Cancer Chemother Pharmacol (2004) 54: 173–177
DOI 10.1007/s00280-004-0810-5

ORIGINAL ARTICLE

**Toshiyuki Tsunoda · Tomonobu Koizumi
Muneharu Hayasaka · Kazuya Hirai · Shigeru Koyama
Yasuki Takabayashi · Keisaku Fujimoto · Keishi Kubo**

Phase II study of weekly docetaxel combined with cisplatin in patients with advanced non-small-cell lung cancer

Received: 15 November 2003 / Accepted: 5 March 2004 / Published online: 4 May 2004

Abstract *Purpose*: To evaluate the safety and efficacy of the combination of cisplatin on day 1 and docetaxel on days 1, 8 and 15 every 4 weeks for the treatment of previously untreated patients with non-small-cell lung cancer (NSCLC). *Patients and methods*: A group of 38 patients with advanced or metastatic NSCLC who had not received prior treatment and who were aged under 75 years were enrolled. The patients received intravenous infusions of docetaxel (25 mg/m^2, days 1, 8, 15) and cisplatin (80 mg/m^2, day 1), followed by a week of rest. *Results*: Six patients had grade 3/4 neutropenia (18%), but there were no episodes of neutropenic fever. Nonhematologic toxicities were also mild. There were 12 partial responses for an objective response rate of 31.6%. The median survival was 11.8 months, and the 1-year survival rate was 46.5%. *Conclusion*: Cisplatin combined with weekly administration of docetaxel is efficacious against NSCLC with low hematotoxicity, and this schedule may be an alternative for the treatment of NSCLC.

Keywords Weekly docetaxel · Cisplatin · Non-small-cell lung cancer · Neutropenia · Neurotoxicity

Introduction

Docetaxel (Taxotere) is a semisynthetic taxoid that possesses significant activity in the treatment of patients with non-small-cell lung cancer (NSCLC) [4, 5, 14, 17, 22]. Docetaxel increases the rate of microtubule assembly and inhibits the depolymerization of microtubules [21]. Due to its unique mechanism of action and an apparent lack of cross-resistance [8], combinations of docetaxel with other active agents have been investigated in numerous clinical studies. Docetaxel combined with cisplatin has been evaluated in large trials in patients with NCSLC [11, 12, 15, 17, 19, 22]. Neutropenia is the main side effect of this combination chemotherapy. In combination with cisplatin, docetaxel has been studied in doses ranging from 60 to 100 mg/m^2. Docetaxel at a dose of 60 mg/m^2 plus cisplatin at 80 mg/m^2 has been recommended on the basis of a phase II/III study conducted in Japan [11, 19]. However, the dose-limiting factor of the regimen is neutropenia with grade 3/4 neutropenia observed in 74–85% of the patients, even with a much lower dose of docetaxel than those used in other studies [11, 12, 15, 17, 22, 24].

How to increase the dose intensity of docetaxel while minimizing its toxicities, including hematotoxicity, by changing the drug administration schedule, have been investigated in several clinical studies using single-agent docetaxel or docetaxel in combination with other agents [1, 3, 6, 9, 17, 18]. We have shown in a phase I study, that weekly docetaxel at 25 mg/m^2 (days 1, 8, 15) and cisplatin at 80 mg/m^2 (day 1) causes mild hematotoxicity in patients with NSCLC, and these doses were recommend for a phase II study [9]. In the present study, we evaluated the efficacy and safety of weekly docetaxel and cisplatin combination chemotherapy for patients with NSCLC.

Materials and methods

Patient eligibility

Patients were eligible if they had histologically or cytologically proven unresectable locally advanced NSCLC (clinical stage IIIB or IV), without a history of prior chemotherapy or radiotherapy. If patients with stage IIIB had malignant pleural effusion or supraclavicular

T. Tsunoda · T. Koizumi (✉) · M. Hayasaka · K. Hirai
S. Koyama · Y. Takabayashi · K. Fujimoto · K. Kubo
First Department of Internal Medicine,
Shinshu University School of Medicine,
3-1-1 Asahi, Matsumoto, 390-8621, Japan
E-mail: tomonobu@hsp.md.shinshu-u.ac.jp
Tel.: +81-263-372631
Fax: +81-263-363722

nodes, or primary tumor size exceeded half of one lung, they were enrolled. Other criteria included: (1) age >20 and <75 years, (2) World Health Organization (WHO) performance status 0–2, (3) measurable disease and an estimated life expectancy over 3 months, (4) adequate bone marrow function (neutrophil count $>2000/\mu l$, hemoglobin 10 g/dl, platelet count $>100{,}000/\mu l$), normal hepatic function (total bilirubin level <1.5 times and AST <2 times the upper normal limits), and renal function (creatinine <1.5 mg/dl, creatinine clearance >60 ml/min).

Patients were excluded from the trial for any of the following reasons: (1) active infection, (2) severe heart disease, (3) past history of hypersensitivity to drugs, (4) pleural or pericardial effusion that required drainage, (5) symptomatic brain metastasis or (6) pregnancy. Patients with a concomitant active malignancy were also excluded. Other concomitant anticancer therapy or experimental drug administration of any type was not permitted. Signed written informed consent was obtained from each patient.

Pretreatment evaluation

Before enrollment in the trial, all patients underwent a clinical and physical examination; evaluation of general condition, history, performance status, blood cell count with differentials, routine laboratory tests, 24-h creatinine clearance and urinalysis. Electrocardiography, chest radiography, chest computed tomographic (CT) scan, abdominal ultrasound and/or CT scan and whole-brain CT scan or magnetic resonance imaging and isotope bone scan were performed in all patients.

Toxicity and response evaluation

During the study, complete blood cell counts with differentials were performed twice a week and every 2 days in the case of grade 3 or more severe neutropenia. Physical examinations and routine chemistry measurements were performed weekly during the chemotherapy. If necessary, additional examinations of blood samples were performed. Toxicity was evaluated according to the National Cancer Institute's common toxicity criteria, version 2.0. Tumor assessment by chest CT was performed after two cycles of chemotherapy. The tumor response was evaluated according to the World Health Organization criteria [13]. All responses were carefully evaluated and confirmed by independent verification. A partial response (PR) was defined as a $>50\%$ decrease in the sum of the products of the longest perpendicular dimensions of all measurable lesions for a period of 4 weeks. Progressive disease (PD) was defined as an increase in tumor growth or appearance of a new site of malignancy. The time to disease progression was defined as the time from the initiation of therapy to the time PD was documented. Overall survival was defined as the interval from the date of the first course of chemotherapy to the date of death or the last follow-up visit (cutoff date: April 2003). The cumulative survival curves were constructed by the Kaplan–Meier method.

Treatment plan

Docetaxel (25 mg/m^2) was diluted with 5% glucose (500 ml) and given intravenously over a 1-h period on days 1, 8 and 15. On day 1, cisplatin (Nihon Kayaku, Tokyo, Japan) was dissolved in 500 ml 0.9% saline solution and administered over a 3-h period after docetaxel infusion. Cisplatin was administered along with a program of forced diuresis that included at least 3500 ml of fluids on days 1–2. Intravenous ondansetron (8 mg) was used prophylactically for nausea or vomiting. Additional antiemetic treatment was given as necessary, using prochlorperazine for a further 5 days after chemotherapy. Docetaxel for administration on days 8 and 15 was diluted in a similar manner as on day 1, and no other fluids were given on that day. Docetaxel was discontinued if the neutrophil count was less than $1000/\mu l$ or the platelet count less than $75{,}000/\mu l$ on day 8 and day 15. The second cycle of chemotherapy was initiated when the neutrophil count was over $2000/\mu l$ and the platelet count was over $100{,}000/\mu l$ after day 28. Therapy was continued for at least two cycles unless the patient experienced unacceptable toxicity or had progressive disease. Dose modification was not performed in the present study.

Results

Patients

Between January 1999 and January 2002, 39 patients were enrolled in the present study. One patient was excluded because of an elevated neutrophil count during staging evaluation and the first chemotherapy (white blood count over $30\times10^3/\mu l$), which suggested a granulocyte-colony stimulating factor (G-CSF)-producing tumor. The clinical characteristics of the remaining 38 patients are summarized in Table 1. The patients comprised 30 men and 8 women, with a median age of 62 years (range 34–73 years). One patient had an ECOG PS score of 2, but the others were PS 0–1. The predominant histologic type was adenocarcinoma ($n=23$), followed by squamous cell carcinoma ($n=15$). Finally, 22 patients had stage IV and 16 patients had stage IIIB disease.

Toxicity

Toxicity was evaluated for 38 patients and in each cycle. The hematologic and other toxicities of the regimen are listed in Table 2. Hematologic toxicity was mild. Grade

Table 1 Patient characteristics

No. of patients enrolled	38
Sex	
Male	30
Female	8
Age (years)	
Median (range)	62 (34–73)
ECOG performance status	
0	24
1	13
2	1
Histologic type	
Squamous	15 (38.5%)
Adenocarcinoma	23 (58.9%)
Stage	
IIIB	16 (42.2%)
IV	22 (57.8%)

Table 2 Incidence of toxicity: number of patients with each grade of toxicity and percent with grade 3/4 ($n=38$)

Toxicity	Grade				Percent grade 3/4
	1	2	3	4	
Hematologic					
Leukopenia	8	7	6	0	15
Neutropenia	8	9	6	1	18
Anemia	7	5	0	0	0
Thrombocytopenia	5	1	2	0	5
Non-hematologic					
Alopecia	18	9	0	0	0
Nausea/vomiting	10	6	1	0	3
Anorexia	16	9	6	2	21
Diarrhea	1	1	0	0	0
Hepatotoxicity	4	1	0	0	0
Nephrotoxicity	3	0	0	0	0
Fatigue	8	5	1	0	3

3/4 neutropenia occurred in only 18% of the patients. Febrile neutropenic infection was not observed. Grade 3/4 thrombocytopenia was only detected in two patients (5%). In addition, before initiation of the second cycle, no patients required a delay to recover from hematologic toxicity. Administration of docetaxel on day 15 was skipped in two patients because the white blood cell count was less than 2000/μl (or the neutrophil count was less than 1000/μl) in both cases.

Non-hematologic toxicity was generally grade 1 or 2. Nausea and vomiting (grade 1/2) related to day 1 chemotherapy was observed in 42% of the patients. However, no patients showed nausea and/or vomiting on the day of docetaxel administration (days 8, 15). Grade 1/2 diarrhea occurred in two patients. One patient developed severe hyponatremia (grade 3) resulting in discontinuation of the following chemotherapy. Mild (grade 1/2) asthenia was observed in 13 patients (36%), but this did not cause any interruption or delay of the treatment. However, one patient developed grade 3 fatigue after the day 15 administration of docetaxel during the second cycle, which appeared to be related to the cumulative docetaxel administration schedule. No patients developed hypersensitivity reactions in the present study, and there were no cases of headache, arthralgia or myalgia. In addition, no patients developed significant renal toxicity.

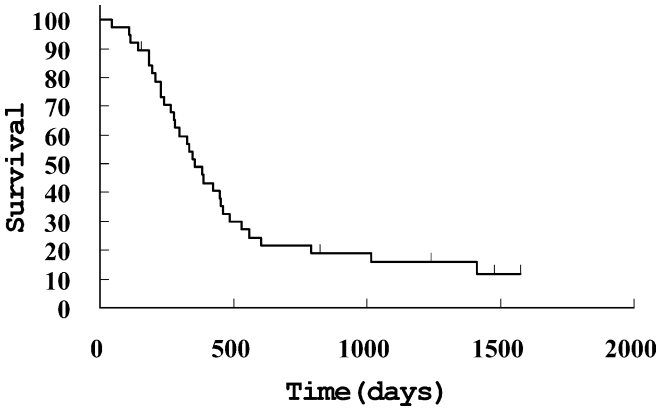

Fig. 1 Overall survival. Each tick mark represents a patient who was alive at last follow up

Efficacy

Analysis of the response rate was performed for 38 patients. Among these patients, two had insufficient chemotherapy. One patient developed pneumothorax during the first chemotherapy and died. Another patient refused the second course of chemotherapy because of hyponatremia, as described above. There were 12 partial responses for an objective response rate of 31.6% (95% confidence limits, CL, 16.8–46.4%). The median survival time was 11.8 months (95% CL, 9.4–15.4 months), and the 1-year survival was 46.5% (95% CL, 30.3–63.8%; Fig. 1).

Discussion

The present study demonstrated the feasibility of weekly administration of 25 mg/m^2 docetaxel for 3 weeks every 4 weeks. This weekly schedule of docetaxel combined with cisplatin was associated with less hematologic toxicity and similar activity against NSCLC compared to the conventional regimen of docetaxel plus cisplatin.

Although docetaxel at a dose of 60–100 mg/m^2 combined with cisplatin is highly active against NSCLC [11, 12, 15, 17, 19, 22, 24], the combination has been somewhat difficult to use because of marked myelosuppression. In general, grade 3/4 neutropenia is observed in 46–85% of patients. However, weekly divided administration of docetaxel at the maximum-tolerated does not cause any severe myelotoxicities in patients with breast cancer [1, 3]. When combined with cisplatin in patients with NSCLC, we selected 25 mg/m^2 docetaxel for 3 weeks for this phase II study [9]. We confirmed that this weekly schedule of docetaxel plus

cisplatin was extremely well tolerated, with rare grade 3/4 neutropenia and neutropenic infection.

Non-hematologic toxicities, including peripheral neuropathy, arthralgia and myalgia, were also mild with weekly docetaxel. It has been reported that the neurotoxic effects of the cisplatin plus docetaxel combination are more severe than with either cisplatin or docetaxel as a single agent [7]. The same group also showed a significant correlation between the severity of peripheral neuropathy and the cumulative dose of both drugs, suggesting that the incidence of neuropathy is dose-dependent. Taken together, a weekly docetaxel schedule may reduce non-hematologic toxicities, including neurotoxicity. However, the important toxicity associated with weekly docetaxel is treatment-related fatigue [1, 3, 6, 8]. Hainsworth et al. [6] have reported that the incidence of this toxicity is higher in elderly patients than in younger patients with advanced breast cancer. In addition, Ohe et al. [18] have reported that the severity of fatigue with weekly docetaxel increases as the weekly dose of docetaxel is increased. We found that therapy-related fatigue and asthenia were not a clinical problem in the present study. This may reflect the fact that the dose per course, the cumulative dosage and the age of the enrolled patients were relatively low in our trial compared with those in other studies [6, 18]. We think that weekly docetaxel at a dose of 25 mg/m^2 would be well tolerated in terms of treatment-related fatigue.

The efficacy of this combination schedule was also important in the present study. The overall response and 1-year survival rates were 31.6% and 46.5%, respectively. These response rates appear to be identical to those in other studies, which were performed using conventional schedules for docetaxel and cisplatin [11, 19, 22, 24]. For example, Zalcberg et al. [24] performed a clinical trial of cisplatin (75 mg/m^2) plus docetaxel (75 mg/m^2) every 3–4 weeks, and found a response rate of 29.8%, mean survival time (MST) of 9.6 months and 1-year survival of 33%, respectively. In another phase II study, a 33.3% response rate, 8.4 months MST and 35% 1-year survival rate were achieved with cisplatin 100 mg/m^2 and docetaxel 75 mg/m^2 [12]. A phase II study [19] and a phase III study [11] in a Japanese group employed 60 mg/m^2 of docetaxel and 80 mg/m^2 of cisplatin and showed response rates of 42% and 37%, MSTs of 11 and 11.3 months and 1-year survival rates of 38.7% and 47.7%, respectively.

Although the dose-intensity of 25 mg/m^2 of docetaxel for three consecutive weeks with a week of rest in our protocol was not higher than in other studies using a conventional schedule of cisplatin plus docetaxel [11, 12, 15, 19, 24], almost identical efficacy was observed in the present study. Out results suggest that even a modified schedule using weekly divided administration of docetaxel is still active against NSCLC. Thus, we speculate that weekly docetaxel combined with cisplatin is still efficacious in patients with advanced NSCLC. A similar study of paclitaxel, another taxane, in combination with platinum was performed in patients with advanced NSCLC. Belani et al. [2] reported that weekly paclitaxel for 3 of 4 weeks with carboplatin administered on day 1 showed a favorable efficacy with a highly tolerable toxicity profile. Thus, weekly administration of taxanes may provide an alternative therapeutic approach for NSCLC with identical efficacy and less toxicity.

In a phase II trial of both weekly administration of docetaxel and cisplatin in NSCLC, Niho et al. [17] administered docetaxel at 35 mg/m^2 and cisplatin at 25 mg/m^2 for three consecutive weeks, followed by a week of rest. They found a response rate of 27% and MST of 12.8 months, with less hematologic toxicity. This regimen appears to be an alternative for chemotherapy involving weekly docetaxel and cisplatin. Our toxicity and survival results were almost identical to those in their study. Thus, although the superiority of the survival benefit in patients with NSCLC remains unknown, a weekly divided schedule of docetaxel and cisplatin is a therapeutic alternative to the standard regimen. However, we think that our administration schedule of docetaxel (days 1, 8, 15) and cisplatin (day 1) is more convenient in simplifying the infusion procedures on days 8 and 15, especially in the outpatient setting, than the three consecutive weeks' infusion protocol of docetaxel and cisplatin.

Recently, weekly docetaxel administration combined with thoracic radiotherapy has been evaluated in NSCLC [10, 16, 20]. Docetaxel was shown to have a radiosensitizing effect by blocking the cell cycle in the most radiosensitive G2/M phase [23]. However, the optimal dose of docetaxel remains unclear [10, 16, 20]. In addition, the survival benefit and the increased risk of radiation pneumonitis remain unknown [20]. Based on the findings of our present study, we think that evaluation of cisplatin plus weekly docetaxel with concurrent thoracic radiotherapy may be warranted in a future study.

In summary, in the present study, weekly docetaxel combined with cisplatin achieved a promising response rate and survival in patients with NSCLC, and was well tolerated, especially in terms of hematologic toxicity.

Acknowledgements The authors would like to acknowledge the participation in the present study of the following investigators and institutions: Dr. Masanori Yasuo, Nagano Red Cross Hospital; Dr. Kazuyoshi Okada, Nagano Municipal Hospital; Dr. Shiro Horie, Okaya Enrei Hospital; Dr. Hikaru Yagi, Iida Municipal Hospital; Dr. Jiro Hirayama and Dr. Shinji Yamaguchi, Toyoshina Red Cross Hospital; Dr. Hiroshi Nomura, Oomati Hospital; and the staff of the First Department of Internal Medicine, Shinshu University School of Medicine.

References

1. Aihara T, Kim Y, Takatsuka Y (2002) Phase II of weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 13:286–292
2. Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D, Clark R, Mills GM (2003) Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol 21:2933–2939

3. Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, Scheib R, Matulonis UA, Garber JE, Clarke KD, Shulman LN, Winer EP (2000) Docetaxel administration on a weekly basis for metastatic breast cancer. J Clin Oncol 18:1212–1219
4. Francis PA, Rigas JR, Kris MG, Pisters KM, Orazem JP, Woolley KJ, Heelan RT (1994) Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. J Clin Oncol 12:1232–1237
5. Gandara DR, Vokes E, Green M, Bonomi P, Devore R, Comis R, Carbone D, Karp D, Belani C (2000) Activity of docetaxel in platinum-treated non-small-cell lung cancer: results of a phase II multicenter trial. J Clin Oncol 18:131–135
6. Hainsworth JD, Burris HA III, Thomas EM, Greco FA (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16:2164–2168
7. Hilkens PHE, Pronk LC, Verweij J, Vecht CJ, van Putten WLJ, van den Bent MJ (1997) Peripheral neuropathy induced by combination chemotherapy of docetaxel and cisplatin. Br J Cancer 75:417–422
8. Kelland LR, Abel G (1992) Comparative in vitro cytotoxicity of taxol and taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. Cancer Chemother Pharmacol 30:444–450
9. Koizumi T, Tsunoda T, Fujimoto K, Nomura H, Hirai K, Koyama S, Okada K, Kubo K (2001) Phase I trial of weekly docetaxel combined with cisplatin in patients with non-small-cell lung cancer. Lung Cancer 34:125–131
10. Koukourakis MI, Kourousis C, Kamilaki M, Koukouraki S, Giatromanolaki A, Kakolyris S, Kotsakis A, Androulakis N, Bahlitzanakis N, Georgoulias V (1998) Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. Eur J Cancer 34:838–844
11. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Yokota S, Yoneda S, Matsui K, Kudo S, Shibuya M, Isobe T, Segawa Y, Nishiwaki Y, Ohashi Y, Niitani H; Japanese Taxotere Lung Cancer Study Group (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
12. Le Chevalier T, Monnier A, Douillard JY, Ruffie P, Sun XS, Belli L, Ibrahim N, Bougon N, Berille J (1998) Docetaxel (Taxotere) plus cisplatin: an active and well-tolerated combination in patients with advanced non-small cell lung cancer. Eur J Cancer 34:2032–2036
13. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
14. Miller VA, Rigas JR, Francis PA, Grant SC, Pisters KM, Venkatraman ES, Woolley K, Heelan RT, Kris MG (1995) Phase II trial of a 75-mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. Cancer 75:968–972
15. Millward MJ, Zalcberg J, Bishop JF, Webster LK, Zimet A, Rischin D, Toner GC, Laird J, Cosolo W, Urch M, Bruno R, Loret C, James R, Blanc C (1997) Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. J Clin Oncol 15:750–758
16. Mudad R, Ramsey M, Kovitz K, Curiel T, Curiel TJ, Hartz R, Nedzi LL, Weiner RS, Zakris EL (2003) Concomitant weekly docetaxel, cisplatin and radiotherapy in locally advanced non-small cell lung cancer: a dose finding study. Lung Cancer 39:173–177
17. Niho S, Ohe Y, Kakinuma R, Kubota K, Matsumoto T, Ohmatsu H, Goto K, Nishiwaki Y (2002) Phase II study of docetaxel and cisplatin administered as three consecutive weekly infusions for advanced non-small cell lung cancer. Lung Cancer 35:209–214
18. Ohe Y, Niho S, Kakinuma R, Kubota K, Matsumoto T, Ohmatsu H, Goto K, Kunitoh H, Saijo N, Nishiwaki Y (2001) Phase I studies of cisplatin and docetaxel administered by three consecutive weekly infusions for advanced non-small cell lung cancer in elderly and non-elderly patients. Jpn J Clin Oncol 31:100–106
19. Okamoto H, Watanabe K, Segawa Y, Ichinose Y, Yokoyama A, Yoneda S, Niitani H (2000) Phase II study of docetaxel and cisplatin in patients with previous untreated metastatic non-small cell lung cancer. Int J Clin Oncol 5:316–322
20. Onishi H, Kuriyama K, Yamaguchi M, Komiyama T, Tanaka S, Araki T, Nishikawa K, Ishihara H (2003) Concurrent two-dimensional radiotherapy and weekly docetaxel in the treatment of stage III non-small cell lung cancer: a good local response but no good survival due to radiation pneumonitis. Lung Cancer 40:79–84
21. Ringer I, Horwitz SB (1991) Studies with RP 56976 (Taxotere): a semi-synthetic analog of taxol. J Natl Cancer Inst 83:288–291
22. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, Eastern Cooperative Oncology Group (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
23. Tishler RB, Schiff PB, Geard CR, Hall EJ (1992) Taxol: a novel radiation sensitization. Int J Radiat Oncol Biol Phys 22:613–617
24. Zalcberg J, Millward MJ, Bishop J, McKeage M, Zimet A, Toner G, Friedlander M, Barter C, Rischin D, Loret C, James R, Bougan N, Berille J (1998) Phase II study of docetaxel and cisplatin in advanced non-small-cell lung cancer. J Clin Oncol 16:1948–1953