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Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials

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There are inadequate data on the outcomes of patients who declined to participate in randomised clinical trials as compared with those of participants. We retrospectively reviewed the patient characteristics and treatment outcomes of both participants and non-participants in the two randomised trials for chemotherapy-naive advanced non-small-cell lung cancer. Trial 1 compared four platinum-based combination regimens. Trial 2 compared two sequences of carboplatin plus paclitaxel and gefitinib therapies. Nineteen of 119 (16%) and 153 (37%) patients declined to participate in Trials 1 and 2, respectively. Among the background patient characteristics, the only variable associated with trial participation or declining was the patients' attending physicians ($P<0.001$). Important differences were not observed in the clinical outcomes between participants and non-participants, for whom the response rates were 30.6 *vs* 34.2% and the median survival times were 489 *vs* 461 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 0.965 (95% confidence interval: 0.73–1.28). In conclusion, there was no evidence to suggest any difference in the characteristics and clinical outcomes between participants and non-participants. Trial designs and the doctor–patient relationship may have an impact on the patient accrual to randomised trials.
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Randomised clinical trials (RCTs) are the definitive method for comparing the efficacy of treatments and a crucial step in the development of new cancer treatments. There has always been a big problem that their low accrual rates limit their progress (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006).

A number of studies have examined the motivations of patients for accepting or declining entry to RCTs (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Ho *et al*, 2006; Albrecht *et al*, 2008). The results of questionnaire surveys administered to patients regarding clinical trials revealed that two of the most common reasons for entering the trial were the hope for personal benefit and the opportunity to contribute to the research knowledge thereby benefiting others in the future (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Albrecht *et al*, 2008). On the other hand, the common reasons for declining participation were worries about the process of randomisation, overestimation of the benefits of standard therapy and fear of the trial's experimental nature (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Ho *et al*, 2006).

However, inadequate data are available on the actual outcomes of non-participants compared with those participating in RCTs (Schmoor *et al*, 1996; Braunholtz *et al*, 2001; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005). Although several reports and their review (Braunholtz *et al*, 2001) have suggested the existence of a 'trial effect', in which participants enjoy favourable outcomes, others, especially those which attempted to exclude the confounding factors, have refuted this finding (Schmoor *et al*, 1996; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005).

On the other hand, if participation in prospective trials is associated with certain clinical characteristics of the patients, generalisability of the conclusion from the data to the clinical practise, even in patients who meet the restrictive eligibility criteria, should be in question.

The purpose of this study was to analyse the characteristics and outcomes of the patients who met the eligibility criteria but declined to participate in RCTs, as compared with those who did participate, and to search for clues to improve patient accrual to clinical trials.

MATERIALS AND METHODS

Between October 2000 and October 2005, each of the 272 patients, who fulfilled the entry criteria of our top priority studies during the period, was informed of all aspects of RCTs on non-small-cell lung cancer (NSCLC) and was invited to participate in one of the two trials to be conducted at the National Cancer Center Hospital, Tokyo, Japan. We make it a rule for each patient with advanced

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lung cancer to be hospitalised for the first-line chemotherapy. All patients are then checked for the eligibility criteria of clinical trials available at the time and recorded in our database, whether or not they are treated on trials.

Signed informed consent was obtained from the patients for future statistical analysis of their clinical courses and outcomes, even when they were treated outside clinical trials.

Trial 1 was conducted to compare the four platinum-based combination regimens (cisplatin–irinotecan, carboplatin–paclitaxel, cisplatin–gemcitabine and cisplatin–vinorelbine) in patients with untreated advanced NSCLC between October 2000 and June 2002 (Ohe *et al*, 2007). When patients declined to participate, cisplatin-based combination regimens, such as cisplatin–irinotecan, the reference arm of the trial, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians.

Trial 2 was conducted between June 2003 and October 2005 to compare the following two treatment arms; (A) four courses of carboplatin and paclitaxel (CP) followed by gefitinib, and (B) gefitinib until disease progression followed by CP, in patients with advanced NSCLC (Nokihara *et al*, 2008). When patients declined to participate, platinum-based combination regimens, such as CP, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians; treatment options included gefitinib as first-line chemotherapy, when the patients and their families wished to start with it.

Patients in each trial had to meet the following criteria: histologically and/or cytologically documented NSCLC; clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy); no earlier systematic chemotherapy; at least one measurable lesion; age 20–74 years old; Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1; adequate haematological, hepatic and renal functions; and partial pressure of arterial oxygen of 60 torr or more. Each patient was required to submit a written informed consent before entry.

Four physicians (A, B, C and D) participated in Trial 1 and five physicians (A, B, C, D and E) in Trial 2. All were male. Physicians A, B, C and D had 16, 14, 11 and 9 years of experience, respectively, at the time of activation of Trial 1 (October 2000), and Physician E had 9 years of experience at the start of Trial 2 (June 2003). One of the five attending staff physicians and one to two residents or trainees attended each consultation. Which doctor actually offered the RCTs depended on each case and was not recorded, but the attending staff physician finally confirmed the decision by the patient.

Paper and/or electronic medical records from the initial visit to our centre to the end of the follow-up were retrospectively reviewed. Demographic data (age, gender, smoking history), medical information (tumour histology, clinical stage, performance status, therapy characteristics), and clinical outcomes (response rate, follow-up time, overall survival time, 1- and 2-year survival rates) were abstracted and analysed. The response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse *et al*, 2000) by the attending physicians. It is our policy to assess clinical responses with RECIST, even in routine practise. Follow-up time at our institution was defined as the period from the initiation of the first day of the initial therapy or decision of no therapy, to the last day at our institution (including death during follow-up). Survival data of the patients who left our institution could be collected by enquiry into official agency for family registry in Japan.

χ^2-tests and logistic regression analysis was used to assess associations between patient characteristics and the rate of declining to participate. Overall survival (OS) curves were produced using the Kaplan–Meier method and compared with the log rank test. All participants (those who agreed to be enroled into the RCT) and non-participants (those who declined to participate in the RCT) were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (age, gender, smoking history, clinical stage and PS) in comparing the OS of participants and non-participants. *P*-values <0.05 were considered statistically significant. The data collected were analysed using an SPSS II statistical package.

Japanese ethics guidelines for clinical and epidemiological studies, which took effect in August 2007, do not mandate institutional review board (IRB) approval for a single-institutional, retrospective data analysis from the medical charts, when the predesignated person of the institution so judges. This study was thus exempted from ethical review of IRB in due process, on the judgment of the responsible official, deputy director of National Cancer Center Hospital.

RESULTS

There were no significant differences in the outcomes between the arms of each trial. In Trial 1, no statistically significant differences in the response rate, progression-free survival and OS were observed between the four regimens. In Trial 2, there were no statistically significant differences in the median survival time (MST) (18.8 and 17.2 months) and the survival rate at 1 year between the two arms. Seventy-five patients declined to participate in those trials, and 1 of the 197 who initially accepted entry withdrew consent, refusing to continue the trial immediately after randomisation.

Table 1 shows the patient characteristics and rate of declining. 100 patients accepted and 19 patients (16%) declined entry to Trial 1, and 96 patients accepted and 57 patients (37%) declined entry to clinical Trial 2 (including the one patient already mentioned who withdrew consent after randomisation) ($P<0.001$). No significant influence on the rate of declining of patient gender, age,

Table 1 Patient characteristics and rate of declining

	Clinical trial 1			Clinical trial 2			Total		
	P	NP	ROD (%)	P	NP	ROD (%)	P	NP	ROD (%)
No.	100	19	16	96	57	37	196	76	28
Gender									
Male	64	12	16	55	34	38	119	46	28
Female	36	7	16	41	23	36	77	30	28
Age									
<60	46	9	16	37	29	44	83	38	31
⩾60	54	10	16	59	28	32	113	38	25
Smoking history									
+	69	9	12	55	33	38	124	43	26
–	31	10	24	41	24	37	72	33	31
Clinical stage									
III	24	6	20	21	19	48	45	25	36
IV	76	13	15	75	38	34	151	51	25
PS									
0	27	4	13	47	19	29	74	23	24
1	73	15	17	49	38	44	122	53	30
Physicians									
A	32	5	14	23	25	52	55	30	35
B	28	0	0	25	1	4	53	1	2
C	18	2	10	34	4	11	52	6	10
D	22	12	35	7	18	72	29	30	51
E	—	—	—	7	9	56	7	9	56

Abbreviations: NP = non-participants, P = participants; PS = performance status; ROD = rate of declining.

Table 2 Prediction of participation or declining to trials

	Univariate analysis[a]		Multivariate analysis[b]	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Gender (male *vs* female)	1.008 (0.586–1.733)	0.977	0.646 (0.300–1.391)	0.264
Age (<60 *vs* ⩾60)	0.735 (0.432–1.250)	0.254	0.701 (0.376–1.310)	0.266
Smoking history (+ *vs* −)	1.394 (0.815–2.386)	0.225	2.538 (1.162–5.541)	0.019
Clinical stage (III *vs* IV)	0.608 (0.339–1.089)	0.093	0.681 (0.346–1.340)	0.266
PS (0 *vs* 1)	1.398 (0.792–2.467)	0.247	0.785 (0.396–1.554)	0.487
Physicians (A–E)		<0.001		<0.001

Abbreviations: NP = non-participant; P = participant; PS = performance status; ROD = rate of declining. [a]By Pearson's χ^2-test. [b]By logistic regression analysis.

Table 3 Number of courses of the first-line chemotherapy

	Clinical trial 1		Clinical trial 2		
	Participants	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
	100	16	96	57	
First-line cycles					
1	10 (10%)	4 (25%)	6 (12%)	4 (9%)	0.418[a]
2	18 (18%)	4 (25%)	8 (16%)	12 (27%)	
3	37 (37%)	7 (44%)	5 (10%)	9 (20%)	
⩾4	35 (35%)	1 (6%)	30 (61%)	20 (44%)	
Gefitinib median duration (day)			73	99	0.118[b]
Range			13–752	34–1065	
IQR			29–204	38.5–512	

Abbreviation: IQR = interquartile range. [a]By Pearson's χ^2-test. [b]By log rank test.

smoking history, tumour histology, clinical stage or PS was observed (Table 2). There were, however, large differences in the rates of decline among the attending physicians who informed the patients about the trials and asked them to participate ($P<0.001$).

The treatment regimens for those who declined participation in the clinical trials were as follows. The majority of those who declined participation in Trial 1 selected one of the four platinum-based combination regimens presented in the trial: cisplatin–irinotecan 4, cisplatin–vinorelbine 3, cisplatin–gemcitabine 1, carboplatin–paclitaxel 4. Three patients in Trial 1 desired to have no more active treatments and opted for supportive care only, but later received active treatment at their referred hospitals. The detail of their therapy is unknown.

The majority of those who declined participation in Trial 2 selected carboplatin-based combination chemotherapy: carboplatin–paclitaxel 34 and carboplatin–gemcitabine 11, there by reflecting the shift to carboplatin for advanced NSCLC in Japan at the time of Trial 2, on the basis of the reports on the activity of the carboplatin-based regimens (Kelly *et al*, 2001; Schiller *et al*, 2002; Ohe *et al*, 2007). Twelve patients (21%) selected gefitinib as first-line chemotherapy.

Survival was analysed for all of the 196 participants and 76 of the non-participants. Post-therapy was analysed for all of the 196 participants and 73 of the non-participants, who were treated at our centre. There was one possible treatment-related death due to perforation of the colon during gefitinib treatment in Trial 2. No other toxic deaths were observed among either participants or non-participants. More participants of both the clinical trials were given four cycles or more of the first-line chemotherapy, probably reflecting protocol regulations (Table 3).

Table 4 summarises the treatment after the initial therapy. There were no significant differences between participants and non-participants in the number of chemotherapy regimens. Six (8%) of those who declined participation in the trial later participated in early-phase clinical trials of experimental therapies.

Table 4 Treatment after the first-line chemotherapy

	Participants 196 (%)	**Non-participants 73 (%)**	***P*-value[a]**
Chemotherapy regimen			
0[b]	26	40	0.108
1	38	26	
2	22	25	
3	9	8	
>4	5	1	
Radiotherapy	49	34	0.031
Pleural or pericardial drainage	10	5	0.227
Operation on metastatic brain tumors	1	3	0.122
Early-phase trials	13	8	0.300

[a]By Pearson's χ^2-test. [b]Patients received first-line chemotherapy only.

We have observed no clinically relevant differences in the clinical outcomes between participants and non-participants (Table 5). Clinical response to the initial therapy was analysed for all of the 196 participants and 73 of the non-participants, excluding three patients who were not treated at our institute. The response rate was 30.6% in participants and 34.2% in non-participants ($P=0.325$). The median follow-up time at our centre was 388 days for participants and 406 days for non-participants, which was not statistically different.

The OS was not different between participants and non-participants (Table 5 and Figure 1), with a hazard ratio of participants *vs* non-participants of 0.998 (95% confidence interval: 0.76–1.32). No significant difference in OS was observed either in Trial 1 (Figure 2) or in Trial 2 (Figure 3).

Table 5 Clinical outcomes

	Clinical trial 1		Clinical trial 2		Total		
	Participants	**Non-participants**	**Participants**	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
Response rate (%)[a]	29 (29/100)	12.5 (2/16)	32.3 (31/96)	40 (23/57)	30.6 (60/196)	34.2 (25/73)	0.569[b]
Median follow-up time (day)	329	339	493	444	388	406	0.846[c]
Range	45–2704	1–2176	36–2036	22–1688	36–2704	1–2176	
IQR	177–665	59–582	213–861	175–658	197–742	146–604	
Median survival time (day)	416	408	573	519	489	461	0.987[c]
Range	34–2704	53–2380	40–2036	35–1688	34–2704	35–2380	
IQR	264–815	140–698	251–938	276–1012	259–863	229–774	
1-year survival (%)	56.0	63.2	65.6	64.9	60.7	64.5	0.567[b]
2-year survival (%)	29.4	21.1	38.5	29.8	33.9	27.6	0.379[b]

Abbreviation: IQR = interquartile range. [a]Excluding three patients who did not receive active treatment at our center. [b]By Pearson's χ^2-test. [c]By log rank test.

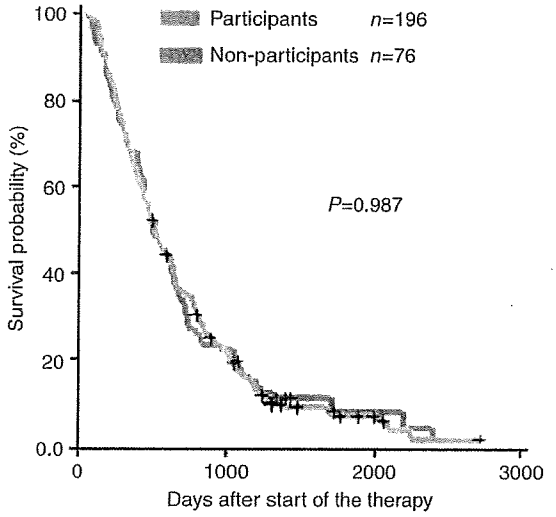

Figure 1 Overall survival of those who declined to participate in randomised trials (blue line, $n = 76$) as compared with the participants (pink line, $n = 196$). No significant difference can be observed.

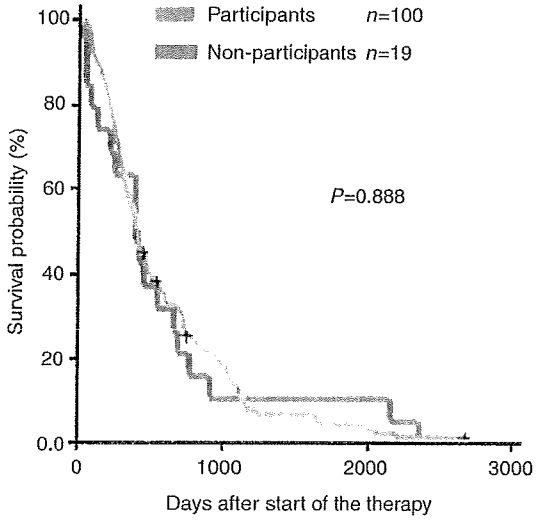

Figure 2 Overall survival of those who declined to participate in Trial 1 (blue line, $n = 19$) as compared with the participants (pink line, $n = 100$). No significant difference can be observed.

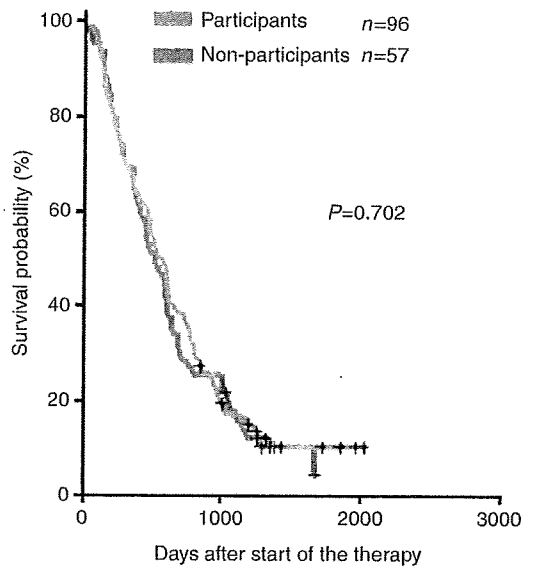

Figure 3 Overall survival of those who declined to participate in Trial 2 (blue line, $n = 57$) as compared with the participants (pink line, $n = 96$). No significant difference can be observed.

With the Cox proportional hazards model adjusted for gender, age, smoking history, clinical stage and PS, the hazard ratio of participants *vs* non-participants was 0.965 (95% confidence interval: 0.73–1.28, $P = 0.805$). Among the patient characteristics, PS was the only significant factor associated with OS in multivariate analysis ($P = 0.006$, by Cox proportional model).

DISCUSSION

It has been argued that trial participants have better outcomes than those who are not enroled in clinical trials. Several investigations have reported a favourable overall trend with trial entry (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004; West *et al*, 2005). This 'trial effect' could derive from several factors, such as protocol effect (the way treatments are delivered), care effect (extra care related to data gathering), Hawthorne effect (changes in doctor or patient behaviour on the basis of the knowledge that they are under observation) or placebo effect (psychologically mediated benefits) (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004).

In majority of the reports comparing outcomes between participants and non-participants of clinical trials, however, the

non-participant 'controls' were chosen from differently pooled database, which could include baseline imbalances between groups and hindsight bias (Davis *et al*, 1985; Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In this study, we compared the characteristics and outcomes of those who met the eligibility criteria but declined to participate in randomised trials, and instead chose to receive standard therapy. We thus aimed at excluding confounding factors as much as possible.

On the other hand, physician triage is pointed out to be one of the barriers to cancer clinical trial accrual (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006; Ho *et al*, 2006). We excluded the barrier by making it a rule to offer clinical trials to every patient with advanced NSCLC who satisfied the eligibility criteria.

The response rate, MST, 1-year and 2-year survival rates were all similar in both groups. We have to admit that response evaluation might not be as strict in off-protocol therapy. However, the hazard ratio for the OS was very close to 1. Although the confidence interval of 0.73 to 1.28 could not rule out the existence of clinically important difference in the treatment effect, it could not by any means be taken as a clinically relevant prognostic factor. We thus believe this confidence interval of the adjusted hazard ratio, 0.73–1.28, was narrow enough to justify the conclusion that the clinical outcomes of trial participants and non-participants were not different in our study. The differences in the number of cycles of chemotherapy given to participants and non-participants may suggest the so-called protocol effect (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), in which explicit careful description of treatment regimens could lead to improvement of outcomes. On the other hand, there clearly existed no 'care effect' representing the differences in incidental aspects of treatment or care between participants and non-participants, which the protocol may require, such as extra follow-up or extra nursing care (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In our cases, the same treatment teams took charge of and followed both groups of patients in the same manner, and found no differences in the post-treatment characteristics or follow-up periods. Thus, our first finding was that the clinical trials themselves seemed to have no influence on the outcomes or pattern of care of the patients.

The second finding was that we could not find any demographic characteristics to influence the patients' willingness to participate in clinical trials. Taken together with the first finding, both the characteristics and outcomes of the non-participants were very similar to the participants. This would imply that the participants ably represented the whole patient population of the disease status who met the eligibility criteria, and that conclusions from the clinical trials could be generalised.

Our study, however, could only show the similarity in the prognosis of the participants and non-participants, and, unlike an earlier report (Link *et al*, 1986), not that of the treatment effect itself. This could not be evaluated because there were no significant differences in the clinical effect between the arms in both Trial 1 and Trial 2. If newer, much more effective experimental treatment were presented in the trials, the outcome could be better in trial participants, which was the case in the adjuvant chemotherapy trial for osteosarcoma (Link *et al*, 1986). In that report, eligible patients who declined randomisation, but were given adjuvant chemotherapy, also had better outcomes. Therefore, a very effective treatment could lead to a better outcome both on and off trial. Ideally, strict comparison of the effects of the study participation itself would require randomised design of the trial participation (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), which is almost impossible to conduct.

Thirdly, the declining rate seemed to be influenced by the trial design. Trial 1 was the comparison of four similar platinum-doublet regimens. On the other hand, Trial 2 was the comparison of two arms with sequentially different types of chemotherapy. In general, people might have the impression that injection therapy would be more effective, and less convenient, than oral administration. It is easy to understand that more patients felt difficulty in accepting the randomisation of different types of therapy, such as Trial 2 (Schmoor *et al*, 1996; Jenkins and Fallowfield, 2000).

The declining rate also seemed to be greatly affected by the attending physician. The attending physician with longer experience as a thoracic oncologist tended to have lower rate of declination. Even though we do not have records on who actually informed the participants regarding the trial, residents or trainees under Physician A seemed to have had more chance to lead the consultation, which might have affected the rate of declination. Trust in the doctor is one of the most important reasons for agreeing to enter an RCT, whereas it has also been cited as the main reason for declining to participate (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Stryker *et al*, 2006). Patients prefer the doctor to make the treatment decisions rather than to be randomised. A recent report emphasises the influence of physicians' clinical communication on patients' decision-making on participation in clinical trials (Albrecht *et al*, 2008). Improving communication and more interventions by clinical research coordinators and other medical staff members in all eligible patients may improve the accrual rate (Fallowfield *et al*, 1998; Wright *et al*, 2004; Stryker *et al*, 2006).

Finally, it was interesting to find that 8% of those who declined the RCTs participated in early-phase trials during follow-up. It is possible that the lack of effective therapies had changed their recognition of clinical trials. However, it might support the psychological states of patients as reported in earlier studies (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Wright *et al*, 2004); patients expect experimental therapies to give them improved effectiveness but with fear of uncertainty. They are reported to have negative opinions regarding the principle of randomisation. Better understanding of the patients' decision-making process and the factors influencing their psychological states may lead to improvement in RCT accrual.

Our study has several limitations. One is that it was conducted at a single academic institution; the situation might well have been different in others or when the research was performed on a multi-institution basis. The second is that we analysed data from only two trials and could not definitely conclude that a trial design would affect the patient accrual. Third, we have no data on the reasons for patient participation. That information would be definitely useful for analysing factors for consent or declining to participate, and would help to improve the accrual rate. Further research is required.

In conclusion, there was no evidence of any difference in the response rates and survival times between participants and non-participants. The declining rate of clinical trials was influenced by the referring physicians and trial designs. Further analysis of the decision-making process of those offered trials is warranted, for it may improve patient accrual to RCTs.

REFERENCES

Albrecht TL, Eggly SS, Gleason MEJ, Harper FWK, Foster TS, Peterson AM, Orom H, Penner LA, Ruckdeschel JC (2008) Influence of clinical communication on patients' decision making on participation in clinical trials. *J Clin Oncol* **26**: 2666–2673

Braunholtz DA, Edwards SJL, Lilford RJ (2001) Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'. *J Clin Epidemiol* **54**: 217–224

Burgers JA, Arance A, Ashcroft L, Hodgetts J, Lomax L, Thatcher N (2002) Identical chemotherapy schedules given on and off trial protocol in small cell lung cancer response and survival results. *Br J Cancer* **87**: 562–566

Corrie P, Shaw J, Harris R (2003) Rate limiting factors in recruitment of patients to clinical trials in cancer research: descriptive study. *BMJ* **327**: 320–321

Davis S, Wright P, Schulman SF, Hill LD, Pinkham RD, Johnson LP, Jones TW, Kellogg HB, Radke HM, Sikkema WW, Jolly PC, Hammar SP (1985) Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. *Cancer* **56:** 1710–1718

Ellis PM, Butow PN, Tattersall MHN, Dunn SM, Houssami N (2001) Randomized clinical trials in oncology: understanding and attitudes predict willingness to participate. *J Clin Oncol* **19:** 3554–3561

Fallowfield LJ, Jenkins V, Brennan C, Sawtell M, Moynihan C, Souhami RL (1998) Attitudes of patients to randomised clinical trials of cancer therapy. *Eur J Cancer* **34:** 1554–1559

Go RS, Frisby KA, Lee JA, Mathiason MA, Meyer CM, Ostern JL, Walther SM, Schroeder JE, Meyer LA, Umberger KE (2006) Clinical trial accrual among new cancer patients at a community-based cancer center. *Cancer* **106:** 426–433

Ho J, Pond GR, Newman C, Maclean M, Chen EX, Oza AM, Siu LL (2006) Barriers in phase I cancer clinical trials referrals and enrollment: five-year experience at the Princess Margaret Hospital. *BMC Cancer* **6:** 263

Jenkins V, Fallowfield L (2000) Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. *Br J Cancer* **82:** 1783–1788

Kelly K, Crowley J, Bunn PA, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) 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* **19:** 3210–3218

Lara PN, Higdon R, Lim N, Kwan K, Tanaka M, Lau DHM, Wun T, Welborn J, Meyers FJ, Christensen S, O'Donnell R, Richman C, Scudder SA, Tuscano J, Gandara DR, Lam KS (2001) Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol* **19:** 1728–1733

Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker AR, Kirkpatrick JA, Ayala AG, Shuster JJ, Abelson HT, Simone JV, Vietti TJ (1986) The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med* **314:** 1600–1606

Madsen SM, Holm S, Davidsen B, Munkholm P, Schlichting P, Riis P (2000) Ethical aspects of clinical trials: the attitudes of participants in two non-cancer trials. *J Intern Med* **248:** 463–474

Madsen SM, Mirza MR, Holm S, Hilsted KL, Kampmann K, Riis P (2002) Attitudes towards clinical research amongst participants and nonparticipants. *J Intern Med* **251:** 156–168

Nokihara H, Ohe Y, Yamada K, Kawaishi M, Kato T, Yamamoto N, Sekine I, Kunitoh H, Saijo N, Tamura T (2008) Randomized phase II study of sequential carboplatin/paclitaxel (CP) and gefitinib (G) in chemotherapy-naïve patients with advanced non-small-cell lung cancer (NSCLC): final results. *J Clin Oncol* **26:** 441s (Suppl; abstr 8069)

Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y, Fukuoka M (2007) 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. *Ann Oncol* **18:** 317–323

Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* **363:** 263–270

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* **346:** 92–98

Schmoor C, Olschewski M, Schumacher M (1996) Randomized and non-randomized patients in clinical trials: experiences with comprehensive cohort studies. *Stat Med* **15:** 263–271

Stryker JE, Wray RJ, Emmons KM, Winer E, Demetri G (2006) Understanding the decisions of cancer clinical trial participants to enter research studies: factors associated with informed consent, patient satisfaction, and decisional regret. *Patient Educ Couns* **63:** 104–109

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Glabbeke MV, Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* **92:** 205–216

West J, Wright J, Tuffnell D, Jankowicz D, West R (2005) Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol. *Qual Saf Health Care* **14:** 175–178

Wright JR, Whelan TJ, Schiff S, Dubois S, Crooks D, Haines PT, DeRosa D, Roberts RS, Gafni A, Pritchard K, Levine MN (2004) Why cancer patients enter randomized clinical trials: exploring the factors that influence their decision. *J Clin Oncol* **22:** 4312–4318

Comparative Chemotherapeutic Efficacy in Non-small Cell Lung Cancer Patients with Postoperative Recurrence and Stage IV Disease

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Background: Whether chemotherapy would be equally effective in non-small cell lung cancer patients with stage IV disease (group A) and postoperative recurrence (group B) remains unclear.

Patients and Methods: In a total of 642 non-small cell lung cancer patients with distant metastases treated by chemotherapy, the baseline patient characteristics, responses to chemotherapy and survival were compared between group A (n = 480) and group B (n = 162).

Results: Adenocarcinoma was the predominant histologic type, accounting for 78% of the patients in group A and 90% of the patients in group B ($p < 0.001$). Bone and brain metastases were more common in group A ($p = 0.034$ and $p = 0.014$, respectively), although pulmonary metastases were more common in group B ($p < 0.001$). The chemotherapy regimens used for the treatment did not differ between groups A and B. The response rates in group A and group B were 32 and 33%, respectively ($p = 0.65$). In contrast, the median progression-free survival (5.5 versus 4.2 months, $p = 0.0065$) and overall survival (21.3 versus 13.3 months, $p < 0.001$) were better in group B than in group A.

Conclusion: Survival was superior in patients with postoperative recurrence than in those with stage IV disease, although the two groups showed comparable responses to chemotherapy.

Key Words: Chemotherapy, Non-small cell lung cancer, Postoperative recurrence, Stage IV disease.

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Until now, non-small cell lung cancer (NSCLC) patients showing disease recurrence after surgery for the primary lesion have been treated with systemic chemotherapy or supportive care alone, in accordance with the treatment offered for patients with stage IV disease,[1] although there have been no comparative studies specifically conducted on these patients. Furthermore, clinical trials conducted to evaluate the efficacy of chemotherapy have, in most cases, included patients with postoperative recurrence as well as those with stage IV disease. However, whether chemotherapy would be equally effective in the two groups of patients remains unclear. The objectives of this retrospective study were to compare the patient characteristics, responses to chemotherapy, and survival between these two patient groups.

PATIENTS AND METHODS

Patient Selection

Patients were retrospectively selected for this study according to the following criteria (1): a histologic or cytologic diagnosis of NSCLC (2); presence of distant metastases at the time of the initial diagnosis (stage IV disease) or postoperative recurrence (3); no prior chemotherapy; and (4) received chemotherapy at the National Cancer Center Hospital between December 2000 and June 2006. Patients were excluded if they had only postoperative local recurrence without distant metastases. All patients underwent systematic evaluation and standardized staging procedures before the start of systemic treatment. Clinical stage was assigned based on the results of physical examination, chest radiography, computed tomography scans of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bone scintigraphy. The histologic classification of the tumor was based on the criteria of the World Health Organization.[2]

Data Collection and Statistical Analyses

Patients' baseline characteristics, including age, sex, performance status, histology, site of distant metastases, number of distant metastases, and chemotherapy regimens were obtained retrospectively from the medical charts. Measurable lesions and objective tumor responses were defined according to Response Evaluation Criteria in Solid Tumors (RECIST).[3] All pretreatment and treatment parameters were compared between the two groups, that is, the group with stage IV disease (group A) and the group with postoperative recurrence (group B). χ^2 and Mann-Whitney tests were used to evaluate the differences in categorical and continuous variables, respectively, between the two groups. The overall and progression-free survivals were evaluated using the

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Kaplan-Meier method and logrank test. Cox proportional hazards models were used to adjust for potential confounding factors.[4] All analyses were performed using the Dr. SPSS II 11.0 for Windows software (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Characteristics

A total of 642 patients met the eligibility criteria for this study. Of these, 480 patients (75%) had stage IV disease (group A) and 162 (25%) had postoperative recurrence (group B). In group B, pathologic stage I, stage II, stage III, and stage IV disease was noted in 49 (30%), 32 (20%), 76 (47%), and 5 (3%) patients, respectively. The median interval from the day of the operation for the primary disease and the first day of chemotherapy was 22.2 months. Baseline characteristics stratified by the groups are summarized in Table 1. Sex distribution did not differ between the two groups, but the median age was 2.5 years higher in group B. Adenocarcinoma was the predominant histologic type, accounting for 78% of patients in group A and 90% of patients in group B ($p < 0.001$). The predominant sites of metastases differed between the two groups; bone and brain metastases were more common in group A ($p = 0.034$ and $p = 0.014$, respectively), although pulmonary metastases were more common in group B ($p < 0.001$). Chemotherapy regimens used for first-line chemotherapy did not differ between the two groups. Platinum-based chemotherapy, nonplatinum doublet chemotherapy, mono-chemotherapy with a third-generation cytotoxic agent, and epidermal growth factor receptor tyrosine kinase inhibitors were administered in 360 (75%), 4 (1%), 29 (6%), and 87 (18%) patients in group A, respectively, and 109 (67%), 5 (3%), 18 (11%), and 30 (19%) patients in group B, respectively.

Responses and Survival

A total of 472 (98%) of the 480 patients in group A, but only 100 (62%) of the 162 patients in group B, had measurable lesions ($p < 0.001$, Table 2). Among patients with measurable lesions, responses to chemotherapy were comparable between the patients of group A and group B (Table 2). Progression-free survival, however, was superior in group B

TABLE 1. Patient Characteristics

	Group A[a] (n = 480)		Group B[a] (n = 162)		
	n	(%)	n	(%)	p
Sex					0.23
Female	173	(36.0)	67	(41.4)	
Male	307	(64.0)	95	(58.6)	
Age median (range)	60	(24–86)	62.5	(32–81)	0.004
Histology					0.001
Adenocarcinoma	375	(78.1)	145	(89.5)	
Nonadenocarcinoma	105	(21.9)	17	(10.5)	
Performance status					0.23
0	137	(28.5)	60	(37.0)	
1	316	(65.8)	95	(58.6)	
2	22	(4.6)	6	(3.7)	
3	5	(1.0)	4	(0.6)	
No. of metastatic organs					0.96
1	303	(63.1)	104	(64.2)	
2	125	(26.0)	39	(24.1)	
3	35	(7.3)	13	(8.0)	
4–6	17	(3.5)	6	(3.7)	
Metastatic sites					
Bone					0.034
No	287	(59.8)	112	(69.1)	
Yes	193	(40.2)	50	(30.9)	
Brain					0.014
No	347	(72.3)	133	(82.1)	
Yes	133	(27.7)	29	(17.9)	
Lung					<0.001
No	256	(53.3)	57	(35.2)	
Yes	224	(46.7)	105	(64.8)	
Liver					0.26
No	423	(88.1)	148	(91.4)	
Yes	57	(11.9)	14	(8.6)	

[a] Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

TABLE 2. Objective Responses to Chemotherapy

	Group A		Group B		
	n	(%)	n	(%)	p
Measurable lesions (n = 642)					<0.001
Yes	472	(98.3)	100	(61.7)	
No	8	(1.7)	62	(38.3)	
Objective responses in patients with measurable lesions (n = 572)					0.65
Complete response	5	(1.1)	1	(1.0)	
Partial response	145	(30.7)	32	(32.0)	
Stable disease	170	(36.0)	29	(29.0)	
Progressive disease	100	(21.2)	23	(23.0)	
Not evaluable[a]	52	(11.0)	15	(15.0)	

[a] In these patients, chemotherapy was discontinued early because of toxicity. Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

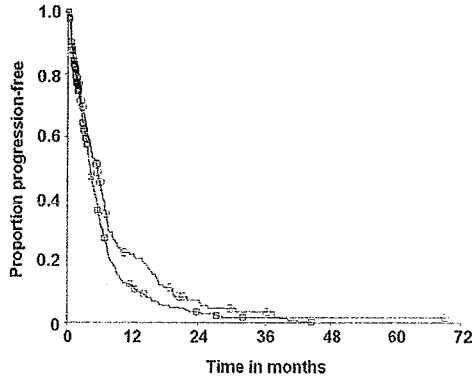

FIGURE 1. Progression-free survival in patients with stage IV disease (open square, n = 480) and in those with postoperative recurrence (open circle, n = 162).

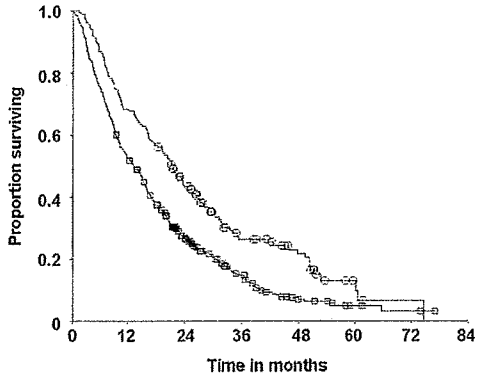

FIGURE 2. Overall survival in patients with stage IV disease (open square, $n = 480$) and in those with postoperative recurrence (open circle, $n = 162$).

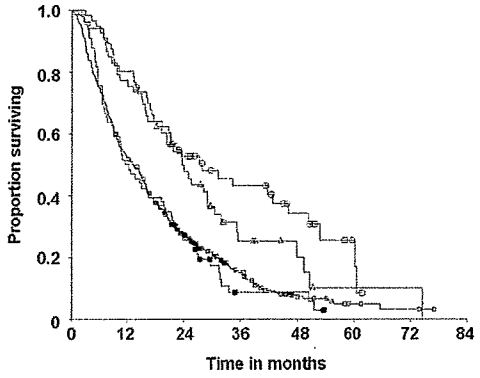

FIGURE 3. Overall survival in patients with stage IV disease (open square, $n = 480$) and in those with postoperative recurrence according to the interval between the day of the operation and the first day of chemotherapy. The interval had a significant impact on the survival from the start of chemotherapy. Open circle ($n = 54$), interval of 30.0 months or longer; open triangle ($n = 53$), interval of 15.0 to 29.9 months, and closed circle ($n = 55$), interval shorter than 15.0 months.

than in group A (5.5 versus 4.2 months, $p = 0.0065$, Figure 1). Overall survival was also superior in group B than in group A (21.3 versus 13.3 months, $p < 0.001$, Figure 2). The interval between the day of operation and the first day of chemotherapy had a significant impact on the survival from the start of chemotherapy. Median survival time (MST) from the start of chemotherapy was 23.6 and 27.8 months, respectively, in patients in whom the interval was 15.0 to 29.9 months and 30 months or longer, respectively. In contrast, the median survival time from the start of chemotherapy was only 11.7 months in the patients in whom the interval was less than 15.0 months ($p < 0.001$), which was comparable with that in patients with stage IV disease (group A; 13.4 months) (Figure 3). Pathologic stage at the time of surgery had no impact on the overall survival of the patients in group B. Other known prognostic factors including male sex, a poor performance status, a large number of metastatic organs, and the presence of bone metastasis were associated with poor patient survival (Table 3), whereas brain metastasis had no

TABLE 3. Factors Associated with Overall Survival

	Hazard Ratio (95% Confidence Interval)			
	Univariate Analysis	p	Multivariate Analysis	p
Sex				<0.001
Female	1		1	
Male	1.56 (1.30–1.86)	<0.001	1.58 (1.32–1.90)	
Performance status				
0	1		1	
1	1.43 (1.19–1.74)	<0.001	1.31 (1.08–1.58)	0.007
2–3	2.76 (1.88–4.05)	<0.001	2.49 (1.67–3.70)	<0.001
Number of metastatic organs[a]	1.25 (1.13–1.37)	<0.001	1.26 (1.12–1.42)	<0.001
Bone metastasis				0.91
No	1		1	
Yes	1.45 (1.22–1.73)	<0.001	1.01 (0.82–1.25)	
Pulmonary metastasis				0.005
No	1		1	
Yes	0.72 (0.61–0.85)	<0.001	0.76 (0.63–0.92)	
Group				<0.001
A	1		1	
B	0.63 (0.51–0.77)	<0.001	0.66 (0.54–0.81)	

[a] With an increment of one. Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

impact on survival (hazard ratio, 1.11; 95% confidence interval, 0.91–1.35; $p = 0.30$) and pulmonary metastasis was associated with a better survival (Table 3). Multivariate analysis using a Cox's proportional hazard model showed that patients in group B had a better prognosis than those in group A with a hazard ratio of 0.66 (95% confidence interval, 0.54–0.81, $p < 0.001$) (Table 3).

DISCUSSION

This study revealed different characteristics of patients with postoperative recurrence who received systemic chemotherapy for tumor recurrence in comparison with those of patients with stage IV disease among NSCLC patients. Considering the interval between the operation and chemotherapy, the median value of which was 22 months, it is understandable that the median age of patients with postoperative recurrence was 2 years higher than that of the patients with stage IV disease. The percentage of patients with adenocarcinoma was higher in the group of patients with postoperative recurrence, probably because recurrence after surgical resection may be more common in patients with adenocarcinoma than in patients with squamous cell carcinoma. This is consistent with a previous report that squamous cell histology was associated with a good prognosis among patients with stage IIIA disease.[5] Recent large-scale randomized trials in previously treated advanced NSCLC patients have shown that epidermal growth factor receptor tyrosine kinase inhibitors are more effective against adenocarcinomas (with response rates of 12–13%) than against nonadenocarcinomas (with response rates of no more than 5%).[6,7] In the current study, these agents were administered as a first-line chemotherapy in

18% of the patients with stage IV disease and in 19% of the patients with postoperative recurrence; no data regarding the use of these agents in second-line or subsequent chemotherapy regimens was available. Thus, the use of this class of agents may have influenced the survival difference between the patients with stage IV disease and those with postoperative recurrence. Brain and bone metastases were significantly less common in patients with postoperative recurrence in this study. These patients may have been less frequently referred to medical oncologists, possibly because of a poor performance status and could therefore be suitable candidates for palliative radiotherapy. However, pulmonary metastases were significantly more common in the group with postoperative recurrence, possibly because these patients can only be treated with systemic chemotherapy.

Thirty-eight percent of patients with postoperative recurrence had no measurable lesions. Many of these patients had multiple small pulmonary metastases, but no evidence of recurrence at other sites. Excluding these patients, evaluation of the response to chemotherapy revealed no difference in percentages of patients showing complete and partial responses between the two groups. Thus, it is reasonable to include patients with postoperative recurrence in studies in which the primary end point is the response rate, such as conventional phase II studies, as long as they have measurable disease.

Patient survival was significantly superior in patients with postoperative recurrence compared with those with stage IV disease in this study, with a hazard ratio of 0.66 ($p < 0.001$). To our knowledge, there are no such data in the medical literature except one report, which showed that prior lung surgery may have been associated with a better prognosis, with a hazard ratio of 0.86.[8] This reported difference, however, was much smaller than that found in this study. Patients with postoperative recurrence constitute a heterogeneous group, and patients with a relatively better prognosis tended to be included in this group in the current study. The disease-free interval between the operation and recurrence has been reported as a prognostic factor.[9] In this study, patients with an interval from the operation to the start of postrecurrence chemotherapy of less than 15.0 months had a survival rate as poor as that in patients with stage IV disease. These patients who showed relatively early recurrence accounted for only one-third of all the patients with postoperative recurrence in this study. In conclusion, the NSCLC patients with postoperative recurrence had characteristics different from those with stage IV disease in this study, but the two groups showed comparable responses to chemotherapy. Survival, both progression-free and overall, was superior in those with postoperative recurrence as compared with those with stage IV disease, especially those having a postoperative disease-free interval of more than 15 months.

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REFERENCES

1. Yoshino I, Yohena T, Kitajima M, et al. Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. *Ann Thorac Cardiovasc Surg* 2001;7:204–209.
2. Travis W, Colby T, Corrin B, Shimosato Y. *Histological Typing of Lung and Pleural Tumors, 3rd Ed.* Berlin: Springer, 1999.
3. Therasse P, Arbuck SG, Eisenhauer EA, 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;92:205–216.
4. Armitage P, Berry G, Matthews J. Survival analysis. In Armitage P, Berry G, Matthews J, (Eds.), *Statistical Methods in Medical Research, 4th Ed.* Oxford: Blackwell Science Ltd, 2002. Pp. 568–590.
5. Sculier JP, Chansky K, Crowley JJ, et al. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008;3:457–466.
6. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
7. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527–1537.
8. Hoang T, Xu R, Schiller JH, Bonomi P, Johnson DH. Clinical model to predict survival in chemonaive patients with advanced non-small-cell lung cancer treated with third-generation chemotherapy regimens based on eastern cooperative oncology group data. *J Clin Oncol* 2005;23:175–183.
9. Ichinose Y, Yano T, Yokoyama H, et al. Postrecurrent survival of patients with non-small-cell lung cancer undergoing a complete resection. *J Thorac Cardiovasc Surg* 1994;108:158–161.

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ORIGINAL ARTICLE

A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer

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Abstract
Purpose Nedaplatin is a second-generation platinum showing favorable activity against non-small cell lung cancer (NSCLC). Dose-limiting toxicity (DLT) is thrombocytopenia, predicted by creatinine clearance (Ccr). This study was conducted to determine the recommended dose, and evaluate the toxicities, pharmacokinetics and efficacy for elderly NSCLC patients.
Methods Patients ≥70 years were stratified into two groups based on renal functions: Group A, Ccr ≥ 60 and Group B, 40 ≤ Ccr < 60. The initial doses were 80 and 60 mg/m^2 in Groups A and B, respectively. The doses were escalated in 20-mg/m^2 increments to 100 mg/m^2 until DLT.
Results Chemotherapy-naïve 39 elderly patients (Group A/Group B: 22/17) received a total of 83 cycles. Major toxicities were hematological. In Group A, one of the 15 patients at 100 mg/m^2 experienced DLT (neutropenia) and the recommended dose was determined at 100 mg/m^2. In Group B, three of the five patients had DLTs (leukopenia, neutropenia, thrombocytopenia and febrile neutropenia) at 100 mg/m^2, and the recommended dose was determined at 80 mg/m^2. The percentage decreases of neutrophil were well correlated with total and free-Pt AUCs. Partial responses were observed in 13 (33%) of the 39 patients, and 12 of the 13 patients who responded had a squamous cell carcinoma.
Conclusions Nedaplatin was administered simply and feasibly by stratifying renal function and exerted favorable antitumor activity for elderly patients with NSCLC, especially on squamous cell carcinoma.

Keywords Nedaplatin · Dose-finding study · Pharmacokinetics · NSCLC · Elderly patient

Introduction

The proportion of elderly patients with non-small cell lung cancer (NSCLC) is increasing [1]. At present, the first-line standard chemotherapy for non-elderly patients with advanced NSCLC is a platinum-based doublet regimen. The efficacy and feasibility of this strategy have been demonstrated in several randomized trials in patients with a good performance status and aged ≤70 years [2–4]. However, platinum-based doublet regimens are not always feasible for elderly patients. Age-related comorbidity and physiologic changes increase inter-individual pharmacokinetic variability, possibly leading to unacceptable severe toxicities. In particular, application of a cisplatin-based regimen to elderly patients is substantially restricted because of the risk of emesis, neurotoxicity and nephrotoxicity.

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Oshita et al. [5] prospectively evaluated the feasibility of cisplatin-based chemotherapy in patients aged 75 years or older. Only 10 (29%) out of the 34 patients fulfilled the eligibility criteria for the cisplatin-based regimen. Furthermore, the majority of these eligible patients had grade 4 neutropenia and infectious episodes requiring antibiotics. In another analysis of cisplatin pharmacokinetics, the area under the plasma concentration versus time curve (AUC) of the ultrafilterable and total plasma platinum increased with age, and this was an independent predictor of cisplatin pharmacokinetics [6]. Therefore, the administration of cisplatin is restricted to highly select elderly patients.

(Glycolate-*O,O'*)-diammine platinum (II) (nedaplatin) is a second-generation platinum analog synthesized by Shionogi & Co., Ltd. (Osaka, Japan). In the preclinical studies, nedaplatin is highly active against solid tumors and has higher aqueous solubility than cisplatin [7–9]. The emesis and nephrotoxicity of nedaplatin are substantially reduced, compared with those of cisplatin, and multiple days of hydration for renal protection are not required [10]. Dose-limiting toxicity (DLT) is thrombocytopenia, and recommended dose in Japanese patient ≤70 years is 100 mg/m^2 every 4 weeks. This agent is active against NSCLC, with a response rate of 20.5% for previously untreated patients [10]. In a pharmacokinetic analysis, thrombocytopenia was significantly correlated with renal function (i.e., creatinine clearance [Ccr]), and nadir platelet count could be predicted from the following formula [11]:

$$[\text{Nadir platelet count}]\left(/\text{mm}^3\right) = -64,264.7 + 2,783.4 \times [\text{Ccr}](\text{mL/min})$$

We conducted a dose-finding and pharmacokinetic study of nedaplatin in elderly patients with NSCLC, stratified into two groups based on renal function. This study was conducted to determine the recommended dose, and evaluate the toxicity profiles, pharmacokinetics and antitumor activity.

Patients and methods

Eligibility

Patients with histologically and cytologically confirmed chemotherapy-naïve advanced or metastatic non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: (1) age ≥70 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) adequate bone marrow (white blood cell [WBC] count ≥4,000/mm^3, absolute neutrophil count [ANC] ≥2,000/mm^3, hemoglobin level ≥9.0 g/dL and platelet [PLT] count ≥100,000/mm^3), hepatic (serum total bilirubin level ≤1.5 mg/dL, serum asparatate aminotransferase [AST] level ≤100 IU/L and serum alanine aminotransferase [ALT] level ≤100 IU/L), renal (serum creatinine [Cr] level ≤1.5 mg/dL, creatinine clearance [Ccr] ≥40 mL/min) and pulmonary (PaO_2 ≥60 torr) functions.

The exclusion criteria were as follows: (1) symptomatic brain metastasis; (2) pleural or pericardial effusions and ascites requiring drainage; (3) serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes and psychogenic disorders; and (4) hepatic B or C virus or human immunodeficiency virus infection.

Written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the National Cancer Center.

Study design, dosage and dose escalation

This study was designed to determine the recommended dose of nedaplatin for elderly patients with advanced NSCLC, stratified into two groups based on renal function. The primary objective was to determine the recommended dose, and the secondary objectives were to evaluate toxicity profiles, pharmacokinetics and antitumor activity.

Patients were stratified into two groups based on their renal function at the time of study entry: Group A, Ccr ≥60 mL/min; and Group B, 40 ≤ Ccr < 60 mL/min. Ccr was measured on three consecutive days, and the mean value was used for stratification. Each Ccr was calculated using the following formula:

$$\text{Ccr}\,(\text{mL/min}) = [\text{urine volume}\,(\text{mL/min}) \times \text{urine creatinine}\,(\text{mg/dL})]/\text{serum creatinine}\,(\text{mg/dL})$$

In Group A, the initial dose of nedaplatin was 80 mg/m^2, and this was escalated to 100 mg/m^2. In Group B, the initial dose was 60 mg/m^2, and this was escalated to 80 and 100 mg/m^2. At least three to six patients were enrolled at each dose level, and the unacceptable dose was defined as the dose level at which >50% of the patients experienced DLT. The definition of DLT was as follows: (1) ≥grade 3 leukopenia, neutropenia or thrombocytopenia; (2) ≥grade 3 non-hematological toxicities except for alopecia, nausea and vomiting; (3) ≥grade 3 nausea and vomiting for ≥5 days. The recommended dose was defined as one dose level below the unacceptable dose level in each treatment arm.

Nedaplatin administration

Nedaplatin (Aqupla, (glycolate-*O,O'*)-diammine platinum (II); Shionogi Pharmaceutical Company, Osaka, Japan) was obtained commercially. Premedication, consisting of

3 mg of granisetron and 16 mg of dexamethasone diluted in 100 mL of 0.9% saline, was administered via a 30-minute intravenous (IV) infusion. The calculated doses of nedaplatin in both treatment groups were diluted in 300 mL of 0.9% saline and were administered using a 1-h IV infusion every 4 weeks. Following the nedaplatin administration, 500 mL of 0.9% saline was administered intravenously to provide minimal hydration.

Pretreatment and follow-up evaluation

On enrollment into the study, history and physical examination was performed. Complete differential blood cell count (including WBC count, ANC, hemoglobin and PLT), and clinical chemistry analysis (including serum total protein, albumin, bilirubin, Cr, AST, ALT, gamma-glutamyltransferase, and alkaline phosphatase) were performed. These above were performed at least twice a week throughout the study. Tumor measurement was planned every cycle, and antitumor response was assessed using the WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

PK study

Pharmacokinetic (PK) evaluations were performed in all patients during the initial cycle of treatment. Heparinized venous blood samples (7 mL) were taken before infusion, at 30 min and just before the end of infusion, as well as at 15 and 30 min and 1, 2, 3, 5, 7, 11, 23 and 47 h after the end of infusion.

Blood samples were centrifuged immediately at 4,000 rpm for 10 min. One milliliter of plasma was stored at −20°C or below in a polyethylene tube until the measurement of total plasma platinum (total-Pt) concentration. Residual plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA, USA) and centrifuged at 4,000 rpm for 20 min. Ultrafiltrate of the plasma was taken and stored at −20°C or below in a polyethylene tube until the measurement of the plasma-free platinum (free-Pt) concentration. The total-Pt and free-Pt concentrations were measured using flameless atomic absorption spectrometry, as previously reported [12].

The PK parameters were estimated using a nonlinear least-squares regression analysis (WinNonlin, Version 5.2; Bellkey Science, Inc., Chiba, Japan) with a weighting factor of $1/year^2$. The individual plasma concentration–time data were fitted to one-, two- and three-exponential equations using a zero-order infusion input and first-order elimination (corresponding to a one-, two- and three-compartment PK model). The model was chosen on the basis of Akaike's information criteria [13]. Fitted parameters (coefficients and exponent of exponential equations) were permitted in the computation of the following PK parameters: half life ($t_{1/2}$), area under the plasma concentration versus time curve (AUC), systemic clearance (CL), and volume of distribution at steady state (V_{dss}).

To assess the pharmacodynamic effect, percentage decrease was calculated in WBC, ANC or PLT according to the following formula:

$$\text{Percentage decrease} = [(\text{pretreatment count} - \text{nadir count})/(\text{pretreatment count})] \times 100.$$

These percentages were related to the AUC according to the sigmoid E_{max} model, as follows:

$$\text{Effect}(\%) = [E_{max}(\text{AUC})^k]/[\text{AUC}_{50}^k + \text{AUC}^k] \times 100.$$

A nonlinear least-squares regression using WinNonlin was used to estimate the AUC that produces 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (k).

Results

Patient characteristics

Between June 1996 and July 2001, 39 patients were stratified into two groups (22 in Group A and 17 in Group B) based on their renal functions at entry into the study (Table 1). They received a total of 83 cycles of therapy. The patients comprised 35 males and 4 females with good performance status, and the median age was 76 years in both treatment groups. All the patients were included in the toxicity evaluation. A total of 28 (72%) patients were included in the PK analysis and the remaining 11 (28%) were excluded because of insufficient PK samplings. Eight patients (two from Group A and six from Group B) had stage IIIA disease, but were not candidates for thoracic radiotherapy because of their poor pulmonary function. Six patients (five from Group A and one from Group B) received surgical resections for primary tumors. As much as 21 patients (54%, 12 from Group A and 9 from Group B) had squamous cell carcinoma. Nine patients (4 from Group A and 5 from Group B) received only one cycle of therapy because of progressive disease (PD) and 22 patients (12 from Group A and 10 from Group B) received two cycles of treatment. Among these 22 patients, partial response (PR), stable disease (SD) and PD were observed in 8, 10 and 4 patients, respectively. Five of eight patients with PR, two of ten with SD and one of four with PD received sequential thoracic radiotherapy for primary lesion following two cycles of treatment. Two of ten patients with SD and one of four with PD received palliative

radiotherapy for metastatic lesion. Two of four patients with PD received second-line chemotherapy. The remaining nine patients received supportive care according to the patients' request.

Toxicity

All the 39 patients were included in the toxicity evaluation. Major toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups, and these hematological toxicities increased in severity with increased dose level of nedaplatin. In Group A, 1 (6.7%) out of the 15 patients treated at a dose level of 100 mg/m^2 had grade 3 neutropenia; this dose level was considered to be acceptable (Table 2). In Group B, three (50%) out of six patients treated at a dose level of 80 mg/m^2 had ≥grade 3 hematological toxicities (one with grade 3 neutropenia, another with grade 4 neutropenia and febrile neutropenia, and the other with grade 3 leukopenia, anemia and grade 4 thrombocytopenia). The patient with grade 4 thrombocytopenia required a platelet transfusion. At a dose level of 100 mg/m^2, three (60%) out of five patients had ≥grade 3 hematological toxicities (one with grade 3 leukopenia and neutropenia, another with grade 3 thrombocytopenia and grade 4 neutropenia, and the other with grade 3 leukopenia, thrombocytopenia and grade 4 neutropenia). These three patients had also febrile neutropenia. In Group B, a dose level of 100 mg/m^2 was considered to be unacceptable (Table 2).

Non-hematological toxicities, mainly nausea and anorexia, were generally mild in severity and were not dose limiting in either group (Table 3). Renal toxicity,

Table 1 Patient characteristics

	Group A (Ccr ≥60 mL/min)		Group B (40 ≤ Ccr < 60 mL/min)	
	No. of patients	Percentage	No. of patients	Percentage
Total patients enrolled	22	100	17	100
Assessable for toxicity	22	100	17	100
Assessable for PK analysis	15	68	13	76
Age, median (range), years	76 (70–82)		76 (70–78)	
Sex				
Male	19	86	16	94
Female	3	14	1	6
ECOG PS				
0	6	27	1	6
1	16	73	15	88
2	0	0	1	6
Stage				
IIIA	2	9	6	35
IIIB	4	18	6	35
IV	11	50	4	24
Postoperative recurrence	5	23	1	6
Pathological subtype				
Squamous cell carcinoma	12	54	9	53
Adenocarcinoma	9	41	8	47
P/D carcinoma	1	5	0	0
Dose of nedaplatin (mg/m^2)				
60	–	–	6	35
80	7	32	6	35
100	15	68	5	30
Treatment cycle				
Median (range)	2 (1–5)		2 (1–4)	
1 cycle	4	18	5	29
2 cycles	12	55	10	59
≥3 cycles	6	27	2	12

PK pharmacokinetics, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *P/D carcinoma* poorly differentiated carcinoma

Table 2 Hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Leukopenia	6	1	0	0	0	12	1	2	0	0
Neutropenia	6	1	0	0	0	8	4	2	1[a]	0
Anemia	4	2	1	0	0	5	7	3	0	0
Thrombocytopenia	7	0	0	0	0	12	2	1	0	0
No. of patients with febrile neutropenia	0					0				
No. of patients with DLT	0					1				

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Leukopenia	5	1	0	0	0	2	1	2	1[a]	0	2	0	1	2[a]	0
Neutropenia	5	1	0	0	0	2	2	0	1[a]	1[a]	1	1	0	1[a]	2[a]
Anemia	4	1	1	0	0	3	1	1	1[a]	0	1	2	2	0	0
Thrombocytopenia	6	0	0	0	0	3	1	1	0	1[a]	2	1	0	2[a]	0
No. of patients with febrile neutropenia	0					1					3				
No. of patients with DLT	0					3					3				

[a] DLT

characterized as an increase in Cr, was also mild, and only one out of five patients treated at a dose level of 100 mg/m^2 in Group B had a grade 2 Cr increase. Considering the toxicity profiles, the recommended doses in Groups A and B were determined to be 100 and 80 mg/m^2, respectively.

Response and survival

The antitumor response was assessed in all the 39 patients (Table 4). Of the 39 patients who achieved PR, 13 had an overall response rate of 33%. Similar antitumor responses were observed in both treatment groups; that is, 6 (27%) of 22 and 7 (41%) of 17 patients had PRs in Groups A and B, respectively. Furthermore, 12 of the 13 patients with PRs in both groups had squamous cell carcinoma, and the response rate among patients with squamous cell carcinoma was 57%. Survival follow-up was completed in all the enrolled patients. The median survival time was 11.2 months (95% confidence interval: 7.7–14.6 months), and the 1-, 2- and 5-year survival rates were 46, 23 and 5%, respectively.

Pharmacokinetics

Pharmacokinetic analysis was performed using data from 28 (72%) of the 39 patients. The first patient enrollment in both treatment groups was started in 1996, and techniques of the sample centrifuging and measurement were not fully developed at the beginning of this pharmacokinetic study. Therefore, the remaining 11 patients (28%) were excluded for pharmacokinetic analysis. The mean plasma concentration–time profiles of total-Pt and free-Pt of nedaplatin are illustrated in Fig. 1. The plasma disappearances of total-Pt and free-Pt were biphasic, and the mean terminal half lives in all the assessable patients averaged 6.28 and 3.57 h, respectively. The C_{max} and AUC of the total-Pt and free-Pt tended to increase with the dose of nedaplatin. The AUCs of the total- and free-Pt at a dose of 100 mg/m^2 in Group A seemed similar to those at a dose of 80 mg/m^2 in Group B (Table 5), and there were no significant differences between these two treatment subgroups (P = 0.293 for total-Pt AUC and P = 0.336 for free-Pt AUC). Furthermore, the AUCs of free-Pt at the recommended doses in both groups (i.e., 100 mg/m^2 in Group A and 80 mg/m^2 in Group B) seemed also similar to that in patients aged 70 years or under who had been treated with 100 mg/m^2 of nedaplatin [14]. In the sigmoid Emax model assessing the pharmacodynamic effect of nedaplatin, the percentage decrease in the neutrophil counts were well correlated with the total-Pt (r = 0.652) and free-Pt (r = 0.723; Fig. 2).

Table 3 Non-hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Nausea	5	1	1	0	0	3	9	3	0	0
Vomiting	6	1	0	0	0	15	0	0	0	0
Anorexia	5	1	1	0	0	7	4	4	0	0
Diarrhea	6	1	0	0	0	14	1	0	0	0
Stomatitis	7	0	0	0	0	15	0	0	0	0
Hyperbilirubinemia	6	0	1	0	0	15	0	0	0	0
AST increase	6	1	0	0	0	13	2	0	0	0
ALT increase	6	1	0	0	0	13	2	0	0	0
ALP increase	7	0	0	0	0	15	0	0	0	0
Cr increase	7	0	0	0	0	15	0	0	0	0

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Nausea	1	4	1	0	0	1	3	2	0	0	1	1	3	0	0
Vomiting	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Anorexia	4	2	0	0	0	1	3	2	0	0	1	1	3	0	0
Diarrhea	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Stomatitis	6	0	0	0	0	6	0	0	0	0	5	0	0	0	0
Hyperbilirubinemia	6	0	0	0	0	6	0	0	0	0	4	0	1	0	0
AST increase	4	2	0	0	0	5	0	1	0	0	4	0	1	0	0
ALT increase	5	1	0	0	0	5	0	1	0	0	4	0	1	0	0
ALP increase	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Cr increase	6	0	0	0	0	4	2	0	0	0	4	0	1	0	0

AST asparatate aminotransferase, *ALT* serum alanine aminotransferase, *ALP* alkaline phosphatase, *Cr* creatinine

Discussion

In this dose-finding study, we evaluated the toxicities, pharmacokinetics as well as antitumor activity, and determined the recommended doses of nedaplatin for elderly patients with advanced NSCLC based on renal function. The predominant toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups. These hematological toxicities tended to increase in severity with the increased dose level of nedaplatin. Non-hematological toxicities were acceptable and those were not dose limiting in either group. The recommended dose was determined as 100 mg/m^2 every 4 weeks in elderly patients with a renal function of Ccr ≥ 60 mL/min, which is the same dose recommended for patients aged ≤70 years. On the other hand, for elderly patients with a renal function of 40 ≤ Ccr < 60 mL/min, the recommended dose was 80 mg/m^2 every 4 weeks. In this study,

Table 4 Response

Group	Dose level (mg/m^2)	No. of patients	Response				PR	
			CR	PR	SD	PD	Sq.	Non–sq.
Group A (Ccr ≥60 mL/min)	80	7	0	2	3	2	2	0
	100	15	0	4	6	5	4	0
Group B (40 ≤ Ccr < 60 mL/min)	60	6	0	3	2	1	2	1
	80	6	0	3	1	2	3	0
	100	5	0	1	1	3	1	0
Total		39	0	13	13	13	12	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *Sq.* squamous cell carcinoma, *Non-sq.* non-squamous cell carcinoma

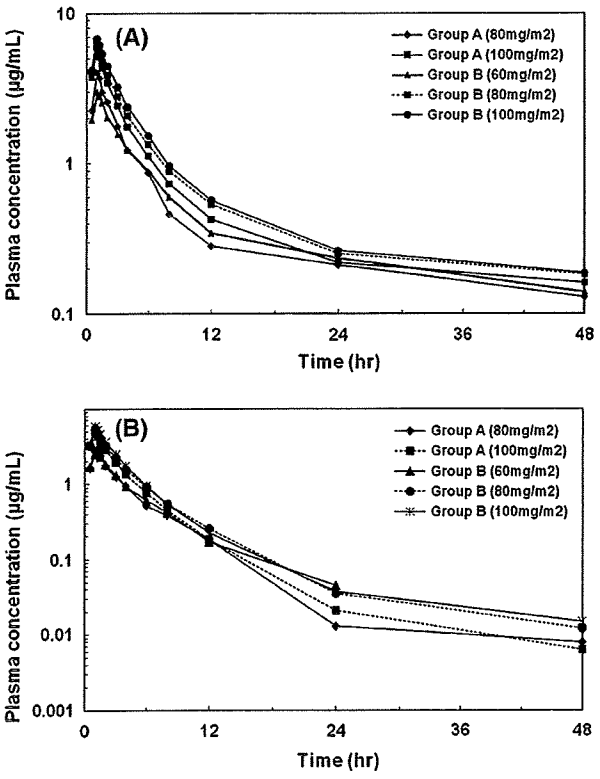

Fig. 1 Mean plasma concentration–time profiles for: **a** total-Pt and **b** free-Pt of nedaplatin

an additional nine patients were enrolled at the dose level of 100 mg/m^2 in Group A. First, the favorable antitumor response was observed in squamous cell carcinoma and we intended to evaluate the antitumor response mainly for squamous cell carcinoma. Then, five of nine additional patients enrolled had squamous cell carcinoma. Second, the recommended dose was determined as 100 mg/m^2 in Group A, which was the same dose in younger patients. We intended to confirm the toxicity and pharmacokinetic profiles in this elderly subgroup.

In the development of chemotherapy for elderly patients, the selection of appropriate agents is extremely important. Candidate agents must have confirmed antitumor activities and acceptable toxicity profiles in younger patients (e.g., aged ≤70 years). In this study, we investigated nedaplatin as it had a lower incidence of associated emesis and nephrotoxicity, compared with cisplatin, and favorable antitumor activity in NSCLC patients aged ≤70 years. Furthermore, the current standard treatment for elderly patients with advanced NSCLC, that is, third-generation single-agent chemotherapy such as vinorelbine, gemcitabine or docetaxel, had not been established at the time of planning of the study [15–17]. The DLT of nedaplatin in patients aged ≤70 years was reported to be thrombocytopenia, which is correlated with renal function; therefore, we expected that nedaplatin could be safely administered to elderly patients by stratifying the patients according to renal function. Patients with a Ccr ≥40 mL/min were eligible for inclusion in this study based on the results of a previous PK analysis examining the correlation between the nadir platelet count and renal function (described in "Introduction") [11]. When younger patients with a Ccr ≥40 mL/min were treated with 100 mg/m^2 of nedaplatin, the predicted nadir platelet count was ≥50,000/mm^3. Therefore, the initial doses of nedaplatin in Group A (Ccr ≥60 mL/min) and Group B (40 ≤ Ccr < 60 mL/min) were determined to be 80 and 60 mg/m^2, respectively. The dose escalation over 100 mg/m^2 was not planned, because the recommended dose in younger patients (aged ≤70 years) had already been determined at 100 mg/m^2.

In this study, milder criteria of DLT was applied, compared with that used in conventional phase I studies. In this developmental strategy, we pursued "the recommended dose with moderate and acceptable toxicities for the majority of elderly patients", instead of "the recommended dose with the severe toxicities in a small and limited number of patients, as per most conventional phase I studies", because the physiological and pharmacological function of elderly patients is highly variable.

Table 5 Pharmacokinetic parameters of total-Pt and free-Pt

Group	Dose level (mg/m^2)	No. of patients	No. of assessables for PK analysis	C_{max} (μg/mL)	AUC (μg/mL h)	V_{dss} (L)	$T_{1/2}$ (h)	CL (L/h)
PK parameters of total-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	4.02 (3.49, 4.57)	22.58 (13.46, 31.69)	64.24 (35.27, 93.21)	14.15 (3.25, 25.04)	6.00 (3.60, 8.40)
	100	15	13	5.94 ± 1.38	21.65 ± 4.54	31.50 ± 13.40	3.28 ± 1.35	7.63 ± 1.74
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	3.02 (2.91, 3.12)	19.78 (14.87, 24.68)	57.05 (33.21, 80.89)	10.77 (4.08, 17.46)	5.21 (4.16, 6.25)
	80	6	6	6.35 ± 1.11	25.99 ± 9.68	29.29 ± 13.18	7.88 ± 8.97	6.10 ± 1.13
	100	5	5	6.83 ± 1.20	32.11 ± 7.86	32.84 ± 22.00	6.62 ± 4.55	5.01 ± 1.57
PK parameters of free-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	2.72 (2.13, 3.31)	10.56 (7.05, 14.06)	42.30 (37.98, 46.62)	3.49 (2.70, 4.28)	12.08 (8.11, 16.04)
	100	15	13	5.11 ± 1.51	16.20 ± 3.34	32.26 ± 11.17	3.51 ± 4.02	10.26 ± 2.46
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	2.55 (2.46, 2.64)	11.59 (11.38, 11.79)	49.33 (33.22, 65.43)	6.16 (2.98, 9.34)	8.45 (7.89, 9.01)
	80	6	6	5.52 ± 1.25	18.53 ± 7.12	29.51 ± 9.11	3.40 ± 0.65	7.25 ± 2.21
	100	5	5	5.91 ± 1.21	20.69 ± 5.52	29.63 ± 12.32	2.92 ± 0.66	7.87 ± 2.71
Patients ≤70 years [14]	100	5	5		15.9			

Data are shown as mean ± SD excepting the dose level of 80 mg/m^2 in Group A and 60 mg/m^2 in Group B

PK pharmacokinetics, *total-Pt* total platinum, *free-Pt*, free platinum, C_{max} maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, V_{dss} volume of distribution at steady-state, $T_{1/2}$ terminal half life, *CL* systemic clearance

[a] Data are shown as mean (actual data)

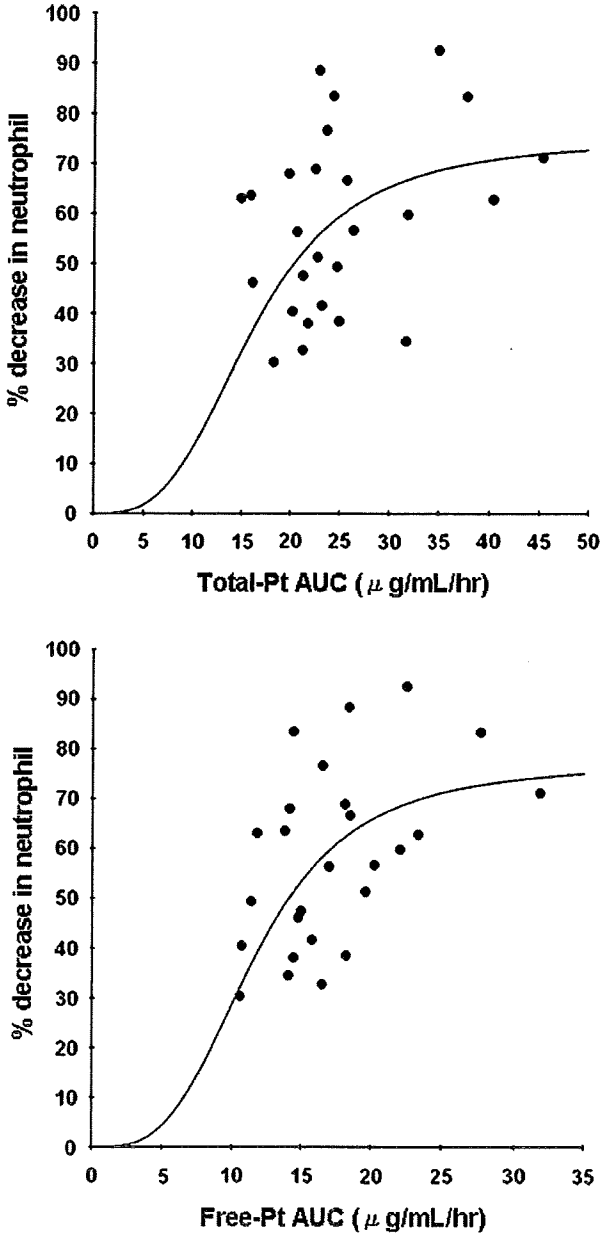

Fig. 2 Relationship between AUCs of total/free-Pt and the percentage decrease in the neutrophil count

In the pharmacokinetic analysis, the free-Pt AUC at a dose of 100 mg/m^2 in Group A seemed similar to that of 80 mg/m^2 in Group B, and there was no significant difference between these two treatment subgroups ($P = 0.336$). These results endorsed an almost equivalent drug exposure in both patient groups, stratified according to renal function. Furthermore, the AUC values in both groups seemed similar to historical data (obtained in a study with a small sample size) for patients aged ≤70 years [14]. However, a significant correlation was not observed between the renal function (i.e., the Ccr value) and the nadir platelet count, as in a previous report examining younger patients. These were possibly attributed to the wide inter-patient physiological and pharmacological variability among elderly patients or just the consequence of the adaptation of dose [11]. For elderly patients, a strict dose calculation of nedaplatin based on renal function, such as the dose calculation for carboplatin using the Calvert formula [18], is not required, and a simple dose selection of nedaplatin stratified according to renal function is considered to be reasonable.

A total of 13 (33%) of the 39 patients achieved partial responses. In this study, 21 patients with squamous cell carcinoma were enrolled, 12 patients achieved PR and the response rate was 57%. The biological mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma of the lung remains unknown. In the pharmacokinetic analysis, no significant differences were observed in responding patients with squamous cell carcinoma compared with non-responding others. However, nedaplatin also has a favorable antitumor activity against head and neck cancer and esophageal cancer, which also have a high frequency of squamous cell histology [19–22]. Although antitumor activity was evaluated only in elderly patients in this study, the development of this activity is worthwhile in the treatment of NSCLC with squamous cell histology. Furthermore, a translational study to identify the biological and/or genetic mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma is also warranted.

In conclusion, the recommended doses of nedaplatin for elderly patients with NSCLC were determined based on renal function, a dose of 100 mg/m^2 every 4 weeks was recommended for patients with a Ccr ≥60 mL/min, and a dose of 80 mg/m^2 every 4 weeks was recommended for patients with 40 ≤ Ccr < 60 mL/min. Nedaplatin can be safely administered to elderly patients with an acceptable level of toxicity and favorable antitumor activities against NSCLC, especially squamous cell carcinoma.

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References

1. Kaneko S, Ishikawa KB, Yoshimi I et al (2003) Projection of lung cancer mortality in Japan. Cancer Sci 94:919–923
2. Schiller JH, Harrington D, Belani CP et al (2002) Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 346:92–98
3. Ohe Y, Ohashi Y, Kubota K et al (2007) 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. Ann Oncol 18:317–323
4. Kubota K, Watanabe K, Kunitoh H et al (2004) 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 22:254–261
5. Oshita F, Kurata T, Kasai T et al (1995) Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. Jpn J Cancer Res 86:1198–1202
6. Yamamoto N, Tamura T, Maeda M et al (1995) The influence of ageing on cisplatin pharmacokinetics in lung cancer patients with normal organ function. Cancer Chemother Pharmacol 36:102–106
7. Kanzawa F, Matsushima Y, Nakano H et al (1988) Antitumor activity of a new platinum compound (glycolate-*O,O'*) diammineplatinum (II) (254-S), against non-small cell lung carcinoma grown in a human tumor clonogenic assay system. Anticancer Res 8:323–327
8. Suzumura Y, Kato T, Ueda R et al (1989) Effect of treatment schedule on antitumor activity of glycolate-*0, 0'*-diammineplatinum(II), a new platinum derivative: comparison with *cis*-diamminedichloroplatinum(II). Anticancer Res 9:1083–1088
9. Hida S, Okada K, Yoshida O (1990) Advantages in combination chemotherapy using cisplatin and its analogues for human testicular tumor xenografts. Jpn J Cancer Res 81:425–430
10. Furuse K, Fukuoka M, Kurita Y et al (1992) A phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for primary lung cancer. Gan To Kagaku Ryoho 19:879–884
11. Sasaki Y, Fukuda M, Morita M et al (1990) Prediction from creatinine clearance of thrombocytopenia and recommended dose in patients receiving (glycolato-*O,O'*)-diammine platinum (II) (NSC 375101D). Jpn J Cancer Res 81:196–200
12. LeRoy AF, Wehling ML, Sponseller HL et al (1977) Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med 18:184–191
13. Yamaoka K, Nakagawa T, Uno T (1978) Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 6:165–175
14. Sasaki Y, Tamura T, Eguchi K et al (1989) Pharmacokinetics of (glycolate-*O,O'*)-diammine platinum (II), a new platinum derivative, in comparison with cisplatin and carboplatin. Cancer Chemother Pharmacol 23:243–246
15. The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer: The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 91:66–72
16. Gridelli C, Perrone F, Gallo C et al (2003) Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 95:362–372
17. Kudoh S, Takeda K, Nakagawa K et al (2006) Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small cell lung cancer: results of the West Japan Thoracic Oncology Group trial (WJTOG 9904). J Clin Oncol 24:3657–3663
18. Calvert AH, Newell DR, Gumbrell LA et al (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
19. Kato H, Fukuchi M, Manda R et al (2003) Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. Anticancer Res 23:3493–3498
20. Kodaira T, Fuwa N, Tachibana H et al (2006) Phase I study of S-1 and nedaplatin for patients with recurrence of head and neck cancer. Anticancer Res 26:2265–2268
21. Yoshioka T, Sakayori M, Kato S et al (2006) Dose escalation study of docetaxel and nedaplatin in patients with relapsed or refractory squamous cell carcinoma of the esophagus pretreated using cisplatin, 5-fluorouracil, and radiation. Int J Clin Oncol 11:454–460
22. Kanai M, Matsumoto S, Nishimura T et al (2007) Retrospective analysis of 27 consecutive patients treated with docetaxel/nedaplatin combination therapy as a second-line regimen for advanced esophageal cancer. Int J Clin Oncol 12:224–227