Table 3 Toxicities (JCOG Toxicity Criteria, Worst Grade of Any Course)

	CE					SPE					
	Grade					Grade					
Toxicity	**1**	**2**	**3**	**4**	**3+4 (%)**	**1**	**2**	**3**	**4**	**3+4 (%)**	***P*-value**
Haematologic											
Leucopenia	5	45	46	13	(54)	8	43	49	7	(51)	0.79
Neutropenia	0	5	46	58	(95)	4	7	41	57	(90)	0.22
Anaemia	9	58	32	—	(29)	20	45	27	—	(25)	0.54
Thrombocytopenia	20	18	29	32	(56)	16	15	12	5	(16)	<.01
Non-haematologic											
Nausea/vomiting	40	24	2	—	(2)	46	28	3	—	(3)	0.68
Diarrhoea	8	9	1	0	(1)	11	3	1	0	(1)	1.0
Bilirubin	—	31	0	0	(0)	—	16	1	0	(1)	0.50
AST	47	9	3	0	(3)	30	8	6	0	(6)	0.33
ALT	40	9	2	0	(2)	38	8	4	0	(4)	0.45
Creatinine	10	2	0	0	(0)	27	3	1	0	(1)	0.50
Hyponatraemia	38	11	7	11	(16)	46	20	6	9	(14)	0.58
PaO2	39	21	7	1	(10)	44	23	2	1	(4)	0.22
Fever	15	15	0	0	(0)	21	16	0	0	(0)	—
Infection	12	15	5	3	(7)	16	7	5	1	(6)	0.78
Bleeding	8	1	0	0	(0)	4	0	0	0	(0)	—
Neurologic-sensory	2	1	0	—	(0)	3	2	0	—	(0)	—
Alopaecia	67	22	—	—		66	15	—	—		

CE, carboplatin plus etoposide; JCOG, Japan Clinical Oncology Group; PaO_2, partial pressure of oxygen; SPE, split doses of cisplatin plus etoposide.

Table 4 Palliation score

	CE		SPE		
	Change from baseline		Change from baseline		
Symptom	**Mean (s.d.)**	**Median (range)**	**Mean (s.d.)**	**Median (range)**	***P*[a]**
Cough	−0.38 (1.16)	0 (−3 to 3)	−0.54 (1.06)	0 (−3 to 3)	0.51
Pain	−0.19 (1.00)	0 (−3 to 3)	−0.19 (0.96)	0 (−3 to 3)	0.96
Anorexia	−0.07 (1.16)	0 (−3 to 3)	0.08 (1.22)	0 (−3 to 3)	0.37
Shortness of breath	−0.05 (1.02)	0 (−2 to 3)	−0.31 (0.95)	0 (−3 to 3)	0.12
Well-being	−0.15 (1.13)	0 (−3 to 3)	−0.02 (1.14)	0 (−3 to 3)	0.48
Nausea	0.16 (0.84)	0 (−2 to 3)	0.26 (0.80)	0 (−1 to 3)	0.21
Diarrhoea or constipation	0.05 (1.07)	0 (−3 to 3)	0.04 (0.99)	0 (−3 to 3)	0.69
Sleep	−0.15 (1.08)	0 (−3 to 3)	−0.04 (0.89)	0 (−3 to 2)	0.10
Total	−0.80 (6.04)	−2 (−12 to 22)	−0.71 (5.35)	−1 (−15 to 21)	0.32

CE, carboplatin plus etoposide; s.d., standard deviation; SPE, split doses of cisplatin plus etoposide. [a]Wilcoxon rank-sum test.

The MST was 5.2 months in the CE arm *vs* 4.7 months in the SPE arm. OS was very similar between the arms ($P=0.54$, one sided). The MST and 1-year survival rate was 10.6 months and 41% in the CE arm *vs* 9.9 months and 35% in the SPE arm.

Second-line chemotherapy

According to an *ad-hoc* survey (not pre-specified in the protocol), 130 (59%) patients (68 (62%) patients in the CE arm and 62 (56%) in the SPE arm) received second-line chemotherapy after relapse and the regimens were almost equally distributed between the arms. The same regimen as the initial chemotherapy, platinum-based combinations, and irinotecan regimens with or without other agents were administered in 17 (15%), 48 (44%), and 40 (36%) patients in the CE arm *vs* 10 (9%), 44 (40%), and 40 (36%) in

Table 5 Therapeutic response (WHO)

	CE	SPE	Total
CR	5	5	10
PR	75	75	150
NC	17	11	28
PD	11	16	27
NE	2	3	5
Total	110	110	220
Response rate	73%	73%	
95% CI	63–81%	63–81%	

CE, carboplatin plus etoposide; CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; SPE, split doses of cisplatin plus etoposide; WHO, World Health Organization.

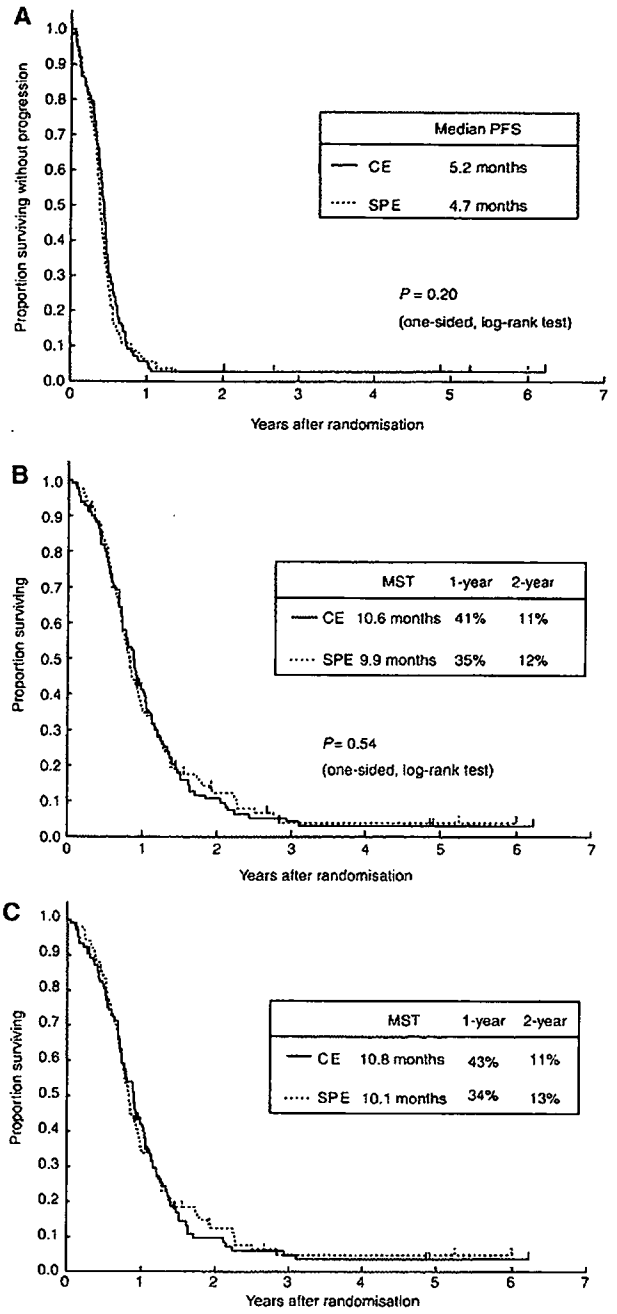

Figure 2 (**A**) PFS curves ($n = 220$). (**B**) OS curves ($n = 220$). (**C**) Survival curves of the patients ⩾70 years of age with a PS of 0–2 ($n = 202$).

the SPE arm. Other chemotherapy regimens included topotecan monotherapy, amrubicin monotherapy, or other regimens.

Subset analysis and multivariate analysis

Subset analysis was performed according to PS and age (Table 6). There were no differences in OS between the arms in any subset; thus, an interaction between treatment and PS is unlikely. The survival curves of the patients ⩾70 years of age with a PS of 0–2 are shown in Figure 2C, and the survival curves were very similar with that of original overall populations. Even in the multivariate analysis with seven selected baseline variables, there was no difference in OS between the arms. High lactate dehydrogenase level was most strongly associated with poor prognosis (Table 7).

Table 6 Subset analysis – overall survival

Subgroup	Number of patients (%)	MST (months) CE	MST (months) SPE
PS 0–1	162 (74)	10.9	10.1
PS 2–3	58 (26)	8.3	8.1
<70 years and PS 3	18 (8)	7.1	6.9
⩾70 years and PS 0–2	202 (92)	10.8	10.0

CE, carboplatin plus etoposide; MST, median survival time; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Table 7 Multivariate analysis with baseline prognostic factors

Variables	P-value	Hazard ratio	95% CI
Treatment arm (CE vs. SPE)	0.99	0.99	0.75–1.33
Alkaline phosphatase level (normal vs abnormal)	0.97	0.99	0.68–1.46
Lactate dehydrogenase level (⩾ × 1.5 vs < × 1.5)	<0.001	1.69	1.23–2.26
Leucocyte count (⩾10000/mm^3 vs <10000/mm^3)	0.06	1.82	0.99–3.36
Age (⩾75 years vs <75 years)	0.77	1.05	0.78–1.41
PS (2–3 vs 0–1)	0.41	1.15	0.82–1.61
Sex (female vs male)	0.13	0.70	0.45–1.11

CE = carboplatin plus etoposide; SPE = split doses of cisplatin plus etoposide; PS = performance status; CI = confidence interval.

DISCUSSION

Until recently, there was no standard chemotherapeutic regimen for elderly SCLC patients. Two phase III (Medical Research Council Lung Cancer Working Party, 1996; Souhami *et al*, 1997) and two randomised phase II trials (Pfeiffer *et al*, 1997; Ardizzoni *et al*, 2005) have shown that suboptimal chemotherapies, such as oral etoposide monotherapy or attenuated doses of combination chemotherapy, may lead to reduced survival in elderly or poor-risk SCLC patients when compared with standard doses of combination chemotherapies. The CE regimen, which has acceptable toxicities and reproducible efficacy, has been used in elderly or poor-risk patients with SCLC worldwide, although there have been substantial differences in toxicities and efficacy between the reported phase II trials. Four trials demonstrated both favourable toxicities and efficacy (Carney, 1995; Evans *et al*, 1995; Matsui *et al*, 1998; Okamoto *et al*, 1999) and three showed somewhat disappointing results because of suboptimal doses of oral etoposide (Larive *et al*, 2002), greater inclusion of patients with poor prognostic factors (Samantas *et al*, 1999), and deterioration of comorbidities as a result of chemotherapy (Quoix *et al*, 2001). No phase III trial evaluating the role of the CE regimen in this population has been reported until now.

This is the first phase III trial comparing carboplatin-based CE and cisplatin-based SPE regimens in elderly or poor-risk patients with ED-SCLC. In addition, this is also the largest randomised trial specifically designed for elderly or poor-risk SCLC patients. Although there was no significant difference in the palliation scores, response rate, and OS between the arms, the efficacy of

both regimens was promising, as this study included only elderly or poor-risk patients with SCLC. Most toxicities were tolerable and the treatment compliance was also favourable in both arms. Approximately two-thirds of the patients received all four cycles of treatment. The CE arm in the current trial had more pronounced thrombocytopenia, which was considered manageable because none of the patients in the CE arm showed grade 3 or 4 bleeding, and the CE arm had a slightly prolonged course interval and a slightly greater incidence of dose reduction. However, in our opinion, these toxicities are less meaningful in clinical practice. More importantly, the CE regimen does not require hydration and can be given in an outpatient setting. Based on the results of this study, many JCOG members prefer the CE regimen to the SPE regimen and consider it to be more suitable for the control arm of future phase III trials.

The MST of each regimen (10.6 months for CE *vs* 9.9 months for SPE) was promising considering that this study included only elderly or frail patients with ED-SCLC. However, some retrospective studies have shown that fit elderly patients who have adequate organ functions, a good PS, and no comorbidity are able to tolerate intensive chemotherapy well and show a similar therapeutic response and survival rate as younger patients (Siu *et al*, 1996; Yuen *et al*, 2000). In fact, in this trial the MST of fit elderly patients $\geqslant 70$ years of age with a PS of 0–1 was 10.9 months for the CE arm and 10.1 months for the SPE arm. In contrast, the MST of patients with a PS of 3 was only approximately 7 months. Furthermore, the group of fit elderly patients comprised 74% of the patients in this study. Therefore, the favourable survival rates in our trial may be attributable to patient selection. In other words, one limitation of this study is that the results of this trial cannot be extrapolated to frail elderly with a poor PS and/or comorbid illness because of the likelihood of greater inclusion of fit elderly patients in this trial.

Although the total dose in both the CE and SPE arms was slightly lower than the standard regimen, 92% of the patients showed grade 3 or 4 neutropenia, and dose reduction and course delay occurred frequently. However, the MST of both regimens was comparable with that of non-elderly or non-selected patients with ED-SCLC in historical reports (Noda *et al*, 2002; Niell *et al*, 2005). These findings suggest that both regimens are not suboptimal, but are near-full and effective doses for elderly or poor-risk patients with ED-SCLC. The CE arm in the current trial had a slightly prolonged course interval and a slightly greater incidence of dose reduction when compared to the SPE regimen. However, 95% of the patients showed grade 3 or 4 neutropenia and 56% showed grade 3 or 4 thrombocytopenia. Therefore, we believe that the dose escalation of the CE regimen may be difficult in this trial.

It remains unclear whether the elderly are able to tolerate a single modest dose of cisplatin (60–80 mg m^{-2} IV) on day 1. We feel that a fit elderly person who passes strict eligibility criteria can receive a modest dose of cisplatin IV on day 1. However, the more common situation is of elderly patients who have comorbidity and a poor PS, and cannot tolerate a standard single dose of cisplatin. Westeel *et al* (1998) and Murray *et al* (1998) reported that split doses of cisplatin were safely and effectively administered in elderly or frail patients with LD-SCLC. The SPE regimen appeared to be an appropriate treatment for elderly patients with SCLC who cannot tolerate a standard single dose of cisplatin. However, it remains unclear whether fit elderly patients in our trial can tolerate a standard single dose of cisplatin, and if so, it also remains unclear whether fit elderly patients who receive a standard single dose of cisplatin are able to achieve a more improved survival than those who receive SPE. Unfortunately, no randomised study comparing a single standard dose of cisplatin with SPE has been reported in fit elderly patients with SCLC.

There are some problems with the design in this study. The hypothesis was that carboplatin would improve survival, and the design of the trial was a superiority design with survival as the primary end point. However, this hypothesis was based on two possible misconceptions. First, carboplatin could be better dosed and might be more efficacious than cisplatin in SCLC. Unfortunately, this hypothesis could not be sustained on the basis of the available literatures. A number of clinical trials have indicated that carboplatin-based combination chemotherapy has a similar or slightly reduced efficacy compared with cisplatin-based combination chemotherapy against various tumours (Go and Adjei, 1999; Hotta *et al*, 2004). Therefore, our trial should have been designed as a non-inferiority trial. However, if this trial were planned as a non-inferiority trial, a total sample size would be about 500 to 1000 patients, with equal expected survival and a non-inferiority margin for hazard ratio ranging from 1.2 to 1.3. Second, the cisplatin dose in the control arm was an attenuated dose. Souhami *et al* (1997) used reduced dose of cisplatin (60 mg m^{-2} IV on day 1) and Murray *et al* (1998) used a single course of a split cisplatin dose in their studies. These regimens were completely different from the control arm in the present study. A standard dose of cisplatin given in 3 days is the best way of giving standard cisplatin (30 mg m^{-2} IV on days 1–3) with etoposide (130 mg m^{-2} IV on days 1–3), according the North Central Cancer Treatment Group (Maksmiuk *et al*, 1994). Had standard SPE been used for the control arm, better survival might have been achieved with increased toxicities. Another problem with the design was the inclusion of patients with a PS of 3, even if they were less than 70 years old. This made the target population heterogeneous. The number of such patients actually recruited was quite small, so emphasising the inappropriateness of their inclusion. A further limitation of this study may be a long accrual period of five-and-a-half years. Because our oncologists might have been afraid of the risk of TRD or increased toxicities in frail elderly with a poor PS and/or comorbid illness, more fit elderly patients were selectively registered and consequently the accrual rate was very slow.

In our trial, although both regimens were well-tolerated and efficacy was promising, over 90% of the patients in both arms showed grade 3 or 4 neutropenia, which may be justified and acceptable for a clinical trial involving elderly or poor risk patients with ED-SCLC, because only 6% of the patients showed grade 3 or 4 infection and TRD occurred in only four (1.8%) patients. Because all TRD occurred after the first course of chemotherapy, careful monitoring and management is necessary, particularly in the first course, if CE or SPE are administered to elderly or frail patients. Several retrospective analyses (Findlay *et al*, 1991; Radford *et al*, 1992) and a prospective study (Timmer-Bonte *et al*, 2005) have shown that standard-dose chemotherapy without G-CSF support causes more risk of early death and sepsis in the older population. Moreover, the American Society of Clinical Oncology (ASCO) guideline recommends the use of prophylactic G-CSF in patients at higher risk for chemotherapy-induced infection, such as those having a poor PS, older age, or comorbid illness (Smith *et al*, 2006). In this trial, the prophylactic use of G-CSF was recommended, but the actual use was left to the discretion of the treating physician because the use of G-CSF leads to increased drug cost. Although G-CSF was administered in only 54% of the total courses, we believe that the prophylactic use of G-CSF with CE regimen should be recommended in a new trial or clinical practice.

In conclusion, although the SPE regimen is still considered to be the standard treatment for elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk-benefit balance. Based on the results of our trial, a phase III trial of the CE regimen *vs* amrubicin monotherapy, supported by a pharmaceutical company, is now ongoing in elderly patients with ED-SCLC in Japan, and a comparative trial of the CE regimen *vs* carboplatin plus irinotecan regimen (Okamoto *et al*, 2006) is being discussed for a future trial in our group.

ACKNOWLEDGEMENTS

We are indebted to Ms Mieko Imai and Ms Tomoko Yamabe for data management, and to Dr Haruhiko Fukuda for direction of the JCOG data center and oversight of management of the study. This work was supported in part by Grants-in-Aid for Cancer Research and for the Second-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare (Tokyo).

REFERENCES

Ardizzoni A, Favaretto A, Boni L, Baldini E, Castiglioni F, Antonelli P, Pari F, Tibaldi C, Altieri AM, Barbera S, Cacciani G, Raimondi M, Tixi L, Stefani M, Monfardini S, Antilli A, Rosso R, Paccagnella A (2005) Platinum-etoposide chemotherapy in elderly patients with small-cell lung cancer: results of a randomized multicenter phase II study assessing attenuated-dose or full-dose with lenograstim prophylaxis-A Forza Operativa Nazionale Italiana Carcinoma Polmonare and Gruppo Studio Tumori Polmonari Veneto (FONICAP-GSTPV) study. *J Clin Oncol* 23: 569-575

Carney DN (1995) Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 12(Suppl 3): S77-S83

DeMets DL, Lan KK (1994) Interim analysis: the alpha spending function approach. *Stat Med* 13: 1341-1352

Evans WK, Radwi A, Tomiak E, Logan DM, Martins H, Stewart DJ, Goss G, Maroun JA, Dahrouge S (1995) Oral etoposide and carboplatin: effective therapy for elderly patients with small cell lung cancer. *Am J Clin Oncol* 18: 149-155

Findlay MP, Griffin AM, Raghavan D, McDonald KE, Coates AS, Duval PJ, Gianoutsos P (1991) Retrospective review of chemotherapy for small cell lung cancer in the elderly: dose the end justify the means? *Eur J Cancer* 27: 1597-1601

Go RS, Adjei AA (1999) Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 17: 409-422

Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M (2004) Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 22: 3838-3852

Larive S, Bombaron P, Riou R, Fournel P, Perol M, Lena H, Dussopt C, Philip-Joet F, Touraine F, Lecaer H, Souquet PJ (2002) Carboplatin-etoposide combination in small cell lung cancer patients older than 70 years: a phase II trial. *Lung Cancer* 35: 1-7

Maksmiuk AW, Jett JR, Earle JD, Su JQ, Diegert FA, Mailliard JA, Kardinal CG, Krook JE, Veeder MH, Wiesenfeld M, Tschetter LK, Levitt R (1994) Sequencing and schedule effects of cisplatin plus etoposide in small-cell lung cancer: results of a North Central Cancer Treatment Group randomized clinical trial. *J Clin Oncol* 12: 70-76

Matsui K, Masuda N, Fukuoka M, Yana T, Hirashima T, Komiya T, Kobayashi M, Kawahara M, Atagi S, Ogawara M, Negoro S, Kudoh S, Furuse K (1998) Phase II trial of carboplatin plus oral etoposide for elderly patients with small-cell lung cancer. *Br J Cancer* 77: 1961-1965

Medical Research Council Lung Cancer Working Party (1996) Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. *Lancet* 348: 563-566

Morita T (2002) A statistical study of lung cancer in the annual of pathological autopsy cases in Japan, from 1958 to 1997, with reference to time trends of lung cancer in the world. *Jpn J cancer Res* 93: 15-23

Murray N, Grafton C, Shah A, Gelmon K, Kostashuk E, Brown E, Coppin C, Coldman A, Page R (1998) Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer. *J Clin Oncol* 16: 3323-3328

Niell HB, Herndon II JE, Miller AA, Watson DM, Sandler AB, Kelly K, Marks RS, Perry MC, Ansari RH, Otterson G, Ellerton J, Vokes EE, Green MR (2005) Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol* 23: 3752-3759

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

Okamoto H, Naoki K, Narita Y, Hida N, Kunikane H, Watanabe K (2006) A combination chemotherapy of carboplatin and irinotecan with granulocyte colony-stimulating factor (G-CSF) support in elderly patients with small cell lung cancer. *Lung Cancer* 53: 197-203

Okamoto H, Watanabe K, Nishiwaki Y, Mori K, Kurita Y, Hayashi I, Masutani M, Nakata K, Tsuchiya S, Isobe H, Saijo N (1999) Phase II study of area under the plasma-concentration-*vs*-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. *J Clin Oncol* 17: 3540-3545

Pfeiffer P, Rytter C, Madesen EL, Moeholt K, Hansen O, Bentzen S, Palshof T, Rose C (1997) Re: five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst* 89: 1892-1893

Quoix E, Breton JL, Daniel C, Jacoulet P, Debieuvre D, Paillot N, Kessler R, Moreau L, Coetmeur D, Lemarie E, Milleron B (2001) Etoposide phosphate with carboplatin in the treatment of elderly patients with small-cell lung cancer: a phase II study. *Ann Oncol* 12: 957-962

Radford JA, Ryder WD, Dodwell D, Anderson H, Thatcher N (1992) Predicting septic complications of chemotherapy: An analysis of 382 patients treated for small cell lung cancer without dose reduction after major sepsis. *Eur J Cancer* 29A: 81-86

Samantas E, Skarlos DV, Pectasides D, Nicolaides P, Kalofonos H, Mylonakis N, Vardoulakis Th, Kosmidis P, Pavlidis N, Fountzilas G (1999) Combination chemotherapy with low doses of weekly carboplatin and oral etoposide in poor risk small cell lung cancer. *Lung Cancer* 23: 159-168

Schoenfeld DA, Richter JR (1982) Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 38: 163-170

Siu LL, Shepherd FA, Murray N, Feld R, Pater J, Zee B (1996) Influence of age on the treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 14: 821-828

Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC (2006) 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 24: 3187-3205

Souhami RL, Spiro SG, Rudd RM, Ruiz de Elvira MC, James LE, Gower NH, Lamont A, Harper PG (1997) Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst* 89: 577-580

Timmer-Bonte JN, de Boo TM, Smit HJ, Biesma B, Wilschut FA, Cheragwandi SA, Termeer A, Hensing CA, Akkermans J, Adang EM, Bootsma GP, Tjan-Heijnen VC (2005) Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a dutch randomized phase III study. *J Clin Oncol* 23: 7974-7984

Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, Narabayashi M, Fukutomi T, Kondo H, Shimoyama M, Suemasu K (1993) Toxicity grading criteria of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 23: 250-257

Westeel V, Murray N, Gelmon K, Shah A, Sheehan F, McKenzie M, Wong F, Morris J, Grafton C, Tsang V, Goddard K, Murphy K, Parsons C, Amy R, Page R (1998) 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* 16: 1940-1947

World Health Organization (1979) *WHO Handbook for Reporting Results of Cancer Treatment* WHO offset publication No. 48 Geneva: World Health Organization

Yuen AR, Zou G, Turrisi AT, Sause W, Komaki R, Wagner H, Aisner SC, Livingston RB, Blum R, Johnson DH (2000) 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* 89: 1953-1960

Appendix

This study was coordinated by the Japan Clinical Oncology Group (N Saijo, Chairperson) and was performed with the cooperation of the following institutions and investigators: Tochigi Cancer Center Hospital, Tochigi (K Mori, M Noda, T Kondo, and Y Kamiyama); National Nishi-Gunma Hospital, Gunma (S Tsuchiya, Y Koike, K Satoh, A Tohi, and K Kaira); Gunma Cancer Center Hospital, Gunma (K Minato); Saitama Cancer Center Hospital, Saitama (H Sakai, K Kobayashi, and R Kuroki); National Cancer Center, Central Hospital, Tokyo (T Tamura, Y Ohe, H Kunitoh, I Sekine, H Nokihara, and H Murakami); National Cancer Center Hospital East, Chiba (R Kakinuma, K Kubota, H Ohmatsu, K Gotoh, and S Niho); National International Medical Center, Tokyo (Y Takeda, S Izumi, A Kawana, M Kamimura, and M Iikura); Toranomon Hospital, Tokyo (K Kishi, and M Kawabata); Kanagawa Cancer Center Hospital, Kanagawa (K Yamada, I Nomura, F Oshita, and M Ikehara), Yokohama Municipal Citizen's Hospital, Kanagawa (K Watanabe, H Kunikane, H Okamoto, A Nagatomo, and H Aono); Niigata Cancer Center Hospital, Niigata (A Yokoyama, H Tsukada, M Makino, T Shinbo, S Kinebuchi, J Tanaka, M Tango, and T Ohara); Gifu City Hospital, Gifu (T Sawa, M Miwa, T Ishiguro, M Sawada, and T Yoshida); Aichi Cancer Center Central Hospital, Aichi (K Yoshida, and T Hida); Aichi Cancer Center Aichi Hospital, Aichi (H Saitoh, and M Okuno); Osaka City University Medical School, Osaka (S Kudoh, S Kyoh, H Kamoi, N Yoshimura, T Kodama, K Ohtani, S Shiraishi, S Nomura, S Enomoto, H Matsuura, and R Wake); Kinki University Medical School, Osaka (T Nogami, N Yamamoto, S Sakai, K Kodama, K Akiyama, J Tsurutani, K Tamura); Osaka Prefectural Adult Disease Center, Osaka (S Nakamura, F Imamura, M Yoshimura, S Yamamoto, K Ueno, H Ohmiya, H Matsuoka, and H Uda); Osaka Prefectural Respiratory and Allergy Medical Center, Osaka (M Furukawa, T Yamadori, T Takimoto, and T Hirashima); National Kinki Central Thoracic Disease Center, Osaka (S Minami, N Naka, T Kawaguchi, and H Ishikawa); National Toneyama Hospital, Osaka (Y Okano); Osaka City General Medical Center, Osaka (N Takifuji, and M Miyazaki); Kobe City Central Hospital, Kobe (T Nishimura, Y Okazaki, D Kinose, H Fujii, S Takakura, and M Hayashi); Sasebo City General Hospital, Nagasaki (J Araki); Kumamoto Regional Medical Center, Kumamoto (H Senba, T Seto, and S Fujii).

Lung Cancer (2007) 58, 362–368

available at www.sciencedirect.com

ScienceDirect

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

Randomized phase II trial of three intrapleural therapy regimens for the management of malignant pleural effusion in previously untreated non-small cell lung cancer: JCOG 9515

Kimihide Yoshida[a,*], Takahiko Sugiura[a], Nobuhide Takifuji[b], Masaaki Kawahara[c], Kaoru Matsui[d], Shinzoh Kudoh[e], Minoru Takada[f], Masahiro Fukuoka[g], Yutaka Ariyoshi[h], Haruhiko Fukuda[i], Nagahiro Saijo[j]

[a] Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
[b] Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan
[c] Department of Internal Medicine, National Kinki Chuo Hospital, Osaka, Japan
[d] Department of Internal Medicine, Osaka Prefectural Habikino Hospital, Habikino, Japan
[e] Department of Internal Medicine, Osaka City University, Osaka, Japan
[f] Department of Pulmonary Diseases, Rinku Genaral Hospital, Izumisano, Japan
[g] Department of Medical Oncology, Kinki University, Sayama, Japan
[h] Department of Internal Medicine, Aichi Prefectural Aichi Hospital, Okazaki, Japan
[i] Japan Clinical Oncology Group Data Center, National Cancer Center, Tokyo, Japan
[j] National Cancer Center Hospital East, Kashiwa, Japan

Received 10 May 2007; received in revised form 9 July 2007; accepted 15 July 2007

KEYWORDS
Non-small cell lung cancer;
Malignant pleural effusion;
Intrapleural therapy;
Management of malignant pleural effusion;
Bleomycin;
OK-432;
Cisplatin plus etoposide

Summary To evaluate the efficacy and toxicity of three intrapleural therapy regimens consisting of bleomycin (BLM), OK-432 (a pulverized product of heat-killed *Streptococcus pyogenes*) or cisplatin plus etoposide (PE) for the management of malignant pleural effusion (MPE) in previously untreated non-small cell lung cancer. Eligible patients were randomized to the BLM arm: BLM 1 mg/kg (maximum 60 mg/body), the OK-432 arm: OK-432 0.2 Klinische Einheit units (KE)/kg (maximum 10 KE/body), or the PE arm: cisplatin (80 mg/m^2) and etoposide (80 mg/m^2). Pleural response was evaluated every 4 weeks according to the study-specific criteria. All responders received systemic chemotherapy consisting of PE every 3–4 weeks for two or more courses. Pleural progression-free survival (PPFS) was defined as the time from randomization to the first observation of pleural progression or death due to any cause. The primary endpoint was the 4-week PPFS rate. Of 105 patients enrolled, 102 were assessed for response. The 4-week PPFS rate for the BLM arm was 68.6%, 75.8% for the OK-432 arm, and 70.6% for PE arm. Median survival time (MST) for the BLM arm was 32.1 weeks, 48.1 weeks for the OK-432 arm, and 45.7 weeks

* Corresponding author. Tel.: +81 52 762 6111; fax: +81 52 763 5233.
E-mail address: 105197@aichi-cc.jp (K. Yoshida).

0169-5002/$ – see front matter
doi:10.1016/j.lungcan.2007.07.009

for the PE arm. However, the outcomes did not differ significantly between groups. Toxicity was tolerable in all arms except for one treatment-related death due to interstitial pneumonia induced by BLM. We will select intrapleural treatment using OK-432 in the management of MPE in NSCLC for further investigation because it had the highest 4-week PPFS rate.

1. Introduction

Malignant pleural effusion (MPE) is a significant problem in the treatment of patients with advanced malignancies and is a major cause of poor prognosis [1]. The most widely used therapy for MPE is tube drainage with intrapleural instillation of sclerosing agents to prevent fluid reaccumulation [2].

Despite many reported trials of chemical pleurodesis, there has been no agreement as to the optimal treatment protocol for MPE [3–5]. The variety of response rates of individual agents among those studies has resulted from heterogeneous patient populations and differences in treatment procedures and response criteria [2,3,6]. To resolve these problems, we conducted a randomized phase II trial in which patient selection was limited to previously untreated patients with MPE due to non-small cell lung cancer (NSCLC) and, in view of adequate estimation of the efficacy of each intrapleural therapy regimen, single instillation of chemical agents and uncomplicated study-specific response criteria were applied. In this study, to select the most promising regimen for intrapleural therapy consisting of sclerosing or chemotherapeutic agents, we chose three regimens—BLM, OK-432 and cisplatin plus etoposide (PE). BLM was chosen because it is one of the most frequently used agents and is considered to have high efficacy, low toxicity and high availability [3,5,7,8]. OK-432 (a preparation of Streptococcus pyogenes, type A3, Chugai Pharmaceutical Co., Tokyo) has been used as an anti-tumor immunomodulator for lung cancer [9,10] and is reported to give superior responses for MPE compared to mitomycin C [11] and BLM [12]. At the beginning of this study, PE regimens were considered one of the standard combination chemotherapy regimens for NSCLC, and a phase II trial using this regimen for intrapleural therapy suggested potential survival benefit as well as local control effects [13].

2. Methods

2.1. Patient selection

The eligibility criteria were as follows: cytologically or histologically proven malignant pleural effusion associated with newly diagnosed NSCLC; no prior chemotherapy, thoracic radiotherapy or thoracic surgery; age of 75 years or less; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 after tube thoracostomy; full lung reexpansion after tube thoracostomy; adequate bone marrow reserve (WBC count $\geq 4000\,\mu L^{-1}$, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100{,}000\,\mu L^{-1}$), and liver (total bilirubin ≤ 1.5 mg/dL and transaminase levels $\leq$ twice the upper limit of the normal value) and renal (BUN ≤ 25 mg/dL, serum creatinine ≤ 1.2 mg/dL, and creatinine clearance ≥ 50 mL/min) functions. All patients gave written, informed consent, and the protocol and the consent form were approved by the Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) and by the institutional review boards of all participating institutions.

The exclusion criteria were bilateral pleural effusion or pericardial effusion, symptomatic brain metastases requiring whole-brain irradiation or administration of corticosteroids, an active synchronous cancer, interstitial pneumonitis, pulmonary fibrosis, uncontrolled angina pectoris or myocardial infarction within the preceding 3 months, uncontrolled diabetes mellitus or hypertension, pregnancy or breast-feeding, and penicillin allergy.

2.2. Treatment and monitoring

All patients were required to have either large-bore chest tubes or small-bore catheters placed, with radiographic evidence of reexpansion of the affected lung following suction or gravity drainage. Patients were stratified by institution and PS after tube drainage and then randomly assigned to the three treatment groups (Fig. 1). Intrapleural therapy was performed as follows. In the BLM and OK-432 arms, following instillation of either BLM (1 mg/kg, maximum 60 mg/body) or OK-432 (0.2 Klinische Einheit units (KE)/kg, maximum 10 KE/body), diluted in 100 ml of physiologic saline, the tube was clamped and the patient's position rotated for 3 h. Then the tube was unclamped and allowed to drain. In the PE arm, cisplatin (80 mg/m^2) and etoposide (80 mg/m^2) diluted in 100 ml of physiologic saline were simultaneously administered into the pleural cavity, the tube was clamped and the patient's position rotated for 3 h. Seventy-two hours later, the tube was unclamped and allowed to drain.

The tube was removed when the pleural effusion decreased to 100 ml or less per day. If more than 100 ml of drained fluid continued for 7 days or the pleural effusion increase by chest radiographs within 4 weeks, the patient was taken off the protocol and considered as a treatment failure.

2.3. Response criteria

The response criteria used were (i) response—disappearance or residual effusion with no need of local treatment (no greater than one quarter of the treated lung field nor remarkable increase compared to baseline chest radiographs) and (ii) pleural progression—a greater than one quarter of the treated lung field increase in pleural effusion compared to baseline chest radiographs.

2.4. Response evaluation and systemic chemotherapy

Pleural response was evaluated at the 4th, 8th, 12th and 24th week according to the study-specific criteria (see

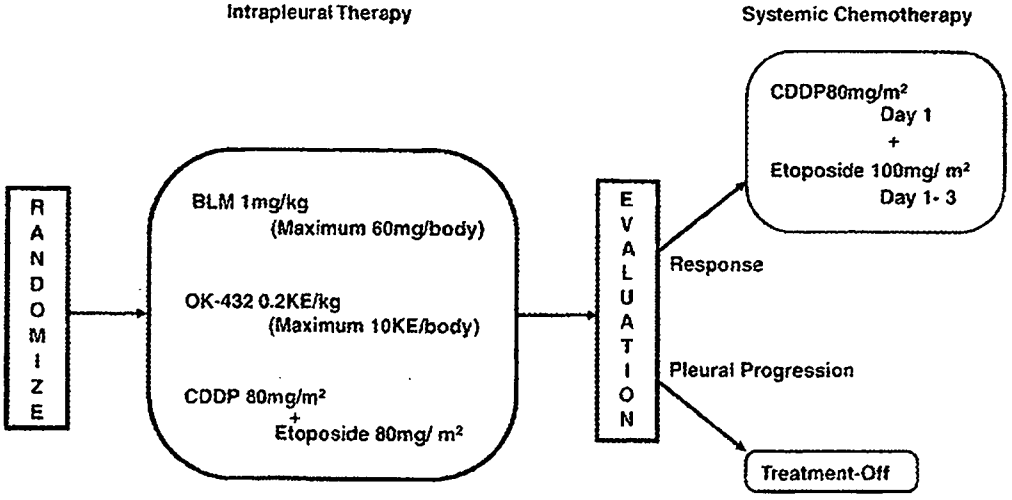

Fig. 1 Treatment schema.

above). A responder identified within 2 weeks after the first (4-week) evaluation received systemic chemotherapy consisting of cisplatin (80 mg/m^2) on day 1 and etoposide (100 mg/m^2) on days 1–3, which was repeated every 3–4 weeks for two or more courses.

2.5. Toxicity criteria and dose modification

Adverse reactions were graded according to the JCOG Toxicity Criteria [14], which are modifications of the National Cancer Institute's common toxicity criteria issued in 1991. The second or subsequent cycles of systemic chemotherapy were delayed if on day 1 the WBC count was less than 3000 μL^{-1} or the platelet count was less than 75,000 μL^{-1}. If grade 4 hematological toxicity occurred during the previous course, the dose of etoposide was reduced to 75%. Cisplatin was permanently discontinued at any time when the serum creatinine level was greater than 2.0 mg/dL. If the serum creatinine level was 1.5–2.0 mg/dL, the next cycle was delayed until it was 1.2 mg/dL or less, and the dose of cisplatin was then reduced to 75%.

2.6. Data management and statistical analysis

This study was designed as a multicenter randomized phase II trial among 21 participating centers in the Lung Cancer Study Group in the JCOG. Pleural progression-free survival (PPFS) was defined as the time from randomization to the first observation of pleural progression or death due to any cause. The primary endpoint of this study was 4-week PPFS rate. Assuming that the 4-week PPFS rate was at least 50% for these arms, the required number for each arm was 30 to select the better arm correctly with 90% probability if the better arm's 4-week PPFS rate was 70% or higher [15]. Planned accrual was set at 35 per arm. Secondary end-points were 8-, 12- and 24-week PPFS rates, overall survival (OS) and toxicity. The duration for OS was measured from the date of randomization to the date of death due to any cause or last follow-up. The mandated time to start treatment following randomization was within a week. Survival distribution was estimated by the Kaplan–Meier method, and confidence intervals were based on Greenwood's formula [16].

Patient randomization and data management were performed by the JCOG Data Center (JCOG DC). In-house interim monitoring was performed by the JCOG Data and Safety Monitoring Committee semiannually. Central review of chest X-rays for all responses in all eligible cases was performed at regular study group meetings by an extramural panel. Statistical analysis was performed by the JCOG DC with SAS software version 6.12 for Windows (SAS Institute Inc., Cary NC).

3. Results

3.1. Patients

From May 1996 to August 1999, 105 patients were enrolled onto this study from the 21 participating institutions. The clinical characteristics of the patients are listed in Table 1. Three patients were later found to be ineligible (one patient per group): one had malignant pleural effusion secondary to colon cancer; one had no reexpansion of the affected lung after tube drainage; and one had poor renal function. Thus, 102 patients were assessable for response and survival. Four patients did not receive intrapleural therapy because of one self-removal of the drain, one obstruction of the drain, and two cases of intrapleural sclerosis. These four patients were excluded from the analysis of toxicity. The three treatment arms were well balanced for age, sex, and PS.

3.2. Treatment compliance and toxicity

Table 2 outlines the compliance with treatment. Fifty-one (50.0%) of the eligible patients completed intrapleural therapy and systemic chemotherapy as defined by the protocol. Forty-one (40.1%) of the eligible patients did not receive systemic chemotherapy because of disease progression. Two

Table 1 Patient Characteristics

Characteristic	BLM	OK-432	PE
All patients	36	34	35
Eligible patients	35	33	34
Age (years)			
Median	64	60.5	61
Range	44–75	31–73	39–75
Sex			
Male	24	21	24
Female	12	13	11
PS (ECOG)[a]			
0	2	4	2
1	30	27	28
2	4	3	5
≥10% weight loss within 6 m			
No	33	27	31
Yes	3	7	4
Histology			
Adenocarcinoma	29	32	32
Squamous cell	4	1	3
Large cell	1	1	0
Other	1	0	0
TNM (N factor)			
N0	14	14	14
N1	2	0	2
N2	16	13	11
N3	3	7	8
Stage			
IIIB	23	17	25
IV	12	17	10

[a] At the time of reexpansion of the affected lung.

patients (5.7%) in the BLM arm had pneumonitis induced by BLM and one of them had treatment-related death. One patient in the PE group did not receive systemic chemotherapy due to elevation of serum creatinine. Other reasons for noncompletion of the protocol treatment were two patient refusals in each for the OK-432 and the PE arms, and one patient in the PE arm who could not receive sufficient drainage due to self-removal of the drain 48 h after intrapleural therapy.

Table 2 Treatment compliance

Variable	BLM	OK-432	PE
Eligible patients	35	33	34
No therapy	1	2	1
End of study protocol	18	19	14
Progressive disease	14	11	16
Toxicity	1	0	1
Death	1	0	0
Patient refusal	0	1	1
Insufficient drainage	0	0	1

Toxicities for intrapleural therapy in the three arms are listed in Table 3. Hematological toxic events were well tolerated in the three arms. Grade 4 nonhematological toxicity was not found in the three arms. Grade 2–3 chest pain occurred almost equally in the three arms. Grade 2–3 fever and nausea/vomiting occurred most frequently in the OK-432 arm (59.4%) and the PE arm (50.0%), respectively.

3.3. PPFS and OS

All eligible patients in the three arms were included in the survival analysis. PPFS and OS data are shown in Figs. 2 and 3, respectively. Median PPFS for the BLM arm was 20.9 weeks (95% confidence interval (CI), 4.7–25.9 weeks); for the OK-432 arm, 27.9 weeks (95% CI, 18.6–50.0 weeks); and for the PE arm, 18.4 weeks (95% CI, 4.4–41.4 weeks). The 4-week PPFS rate, which was the primary endpoint of this study, was 68.6% for the BLM arm (95% CI, 53.2–84.0%); 75.8% for the OK-432 arm (95% CI, 61.1–90.4%); and 70.6% for the PE arm (95% CI, 55.3–85.9%). The median survival time (MST) for the BLM arm was 32.1 weeks (95% CI, 21.6–37.9 weeks); 48.1 weeks for the OK-432 arm (95% CI, 26.7–58.4 weeks); and 45.7 weeks for the PE arm (95% CI, 34.4–57.1 weeks). The 48-week survival rate for the BLM arm was 29.9% (95% CI, 14.4–45.3%); 51.1% for the OK-432 arm (95% CI,

Table 3 Toxicity (JCOG grade) for Intrapleural Therapy

	BLM ($n=35$)				OK-432 ($n=32$)				PE ($n=34$)			
	1	2	3	4	1	2	3	4	1	2	3	4
Leukocytes	3	3	0	1	1	0	1	0	8	3	2	1
Neutrophils	1	0	2	1	0	0	1	0	5	5	1	2
Hemoglobin	3	5	3	ND	3	6	1	ND	6	6	3	ND
Platelet	0	0	1	0	0	0	0	0	1	1	0	0
AST	8	0	0	0	15	2	0	0	6	0	0	0
ALT	11	0	0	0	14	7	0	0	10	2	0	0
Serum creatinine	1	0	0	0	0	0	0	0	4	1	0	0
Chest pain	10	5	4	0	15	8	1	0	13	6	1	0
Fever	12	13	0	0	6	18	1	0	9	7	2	0
Nausea/vomiting	7	3	0	ND	5	0	0	ND	10	13	4	ND

Abbreviation: ND, not defined.

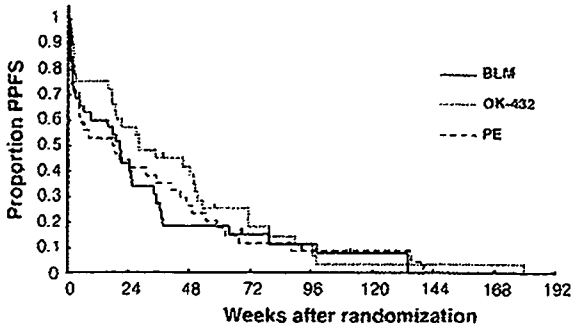

Fig. 2 Pleural progression-free survival (PPFS) in all eligible patients ($n = 102$).

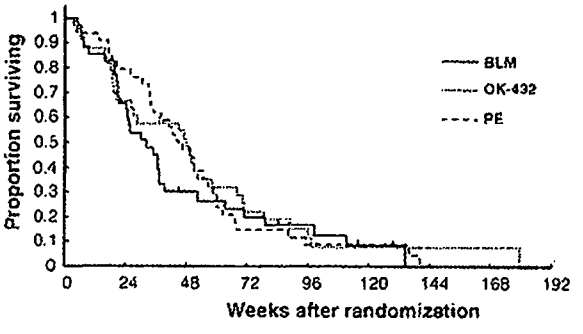

Fig. 3 Overall survival in all eligible patients ($n = 102$).

34.0–68.3%); and 47.1% for the PE arm (95% CI, 30.3–63.8%). Both the PPFS and OS for the OK-432 arm were superior to those for other two arms; however, the outcomes did not differ significantly between groups.

4. Discussion

To date, numerous chemical agents for treatment of MPE have been studied. These were antibiotics, antineoplastic agents, biological response modifiers (BRMs) and others that showed varied degrees of chemical sclerosis. Among them, BLM and talc are most frequently used for the management of MPE [5,7,17,18]. BLM is an antineoplastic antibiotic used in sclerotherapy with a success rate of 63–85% [7,8,18–21]. Talc applied as either slurry or poudrage is superior to other commonly used sclerosing agents with a success rate of 71–100% [5,7,22–24]. Because talc has not been available commercially in Japan and the use of talc was considered controversial at the beginning of this study because of severe complications, such as acute respiratory distress syndrome [25,26], we selected BLM as the sclerosing agent. A recent report demonstrated that the safety of talc pleurodesis and that acute respiratory distress syndrome can be avoided by using large-particle talc applied as thoracoscopic poudrage [27]. The thoracoscopic pleurodesis with talc is now considered to be the gold standard treatment for MPE [28,29].

OK-432 has been used as a BRM for gastric and lung cancer [9,10,30,31]. OK-432 has been reported to be effective in controlling MPE in two prospective randomized trials. One study reported a 73% success rate with OK-432 compared to 41% with mitomycin C treatment ($p = 0.03$) [11]. The other comparison found OK-432 70% effective compared to 46% in BLM subjects (statistical data not reported) [12]. OK-432 has been reported to induce various cytokines, such as tumor necrosis factor-α, interferon-γ, interleukin (IL)-1, IL-8 and IL-12 [32] and also to enhance cytotoxicity against tumor cells [33,34]. It is suggested that the main therapeutic effects of OK-432 for malignant effusion depend on increased expression of intercellular adhesion molecule-1 on tumor cells induced by interferon-γ [35].

Intrapleural combination chemotherapy is focused on achieving higher concentrations in the pleural cavity with less toxicity than systemic chemotherapy [36]. Two phase II studies with intrapleural cisplatin and cytarabine had success rates of 49% [2] and 73% [37]. Tohda et al. [13] reported that intrapleural instillation of cisplatin and etoposide for NSCLC with MPE resulted in a 46.2% overall response rate and the MST of 8 months was found to be improved, compared with previous reports for NSCLC with MPE of 3–6 months [11,18,38]. The reason for this was assumed to be that intrapleural combination chemotherapy of cisplatin and etoposide produced systemic as well as local effects. The overall response rates of intrapleural combination chemotherapy are variable and there are no prospective randomized studies compared modality of intrapleural combination chemotherapy with that of sclerotherapy.

There have been several special problems raised in the clinical trials for MPE, such as patient selection, response criteria, treatment procedures, short life expectancy, small sample sizes, and different endpoints [2–7,11,39]. To minimize the bias of patient selection, NSCLC patients with MPE who had received no prior therapy were entered into this study. Furthermore, justifiable and simplified response criteria and whether further treatment was required or not, as suggested by Ruckdeschel [18] and Rusch [40] were used and single intrapleural instillation of each agent was permitted to allow uniform estimation of responses. In many trials, successful pleurodesis was determined by assessing clinical and radiological findings. The positive response criteria have been defined generally as no pleural re-accumulation, 50% less effusion than that observed in the baseline radiograph taken immediately after the procedure, or no requirement for further thoracentesis. To determine the efficacy, we used the criterion that a decrease in effusion over one-quarter of the treated lung provides a stricter assessment of chemical pleurodesis that may relieve the symptoms of MPE. The position rotation after intrapleural instillation was recommended traditionally because it was thought to allow the agents to be distributed thoroughly throughout the entire pleural space. In contrast, studies using tetracycline and talc [41,42] demonstrated that rotation does not affect the overall intrapleural dispersion. It is unclear whether rotation is beneficial or not when applying the agents used in this study. Because a previous phase II study [13] showed that etoposide remains for a long period (β-phase half-life = 62.53 h) in intrapleural fluids, we applied the longer duration of clamping in the PE arm (72 h) than the other two arms (3 h) to provide enough exposure to the cancer cells. We found no major safety concerns such as excess pleural effusion as a result of the longer duration of clamping.

In this study, all three regimens were feasible. One treatment-related death occurred in the BLM arm 9 weeks after intrapleural instillation of BLM. Treatment compliance

rates for both intrapleural and systemic therapy was 50% (51 of the 102 eligible patients). This study lacks sufficient power to demonstrate differences between treatment arms; however, the OK-432 arm seemed to demonstrate modest benefit compared with the other two arms in terms of PPFS. It is assumed that the favorable efficacy in the OK-432 arm suggests that OK-432 has clinically meaningful activity for controlling MPE in NSCLC patients. NSCLC patients with MPE have been treated as patients with stage IV disease even when without metastasis, and systemic chemotherapy should be recommended when they have a good PS [43]. We prescribed systemic PE chemotherapy regimens, which were considered one of the standard regimens at the beginning of the study, following successful pleurodesis. However, we expect that platinum-based systemic combination chemotherapy regimens with several active new chemotherapeutic agents such as taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine and irrinotecan, which are the current standard treatment options for patients with advanced NSCLC, should enhance the survival benefit more than PE regimens.

This is the first fully reported randomized study that has evaluated the efficacy of intrapleural therapy for previously untreated patients with NSCLC and compliance with sequential systemic chemotherapy. As the results of this study demonstrate that intrapleural therapy with OK-432 shows a tendency to be more effective than BLM or PE in the management of MPE in NSCLC, in terms of PPFS, further studies are needed to compare OK-432 with talc.

Conflict of interest

None declared.

Acknowledgements

We are indebted to Ms. M. Imai and Dr. M. Niimi for data management and to Dr. N. Ishizuka for statistical analysis. We thank all of the investigators who contributed to study development and patient enrollment.

Supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare of Japan.

References

[1] Figlin R, Mendoza E, Piantadosi S, Rusch V. Intrapleural chemotherapy without pleurodesis for malignant pleural effusions. LCSG Trial 861. Chest 1994;106:363S–6S.

[2] Rusch VW, Figlin R, Godwin D, Piantadosi S. Intrapleural cisplatin and cytarabine in the management of malignant pleural effusions: a Lung Cancer Study Group trial. J Clin Oncol 1991;9:313–9.

[3] Windsor PG, Como JA, Windsor KS. Sclerotherapy for malignant pleural effusions: alternatives to tetracycline. South Med J 1994;87:709–14.

[4] Walker-Renard PB, Vaughan LM, Sahn SA. Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994;120:56–64.

[5] Grossi F, Pennucci MC, Tixi L, et al. Management of malignant pleural effusions. Drugs 1998;55:47–58.

[6] Ruckdeschel JC. Management of malignant pleural effusions. Semin Oncol 1995;22:58–63.

[7] Zimmer PW, Hill M, Casey K, et al. Prospective randomized trial of talc slurry vs bleomycin in pleurodesis for symptomatic malignant pleural effusions. Chest 1997;112:430–4.

[8] Sartori S, Tassinari D, Ceccotti P, et al. Prospective randomized trial of intrapleural bleomycin versus interferon alfa-2b via ultrasound-guided small-bore chest tube in the palliative treatment of malignant pleural effusions. J Clin Oncol 2004;22:1228–33.

[9] Kimura I, Ohnoshi T, Yasuhara S, et al. Immunochemotherapy in human lung cancer using the streptococcal agent OK-432. Cancer 1976;37:2201–3.

[10] Sakamoto J, Teramukai S, Watanabe Y, et al. Meta-analysis of adjuvant immunochemotherapy using OK-432 in patients with resected non-small-cell lung cancer. J Immunother 2001;24:250–6.

[11] Luh KT, Yang PC, Kuo SH, et al. Comparison of OK-432 and mitomycin C pleurodesis for malignant pleural effusion caused by lung cancer. A randomized trial. Cancer 1992;69:674–9.

[12] Saka H, Shimokata K, Watanabe A, Saito H, Minami H, Sakai S. Randomized comparison of OK-432 and Bleomycin in intrapleural therapy for malignant effusions. Proc Am Soc Clin Oncol 1994;450a [Abstr 1555].

[13] Tohda Y, Iwanaga T, Takada M, et al. Intrapleural administration of cisplatin and etoposide to treat malignant pleural effusions in patients with non-small cell lung cancer. Chemotherapy 1999;45:197–204.

[14] Tobinai K, Kohno A, Shimada Y, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 1993;23:250–7.

[15] Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1985;69:1375–81.

[16] Armitage P, Berry G. Survival analysis. In: Statistical Methods in Medical Research. Oxford, United Kingdom: Blackwell Scientific Publications; 1994.

[17] Ostrowski MJ. Intracavitary therapy with bleomycin for the treatment of malignant pleural effusions. J Surg Oncol Suppl 1989;1:7–13.

[18] Ruckdeschel JC, Moores D, Lee JY, et al. Intrapleural therapy for malignant pleural effusions. A randomized comparison of bleomycin and tetracycline. Chest 1991;100:1528–35.

[19] Paladine W, Cunningham TJ, Sponzo R, et al. Intracavitary bleomycin in the management of malignant effusions. Cancer 1976;38:1903–8.

[20] Bitran JD, Brown C, Desser RK, et al. Intracavitary bleomycin for the control of malignant effusions. J Surg Oncol 1981;16:273–7.

[21] Ostrowski MJ, Priestman TJ, Houston RF, Martin WM. A randomized trial of intracavitary bleomycin and *Corynebacterium parvum* in the control of malignant pleural effusions. Radiother Oncol 1989;14:19–26.

[22] Hamed H, Fentiman IS, Chaudary MA, Rubens RD. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. Br J Surg 1989;76:1266–7.

[23] Hartman DL, Gaither JM, Kesler KA, et al. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. J Thorac Cardiovasc Surg 1993;105:743–7 [Discussion747–8].

[24] Dresler CM, Olak J, Herndon II JE, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 2005;127:909–15.

[25] Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. J Thorac Cardiovasc Surg 1983;85:523–6.

[26] Bouchama A, Chastre J, Gaudichet A, et al. Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. Chest 1984;86:795–7.
[27] Janssen JP, Collier G, Astoul P, et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet 2007;369:1535–9.
[28] Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev (database online) 2004.
[29] Aelony Y. Talc pleurodesis and acute respiratory distress syndrome. Lancet 2007;369:1494–6.
[30] Yasue M, Murakami M, Nakazato H, et al. A controlled study of maintenance chemoimmunotherapy vs immunotherapy alone immediately following palliative gastrectomy and induction chemoimmunotherapy for advanced gastric cancer. Tokai cooperative study group for adjuvant chemoimmunotherapy of stomach cancer. Cancer Chemother Pharmacol 1981;7:5–10.
[31] Watanabe Y, Iwa T. Clinical value of immunotherapy with the streptococcal preparation OK-432 in non-small cell lung cancer. J Biol Response Mod 1987;6:169–80.
[32] Katano M, Morisaki T. The past, the present and future of the OK-432 therapy for patients with malignant effusions. Anticancer Res 1998;18:3917–25.
[33] Uchida A, Micksche M. Lysis of fresh human tumor cells by autologous peripheral blood lymphocytes and pleural effusion lymphocytes activated by OK432. J Natl Cancer Inst 1983;71:673–80.
[34] Wei Y, Zhao X, Kariya Y, et al. Induction of autologous tumor killing by heat treatment of fresh human tumor cells: involvement of gamma delta T cells and heat shock protein 70. Cancer Res 1996;56:1104–10.
[35] Kitsuki H, Katano M, Ikubo A, et al. Induction of inflammatory cytokines in effusion cavity by OK-432 injection therapy for patients with malignant effusion: role of interferon-gamma in enhancement of surface expression of ICAM-1 on tumor cells in vivo. Clin Immunol Immunopathol 1996;78:283–90.
[36] Markman M. Intracavitary chemotherapy. Curr Probl Cancer 1986;10:401–37.
[37] Aitini E, Cavazzini G, Pasquini E, et al. Treatment of primary or metastatic pleural effusion with intracavitary cytosine arabinoside and cisplatin. A phase II study. Acta Oncol 1994;33:191–4.
[38] Sugiura S, Ando Y, Minami H, et al. Prognostic value of pleural effusion in patients with non-small cell lung cancer. Clin Cancer Res 1997;3:47–50.
[39] Miles DW, Knight RK. Diagnosis and management of malignant pleural effusion. Cancer Treat Rev 1993;19:151–68.
[40] Rusch VW. The optimal treatment of malignant pleural effusions. A continuing dilemma. Chest 1991;100:1483–4.
[41] Dryzer SR, Allen ML, Strange C, et al. A comparison of rotation and nonrotation in tetracycline pleurodesis. Chest 1993;104:1763–6.
[42] Mager HJ, Maesen B, Verzijlbergen F, et al. Distribution of talc suspension during treatment of malignant pleural effusion with talc pleurodesis. Lung Cancer 2002;36:77–81.
[43] Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330–53.

original article

Annals of Oncology 18: 317–323, 2007
doi:10.1093/annonc/mdl377
Published online 1 November 2006

Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan

Y. Ohe[1]*, Y. Ohashi[2], K. Kubota[3], T. Tamura[1], K. Nakagawa[4], S. Negoro[5], Y. Nishiwaki[3], N. Saijo[3], Y. Ariyoshi[6] & M. Fukuoka[4]
For the FACS Cooperative Group

[1]*Department of Internal Medicine, National Cancer Center Hospital, Tokyo;* [2]*Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, The University of Tokyo, Tokyo;* [3]*Thoracic Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba;* [4]*Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Osaka;* [5]*Department of Thoracic Oncology, Hyogo Medical Center for Adults, Akashi, Hyogo;* [6]*Aichi Cancer Center Aichi Hospital, Okazaki, Aichi, Japan*

Received 16 May 2006; revised 13 August 2006; accepted 30 August 2006

Background: To compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.
Patients and methods: A total of 602 patients were randomly assigned to one of four regimens: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP) carboplatin AUC 6.0 min × mg/mL (area under the concentration–time curve) on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP).
Results: The response rate, median survival time, and 1-year survival rate were 31.0%, 13.9 months, 59.2%, respectively, in IP; 32.4%, 12.3 months, 51.0% in TC; 30.1%, 14.0 months, 59.6% in GP; and 33.1%, 11.4 months, 48.3% in NP. No statistically significant differences were found in response rate or overall survival, but the non-inferiority of none of the experimental regimens could be confirmed. All the four regimens were well tolerated.
Conclusion: The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Key words: carboplatin, cisplatin, gemcitabine, irinotecan, non-small-cell lung cancer, paclitaxel, randomized phase III study, vinorelbine

original article

introduction

Nearly 60 000 patients in Japan died of lung cancer in 2004, and the mortality rate is still increasing [1]. Even old-generation cisplatin-based chemotherapy provides a survival benefit and symptom relief in patients with inoperable non-small-cell lung cancer (NSCLC) [2]. Several anticancer agents including irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine, were developed in the 1990s and most of them have mechanisms of action that differ from those of the old-generation agents [3–7]. The combinations of platinum and these new agents developed in the 1990s are more useful against advanced NSCLC than old-generation combination chemotherapy, and doublets of platinum and new-generation anticancer agents are considered standard chemotherapy regimens for advanced NSCLC, although no consistent standard regimens have yet been established [8–17].

Two phase III studies comparing cisplatin plus irinotecan (IP) with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan [18, 19]. Fukuoka et al. [20] reported the results of a combined analysis of the 358 eligible stage IV patients in these studies. They carried out a multivariate analysis using the Cox regression model with adjustment for well-known prognostic factors, and the Cox regression analysis demonstrated that treatment with IP was one of significant independent favorable factor. Based on their data, we selected IP for the reference arm in our study.

The Ministry of Health, Labour and Welfare of Japan approved the prescription of paclitaxel, gemcitabine, and

Correspondence to: Dr Y. Ohe, Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: x+81-3-3542-7006; E-mail: yohe@ncc.go.jp

vinorelbine for NSCLC in 1999 and requested a phase III study to confirm the efficacy and safety of these agents. The Japanese investigators and the pharmaceutical companies decided to conduct a four-arm randomized phase III study for NSCLC, the so-called FACS, Four-Arm Cooperative Study. The purpose of the study was to compare the efficacy and toxicity of three platinum-based combination regimens, carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP), with IP as the reference arm.

patients and methods

patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion >2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate hematological, hepatic and renal functions, partial pressure of arterial oxygen (paO_2) ≥60 torr, expected survival >3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

treatment schedule

All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m^2 of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m^2 of cisplatin on day 1 and 25 mg/m^2 of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.

response and toxicity evaluation

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors, and tumor markers were excluded from the criteria [21]. Objective tumor response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.

quality of life assessment

Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL-ACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment [22–24].

statistical analysis and monitoring

The primary end point of this study was overall survival (OS), and the secondary end points were response rate, response duration, time to progressive disease (TTP), time to treatment failure (TTTF), adverse event, and QoL. The 1-year survival rate of the control group in this study was estimated to be 43% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as '−10%'. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the non-inferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm).

Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).

results

patient characteristics

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for >2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumor progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumor progression, and nephritic syndrome in NP. Two patents were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP. Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinona were, however, entered in three experimental arms than in IP.

objective tumor response and response duration

Objective tumor response is shown in Table 2. Forty-five partial responses occurred in the 145 assessable patients in the reference arm, IP, for an objective response rate of 31.0% with a median response duration of 4.8 months. The response rate and median response duration were 32.4% and 4.0 months in TC, 30.1% and 3.5 months in GP, and 33.1% and 3.4 months in NP. The response rates in TC, GP, and NP were not statistically different from the rate in IP according to the results of the χ^2 test.

Table 1. Patient characteristics and treatment delivery

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine
Assessable patients	145	145	146	145
Gender (male/female)	97/48	99/46	101/45	101/44
Age, median (range)	62 (30–74)	63 (33–74)	61 (34–74)	61 (28–74)
PS (0/1)	44/101	44/101	45/101	45/100
Histology				
Adenocarcinoma	121	104	108	109
Squamous cell carcinoma	16	31	29	29
Others	8	10	9	7
Stage (IIIB/IV)	31/114	28/117	30/116	26/119
No. of cycles				
Mean ± SD	3.0 ± 1.3	3.5 ± 1.5	3.2 ± 1.2	3.1 ± 1.3
Median	3	3	3	3
Range	1–7	1–10	1–7	1–8

PS, performance status; SD, standard deviation.

Table 2. Survival, TTP, TTTF, response rate, and response duration

	N	Median survival, months	1-year survival (%)	Difference in 1-year survival from IP	2-year survival (%)	TTP (median), months	TTTF (median), months	Response rate (%)	Response duration (median), months
Cisplatin + irinotecan	145	13.9	59.2	–	26.5	4.7	3.3	31.0	4.8 (n = 45)
Carboplatin + paclitaxel	145	12.3	51.0	−8.2% (95% CI −19.6% to 3.3%)	25.5	4.5 (P = 0.355)[a]	3.2 (P = 0.282)[a]	32.4 (P = 0.801)[b]	4.0 (n = 47)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI −10.9% to11.7%)	31.5	4.0 (P = 0.170)[a]	3.2 (P = 0.567)[a]	30.1 (P = 0.868)[b]	3.5 (n = 44)
Cisplatin + vinorelbine	145	11.4	48.3	−10.9% (95% CI −22.3% to 0.5%)	21.4	4.1 (P = 0.133)[a]	3.0 (P = 0.091)[a]	33.1 (P = 0.706)[b]	3.4 (n = 48)

[a]Compared with IP by the generalized Wilcoxon test.
[b]Compared with IP by the χ^2 test.
CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.

OS, TTP disease, and TTTF

OS and TTP are shown in Figure 1. Median survival time (MST), the 1-year, and 2-year survival rate in IP were 13.9 months, 59.2%, and 26.5%, respectively. The MSTs, 1-year, and 2-year survival rates were, respectively, 12.3 months, 51.0%, and 25.5% in TC; 14.0 months, 59.6%, and 31.5% in GP; and 11.4 months, 48.3%, and 21.4% in NP. The lower limits of the 95% CI of the difference in 1-year survival rate between IP and TC (−19.6%), GP (−10.9%), and NP (−22.3%) were below −10%, which was considered the lower equivalence limit (Table 2). Thus, the results did not show non-inferiority in three experimental regimens compared with reference treatment. Median TTP and median TTTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTTF were, respectively, 4.5 and 3.2 months in TC, 4.0 and 3.2 months in GP, and 4.1 and 3.0 months in NP. There were no statistical differences in either TTP or TTTF in TC, GP, or NP, compared with IP according to the results of the generalized Wilcoxon test (Table 2).

hematologic and non-hematologic toxicity

In IP, 47.6% and 83.7% of patients developed grade 3 or worse leukopenia and neutropenia, respectively (Table 3). The incidences of grade 3 or worse leukopenia (33.1%, P = 0.010) and neutropenia (62.9%, P < 0.001) were significantly lower in GP than in IP. The incidence of grade 3 or worse leukopenia (67.1%, P < 0.001) was significantly higher in NP than in IP. Grade 3 or worse thrombocytopenia developed in 5.4% of the patients in IP, and the incidence was significantly higher in GP (35.1%, P < 0.001). The incidence of febril neutropenia in IP was 14.3%, and was significantly lower in GP (2.0%, P < 0.001).

Grade 2 or worse nausea, vomiting, anorexia, and fatigue occurred in 60.5%, 51.0%, 65.3%, and 38.8%, respectively, of the patients in IP. The incidences of grade 2 or worse nausea (TC: 25.0%, P < 0.001, NP: 47.3%, P = 0.022), vomiting (TC: 22.3%, P < 0.001, NP: 36.3%, P = 0.011), and anorexia (TC: 32.4%, P < 0.001, NP: 49.3%, P = 0.005) were significantly lower in TC and NP than in IP. Grade 2 or worse diarrhea was

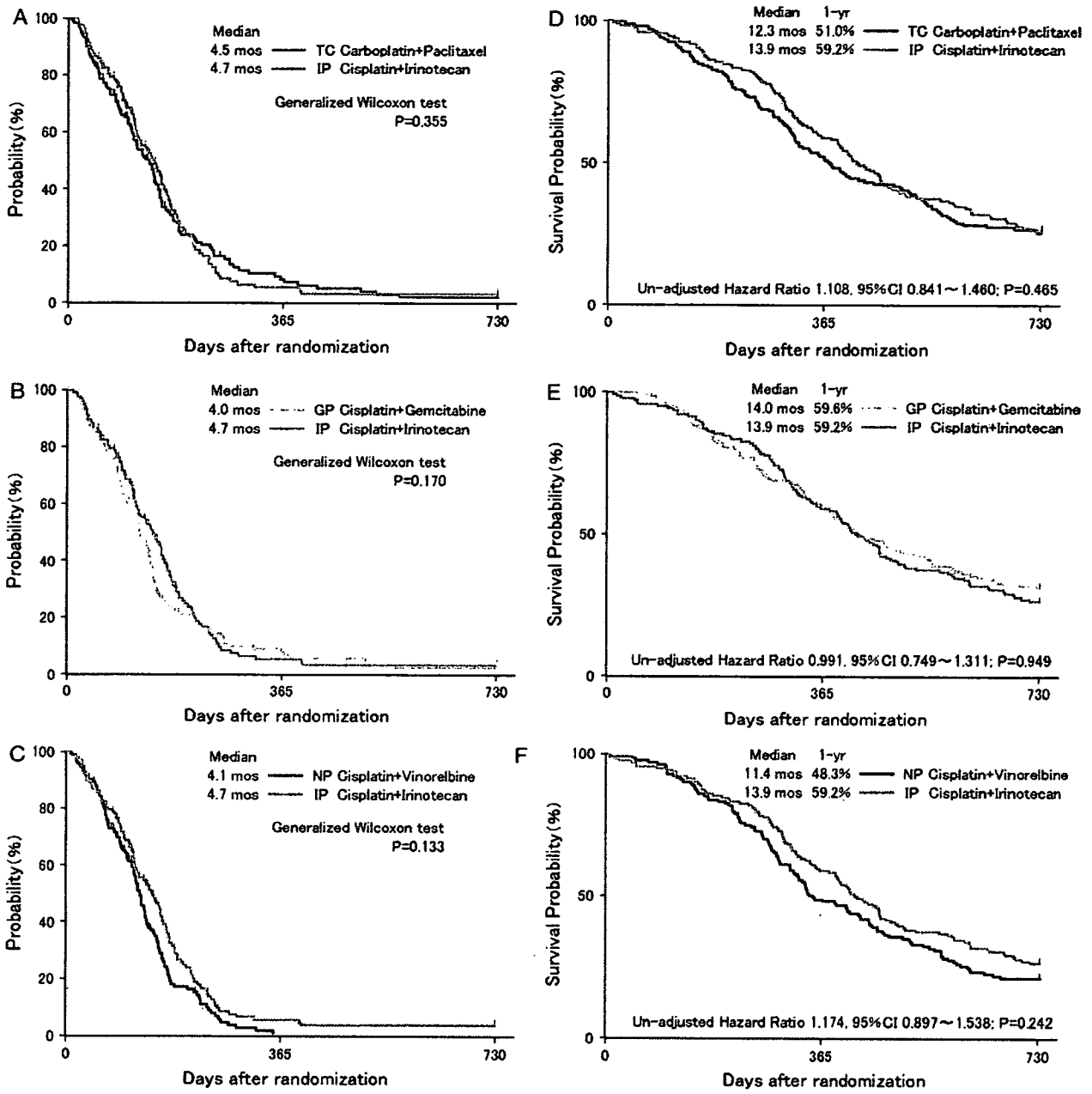

Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

significantly less frequent in TC (6.8%), GP (8.6%), and NP (11.6%) than in IP (48.3%, $P < 0.001$). The incidences of grade 2 or worse sensory neuropathy (16.9%, $P < 0.001$), arthralgia (21.6%, $P < 0.001$), and myalgia (17.6%, $P < 0.001$) were significantly higher in TC than in IP. Grade 2 alopecia occurred in 30.6% of the patients in IP, and its incidence was significantly higher in TC (44.6%, $P = 0.013$) and significantly lower in GP (15.2%, $P = 0.001$) and NP (8.9%, $P < 0.001$). Grade 2 injection site reactions were more frequent in NP (26.7%) than in IP (4.8%, $P < 0.001$).

A total of five patients died of treatment-related toxicity: three in IP (cerebral hemorrhage, interstitial pneumonia, acute circulatory failure/disseminated intravascular coagulation: 2.0%), one in TC (acute renal failure: 0.7%), and one in NP (pulmonary embolism: 0.7%).

second-line treatment

Data on second-line treatment, but not third-line or later treatment, was available in this study, and they showed that

Table 3. Toxicity

	IP ($n = 147$)			TC ($n = 148$)			GP ($n = 151$)			NP ($n = 146$)		
	Grade (%)			Grade (%)			Grade (%)			Grade (%)		
	2	3	4	2	3	4	2	3	4	2	3	4
Leukocytes	42	43	5	39	42	3	40	31[a]	2[a]	25	51[b]	16[b]
Neutrophils	11	39	45	5	19	69	21	40	23[a]	5	16	72
Hemoglobin	42	24	7	42	13[a]	2[a]	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35[b]	0[b]	3	1[a]	0[a]
Febrile neutropenia	–	14	0	–	18	0	–	2[a]	0[a]	–	18	0
Nausea	32	29	–	14[c]	11[c]	–	35	23	–	33[c]	14[c]	–
Vomiting	38	13	0	17[c]	5[c]	0[c]	34	14	0	29[c]	7[c]	0[c]
Anorexia	30	33	2	15[c]	17[c]	1[c]	31	26	1	29[c]	20c	1[c]
Fatigue	27	12	1	26	2	1	17[c]	3[c]	0[c]	23[c]	3[c]	0[c]
Diarrhea	33	15	1	4[c]	3[c]	0[c]	7[c]	2[c]	0[c]	8[c]	4[c]	0[c]
Constipation	27	7	0	30	8	0	33	9	0	40[d]	14[d]	0[d]
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14[d]	3[d]	0[d]	0	0	0	0	0	0
Alopecia	31	–	–	45[d]	–	–	15[c]	–	–	9[c]	–	–
Arthralgia	2	0	0	20[d]	2[d]	0[d]	0	0	0	1	0	0
Myalgia	1	0	0	16[d]	2[d]	0[d]	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27[d]	0[d]	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2[c]	0[c]	0[c]	7	0	0	8	1	0
AST	7	1	1	5	1	0	6	3	0	1	3	0
Fever	2	0	0	5	1	0	1	0	0	1	0	0
Treatment-related death	3 (2.0%)			1 (0.7%)			0			1 (0.7%)		

[a]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.
[b]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.
[c]Incidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.
[d]Incidence of grade 2 or worse toxicity significantly ($P < 0.05$) higher than that with IP.
GP, cisplatin plus gemcitabine; IP, cisplatin plus irinotecan; NP, cisplatin plus vinorelbine; TC, carboplatin plus paclitaxel.
AST, aspartate aminotransferase; –, no category in the criteria.

60%–74% of the patients received chemotherapy and 6%–9% received thoracic irradiation as second-line treatment (Table 4). The percentages of patients in each treatment group who received second-line chemotherapy were not significantly different ($P = 0.081$).

quality of life

The details of the QoL analysis will be reported elsewhere. No statistically significant difference in global QoL was observed among the four treatment groups based on either the FACT-L Japanese version or the QoL-ACD. Only the physical domain evaluated by QoL-ACD was significantly better in TC, GP, and NP than in IP.

discussion

Many randomized phase III studies have compared platinum-plus-new-agent doublets in NSCLC, but, this is the first to evaluate the efficacy of an irinotecan-containing regimen in comparison with other platinum-plus-new-agent doublets in NSCLC [14–17]. Although non-platinum-containing chemotherapy regimens are used as alternatives, doublets of platinum and a new-generation anticancer agent, such as TC, GP, and NP, are considered standard chemotherapy regimens for advanced NSCLC worldwide [13–17, 25]. Although the non-inferiority of none of the three experimental regimens could be confirmed in this study, no statistically significant differences in response rate, OS, TTP, or TTTF were observed between the reference regimen and the experimental regimens. All four platinum-based doublets have similar efficacy against advanced NSCLC but different toxicity profiles. Nevertheless, IP was still regarded as the reference regimen in this study because the non-inferiority of none of the three experimental regimens could be confirmed.

OS in this study was relatively longer than previously reported. The estimated 1-year survival rate in the reference arm was 43%, but the actual 1-year survival rate was 59.2%, much higher than expected. The MSTs reported for patients treated with TC, GP, and NP in recent phase III studies have ranged from 8 to 10 months, and in the present study they were 12.3, 14.0, and 11.4 months, respectively [14–17]. One reason for the good OS in this study was the difference in patient selection criteria, for example exclusion of PS2 patients. Ethnic differences in pharmacogenomics have also been indicated as a possible reason for the good OS in this study [26]. The OS in IP in this study, however, was better than in previous Japanese studies [18, 19]. TTP in this study ranged from 4.0 to 4.7 months, and was similar to the TTP of 3.1–5.5 months reported in the literature [15, 16]. OS not TTP was longer in this study

Table 4. Second-line treatment

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine	
Number of patients	145	145	146	145	
Chemotherapy	107 (74%)	87 (60%)	101 (69%)	95 (66%)	$P = 0.081$
Docetaxel	39	25	50	51	
Gefitinib	11	9	18	12	
Paclitaxel	15	14	7	11	
Gemcitabine	24	28	17	28	
Vinorelbine	9	12	2	9	
Irinotecan	15	4	3	3	
Thoracic irradiation	8	10	13	10	

than previously reported, and higher 2-year survival rates, 21.4%–31.5%, were observed in the minimum 2-year follow-up in this study. Second-line or later treatments may affect survival, because docetaxel has been established as standard second-line chemotherapy for advanced NSCLC [27, 28]. Gefitinib is also effective as second-line or later chemotherapy for advanced NSCLC, especially in Asian patients, never smokers and patients with adenocarcinoma [29–32].

The toxicity profile of each treatment differed and the toxicity of all four regimens was well tolerated. Overall QoL was similar in the four platinum-based doublets. Only physical domain QoL evaluated by the QoL-ACD was statistically better in TC, GP, and NP than in IP. This finding is presumably attributable to the fact that diarrhea is a statistically less frequent adverse effect of TC, GP, and NP than of IP.

In conclusion, all four platinum-based doublets had similar efficacy for advanced NSCLC but different toxicity profiles. All the four regimens can be used to treat advanced NSCLC patients in clinical practice.

appendix

Institutions of the FACS Cooperative Group: National Hospital Organization (NHO) Hokkaido Cancer Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Niigata Cancer Center Hospital, Tochigi Cancer Center, NHO Nishigunma National Hospital, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Japanese Foundation for Cancer Research, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kanagawa Cardiovascular and Respiratory Center, Aichi Cancer Center Hospital, Prefectural Aichi Hospital, Nagoya City University Hospital, NHO Nagoya Medical Center, Nagoya University Hospital, Gifu Municipal Hospital, NHO Kyoto Medical Center, Osaka City General Hospital, Osaka City University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, NHO Toneyama Hospital, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Kinki University School of Medicine, Rinku General Medical Center Izumisano Municipal Hospital, Kobe Central General Hospital, The Hospital of Hyogo College of Medicine, Hyogo Medical Center for Adults, Tokushima University Hospital, Kagawa Prefectural Central Hospital, NHO Shikoku Cancer Center Hospital, Hiroshima University Medical Hospital, NHO Kyushu Cancer Center Hospital, Kyushu University Hospital, National Nagasaki Medical Center, Nagasaki Municipal Hospital, Nagasaki University Hospital of Medicine and Dentistry, Kumamoto Chuo Hospital, Kumamoto Regional Medical Center, NTT West Osaka Hospital.

acknowledgements

This study was supported by Bristol-Myers K.K., Tokyo; Eli Lilly Japan K.K., Kobe; and Kyowa Hakko Kogyo Co. Ltd, Tokyo, Japan.

references

1. Cancer Statistics in Japan 2005: The Editorial Board of the Cancer Statistics in Japan. Tokyo, Japan: Foundation for Promotion of Cancer Research 2005.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995; 311: 899–909.
3. Fukuoka M, Niitani H, Suzuki A et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 1992; 10: 16–20.
4. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med 1995; 332: 1004–1014.
5. Gelmon K. The taxoids: paclitaxel and docetaxel. Lancet 1994; 344: 1267–1272.
6. Hertel LW, Border GB, Kroin JS et al. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). Cancer Res 1990; 50: 4417–4422.
7. Binet S, Fellous A, Lataste H et al. Biochemical effects of navelbine on tubulin and associated proteins. Semin Oncol 1989; 16 (2 Suppl 4): 9–14.
8. Kubota K, Watanabe K, Kunitoh H et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 2004; 22: 254–261.
9. Le Chevalier T, Brisgand D, Douillard JY 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: 360–367.
10. Belani CP, Lee JS, Socinski MA et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005; 16: 1069–1075.
11. Yana T, Takada M, Origasa H et al. New chemotherapy agent plus platinum for advanced non-small cell lung cancer: a meta-analysis. Proc Am Soc Clin Oncol 2002; 21: 328a.
12. Baggstrom MQ, Socinski MA, Hensing TA et al. Third generation chemotherapy regimens (3GR) improve survival over second generation regimens (2GR) in stage IIIB/IV non-small cell lung cancer (NSCLC): a meta-analysis of the published literature. Proc Am Soc Clin Oncol 2002; 21: 306a.

13. Hotta K, Matsuo K, Ueoka H et al. Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials. Ann Oncol 2004; 15: 1782–1789.
14. Kelly K, Crowley J, Bunn PA et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group Trial. J Clin Oncol 2001; 19: 3210–3218.
15. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92–98.
16. Scagliotti GV, De Marinis F, Rinaldi M et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002; 20: 4285–4291.
17. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 Study Group. J Clin Oncol 2003; 21: 3016–3024.
18. Negoro S, Masuda N, Takada Y et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. Br J Cancer 2003; 88: 335–341.
19. Niho S, Nagao K, Nishiwaki Y et al. Randomized multicenter phase III trial of irinotecan (CPT-11) and cisplatin (CDDP) versus CDDP and vindesine (VDS) in patients with advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 1999; 18: 492a.
20. Fukuoka M, Nagao K, Ohashi Y et al. Impact of irinotecan (CPT-11) and cisplatin (CDDP) on survival in previously untreated metastatic non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2000; 19: 495a.
21. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205–216.
22. Cella DF, Bonomi AE, Lloyd SR et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995; 12: 199–220.
23. Kurihara M, Shimizu H, Tsuboi K et al. Development of quality of life questionnaire in Japan: quality of life assessment of cancer patients receiving chemotherapy. Psychooncology 1999; 8: 355–363.
24. Matsumoto T, Ohashi Y, Morita S et al. The quality of life questionnaire for cancer patients treated with anticancer drugs (QOL-ACD): validity and reliability in Japanese patients with advanced non-small-cell lung cancer. Qual Life Res 2002; 11: 483–493.
25. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004; 22: 330–353.
26. Gandara DR, Ohe Y, Kubota K et al. Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of cooperative group trials. Proc Am Soc Clin Oncol 2004; 22: 618a.
27. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095–2103.
28. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18: 2354–2362.
29. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003; 290: 2149–2158.
30. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). Clin Oncol 2003; 21: 2237–2246.
31. Takano T, Ohe Y, Kusumoto M et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. Lung Cancer 2004; 45: 93–104.
32. Takano T, Ohe Y, Sakamoto H et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005; 23: 6829–6837.

Lung Cancer (2007) 55, 337–341

available at www.sciencedirect.com

ScienceDirect

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

Randomized trial of drip infusion versus bolus injection of vinorelbine for the control of local venous toxicity

Kiyotaka Yoh*, Seiji Niho, Koichi Goto, Hironobu Ohmatsu, Kaoru Kubota, Ryutaro Kakinuma, Nagahiro Saijo, Yutaka Nishiwaki

Division of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Received 6 April 2006; received in revised form 31 July 2006; accepted 25 October 2006

KEYWORDS
Vinorelbine;
Non-small cell lung cancer;
Chemotherapy;
Toxicity;
Phlebitis;
Randomized trial

Summary Vinorelbine is a moderate vesicant that is well known to cause local venous toxicity such as drug induced-phlebitis. We conducted a prospective randomized trial to determine whether a 1-min bolus injection (1 min bolus) of vinorelbine reduced the incidence of local venous toxicity compared with a 6-min drip infusion (6 min infusion). Non-small cell lung cancer patients who were to receive chemotherapy containing vinorelbine were randomly assigned to receive either 6 min infusion or 1 min bolus of the drug. All infusions were administered through a peripheral vein. Local venous toxicity was evaluated at each infusion up to two cycles. Eighty-three patients were randomized into the study and 81 of them assessable for analysis. One hundred thirty-eight infusions to 40 patients in 6 min infusion and 135 infusions to 41 patients in 1 min bolus were delivered. Vinorelbine induced-local venous toxicity was observed in 33% of patients in 6 min infusion and 24% in 1 min bolus. There was no statistically significant difference between the two arms ($P=0.41$). The incidence of local venous toxicity per infusions was 16% (22 of 138 infusions) in 6 min infusion and 11% (15 of 135 infusions) in 1 min bolus ($P=0.47$). No severe local venous toxicity was seen in either arm. In this study, the administration of in 1 min bolus of vinorelbine did not significantly reduce the incidence of local venous toxicity compared with 6 min infusion. Further studies for the control of local venous toxicity of vinorelbine are warranted.

1. Introduction

Vinorelbine is a second-generation semi-synthetic vinca alkaloid whose antitumor activity is related to its ability to depolymerize microtubules and disrupt the mitotic spindle apparatus [1]. Vinorelbine has been shown to have clearly higher activity and lower neurotoxicity than the other vinca

* Corresponding author. Tel.: +81 4 7133 1111; fax: +81 4 7131 4724.
E-mail address: kyoh@east.ncc.go.jp (K. Yoh).

0169-5002/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2006.10.016