severe neutropenia in patients receiving 350 mg/m^2 of irinotecan (8). We extended this observation in patients receiving cisplatin and irinotecan to clarify the association between PTB and severe toxicity, including neutropenia and diarrhea, in these patients.

PATIENTS AND METHODS

Treatment Schedule

The subjects consisted of consecutive lung cancer patients who had received cisplatin and irinotecan therapy at the National Cancer Centre Hospital between February 1999 and May 2004. Irinotecan, diluted in 500 ml of normal saline, was given intravenously over 90 min at a dose of 60 mg/m^2 on days 1 and 8 or on days 1, 8 and 15. Cisplatin was given intravenously over 60 min after the irinotecan infusion at a dose of 60 or 80 mg/m^2 on day 1 with at least 2500 ml of hydration. The first phase I trial of irinotecan and cisplatin showed that 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15 were the recommended dose for phase II trials (12), and this dose schedule was used for subsequent phase II and phase III trials of non-small cell lung cancer (NSCLC) (13,4,14). The second phase I trial of this combination showed that 60 mg/m^2 of cisplatin on day 1 and 80 mg/m^2 of irinotecan on days 1, 8, and 15 were the recommended dose (15). A phase II trial for small cell lung cancer, however, showed that this dose schedule was too toxic, and thereafter the dose of irinotecan was reduced from 80 to 60 mg/m^2 (16). From the above, we used 80 mg/m^2 of cisplatin and 60 mg/m^2 of irinotecan for patients with NSCLC, and 60 mg/m^2 of cisplatin and 60 mg/m^2 of irinotecan for the other patients. Administration of irinotecan was omitted if any of the following toxicities were noted on days 8 and 15: a white blood cell count $<2.0 \times 10^9$/l, a platelet count $<75 \times 10^9$/l, or grade 1–3 diarrhea. Each course was repeated every 3 or 4 weeks until the occurrence of unacceptable toxicity, disease progression, patient's refusal to continue treatment, or the investigator's medical decision to stop treatment. To control for cisplatin-induced emesis, a 5-HT3 receptor antagonist and dexamethasone were given prior to cisplatin administration.

Study Design

We retrospectively reviewed the patients' clinical records, including patient characteristics (age, sex, Eastern Cooperative Oncology Group performance status, histology of primary disease, clinical stage, prior treatment, evidence of liver metastasis), the dose and schedule of chemotherapy, and pre-treatment complete blood counts and serum chemistry profiles. We defined 'severe toxicity' as grade 4 neutropenia or grade 3–4 diarrhea during the first cycle of chemotherapy, in accordance with the NCI-CTC Version 2.0 criteria. All patients were treated as in-patients, and complete blood counts and serum chemistry profiles were assessed at least once a week. PTB was defined as the serum total bilirubin level at fasting just prior to the administration of cisplatin and irinotecan.

Table 1. Patient characteristics

		No. of patients
Sex	Male/female	93/34
Age	Median (range)	61 (24–74)
Performance status	0/1/2	34/91/2
Histology	Non-small cell lung cancer	57
	Small cell lung cancer	63
	Others	7
Liver metastasis	Yes/no	18/109
Prior chemotherapy	Yes/no	17/110
PTB (mg/m^2)	Median (range)	0.6 (0.2–2.4)
PNC ($\times 10^9$/l)	Median (range)	4.1 (1.8–8.5)
Chemotherapy	CDDP (60) day 1 + CPT-11 (60) days 1.8 q3w	32
Regimens (mg/dl)	CDDP (60) day 1 + CPT-11 (60) days 1.8.15 q4w	39
	CDDP (80) day 1 + CPT-11 (60) days 1.8 q3w	24
	CDDP(80) day1 + CPT-11 (60) days 1.8.15 q4w	32

PTB, pre-treatment total bilirubin; PNC, pre-treatment neutrophil count.

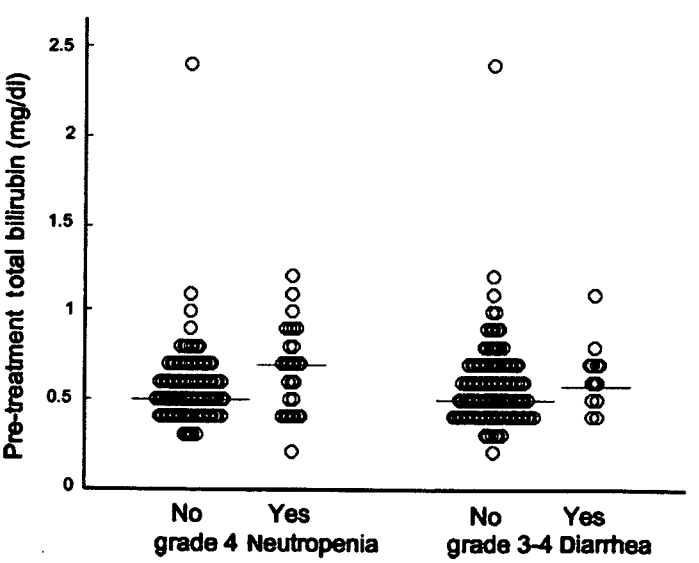


Figure 1. Association of PTB in patients who developed severe toxicity and in those who did not. The median PTB in patients who developed grade 4 neutropenia and those who did not was 0.7 (range, 0.2–1.2) mg/dl and 0.5 (range, 0.3–2.4) mg/dl, respectively ($P = 0.03$, Mann–Whitney U test). The median PTB in patients who developed grade 3–4 diarrhea and those who did not was 0.6 and 0.5 mg/dl, respectively ($P = 0.22$). The bars represent the median values.

Table 2. Univariate analysis of association between grade 4 neutropenia and pre-treatment clinical variables

	Neutropenia grade		Odds ratio (95% CI)
	Grade <4 ($n = 98$)	Grade 4 ($n = 29$)	
Sex			
Male	70	23	1
Female	28	6	0.65 (0.24–1.77)
Age			
Median (range)	61 (24–74)	65 (38–73)	1.04 (0.99–1.09)
Performance status			
0	29	5	1
1, 2	69	24	2.02 (0.70–5.80)
Liver metastasis			
No	82	27	1
Yes	16	2	0.38 (0.08–1.76)
Prior chemotherapy			
No	84	26	1
Yes	14	3	0.69 (0.19–2.60)
Treatment schedule			
Every 3 weeks	41	15	1
Every 4 weeks	57	14	0.67 (0.29–1.54)
Cisplatin dose (mg/m^2)			
60	56	15	1
80	42	14	1.24 (0.54–2.86)
AST (IU/l)			
Median (range)	22 (11–161)	22 (11–56)	0.98 (0.95–1.01)
ALT (IU/l)			
Median (range)	18 (6–266)	20 (5–67)	0.99 (0.97–1.02)
PNC ($\times 10^9$/l)			
Median (range)	4.4(2.0–8.5)	3.9 (1.8–8.3)	0.84 (0.61–1.14)
PTB (mg/dl)			
Median (range)	0.5 (0.3–2.4)	0.7 (0.2–1.2)	3.74 (0.70–19.9)
≤0.7	87	20	1
>0.7	11	9	3.56 (1.30–9.73)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

Statistical Methods

The Mann–Whitney U test was used to compare the PTB levels of patients who developed severe toxicity and those who did not. Possible explanatory factors were compared using a logistic regression model. A PTB threshold of ≤0.7 mg/dl was selected to categorize this variable because a total bilirubin level higher than 0.7 mg/dl has been correlated with a mutated UGT1A1 genotype and the occurrence of grade 4 neutropenia (8). Furthermore, sex, performance status, liver metastasis, prior chemotherapy, treatment schedule and cisplatin dose were defined as categorized variables, and age, AST, ALT and pre-treatment neutrophil count (PNC) were examined as continuous variables. Variables that seemed to be associated with severe toxicity ($P < 0.1$) were considered for inclusion in a multivariate analysis using a backward stepwise regression model. We performed these analyses using the SPSS statistical package (SPSS version 11.0 for Windows; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 127 consecutive patients with thoracic malignancy received cisplatin and irinotecan therapy. The patient characteristics are listed in Table 1. In all, two patients (1.5%) had

Table 3. Backward stepwise regression analysis of association between severe toxicity and pre-treatment clinical variables

Variable	Co-efficient	*P*	Odds ratio (95% CI)
Grade 4 neutropenia			
Cisplatin dose	1.04	0.04	2.84 (1.03–7.81)
PNC	0.42	0.04	1.53 (1.02–2.27)
PTB	1.59	0.02	4.93 (1.37–17.7)
Grade 3–4 diarrhea			
Liver metastasis	2.41	0.004	11.2 (2.18–57.4)
Cisplatin dose	1.61	0.03	5.00 (1.18–21.3)
PNC	0.67	0.03	1.96 (1.07–3.60)

Adjusted for age and PS.
PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

stage IIA disease, seven patients (5.5%) had stage IIIA disease, 26 patients (20%) had stage IIIB disease and 85 patients (67%) had stage IV disease. The median PTB level was 0.6 (range, 0.2–2.4) mg/dl and the median PNC was 4.1 (range 1.8–8.5) $\times 10^9$/l. A total of 93 patients (73%) received the planned doses without skipping the irinotecan administrations on day 8 or 15. Among the remaining 34 patients, the irinotecan on day 8 or 15 was omitted in 27 of 164 (16.5%) planned doses in patients with PTB level $\leq$0.7 mg/dl, while in 11 of 34 (32.4%) planned doses in patients with PTB level >0.7 mg/dl ($P = 0.053$). Thus, the actual irinotecan dose delivered was lower with marginal significance in patients with PTB level >0.7 mg/dl. Grade 4 neutropenia occurred in 29 (23%) patients and grade 3–4 diarrhea occurred in 13 (10%) patients.

The median PTB level was higher in patients who developed grade 4 neutropenia than in those who did not (0.7 and 0.5 mg/dl, respectively; $P = 0.03$) (Fig. 1), but PTB was not correlated with the presence or absence of grade 3–4 diarrhea ($P = 0.22$).

In a univariate analysis, grade 4 neutropenia was associated with only the PTB level ($\leq$0.7 versus >0.7 mg/dl; $P = 0.01$, Table 2). When PTB level was analyzed as a continuous variable, the association was not significant (OR: 3.74; 95% CI: 0.70–19.9; $P = 0.12$). In a multivariate analysis, grade 4 neutropenia was associated with the PTB level ($\leq$0.7 versus >0.7 mg/dl; $P = 0.02$), the cisplatin dose ($P = 0.04$), and PNC ($P = 0.04$, Table 3). In a univariate analysis, grade 3–4 diarrhea was associated with only liver metastasis ($P = 0.01$, Table 4). We analyzed serum levels of PTB and pre-treatment AST and ALT between patients with ($n = 18$) or without ($n = 109$) liver metastasis. The median (range) PTB was 0.6 (0.4–2.4) mg/dl in patients with liver metastasis and 0.6 (0.2–1.2) mg/dl in patients without liver metastasis ($p = 0.19$). In contrast, the median (range) levels of pre-treatment AST and ALT were 30 (16–114) IU/l and 30 (11–84) IU/l, respectively, in patients with liver metastasis and 21 (11–161) IU/l and 17 (5–266) IU/l, respectively, in patients without liver metastasis ($P = 0.0054$). In a multivariate analysis, grade 3–4 diarrhea was associated with liver metastasis ($P = 0.004$), the cisplatin dose ($P = 0.03$) and PNC ($P = 0.03$, Table 4).

DISCUSSION

This study showed that the PTB level was significantly associated with severity of neutropenia in patients treated with cisplatin and weekly irinotecan. Although irinotecan-induced toxicity can be reduced by skipping irinotecan on day 8, 15, or both, this dose modification is not enough to eliminate severe toxicity completely. In this study irinotecan was more frequently omitted on days 8 and 15 in patients with PTB level >0.7 mg/dl, and therefore, the association between PTB and irinotecan-induced toxicity may be underestimated. Thus, the PTB level, a simple routine measure in clinical practice, can be a useful predictive marker for irinotecan-induced toxicity.

The most compelling evidence for a genetic marker of toxicity caused by irinotecan therapy is seen with the *UGT* gene. In some retrospective pharmacogenetic studies, patients with at least one *UGT*1A1*28 allele encountered severe irinotecan-induced toxicity, compared with those with the wild-type genotype who were homozygous for the 6 TA repeat allele (6,9,10). In a prospective study, the *UGT*1A1 genotype was strongly associated with severe neutropenia in patients treated with irinotecan (8). More than 30 polymorphic variations have been reported to date for the *UGT*1A1 gene (17). Novel polymorphisms (*1, *6, *28,*60 and so on) in *UGT*1A1 and the functional characterization of known variants are helpful in elucidating the role of *UGT*1A1 genetic variation in irinotecan toxicity (18). The FDA has approved a *UGT*1A1 molecular assay test to detect polymorphisms in the *UGT*1A1 gene in clinical practice, so that patients with particular *UGT*1A1 gene variations that raise the risk of certain adverse effects can receive safer doses of irinotecan. This assay is intended to aid physicians to make decisions for individualized patient. Nevertheless, other important factors that affect dosing should also be considered, because severe toxicity sometimes occurs even in patients without particular *UGT*1A1 gene variations that place them at risk.

The *UGT*1A1 enzyme is responsible for hepatic bilirubin glucuronidation. A polymorphism in the *UGT*1A1 promoter has been linked with reduced *UGT*1A1 expression and is consequently associated with familiar hyperbilirubinemia. Accordingly, bilirubin levels may be associated with *UGT*1A1 function. The PTB level may reflect the total function of some polymorphisms in the *UGT*1A1 region and may be used as a simple and available surrogate marker for *UGT*1A1 function.

Recent studies have revealed that two major hepatic UGT, *UGT*1A1 and *UGT*1A9, and extra-hepatic *UGT*1A7 are involved in SN-38 glucuronidation (SN-38G) (7,19). The

Table 4. Univariate analysis of association between grade 3–4 diarrhea and pre-treatment clinical variables

	Diarrhea grade		Odds ratio (95% CI)
	Grade 0–2 ($n = 114$)	Grade 3–4 ($n = 13$)	
Sex			
Male	84	9	1
Female	30	4	1.24 (0.36–4.34)
Age			
Median (range)	65 (24–74)	65 (53–73)	1.07 (0.99–1.16)
Performance status			
0	29	5	1
1, 2	85	8	0.55 (0.17–1.80)
Liver metastasis			
No	101	8	1
Yes	13	5	4.86 (1.38–17.1)
Prior chemotherapy			
No	99	11	1
Yes	15	2	1.20 (0.20–7.04)
Treatment schedule			
Every 3 weeks	50	6	1
Every 4 weeks	64	7	0.91 (0.29–2.88)
Cisplatin dose (mg/m^2)			
60	66	5	1
80	48	8	2.20 (0.68–7.14)
AST (IU/l)			
Median (range)	21 (11–161)	23 (15–65)	1.00 (0.98–1.03)
ALT (IU/l)			
Median (range)	17 (5–266)	21 (14–84)	1.01 (0.99–1.02)
PNC ($\times 10^9$/l)			
Median (range)	4.2 (1.8–8.5)	3.5 (2.2–5.2)	0.77 (0.49–1.20)
PTB (mg/dl)			
Median (range)	0.55 (0.2–2.4)	0.6 (0.4–1.1)	1.95 (0.29–13.2)
≤ 0.7	96	11	1
>0.7	18	2	0.97 (0.20–4.75)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

efficacy of irinotecan is possibly affected by the activity of these genes. Thus, the product of some genetic polymorphisms in several genes may be a better pharmacogenetic marker for selecting patients who may not respond favorably to irinotecan-containing chemotherapy.

Cisplatin and irinotecan therapy is a standard regimen for both advanced non-small cell and small cell lung cancer (4). A randomized trial of irinotecan with or without cisplatin in patients with non-small cell lung cancer showed that grade 4 neutropenia was observed more frequently in the cisplatin–irinotecan arm (37%) than in the irinotecan-alone arm (8%), whereas grade 3 and 4 diarrhea was observed at the same frequency in both arms. In the present study, a higher cisplatin dose was associated with both grade 4 neutropenia and grade 3 and 4 diarrhea. The addition of cisplatin to another anti-cancer agent aggravated diarrhea in phase III studies (20), although diarrhea was moderate in cisplatin monotherapy observed in clinical trials (21). Thus, a higher dose of cisplatin seems to be associated with diarrhea, but the mechanism for this association remains unclear.

In this study PTB level was associated with the severity of neutropenia, but not with severity of diarrhea. When SN-38G is excreted in the bile and intestines, the bacteria-derived enzyme beta-glucuronidase converts SN-38G back

into SN-38 (22,23). Presence of SN-38 in the stool is associated with the occurrence of severe diarrhea as a result of the direct enteric injury caused by SN-38 (24). This phenomenon probably occurs because UGT1A1 is not involved in this step.

Liver metastasis was associated with the development of grade 3–4 diarrhea in both univariate and multivariate analyses in this study. This may be explained by small, but statistically significant differences in the pre-treatment transaminase levels between patients with or without liver metastasis. However, in contradiction to this explanation are that: (1) neither the pre-treatment AST nor ALT level was associated with grade 3–4 diarrhea in this study, and (2) in dose-finding studies of irinotecan monotherapy in patients with liver dysfunction, patients were categorized into subgroups by the PTB and serum AST and ALT levels, criteria of which were three times or five times the upper limit of normal (25,26). Thus, the small difference in the AST and ALT levels in this study is unlikely to be significant from the medical point of view.

The PNC in patients who developed grade 3–4 diarrhea was slightly lower than that in the other patients and the PNC was associated with grade 3–4 diarrhea in the multivariate analysis. Neutrophils play an important role in maintaining the mucosal barrier of the intestine and inflammatory responses against mucosal damage (27). Thus, reduced number, dysfunction, or both, of neutrophils may lead to impairment of the mucosal integrity, rendering these patients prone to develop diarrhea. In addition, the decreased number of neutrophils in the blood is closely related to malnutrition associated with cancer (28), which may in turn be associated with enhanced toxicity during chemotherapy with irinotecan and cisplatin.

In conclusion, the PTB level was significantly associated with severity of neutropenia in patients treated with cisplatin and weekly irinotecan. This will provide a simple and useful marker required for individualized therapy to reduce the risk of harmful chemotherapy.

Acknowledgments

We thank Mika Nagai for her assistance with the preparation of the manuscript.

Conflict of interest statement

None declared.

References

1. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, et al. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991;83:1164–8.
2. Rothenberg ML, Kuhn JG, Burris HA, Nelson J, 3rd, Eckardt JR, Tristan-Morales M, et al. Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993;11:2194–204.
3. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;343:905–14.
4. Negoro S, Masuda N, Takada Y, Sugiura T, Kudoh S, Katakami N, et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. *Br J Cancer* 2003;88:335–41.
5. Iyer L, King CD, Whitington PF, Green MD, Roy SK, Tephly TR, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Roleof uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J Clin Invest* 1998;101:847–54.
6. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 2000;60:6921–6.
7. Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). *Mol Pharmacol* 2002;62:608–17.
8. Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004;22:1382–8.
9. Iyer L, Das S, Janisch L, Wen M, Ramirez J, Karrison T, et al. *UGT*1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. *Pharmacogenomics J* 2002;2:43–7.
10. Marcuello E, Altes A, Menoyo A, Del Rio E, Gomez-Pardo M, Baiget M. *UGT*1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. *Br J Cancer* 2004;91:678–82.
11. Rouits E, Boisdron-Celle M, Dumont A, Guerin O, Morel A, Gamelin E. Relevance of different *UGT*1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. *Clin Cancer Res* 2004;10:5151–9.
12. Masuda N, Fukuoka M, Takada M, Kusunoki Y, Negoro S, Matsui K, et al. CPT-11 in combination with cisplatin for advanced non-small-cell lung cancer. *J Clin Oncol* 1992;10:1775–80.
13. Masuda N, Fukuoka M, Fujita A, Kurita Y, Tsuchiya S, Nagao K, et al. A phase II trial of combination of CPT-11 and cisplatin for advanced non-small-cell lung cancer. CPT-11 Lung Cancer Study Group. *Br J Cancer* 1998;78:251–6.
14. Niho S, Nagao K, Nishiwaki Y, Yokoyama A, Saijo N, Ohashi Y, et al. Randomized multicenter phase III trial of irinotecan and cisplatin versus cisplatin and vindesine in patients with advanced non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 1999;18:p492a.
15. Masuda N, Fukuoka M, Kudoh S, Kusunoki Y, Matsui K, Takifuji N, et al. Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. *Br J Cancer* 1993;68:777–82.
16. Kudoh S, Fujiwara Y, Takada Y, Yamamoto H, Kinoshita A, Ariyoshi Y, et al. Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. West Japan Lung Cancer Group. *J Clin Oncol* 1998;16:1068–74.
17. Burchell B, Hume R. Molecular genetic basis of Gilbert's syndrome. *J Gastroenterol Hepatol* 1999;14:960–6.
18. Sai K, Saeki M, Saito Y, Ozawa S, Katori N, Jinno H, et al. *UGT*1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. *Clin Pharmacol Ther* 2004;75:501–15.
19. Jinno H, Tanaka-Kagawa T, Hanioka N, Saeki M, Ishida S, Nishimura T, et al. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human *UGT*1A1 variants, G71R, P229Q, and Y486D. *Drug Metab Dispos* 2003;31:108–13.
20. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;12:360–7.
21. Arnold RJ, Gabrail N, Raut M, Kim R, Sung JC, Zhou Y. Clinical implications of chemotherapy-induced diarrhea in patients with cancer. *J Support Oncol* 2005;3:227–32.
22. Mathijssen RH, Loos WJ, Verweij J, Sparreboom A. Pharmacology of topoisomerase I inhibitors irinotecan (CPT-11) and topotecan. *Curr Cancer Drug Targets* 2002;2:103–23.

23. Yokoi T, Narita M, Nagai E, Hagiwara H, Aburada M, Kamataki T. Inhibition of UDP-glucuronosyltransferase by aglycons of natural glucuronides in kampo medicines using SN-38 as a substrate. *Jpn J Cancer Res* 1995;86:985–9.
24. Araki E, Ishikawa M, Iigo M, Koide T, Itabashi M, Hoshi A. Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. *Jpn J Cancer Res* 1993;84:697–702.
25. Venook AP, Enders Klein C, Fleming G, Hollis D, Leichman CG, et al. A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. *Ann Oncol* 2003;14:1783–90.
26. Schaaf LJ, Hammond LA, Tipping SJ, Goldberg RM, Goel R, Kuhn JG, et al. Phase 1 and pharmacokinetic study of intravenous irinotecan in refractory solid tumor patients with hepatic dysfunction. *Clin Cancer Res* 2006;12:3782–91.
27. Sartor RB. Mucosal immunology and mechanisms of gastrointestinal inflammation. In: Feldman M, Friedman LS, Sleisenger MH editors. Gastrointestinal and Liver Disease, 7th edn. Philadelphia, PA: Saunders 2002; 21–51.
28. Balducci L, Little DD, Glover NG, Hardy CS, Steinberg MH. Granulocyte reserve in cancer and malnutrition. *Ann Intern Med* 1983;98:610–1.

Jpn J Clin Oncol 2007;37(3)175–180
doi:10.1093/jjco/hym008

Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Terufumi Kato[1], Yasuhito Fujisaka[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Divisions of Internal Medicine and Thoracic Oncology and [2]Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Received September 6, 2006; accepted November 1, 2006; published online April 23, 2007

Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.
Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m^2) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m^2 in level 1, 135 mg/m^2 in level 2 to 150 mg/m^2 in level 3.
Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.
Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4). Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (*cis*-diammine-glycolate-O,O′-platinum II, 254-S) is a second-generation platinum derivative that has an

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m^2 and 180 mg/m^2, respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V_{20}) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status (14) 0 or 1; adequate bone marrow function (12.0×10^9/L $\geq$ white blood cell (WBC) count $\geq 4.0 \times 10^9$/L, neutrophil count $\geq 2.0 \times 10^9$/L, hemoglobin $\geq$ 10.0 g/dL and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin $\leq$ 1.5 mg/dL and transaminase $\leq$ twice the upper limit of the normal value), and renal function (serum creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 60 mL/min); and a PaO_2 of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

Treatment Schedule

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m^2 (level 1), 135 mg/m^2 (level 2), and 150 mg/m^2 (level 2). The dose of nedaplatin was 80 mg/m^2 through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensional conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level $\geq$1.6 mg/dL, infection $\geq$ grade 2, elevated hepatic transaminase level or total serum bilirubin $\geq$ grade 2, pneumonitis $\geq$ grade 2, peripheral neuropathy, musculoskeletal pain $\geq$ grade 3, fever $\geq$ 38°C, or performance status $\geq$ 2. Chemotherapy was terminated if the toxicities did not

recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever $\geq 38^{\circ}C$, infection $\geq$ grade 2, esophagitis of grade 3, performance status ≥ 3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, Maximum Tolerated Dose (MTD), and Recommended Dose For Phase II Trials

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count $<20 \times 10^9$/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

Study Design, Data Management and Statistical Analyses

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of The Patients

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

Treatment Delivery

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

Toxicity, DLT and MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid

Table 1. Patient characteristics

	n	(%)
Number of patients	18	
Gender		
male	14	(78)
female	4	(22)
Age		
median (range), years	62.5	(46–69)
PS		
0	11	(61)
1	7	(39)
Body weight loss		
< 5%	15	(83)
5–9%	2	(11)
≥ 10%	1	(6)
Clinical stage		
IIIA	10	(56)
IIIB	8	(44)
Histology		
adenocarcinoma	8	(44)
squamous cell carcinoma	6	(33)
non-small cell, not specified	4	(22)

PS, performance status.

replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The V_{20} and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Table 2. Treatment delivery

Dose level	Level 1	Level 2	Level 3
	(*n* = 6)	(*n* = 8)	(*n* = 4)
Number of chemotherapy cycles			
3–4	5	4	2
2	1	3	1
1	0	1	1
Total radiation dose (Gy)			
60	6	7	3
50–59	0	1	0
NE	0	0	1
Radiotherapy delay (days)			
0–4	5	7	2
5–9	1	0	1
NE	0	1	1

NE, not evaluable.

Table 3. Toxicity in all patients

Dose level	Level 1 (*n* = 6)			Level 2 (*n* = 8)			Level 3 (*n* = 4)		
Toxicity grade	2	3	4	2	3	4	2	3	4
Leukopenia	2	3	0	3	3	0	1	2	1
Neutropenia	0	4	1	2	3	1	0	2	2
Anemia	0	0	0	2	0	0	2	0	0
GPT elevation	1	0	0	2	0	0	0	0	0
Total bilirubin elevation	1	0	0	1	0	0	1	0	0
Infection	0	0	0	1	1	0	0	0	0
Allergic reaction	1	0	0	2	0	1	0	0	0
Anorexia	1	0	0	2	0	0	0	0	0
Nausea	0	0	0	1	0	0	0	0	0
Constipation	0	0	0	2	0	0	0	0	0
Esophagitis	1	0	0	2	1	0	0	0	0
Pneumonitis	0	0	1*	1	0	1*	0	0	0
Musculoskeletal pain	1	0	0	1	0	0	1	0	0
Alopecia	4	0	0	4	0	0	0	0	0

GPT, glutamic pyruvic transaminase.
*Pneumonitis was fatal in these patients.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL_{CO}) was not done in this patient. The PaO_2 was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l). The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), % DL_{CO} was 111%, and PaO_2 was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose V_{20} and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.

To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

Objective Response and Survival

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

DISCUSSION

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m^2 and nedaplatin 80 mg/m^2 every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m^2 and cisplatin 80 mg/m^2 were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V_{20} and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subclinical micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.

Acknowledgements

We thank Yuko Yabe and Mika Nagai for preparation of the manuscript. This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement

None declared.

References

1. Vokes EE, Crawford J, Bogart J, Socinski MA, Clamon G, Green MR. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2005;11:5045s–50s.
2. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2005;23:5910–7.
3. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–9.
4. Curran W, Scott CJ, Langer C, Komaki R, Lee J, Hauser S, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:p621 (abstr 2499).
5. Sekine I, Noda K, Oshita F, Yamada K, Tanaka M, Yamashita K, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–5.
6. Vokes EE, Herndon JE, 2nd, Crawford J, Leopold KA, Perry MC, Miller AA, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;20:4191–8.
7. Choy H, Akerley W, Safran H, Graziano S, Chung C, Williams T, et al. Multiinstitutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* 1998;16:3316–22.
8. Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Nakamura M, Gemba M. Nephrotoxicity of a new platinum compound, 254-S, evaluated with rat kidney cortical slices. *Toxicol Lett* 1990;52:15–24.
9. Furuse K, Fukuoka M, Kurita Y, Ariyoshi Y, Niitani H, Yoneda S, et al. A phase II clinical study of cis-diammine glycolato platinum, 254-S, for primary lung cancer. *Gan To Kagaku Ryoho* 1992;19:879–84.
10. Yamamoto N, Tamura T, Kurata T, Yamamoto N, Sekine I, Kunitoh H, et al. Phase I and pharmacokinetic (PK) study of (Glycolate-0, 0')-diammine platinum (II) (Nedaplatin: 254-S) in elderly patients with non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000;19:203a (abstr 792).
11. Nemoto K, Matsushita H, Ogawa Y, Takeda K, Takahashi C, Britton KR, et al. Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. *Am J Clin Oncol* 2003;26:46–9.
12. Sekine I, Nokihara H, Horiike A, Yamamoto N, Kunitoh H, Ohe Y, et al. Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma. *Br J Cancer* 2004;90:1125–8.
13. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–9.
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
16. Armitage P, Berry G, Matthews J. Survival analysis. In: Armitage P, Berry G, Matthews J editors. Statistical Methods in Medical Research, 4th edn. Oxford: Blackwell Science 2002; 568–90.
17. Hasegawa Y, Takanashi S, Okudera K, Aoki M, Basaki K, Kondo H, et al. Weekly paclitaxel and nedaplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a phase I/II study. *Jpn J Clin Oncol* 2004;34:647–53.
18. Nemoto K, Matsushita H, Ogawa Y, Takeda K, Takahashi C, Britton KR, et al. Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. *Am J Clin Oncol* 2003;26:46–9.
19. Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD, Jr, Morse D, et al. United States Food and Drug Administration drug approval summary: Gefitinib (ZD1839; Iressa) tablets. *Clin Cancer Res* 2004;10:1212–8.
20. Edelman MJ, Sekine I, Tamura T, Saijo N. Geographic variation in the second-line treatment of non-small cell lung cancer. *Semin Oncol* 2006;33(1 Suppl 1):39–44.
21. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–56.
22. Sekine I, Takada M, Nokihara H, Yamamoto S, Tamura T. Knowledge of efficacy of treatments in lung cancer is not enough, their clinical effectiveness should also be known. *J Thorac Oncol* 2006;1:398–402.
23. Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose – volume histogram parameters in lung cancer – a systematic review. *Radiother Oncol* 2004;71:127–38.
24. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005;63:5–24.
25. Machtay M. Pulmonary complications of anticancer treatment. In Abeloff MD, Armitage JO, Niederhuber JE, Kastran MB, McKenna WG editors. *Clinical Oncology*, 3rd edn. Philadelphia, PA: Elsevier Churchill Livingstone 2004; 1237–50.
26. Grills IS, Yan D, Martinez AA, Vicini FA, Wong JW, Kestin LL. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. *Int J Radiat Oncol Biol Phys* 2003; 57:875–90.

Jpn J Clin Oncol 2007;37(3)181–185
doi:10.1093/jjco/hym005

Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

Toshio Shimizu[1,3], Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Kazuhiko Yamada[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Divisions of Internal Medicine and Thoracic Oncology and [2]Radiation Oncology, National Cancer Center Hospital, Tokyo and [3]Department of Medical Oncology, Kinki University Nara Hospital, Ikoma, Nara, Japan

Received July 19, 2006; accepted November 8, 2006; published online April 10, 2007

Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo, 104-0045, Japan. E-mail: isekine@ncc.go.jp

70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever ≥ 38°C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles

of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

Acknowledgment

We would like to thank Mika Nagai for her assistance in the preparation of this manuscript.

Conflict of interest statement

None declared.

References

1. Sekine I, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, et al. Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. *Cancer Treat Rev* 2004;30:359–68.
2. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–60.
3. Turrisi AT, 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–71.
4. Sekine I, Fukuda H, Kunitoh H, Saijo N. Cancer chemotherapy in the elderly. *Jpn J Clin Oncol* 1998;28:463–73.
5. Yuen AR, Zou G, Turrisi AT, Sause W, Komaki R, Wagner H, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–60.
6. Siu LL, Shepherd FA, Murray N, Feld R, Pater J, Zee B. Influence of age on the treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 1996;14:821–8.
7. Quon H, Shepherd FA, Payne DG, Coy P, Murray N, Feld R, et al. The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1999;43:39–45.
8. Japan Clinical Oncology Group. Common Terminology Criteria for Adverse Events v3.0 Japanese edition. Available at: http://www.jcog.jp/SHIRYOU/fra_ma_guidetop.htm 2005.
9. World Health Organization. Handbook for reporting results of cancer treatment. Geneva: WHO Offset Publication No. 48, 1979.
10. Okamoto H, Watanabe K, Kunikane H, Yokoyama A, Kudoh S, Ishizuka N, et al. Randomized phase III trial of carboplatin(C) plus etoposide (E) vs. split doses of cisplatin (P) plus etoposide (E) in elderly or poor-risk patients with extensive disease small cell lung cancer (ED-SCLC): JCOG9702. *Proc Am Soc Clin Oncol* 2005;23:623s.
11. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–24.
12. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. *Cancer* 1998;82:836–41.
13. Westeel V, Murray N, Gelmon K, Shah A, Sheehan F, McKenzie M, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: a phase II study of the PAVE regimen. *J Clin Oncol* 1998;16:1940–7.

臨床画像別刷

CLINICAL IMAGIOLOGY

メジカルビュー社
〒162-0845 東京都新宿区市谷本村町2番30号
TEL 03(5228)2050

胸部

肺転移の診断に関してはCTが最も優れた画像診断法である。悪性腫瘍の肺転移は境界明瞭な結節影としてみられることが多いが非典型例も多く，原発巣の種類に応じた対応が必要である。肺に比べて一般に縦隔や胸膜は転移しにくい部位ではあるが，これらの部位に転移しやすい腫瘍もあり，診断には注意を要する。

楠本昌彦　渡辺裕一　立石宇貴秀　荒井保明

胸部の臓器のうち，肺は多くの悪性腫瘍の転移の部位となる臓器である。したがって種々の悪性腫瘍の肺転移は日常診療においてしばしば遭遇する疾患である。この転移性肺腫瘍の診断は，治療方針を立てるうえで，また悪性腫瘍の病期診断において重要であり，その診断に画像診断の果たす役割は必要で欠かすことのできないものである。

転移性肺腫瘍の画像診断は，①すでに悪性腫瘍の存在が明らかで，肺転移の存在診断が必要となる場合(病期診断)，②悪性腫瘍の存在が明らかでなく，スクリーニングの胸部単純X線写真やCTで肺に多発結節や孤立結節がみられる場合に重要となりうる[1]。

本稿では，画像診断上の肺転移の検出と特異性，さまざまな転移性肺腫瘍の画像所見に加え，縦隔，胸膜転移などについても概説する。

肺転移の画像診断法の選択

肺転移の画像上でのスクリーニング検査法としては，簡便でかつ安価しかも情報量が比較的多いという点で，胸部単純X線撮影が行われる。単純X線写真で，多発性の腫瘤影や結節影を認めた場合，転移性肺腫瘍を強く疑う。肺転移があるという存在診断には，単純X線写真のみで十分なこともある。また，抗癌剤を用いた化学療法後の治療効果の監視(モニター)にも適している。

しかしながら，肺結節影の検出に関しては，CTと比べて単純X線写真には限界もある。単純X線写真は，CTと比べて微小病変の描出に劣り，また心臓，横隔膜，骨，肺血管などの既存構造の重なりのために一定の大きさをもった結節でも検出されにくい，などの欠点がある。

したがって，胸部単純X線写真で肺転移が疑われた場合に限らず，単純X線写真で肺転移が明らかでない場合でも，原発巣の悪性腫瘍が肺転移を高頻度に起こしやすい腫瘍の場合や，原発巣が進行しており肺転移が予測される場合，あるいは肺転移の有無が治療方針の決定に大きな影響を及ぼすような場合は，CTが施行されることが推奨される。

CTの肺転移発見率に関しては，1970年代の切除例からの検討では，CTで51%，断層撮影で35%，単純X線写真では23%の描出率であったとされている[2]。また80年代には，当時のCT装置の改善により，同様の切除例からの検討でCTでのsensitivityは73%と報告されている[3]。90年代に入るとヘリカルCTの登場により，肺転移の検出はさらに向上し，転移性肺腫瘍の手術所見と対比したCTの検出能は，径5mm以上ではほぼ100%の検出率に達した[4]。

ヘリカルCTの登場で1回の呼吸停止下で全肺が

Kusumoto M, Watanabe H, Tateishi U, Arai Y：国立がんセンター中央病院放射線診断部

 0911-1069/07/¥400/論文/JCLS

スキャンできるようになったため，呼吸停止相のずれの問題はほぼ解決し，従来型CTとヘリカルCTとで転移性肺腫瘍の検出率を比較した報告では，ヘリカルCTが肺結節描出に優れていることが明らかとなった[5]。さらに，マルチスライスCTが普及している現状では，1回の呼吸停止下で全肺をより薄層でスライスできるようになったため，小結節描出率は明らかに向上しており，肺転移の検索にはCTが最も存在診断の精度が高い。

肺転移の特異性について

単純X線写真と断層写真の時代に比べて，CTにより肺転移の検出率が向上したのは疑う余地のないことである。しかしCTによって微小結節も同時に描出されるため，必ずしも特異性の向上につながっているとはいえない。すなわち，CTによってより小さな結節が描出されるが，それが必ずしも肺転移とは診断できない場合がある。

悪性腫瘍の存在が明らかでCTで結節が描出されても，過誤腫，結核腫，形質細胞腫，炎症性偽腫瘍，肺内リンパ節などの良性腫瘤であることが切除にて確認される場合が少なからず存在する。

それ以外にも，悪性腫瘍に対する化学療法後状態の日和見感染が，多発性の円形の肺結節様陰影としてみられることがしばしばある[6]。また，抗癌剤そのものの肺に対する毒性が，結果として肺限局性間質性肺炎や線維化を起こし，CTなどで結節影としてみられるという報告もある[7]。反対に，悪性腫瘍の患者で孤立性肺結節がみられても，原発性肺癌であった例もしばしば経験される。

このように，悪性腫瘍の症例で肺結節がみられた場合の肺転移である特異度は必ずしも高くはない。特異度に関する因子としては，悪性腫瘍の種類，年齢，結節影のサイズなどが関係する[8]。悪性腫瘍の種類としては，肺に転移しやすい腫瘍，骨軟部の肉腫や悪性黒色腫などでは肺転移の特異度が高く，また原発巣がかなり進行している場合や再発している場合も肺転移の特異度が高い。

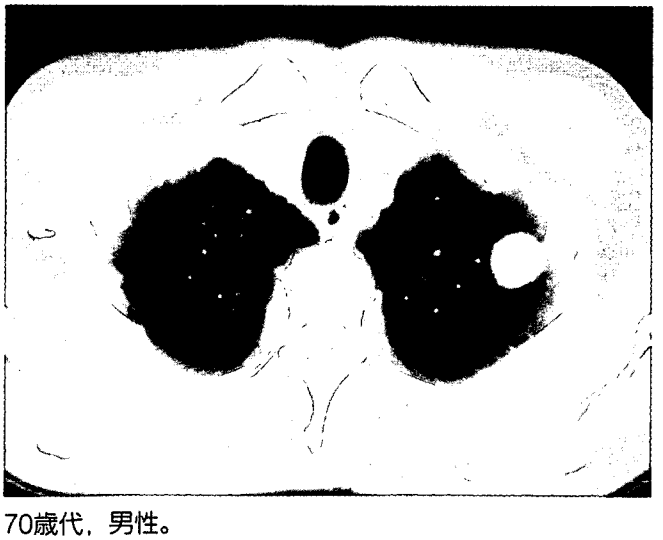
また，高齢者の場合に比べて若年者で見つかった肺結節のほうが，肺転移である可能性が高い[9]。結節のサイズとしては，小さな結節のほうがより良性の可能性が高くなり，大きいほうが肺転移の可能性が高くなる。

以上のように，肺結節が転移であるかどうかは，特に結節が小さい場合や1個の場合，診断に難渋し画像所見のみからは診断が困難であることが多い。この際，経過のX線写真やCTの比較読影がきわめて有用である。当然のことながら，以前にみられない結節影が出現したり，結節が大きくなったりしている場合は転移の可能性が高くなる。また，腫瘍マーカの上昇が診断に有用な場合もある。

肺転移の画像所見

肺転移は多くは肺動脈を介する血行性転移の形式をとり，そのX線所見として辺縁平滑で明瞭な円形の結節影，腫瘤影としてみられることが多い(**図1**)。通常は多発性で両側肺野にみられることが多く，サイズも大小不同である。好発部位としては，上肺野よりも下肺野で，また肺野中央部より末梢肺野に位置することが多い(**図2**)。下肺野に多いのは重力による影響，胸膜近くの肺末梢部に多いのは，肺血流の影響と考えられている。このような典型的な画像所見を呈する場合は，診断

図1　肝細胞癌の肺転移



70歳代，男性。
CT
左肺上葉に境界明瞭で辺縁平滑な結節を認める。典型的な血行性肺転移の画像所見である。