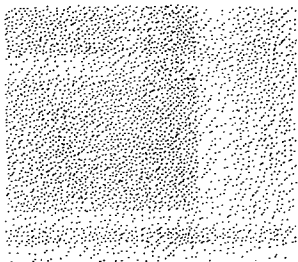
received two or more cycles of chemotherapy, and the median actual delivery of irinotecan was 84% of the projected dose. Grade 3/4 neutropenia, anemia, and diarrhea occurred in 50%, 33% and 6% of patients, respectively. Other toxicities were mild and no treatment-related deaths occurred. The response rate was 89%, with two complete responses and 14 partial responses. The median survival time was 13.3 months and the 1-year survival rate was 62%.

Conclusions: The combination of carboplatin and irinotecan with G-CSF support was an effective and non-toxic regimen in elderly SCLC patients and should be further evaluated in phase III trials.

1. Introduction

Approximately half of the patients with small cell lung cancer (SCLC) are older than 70 years, and this proportion of elderly SCLC patients is expected to increase in Japan [1—3]. Commonly used combination chemotherapy regimens for non-elderly SCLC include: cyclophosphamide, doxorubicin, and vincristine (CAV); cisplatin and etoposide (PE); alternating PE/CAV; and irinotecan plus cisplatin (IP) [4—6]. However, since many studies arbitrarily exclude elderly patients from clinical trials, no standard chemotherapeutic regimen has yet been established for elderly SCLC patients.

The Japan Clinical Oncology Group (JCOG) concluded that carboplatin plus etoposide (CE) represented an effective regimen with low toxicity in elderly SCLC patients in a phase II trial [7], and showed that IP was more effective than PE in the treatment of non-elderly patients with extensive disease (ED)-SCLC in a phase III trial [6]. As few clinical trials have evaluated the role of irinotecan in elderly patients with SCLC, we decided to conduct a prospective feasibility study designed to evaluate the efficacy of the carboplatin plus irinotecan (CI) regimen in elderly SCLC patients.

2. Patients and methods

2.1. Patient selection

Eligibility criteria were previously treated or untreated patients with histologically or cytologically confirmed SCLC, ≥70 years in age, and with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0—2. Additional criteria were the presence of limited disease (LD) or ED (all stages of SCLC were eligible), presence of evaluable or measurable disease, expected survival ≥2 months, adequate organ function [leukocyte count ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin level ≥9.0 g/dl, AST/ALT ≤2 × upper limit of normal range, total bilirubin ≤1.5 mg/dl, creatinine ≤1.5 mg/dl, creatinine clearance (Ccr) ≥50 ml/min, and PaO$_2$ ≥60 mmHg], absence of pericardial or pleural effusions requiring drainage, absence of active concomitant malignancy, no senile dementia, and written informed consent. ED was defined as presence of distant metastases, contralateral hilar-node metastases, or pleural effusion. Exclusion criteria included brain metastases or superior vena cava (SVC) syndrome that required radiotherapy, and serious medical or psychiatric illness. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance imaging (MRI) of the brain, CT scan or ultrasound of the abdomen, and isotope bone scanning.

2.2. Treatment protocol

Treatment consisted of carboplatin administered intravenously on day 1 plus irinotecan administered intravenously on days 1, 8, and 15. Granulocyte colony-stimulating factor (G-CSF) at 50 μg/m^2 or 2 μg/kg was administered daily except on days 1, 8, 15, until leukocyte counts exceeded 10,000/mm^3, at which point the G-CSF was discontinued. If leukocyte counts decreased to less than 3000/mm^3, G-CSF treatment was restarted. Cycles were repeated every 4 weeks for up to four courses. This trial used three carboplatin area under the curve (AUC) and irinotecan dose levels of 4 mg/ml × min carboplatin and 50 mg/m^2 irinotecan (level 1), 5 mg/ml × min carboplatin and 50 mg/m^2 irinotecan (level 2), and 5 mg/ml × min carboplatin and 60 mg/m^2 irinotecan (level 3). Based on a phase I trial of combined carboplatin and irinotecan for non-SCLC performed at our institution, level 3 was determined to be the recommended dose [8]. However, as the current trial included only elderly patients, the starting dose was reduced to level 2. If a patient had history of prior chemotherapy, performance status (PS) of 2, or was 75 or more years old, the dose administered was reduced by 1 level. If a patient had a PS of 0, the dose was increased by one level. For example, if a patient had a PS of 0 and was 78-years old, the patient received level 2 dose. If a patient had a PS of 2 and was 73-years old, the patient received level 1 dose. The 24 h Ccr was substituted for glomerular filtration rate (GFR) in Calvert's formula [9]. Antiemetic prophylaxis with 5-HT$_3$ antagonists plus dexamethasone was routinely used. In cases of irinotecan-induced diarrhea, high dose loperamide treatment was given as described in Abigerges et al. [10]. Irinotecan was withdrawn if leukocyte counts were less than 3000/mm^3, platelet counts less than 75,000/mm^3, or if diarrhea of grade 1 or more occurred on days 8 and 15. Subsequent courses of chemotherapy were initiated when leukocyte counts reached 4000/mm^3 and platelet counts 100,000/mm^3 after day 28 and for 2 or more days after the discontinuation of G-CSF. If the above criteria were not satisfied by the first day of the next course, treatment was withheld until full recovery. If more than 6 weeks passed from the first day of the last course, the patient was taken out of the study. Dose modifications were made for both carboplatin and irinotecan based on toxicity. Patients that experienced grade 4 leukopenia or neutropenia, grade 2 diarrhea, or neutropenic fever received a 25% reduction in irinotecan dose for the next course. Patients that experienced grade 3 or 4 thrombocytopenia received a 20% reduction in target carboplatin AUC for the next course. If the same toxicity occurred following dose reduction, the patient was taken out of the study. If grade 3 or 4 non-hematologic toxici-

ties, except for nausea/vomiting and hyposodium, occurred, the patient was taken out of the study even if the toxicities improved thereafter. Patients with LD received thoracic irradiation after chemotherapy. Palliative radiotherapy of less than 20 Gy total dose was allowable to control persistent pain associated with bone metastasis during the study period. After the completion of four courses, responders did not receive further chemotherapy unless progressive disease (PD) developed. Post-protocol treatments were left at the discretion of the physician. Prophylactic cranial irradiation (PCI) was an option for patients that achieved a complete response (CR).

2.3. Evaluation

Tumor responses were evaluated according to World Health Organization criteria [11]. A CR was defined as the complete disappearance of tumor for at least 4 weeks. A partial response (PR) was defined as a $\geq$50% reduction in the sum of the products of the two greatest perpendicular diameters of all indicator lesions or a reduction of more than 50% in assessable disease for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. PD was defined as a $\geq$25% increase in tumor area or the appearance of new lesions. All other outcomes were classified as no change (NC). At the time of study initiation in March 1998, response evaluation criteria in solid tumors (RECIST) [12] was not yet available, such that toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

2.4. Study design and statistics

This trial was designed as a prospective non-phase I study and the main objective is to see feasibility and efficacy. The study protocol was approved by the institutional review board at our institution prior to the initiation of the study. Study objectives were to detect and quantify the clinical toxicities of the carboplatin and irinotecan combination and to assess its therapeutic efficacy in elderly patients with SCLC. Because this feasibility study included a heterogeneous patient population, (e.g. in terms of presence of prior chemotherapy and disease stage), the study was not designed as a phase I or II study. Therefore, sample size calculations based on Simon's minimax design were not applied to this study. Analysis of the trial was based on the intention-to-treat principle. Overall survival, determined from the time of registration to death or the last follow-up evaluation, was calculated using the Kaplan and Meier method.

3. Results

3.1. Patient characteristics

Between March 1998 and December 2003, 18 patients were registered for the study, and all received chemotherapy. Patient characteristics are listed in Table 1. Patients consisted of 4 women and 14 men, with a median age of 75 years (range, 70–85 years) and a median 24 h Ccr of 74 ml/min (range, 28–134 ml/min). Thirteen patients

Table 1   Patient characteristics

No. of patients	18
Male/female	14/4
Median age, years (range)	75 (70–85)
Stage: LD/ED	8/10
PS (ECOG): 0/1/2	4/9/5
Prior chemotherapy: present/absent	9/9
Sensitive/refractory cases	5/4
Median 24 h Ccr, ml/min (range)	74 (28–134)

LD, limited disease; ED, extensive disease; PS, performance status; ECOG, Eastern Cooperative Oncology Group; Ccr, creatinine clearance.

Table 2   Dose level

Level	No. of patients	AUC of carboplatin (mg/ml × min)	Dose of irinotecan (mg/m²)
1	9	4	50
2	7	5	50
3	2	5	60

AUC, area under the curve.

(72%) had an ECOG PS of 0 or 1. Eight patients had LD and 10 had ED. Nine patients had a history of prior chemotherapy (five with sensitive relapses, four with refractory relapses) and nine were chemo-naïve. Of the previously treated patients, five had received one regimen of CE and two had received one regimen of PE. One patient had received two regimens consisting of CE and CODE (cisplatin + oncovin + doxorubicin + etoposide), and one patient had received three regimens consisting of CE, CODE and IP. The numbers of patients that started at dose levels 1, 2 and 3 were nine, seven and two, respectively (Table 2).

3.2. Treatment delivery

Nine patients (50%) received four courses of treatment, two (11%) received three courses, six (33%) received two courses, and one (6%) received one course. The reasons for termination of treatment included completion of two or more courses of chemotherapy (16 patients, 89%), and NC (two patients, 11%). One patient experienced grade 3 diarrhea after receiving a single course of chemotherapy and was taken off the study. No treatment-related deaths (TRDs) occurred. Course intervals and dose reductions are listed in Table 3. The median interval of each round of chemotherapy was 28–29 days. Only four patients received a reduced dose

Table 3   Course interval and dose reduction

Interval of each chemotherapy course	No. of patients	Median days (range)	No. of patients with dose reduction
1–2	17	28 (21–35)	4[a]
2–3	10	29 (25–36)	0
3–4	9	28 (27–35)	0

[a] Thrombocytopenia, two patients; neutropenia, one patient; both, one patient.