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ORIGINAL ARTICLE

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Phase I/II study of escalating doses of nedaplatin in combination with irinotecan for advanced non-small-cell lung cancer

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Abstract We conducted a phase I/II study of combination chemotherapy with nedaplatin (NDP) and irinotecan to determine the effects against advanced non-small-cell lung cancer (NSCLC) and to determine the qualitative and quantitative toxicities of the combination chemotherapy. NDP was given on day 1 and irinotecan on days 1 and 8. The treatment cycle was designed to be repeated every 3 weeks. We fixed the dose of irinotecan as 60 mg/m^2 and escalated the NDP dose from a starting dose of 50 mg/m^2 by 10-mg/m^2 increments until the maximum tolerated dose (MTD) was reached. The MTD was defined as the dose level at which at least two of three or three of six patients experienced a dose-limiting toxicity (DLT). Between April 1997 and November 2000, 42 patients were registered in the study. Of the 42 patients, 37 had no prior treatment, 3 had received whole-brain irradiation, 1 had undergone surgical resection, and 1 had had one regimen of chemotherapy before enrolling in this study. In the phase I study, we observed DLTs such as grade 4 neutropenia lasting 7 days and grade 3 diarrhea lasting 1 day in one patient at level 2, grade 3 elevated of GPT in one patient at level 3, and acute myocardial infarction in one patient at level 6. We could not determine the MTD until dose level 6 was reached, so decided on a recommended dose of 100 mg/m^2 NDP, which is recommended for NDP-alone chemotherapy. Because of prolonged neutropenia in the phase I study, we repeated the treatment every 4 weeks in the phase II study. In the phase II study, a total of 16 patients, including 6 patients from the phase I study, were registered and a total of 42 cycles were administered. Grade 3 or 4 neutropenia, grade 3 anemia and grade 3 or 4 thrombocytopenia occurred in 50%, 12% and 7% of cycles, respectively. Febrile neutropenia occurred in eight cycles (19%) but there were no severe infections. Grade 3 elevation of GPT occurred in one patient. Of the 16 patients, 7 had an objective response. Of the 42 patients, 13 achieved a partial response (PR) and the overall response rate was 31.0%. The median duration of PRs was 226 days (range 59 to 646 days). The median survival time was 341 days and the 1-year survival rate was 45.2%. In conclusion, the combination of NDP and irinotecan was highly effective and well tolerated in NSCLC.

Keywords Adenocarcinoma · Squamous cell carcinoma

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Introduction

Current chemotherapy regimens for metastatic non-small-cell lung cancer (NSCLC) are not particularly effective. The disease cannot be cured, even with the most effective cisplatin-based combination chemotherapy. New agents and new combination chemotherapies have been investigated for metastatic NSCLC. In the past decade, a number of new anticancer agents have been approved for the treatment of advanced NSCLC, including vinorelbine, gemcitabine, docetaxel and paclitaxel. Regimens based on combinations of these drugs with platinum compounds have shown interesting new possibilities for treating patients with NSCLC. Randomized studies comparing these platinum-based combinations with single-agent treatment have demonstrated a small but significant survival benefit for the combination treatment [1, 2]. Recently, a trial of non-platinum combination chemotherapy has commenced [3]. However, cisplatin is still a key drug in chemotherapy against NSCLC. Nedaplatin (NDP) is an analogue of cisplatin, whose in vitro and in vivo cytotoxicity, relatively low neurotoxicity and nephrotoxicity,

and large in vivo bioavailability have ensured its position as a promising platinum analogue and as a primary chemotherapeutic agent for the treatment of patients with advanced lung cancer [4]. A phase I study has demonstrated 100 mg/m^2 of NDP to be the recommended dose and its dose-limiting toxicity is thrombocytopenia [5]. A phase II study against NSCLC in which NDP was given at a dose of 100 mg/m^2 every 4 weeks has demonstrated a 14.7% objective response rate (RR) [6].

Agents which inhibit topoisomerase activity lead to the DNA strands being broken and the topoisomerase being covalently attached to the target DNA molecule [7, 8]. Thus, DNA topoisomerase I has been identified as an important target for anticancer agents. The camptothecin derivative, irinotecan, is a topoisomerase I inhibitor and is effective against small-cell lung cancer and NSCLC [9, 10]. Platinum and irinotecan have shown a synergistic effect against human lung cancer [11]. Moreover, three-dimensional analysis models have demonstrated a remarkable synergistic interaction between concurrently administered NDP and irinotecan [12].

We conducted a phase I/II study of NDP and irinotecan against NSCLC. We fixed the dose of irinotecan as 60 mg/m^2, which is the dose used in combination with cisplatin [13], and escalated the NDP dose from 50 mg/m^2 in 10-mg/m^2 increments. We omitted irinotecan on day 15 and aimed to repeat this combination chemotherapy every 3 weeks. The aims of this study were:

1. to determine a recommended dose of NDP with irinotecan
2. to determine the effects of combination chemotherapy against advanced NSCLC, with evaluation of the objective response and survival rate
3. to determine the qualitative and quantitative toxicities of the combination chemotherapy.

Patients and methods

Patients

Patients with histologically or cytologically proven unresectable NSCLC were registered for NDP and irinotecan combination chemotherapy. Eligibility criteria for the chemotherapy were: an expected survival of at least 6 weeks, age <70 years, Eastern Cooperative Oncology Group performance status (PS) score not more than 1, white blood cell count at least 4000/μl, hemoglobin at least 10 g/dl, platelet count at least 100,000/μl, total serum bilirubin not more than 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase not more than 90 IU/l, serum creatinine not more than 1.5 mg/dl, and creatinine clearance more than 40 ml/min.

Patients experiencing postoperative recurrence and patients who had received radiotherapy or chemotherapy were eligible for the present study, but only one regimen of chemotherapy was allowed and 4 weeks or more rest was required after prior chemotherapy or radiation therapy. Written informed consent was obtained from every patient.

Chemotherapy

All patients without disease progression were to be treated every 3 weeks with two or more courses of chemotherapy comprising 60 mg/m^2 irinotecan on days 1 and 8, and NDP on day 1. Patients received intravenous (i.v.) 5-HT$_3$ antagonist and 8 mg dexamethasone before administration of the anticancer drugs on day 1. Irinotecan was administered on day 8 when the following criteria were satisfied: leukocyte count ≥3000/μl, neutrophil count ≥1500/μl, platelets ≥75,000/μl, and less than grade 2 non-hematologic toxicity except for emesis and alopecia. Recombinant human granulocyte colony-stimulating factor (rhG-CSF), 50 mg/m^2 per day or 2 μg/kg per day, was administered subcutaneously once a day when the leukocyte or neutrophil counts were below 2000/μl or 1000/μl, respectively. The use of rhG-CSF was stopped if the leukocyte or neutrophil counts were more than 10,000/μl or 5000/μl, respectively. Subsequent courses of chemotherapy were started when patients could satisfy the organ function eligibility criteria, except for hemoglobin, for entry to the study. The doses of irinotecan and NDP were reduced by 10 mg/m^2 for the subsequent course if the dose-limiting toxicity (DLT) was reached. The chemotherapy was repeated for a maximum of four courses unless the disease progressed, but was stopped if the tumor response was defined as no change (NC) after two courses. Physical examination, complete blood cell counts, biochemical tests and chest radiographs were obtained weekly.

Tumor responses were evaluated according to World Health Organization criteria [14]. Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response (PR) was defined as at least a 50% reduction in the sum of the products of the two greatest perpendicular diameters of all indicator lesions or a reduction of more than 50% in evaluable disease for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. Progressive disease (PD) was defined as at least a 25% increase in the tumor area or the appearance of new lesions. All other outcomes were classified as NC. Toxicities were evaluated according to the Japan Clinical Oncology Group (JCOG) criteria [15].

DLT was defined as toxicity in the first two courses consisting of grade 4 neutropenia lasting for 4 days or more, or grade 4 neutropenia with fever of 38°C or above, or grade 4 thrombocytopenia, or grade 2 or more depression of PaO_2, or grade 2 or more dyspnea, or grade 3 or 4 non-hematologic toxicity except for alopecia, nausea and vomiting, or failure to recover to eligibility criteria for starting the second course within 6 weeks, or skipping day-8 chemotherapy because of toxicity. Patient refusal was also defined as a DLT. When a patient had experienced a DLT, subsequent patients were eligible for entry to the study only if they had no prior chemotherapy.

At least three patients assessable for toxicity were treated at each dose level. If none of the first three patients experienced a DLT, then the next dose level was opened. If one patient developed a DLT, the cohort was expanded to six patients. The maximum tolerated dose (MTD) was defined as the dose level at which at least two of three patients or three of six patients experienced a DLT. The recommended dose of NDP for phase II was defined one level below the MTD. If the MTD was not defined by the NDP dose level at 100 mg/m^2, which is the recommended dose for NDP alone, 100 mg/m^2 of NDP was recommended as the dose for phase II.

In the phase II study, 16 patients were treated at the recommended dose level. We decided to stop the study if fewer than 4 of 16 patients responded in the first stage. If 7 or more patients responded in first stage, this regimen was considered to be active. If 4 to 6 of 16 patients responded, a total of 35 patients at the recommended dose level were required. This regimen was defined as active if there were 12 or more responders and inactive if there were 11 or fewer responders (Simon optimal two stage; $\alpha < 0.05$ and $\beta < 0.10$) [16, 17]. Overall survival was estimated using the method of Kaplan and Meier The Committee of JCOG and the Institutional Review Board of Kanagawa Cancer Center reviewed and approved the protocol prior to commencement.

Table 1 Patient characteristics

Total no. of patients	42
Age (years)	
Median	55
Range	29–69
Gender	
Male	27
Female	15
Performance status (ECOG)	
0	7
1	35
Clinical stage	
IIIA/B	5
IV	36
Postoperative recurrence	1
Histology	
Adenocarcinoma	30
Squamous cell carcinoma	8
Others	4
Prior treatment	
Whole-brain irradiation	3
Chemotherapy	1
Surgery	1

Table 2 Planned and administered nedaplatin and irinotecan

Dose level	Nedaplatin (mg/m^2)	Irinotecan (mg/m^2)	No. of patients	No. of cycles
1	50	60	6	13
2	60	60	7	14
3	70	60	7	14
4	80	60	3	7
5	90	60	3	7
6	100	60	16	42

Results

Between April 1997 and November 2000, 42 patients were registered in the study. The patient characteristics are summarized in Table 1. Of the 42 patients: 27 were male and 15 female; their median age was 55 years (range 29–69 years); 7 had a PS of 0 and 35 had a PS of 1; 30 had adenocarcinoma, 8 had squamous cell carcinoma, and 4 had other cancers; and 37 had no prior treatment, 3 had received whole-brain irradiation, 1 had undergone surgical resection, and 1 had had one regimen of chemotherapy before enrolling in this study. A total of 97 cycles were administered. The number of patients and cycles at each dose level are listed in Table 2. A total of 40 patients were assessable for toxicity following the drop-out of two patients in the first cycle, one at level 2 because of a violation of chemotherapy, and one at level 3 because of bleeding from a metastatic tumor in the duodenum. There were no treatment-related deaths in either the phase I or the phase II study.

Phase I study

At dose level 1, one of the first three patients could not receive irinotecan on day 8 because of neutropenia (a DLT); another three patients were registered and no other DLT was observed at level 1. At dose level 2, a third patient received irinotecan on day 15 in the first cycle and was considered a protocol violation; another patient was registered. The additional patient experienced DLTs including grade 4 neutropenia lasting 7 days and grade 3 diarrhea lasting 1 day. No DLT was observed in the other registered three patients. At dose level 3, a third patient experienced DLTs including grade 3 elevated GPT and so another three patients were registered. One of the additional three patients experienced massive bleeding from metastatic tumors in the duodenum on day 8 in the first cycle and was dropped from the protocol, and a total of seven patients entered at dose level 3. One of the additional four patients could not receive irinotecan on day 8 because of neutropenia. Only two of the six patients assessable for toxicity at dose level 3 experienced DLT and so dose level 4 was opened. Three patients were registered at dose level 4 and three at dose level 5. One patient developed disease progression during the first cycle at each level, but the other two at each level did not experience a DLT, and so dose level 6 was opened. One patient at dose level 6 experienced acute myocardial infarction on day 7 in the first cycle (a DLT) and a total of six patients were assessable for toxicity. The sixth patient could not receive irinotecan on day 8 in the first cycle because of neutropenia, but the other four patients did not experience DLTs and we could not determine the MTD until dose level 6. The recommended dose of NDP was determined as 100 mg/m^2, which is the recommended dose for NDP-alone chemotherapy. We planned to treat patients every 3 weeks, but neutropenia induced by chemotherapy was prolonged and most patients were treated every 4 weeks in the phase I study (Table 2). Therefore, NDP 100 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1 and 8 every 4 weeks were recommended for the phase II study.

Phase II study

A total of 16 patients, including 6 patients from the phase I study, were registered for assessment of response in the phase II study. A total of 42 cycles were administered. Hematologic toxicities are summarized in Table 3. Grade 3 or 4 neutropenia, grade 3 anemia and grade 3 or 4 thrombocytopenia occurred in 50%, 12% and 7% of cycles, respectively. Febrile neutropenia occurred in 8 cycles (19%) but there were no severe infections. Non-hematologic toxicities are summarized in Table 4. Grade 3 elevation of GPT occurred in one patient. Of the 16 patients in phase II, 7 responded and patient registration was stopped.

Table 3 Hematologic toxicities by cycle

Dose level	No. of patients	No. of cycles	No. of cycles with toxicity (JCOG grade)											
			Neutropenia					Hemoglobin			Platelets			
			1	2	3	4	Febrile	1	2	3	1	2	3	4
1	6	13	0	5	6	1	0	4	2	0	0	0	0	0
2	7	14	4	3	3	1	1	5	5	1	1	1	0	0
3	7	14	3	5	4	0	1	2	4	0	1	1	0	0
4	3	7	2	1	3	0	0	0	0	0	0	0	0	0
5	3	7	2	1	0	0	2	4	1	0	0	0	0	0
6	16	42	5	9	14	7	8	10	11	5	2	1	2	1

Table 4 Grade 3 or 4 nonhematologic toxicity

Dose level	No. of patients	No. of cycles	No. of cycles with toxicity (JCOG grade)							
			Total bilirubin	GOT	GPT	Creatinine	Diarrhea	Dyspnea	Emesis	Neuropathy
1	6	13	0	0	0	0	0	0	0	0
2	7	14	0	0	0	0	1	0	0	0
3	7	14	0	0	1	0	0	0	0	0
4	3	7	0	0	0	0	0	0	0	0
5	3	7	0	0	0	0	0	0	0	0
6[a]	16	42	0	0	1	0	0	0	0	0

[a]One patient at level 6 experienced acute myocardial infarction

Table 5 Antitumor activity by dose level

Dose level	No. of patients	Partial response	No change	Disease progression	Not evaluable
1	6	1	4	1	0
2	7	2	3	1	1
3	7	1	4	1	1
4	3	1	1	1	0
5	3	1	1	1	0
6	16	7	6	2	1
Total	42	13	19	7	3

The outcome of chemotherapy in 42 patients with measurable lesions is shown in Table 5. Of the 42 patients, 13 achieved PR, 19 NC and 7 PD, and the overall RR was 31.0%. The median duration of PR was 226 days (range 59 to 646 days). Seven patients were alive and the other 35 patients died during the follow-up period. The median survival time was 341 days and the 1-year survival rate was 45.2%.

Discussion

The combination of NDP with irinotecan showed high activity in NSCLC, and did not result in renal toxicity or emesis in the present study. Unexpectedly, severe hematologic toxicities were not observed and we could not determine the MTD in the phase I study. The phase II study was conducted with irinotecan 60 mg/m^2, plus NDP 100 mg/m^2, which is the recommended dose for chemotherapy with NDP alone. In a phase II study, 50% grade 3 or 4 neutropenia is considered acceptable. rhG-CSF was used for a mean of 6.6 days in 14 of total 42 courses in the phase II study according to Japanese recommendations [18]. Eight episodes of infection in five patients were observed. One episode of grade 3 infection occurred; the lesion of the patient progressed in one cycle of chemotherapy, and was found to be obstructive pneumonia due to tumor progression. The other seven episodes of infection were mild. Anemia and thrombocytopenia were also mild in the phase II study. Non-hematologic toxicities were mild except for one case of gastrointestinal bleeding from metastatic lesion (level 3 of phase I) and one of acute myocardial infarction (level 6 of phase I). The patient experienced gastrointestinal bleeding on day 8 just before irinotecan infusion. The patient responded to hemostatic therapy but died of tumor progression on day 52. The acute myocardial infarction occurred on day 7 of the first cycle of chemotherapy and was treated with anticoagulant therapy. The patient improved from the myocardial infarction but died of tumor progression 5 months from chemotherapy. These

two episodes were considered sporadic and non-specific for the NDP and irinotecan combination chemotherapy.

The median survival time of 341 days and the 1-year survival rate of 45.2% were both good results in the present study. Of 42 patients in the phase I and phase II studies, 13 responded, a RR of 31.0%, and in particular there were 7 responders among 16 patients in the phase II study (RR 43.8%), indicating a high activity in NSCLC. Considering the relationship between pathology of tumor and response to chemotherapy, NDP was shown to be more effective against squamous cell carcinoma than against adenocarcinoma. Of 8 patients with squamous cell carcinoma and 30 patients with adenocarcinoma, 3 (37.5%) and 8 (26.7%) responded, respectively, in the present study. We conclude that both pathological types are sensitive to NDP with irinotecan. Furthermore, responses were observed with low doses of NDP with irinotecan; this is because these two drugs act synergistically. The synergy between NDP and irinotecan seems to be affected by the drug treatment because of their differing mechanisms. One study has shown schedule-dependent synergism between NDP and irinotecan [12]. A marked synergistic interaction was observed when the cells were simultaneously exposed to NDP and irinotecan. The topoisomerase I-inhibitory effect of irinotecan has been reported to be enhanced tenfold in the presence of NDP in an analysis of the effects of NDP and SN-38 on the activity of DNA topoisomerase I using nuclear protein extract of SBC-3 cells [12]. In that study, neither the catalytic activity of topoisomerase I nor its susceptibility to topoisomerase I inhibitors was affected by pretreatment with NDP. The effect of the combination of NDP and irinotecan was correlated with the effect of NDP on the irinotecan-induced inhibition of topoisomerase I. It is very interesting that this synergistic action of NDP and irinotecan resulted in high activity in NSCLC but did not induce severe toxicities in the present study.

The characteristics of this combination of the platinum derivative NDP and irinotecan differ from that of combination chemotherapy with cisplatin or carboplatin. The combination of NDP and irinotecan did not result in renal toxicity and emesis, in contrast to cisplatin and irinotecan. Moreover, myelosuppression with NDP and irinotecan was mild, which is in contrast to the effect of carboplatin and irinotecan. Neutropenia is a DLT of the combination of carboplatin and irinotecan and the recommended dose of irinotecan is 50 mg/m^2 with that combination [19, 20]. We showed that the combination of 60 mg/m^2 of irinotecan with NDP was safe and feasible in NSCLC. Furthermore, the antitumor activity was high (43.8% in phase II), and not less than that of cisplatin combination chemotherapy. These results indicate that the combination chemotherapy of NDP and irinotecan is useful not only for patients at low risk, but also for patients at high risk such as those with a poor PS or the elderly. Further studies are required, not only a large phase II study to examine the activity of the combination in NSCLC, but also a study to examine the feasibility and activity in elderly patients with NSCLC.

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References

1. Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, Albain K S, Kelly K, Taylor SA, Gandara DR, Livingston RB (1998) Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol 16:2459
2. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, Mattson K, Manegold CH, Palmer MC, Gregor A, Nguyen B, Niyikiza C, Einhorn LH (2000) Phase III study of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122
3. Geogoulias V, Papadakis E, Alexoupoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas Ph, Vlachonikolis I, for the Greek Oncology Cooperative Group (GOCG) for Lung Cancer (2001) Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicenter trial. Lancet 357:1478
4. Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Akamura M, Gemaba M (1990) Nephrotoxicity of a new platinum compound, 254S, evaluated with rat kidney cortical slices. Toxicol Lett 52:15
5. Ariyoshi Y, Ota K, Wakui A, Majima H, Niitani H, Ogawa M, Inuyama Y, Yoshida O, Taguchi T, Kimura I, Kato T (1988) Phase I study of (glycolato-O,O′)diammineplatinum(II) (254S). Proc Am Soc Clin Oncol 7:59
6. Fukuda M, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Ohe Y, Kojima A, Oshita F, Hara K, Saijo N (1990) Phase II study of (glycolate-O,O′)diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. Cancer Chemother Pharmacol 26:393
7. Osheroff N, Zechiedrich EL, Gale KC (1991) Catalytic function of topoisomerase II. Bioassays 13:269
8. Liu LF (1989) DNA topoisomerase poisons as anti-tumor drugs. Annu Rev Biochem 58:51
9. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N, Nakajima S, Taguchi T for the CPT-11 Lung Cancer Study Group (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 10:16
10. Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, Nakagawa K, Takada M (1992) CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225
11. Kudoh S, Takada M, Masuda N, Nakagawa K, Itoh K, Kusunoki Y, Negoro S, Matsui K, Takifuji N, Morino H, Fukuoka M (1993) Enhanced antitumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against lung tumor xenografts. Jpn J Cancer Res 84:203
12. Kanzawa F, Koizumi F, Koh Y, Nakamura T, Tatsumi Y, Fukumoto H, Saijo N, Yoshida T, Nishio K (2001) In vitro synergistic interactions between the cisplatin analogue nedapl-

atin and the DNA topoisomerase I inhibitor irinotecan and the mechanism of this action. Clin Cancer Res 7:202
13. Fukuoka M, Nagao K, Ohhashi H, Niitani H (2000) 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 19:495a
14. World Health Organization (1979) Handbook for reporting results of cancer treatment (offset publication no. 48). World Health Organization, Geneva
15. Tobina K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, Narabayashi M, Fukutomi T, Kondo H, Shimoyama M, Suemasu K, members of the Clinical Trial Review Committee of the Japan Clinical Oncology Group (1993) Toxicity grading criteria of the Japan Clinical Oncology Group. Jpn J Clin Oncol 23:250
16. Simon R (1989) Optimal two-stage designs for phase II clinical trial. Control Clin Trials 10:1
17. Lee YJ, Staquet M, Simon R, Cantane R, Muggia F (1979) Two stage plans for patient accrual in phase II cancer clinical trials. Cancer Treat Rep 63:1721
18. Ota K, Ariyoshi Y, Fukuoka M, Furuse K, Niitani H (1990) Clinical effect of recombinant human G-CSF on neutropenia induced by the chemotherapy for lung cancer. Jpn J Cancer Chemother 17:65
19. Takeda K, Negoro S, Takifuji N, Nitta T, Yoshimura N, Terakawa K, Fukuoka M (2001) Dose escalation study of irinotecan combined with carboplatin for advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 48:104
20. Fukuda M, Oka M, Soda H, Terashi K, Kawabata S, Nakatomi K, Takatani H, Tsurutani J, Tsukamoto K, Noguchi Y, Fukuda M, Kinoshita A, Kohno S (1999) Phase I study of irinotecan combined with carboplatin in previously untreated solid cancers. Clin Cancer Res 5:3963