Yamanashi Med. J. **27**(2), 51 ～ 58, 2013

Original article

Gemcitabine Plus Carboplatin in Patients with Advanced Non-Small-Cell Lung Carcinoma: Phase I/II Study of 28-Day Schedule

Kazuyoshi Watanabe[1)], Hiroshi Ishihara[1)]*, Keiichi Nishikawa[2)], Sensuke Hishiyama[2)], Masaki Kanazawa[3)], Satoshi Yamaga[2)], Junya Miyaki[4)], Hiroshi Yamaguchi[5)], Yasuyuki Narumiya[4)], Zennosuke Ooki[2)], Katsura Ozawa[2)] and Kiyotaka Kugiyama[1)]

[1)] Department of Internal Medicine II, University of Yamanashi, Faculty of Medicine, Chuo [2)] Department of Respiratory Medicine, Kofu Municipal Hospital, Kofu [3)] Department of Internal Medicine, Kanoiwa General Hospital, Yamanashi

[4)] Department of Respiratory Medicine, Yamanashi Kousei Hospital, Yamanashi

[5)] Department of Internal Medicine, Fuefuki Central Hospital, Fuefuki, Yamanashi, Japan

Abstract: Carboplatin plus gemcitabine is a standard regimen for advanced non-small-cell lung carcinoma (NSCLC) but has been frequently accompanied by significant hematologic toxicities. A 28-day schedule of this combination was evaluated in the phase I/II study. For NSCLC patients who were chemotherapy-naïve and having stage IIIB/IV disease, a fixed dose of gemcitabine (1,000 mg/m^2) was administered on days 1 and 8 and an escalating dose of carboplatin was administered on day 8 of a 28-day schedule in the phase I study. With the established recommended dose, the phase II study was undertaken. In the phase I study, the recommended dose of carboplatin was established at an area under the concentration-time curve (AUC) of 6 mg/ml·min. Twenty-seven patients were treated in the phase II study. The response rate was 33.3% and the median survival time was 54.0 weeks, both of which were similar to those seen for 21-day schedules that are currently widely used. The most common grade 3/4 hematologic toxicities were neutropenia (33.3%) and thrombocytopenia (22.2%). Non-hematologic toxicities were mild. The 28-day schedule of this combination should be considered for treatment of advanced NSCLC.

Key Words: non-small cell lung carcinoma, carboplatin, gemcitabine, phase I/II

Introduction

Non-small cell lung carcinoma (NSCLC) is the leading cause of cancer-related death worldwide. The majority of patients have metastatic or locally advanced disease at the time of diagnosis. For these patients, standard treatments have been systemic platinum-based chemotherapies, which have been proved to palliate symptoms, improve quality of life, and prolong survival[1,2)]. New chemotherapeutic agents were introduced in the last decade of the 20th century, and platinum-based doublets employing one of these third generation drugs have yielded improved response rates and survival times compared to the old regimens[3,4)].

Gemcitabine, a nucleoside anti-metabolite prodrug, is a third generation chemotherapeu-

*Address for correspondence: Hiroshi Ishihara, Department of Internal Medicine II, University of Yamanashi, Faculty of Medicine, 1110 Shimokato, Chuo, Yamanashi, 409-3898, Japan.
E-mail: ihiroshi@yamanashi.ac.jp.
Received August 17, 2012
Accepted October 4, 2012

tic agent, and a combination of carboplatin with gemcitabine has become one of the standard regimens. In early trials, gemcitabine was administered on days 1, 8, and 15, and monthly carboplatin was administered on day 1 or 2 of a 28-day schedule[5,6]. However, this regimen was found to be associated with severe myelosuppression, especially thrombocytopenia, and frequently led to omission of gemcitabine on day 15. To circumvent these toxicities, investigations have been undertaken to determine appropriate dosing schedules. Currently, a 21-day schedule where carboplatin is administered on day 1 and gemcitabine on days 1 and 8 is widely used, but hematologic toxicities are still significant[7–12]. An attractive alternative 28-day regimen administering gemcitabine on days 1 and 8 and carboplatin on day 8 has been proposed[13,14] but has not been fully evaluated.

We conducted a multicenter phase I/II study to further investigate the efficacy and feasibility of the 28-day schedule, using a fixed dose of gemcitabine (1,000 mg/m^2) on days 1 and 8 and an escalating dose of carboplatin on day 8 in chemotherapy-naïve, stage IIIB/IV NSCLC patients.

PATIENTS AND METHODS

Patient selection

Patients with stage IIIB or IV (based on the 6th edition of the Union Internationale Contre le Cancer-TNM staging system) NSCLC who fulfilled the following criteria were considered eligible: (1) histologic or cytologic documentation of non-small-cell lung carcinoma; (2) measurable disease; (3) no prior chemotherapy or radiotherapy; (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; (5) age 20 to 75 years; (6) adequate baseline organ function defined as white blood cell (WBC) count of ≧ 4,000/μL, neutrophil count of ≧ 2,000/μL, Hb level of ≧ 9.5 g/dL, serum transaminase levels of < 2.5 times the upper limit of normal, serum creatinine value of < upper limit of normal, PaO_2 of ≧ 70 torr or SpO_2 level of ≧ 92%; (7) life expectancy of ≧ 3 months; and (8) written informed consent.

Patients were excluded from the trial for any of the following reasons: (1) symptomatic interstitial pneumonia or pulmonary fibrosis identified by chest X-ray; (2) malignant pleural or pericardial effusion; (3) superior vena cava syndrome; (4) uncontrolled diabetes mellitus, liver dysfunction, angina pectoris, recent acute myocardial infarction; (5) severe infectious disease; (6) symptomatic brain metastasis; (7) pregnant or lactating; (8) active second malignancy; or (9) any other serious morbidity incompatible with this trial. This was a multicenter study, and the protocol was approved by the ethics committees of participating institutions.

Treatment schedule

Gemcitabine at a dose of 1,000 mg/m^2 was administered intravenously over 30 min on days 1 and 8, and carboplatin was administered over 60 min or more immediately after the gemcitabine infusion on day 8 of a 28-day schedule. The carboplatin dose was calculated using the Calvert formula (total dose [mg] = target AUC x [glomerular filtration rate+25]). In the phase I study, the dose of carboplatin was initially set at AUC 4 mg/ml·min (level 1), subsequently increased to AUC 5 (level 2) and then to 6 (level 3). The glomerular filtration rate was calculated using the Cockcroft and Gault equation.

Dose-limiting toxicity (DLT) was defined using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 2.0) as follows: (1) grade 4 leukopenia or neutropenia lasting 3 days or more; (2) neutropenia of grade 3 with

fever higher than 38°C or infection; (3) platelet count < 20,000/μL or platelet infusion; (4) any non-hematologic grade 3 or 4 toxicities except for nausea, vomiting, or fatigue; and (5) omission of treatment on day 8.

For the phase I study, 3 patients were initially to be treated at each of the 3 dose levels. If no DLT was seen among all 3 patients, the dose level was to be escalated. If DLT was seen in 1 or 2 patients, 3 more patients were to be enrolled at this cohort level. If DLT was observed in ≦ 2 of these 6 patients, the dose level was to be escalated. If DLT was observed in ≧ 3 patients, the study was to be withdrawn and this level was considered to be the MTD, and the preceding dose level was defined as the recommended dose (RD). If DLT was not observed at dose level 3, this level was defined as the RD.

During the study, patients were not allowed to receive any other chemotherapy, hormone therapy, biological response modifier, radiotherapy, or any surgical treatment. Granulocyte colony-stimulating factor (G-CSF) was not allowed prophylactically, but was allowed to be used therapeutically at the discretion of the treating investigator. Platelet infusions were allowed for patients with hemorrhagic tendencies or platelet counts < 20,000 /μL. No prophylactic treatments for possible adverse effects were allowed except for antiemetic agents such as 5-HT3 receptor antagonists.

Day 8 chemotherapy infusions were administered if the patient's neutrophil count was ≧ 2,000 /μL, platelet count ≧ 100,000 /μL, and non-hematologic toxicities were grade 0-2. The second chemotherapy cycle was initiated if the PS was 0-2, WBC count ≧ 3,000 /μL, neutrophil count ≧ 1,500 /μL, platelet count ≧ 100,000 /μL, serum creatinine value < upper limit of normal, creatinine clearance ≧ 60 mL/min, serum transaminase levels < 100 IU/L, total bilirubin < 2.0 mg/dL, and non-hematologic toxicities of grade 0-1. Patients were withdrawn from the study if scheduled infusions were delayed more than 2 weeks because of incomplete recovery from hematologic and non-hematologic toxicities, or for patients' refusal.

In the phase II study, patients were treated with the carboplatin dose established in the phase I study. Responses and toxicities were assessed after 2 cycles of treatment. The primary endpoints were tumor response and development of toxicity, and the secondary endpoint was survival. The study patients usually underwent the first course of treatment as in-patients, and underwent subsequent courses as out-patients. Dose modification was carried out according to hematologic and non-hematologic toxicities occurring during the preceding course of treatment. Gemcitabine was to be reduced to 80% of the protocol dose if the leukocyte count was < 1,000 /μL or grade 3 neutropenia and fever higher than 38°C or infection occurred. Carboplatin was to be reduced from AUC 6 to 5 if grade 2 or higher serum creatinine elevation occurred. Both drugs were to be reduced to their respective levels if the platelet count was < 20,000 /μL or any non-hematologic toxicity of grade > 3 occurred, except for nausea, vomiting, and alopecia.

Results

Phase I study

The phase I study was begun in October 2000. Eleven patients were enrolled and their characteristics are summarized in Table 1. In level 1 grade 4 thrombocytopenia was observed in 1 of the initial 3 patients, but there were no serious sequelae or need for platelet infusions in that patient. Two additional patients underwent treatment at level 1, and because no other DLT

Table 1. Patient characteristics (phase I study, n = 11)

Characteristics	No. of patients
Age (years)	
Mean	63.2
Range	43-75
Gender	
Male	9
Female	2
Performance status*	
0	6
1	5
2	0
Histology	
Adenocarcinoma	8
Squamous cell carcinoma	2
Large cell carcinoma	1
Clinical stage	
IIIB	5
IV	6

*Eastern Cooperative Oncology Group

Table 2. Patient characteristics (phase II study, n = 27)

Characteristics	No. of patients
Age (years)	
Mean	64.6
Range	35-75
Gender	
Male	18
Female	9
Performance status*	
0	24
1	3
2	0
Histology	
Adenocarcinoma	21
Squamous cell carcinoma	6
Large cell carcinoma	0
Clinical stage	
IIIB	12
IV	15

*Eastern Cooperative Oncology Group

developed, the 3 subsequent patients underwent treatment at level 2. Of these patients, 2 developed grade 3 neutropenia and 1 developed grade 3 thrombocytopenia. Among level 3 patients, 2 developed grade 2 neutropenia and 1 developed grade 2 thrombocytopenia.

The most frequent non-hematologic toxicities were nausea in 8, anorexia in 5, and elevated transaminases in 3 patients. Elevated serum total bilirubin, hiccoughs, headache, alopecia, were each observed in 2 patients. Skin rash, constipation, numbness, insomnia, abnormal taste, fever were each observed in 1 patient. All of these toxicities were $\leqq$ grade 2. Accordingly, the MTD was not achieved, and the recommended dose of carboplatin was chosen to be AUC 6. One patient at each of these 3 dose levels achieved a partial response, for a response rate of 27.3%.

Phase II study

The phase II study was begun in March 2003. Twenty-seven patients were enrolled and their characteristics are summarized in Table 2. Drug doses were reduced in 3 patients for the second cycle of chemotherapy in accordance with the protocol as follows: in 1 patient, gemcitabine was reduced because of grade 4 leukopenia; and in 2 patients, both carboplatin and gemcitabine were reduced because of platelet counts < 20,000 /μL. For the first cycle, all patients were treated as in-patients, and for the second cycle, 14 patients (51.9%) were treated as out-patients.

Hematologic toxicities are shown in Table 3. Grade 3 or 4 neutropenia occurred in 18 of 54 chemotherapy cycles (33.3%) and neutropenic fever occurred in 1 cycle (1.9%). Grade 3 thrombocytopenia occurred in 12 cycles (22.2%) but grade 4 thrombocytopenia was not seen. Grade 3 anemia occurred in 4 cycles (7.4%). Grade 3 or 4 non-hematologic toxicities consisting of nausea and anorexia occurred during 6 cycles (11.1%).

All 27 patients were evaluated for response ac-

Table 3. Hematologic toxicities occurring in 54 chemotherapy cycles (phase II study)

	Grade 3 (%)	Grade 4 (%)	Grade 3 + 4 (%)
Neutropenia	17 (31.6)	1 (1.9)	18 (33.3)
Thrombocytopenia	12 (22.2)	0 (0)	12 (22.2)
Anemia	4 (7.4)	0 (0)	4 (7.4)

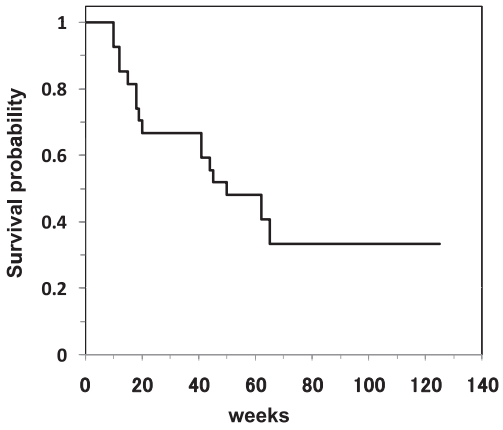

Fig. 1. Kaplan Meier estimate of overall survival.

cording to the Response Evaluation Criteria in Solid Tumor. None of the patients achieved complete response. There were 9 patients (33.3%) who achieved partial response, 16 (59.3%) with stable disease and 2 (7.4%) who developed progressive disease. The overall response rate was 33.3% and the disease control rate was 92.6%. By Kaplan-Meier analysis, the median survival time was 54.0 weeks (Fig. 1).

Discusssion

Gemcitabine/carboplatin is a standard regimen for the treatment of advanced-stage NSCLC, but its hematologic toxicities are significant. Several dosing schedules for reducing those toxicities have been investigated. We evaluated a 28-day schedule, in which carboplatin was administered on day 8 and gemcitabine on days 1 and 8, for efficacy and feasibility in a phase I/II study. The results demonstrated that carboplatin was safely increased to AUC of 6 mg/ml·min in combination with 1,000 mg/m^2 of gemcitabine. This regimen yielded a response rate of 33.3% and median survival time of 54.0 weeks with mild hematologic and non-hematologic toxicities.

Because gemcitabine as a single agent was originally administered on days 1, 8, and 15 of a 28-days cycle in the phase II study[15,16], it was also administered according to the same schedule when combined with monthly cisplatin in the early trials[17–19]. When cisplatin was administered on day 2, severe myelosuppression frequently occurred, resulting in dose-reduction or omission of gemcitabine on day 15 in at least 50% of patients[17]. Administering cisplatin on day 15 of a 28-day schedule[18,19] or by using a 21-day schedule in which gemcitabine on day 15 was omitted and cisplatin was given on day 1[20], reduced the occurrence of myelosuppression and improved compliance, while providing an almost similar response rate.

With the increasing need for ambulatory chemotherapy and in order to avoid the gastrointestinal and renal toxicities associated with cisplatin, carboplatin has been widely used as the partner of third generation chemotherapeutic agents. In parallel with gemcitabine/cisplatin, gemcitabine was initially given on days 1, 8, and 15 with monthly carboplatin administered on day1 or 2 of a 28-day schedule[5,6]. In spite of reduced non-hematologic toxicities, carboplatin has increased hematologic toxicities. Combinations of carbopl-

atin and gemcitabine in these schedules resulted in considerable myelosuppression, in particular, thrombocytopenia, leading to frequent omission of gemcitabine on day 15.

Therefore, alternative schedules for reducing these toxicities have been investigated. One regimen consisted of a 21-day schedule in which carboplatin was administered on day 1 or 2 and gemcitabine on days 1 and 8. The results of phase I[7,8] and phase II[9] studies indicated that this schedule tended to produce lower rates of thrombocytopenia, and currently it seems to be one of the standard regimens, but reports from subsequent studies showed that it was associated with significant myelosuppression[10–12]. Myelotoxicities were not significantly improved by another 21-day schedule, in which carboplatin was administered on day 8 and gemcitabine on days 1 and 8[21–23]. A 28-day schedule employed by Iaffaioli *et al.*, in which gemcitabine was administered on days 1 and 8 and carboplatin was administered on day 8, resulted in reduced myelotoxicities, and neutropenia instead of thrombocytopenia was observed as the DLT[13]. Mott *et al.* confirmed the mild hematologic toxicities of that schedule, but the response rate was reported to be 10%, which was inferior to other schedules[14]. This 28-day schedule has not been further evaluated until recently.

Because the maximum dose of gemcitabine has been restricted to 1,000 mg/m^2 in Japan, we planned this phase I/II trial using a fixed dose of gemcitabine (1,000 mg/m^2) on days 1 and 8 and an escalating dose of carboplatin on day 8 of a 28-day schedule. We confirmed that this schedule had mild hematologic toxicities, especially reduced occurrence of thrombocytopenia, as previously demonstrated by Iaffaioli *et al.*[13] and Mott *et al.*[14], and observed anticancer activity similar to that demonstrated in the 21-day schedule[7–9] or the original 28-day schedule[6].

After our trial was completed, results of 2 randomized phase II trials comparing this same 28-day schedule with a 21-day schedule in which carboplatin was given on day 1 and gemcitabine on days 1 and 8 were published[24,25]. Although survival times tended to be longer in the 21-day schedule and toxicities were milder in the 28-day schedule, the differences were not statistically significant.

Anticancer molecular targeting agents such as bevacizumab and bortezomib have been recently introduced for the treatment of NSCLC, and some have been used in combination with gemcitabine /carboplatin[26–28]. To the best of our knowledge, a targeting agent has not been evaluated in this 28-day schedule. Because some molecular agents have been reported to increase hematologic toxicities[29], evaluation of the addition of a molecular targeting agent to this 28-day schedule warrants consideration because of the reduced myelotoxicity seen with this regimen.

In conclusion, with the administration of 1,000 mg/m^2 of gemcitabine on days 1 and 8, day-8 carboplatin could be safely increased to AUC 6 mg/ml·min in a 28-day schedule. This regimen provided response rate and survival time similar to those in previously reported trials, and reduced hematologic and non-hematologic toxicities, especially thrombocytopenia. This schedule of gemcitabine/carboplatin should be considered for the treatment of NSCLC, in addition to its combination with molecular targeting agents.

REFERENCES

1) Non-small cell lung cancer collaborative group: Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ, 311: 899–909, 1995.
2) NSCLC meta-analyses collaborative group: Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer:

a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol, 26: 4617–4625, 2008.
3) Yana T, Takada M, Origasa H, Ijima T, Yamamoto N, *et al.*: New chemotherapy agent plus platinum for advanced non-small cell lung cancer: a meta-analysis. Proc Am Soc Clin Oncol, 21: (abstr 1309), 2002.
4) Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, *et al.*: Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. J Thorac Oncol, 2: 845–853, 2007.
5) Carmichael J, Allerheiligen S, Walling J: A phase I study of gemcitabine and carboplatin in non-small cell lung cancer. Semin Oncol, 23 (Suppl 10): 55–59, 1996.
6) Masotti A, Zannini G, Gentile A, Morandini G: Activity of gemcitabine and carboplatin in advanced non-small cell lung cancer: a phase II trial. Lung Cancer, 36: 99–103, 2002.
7) Gajra A, Mehdi SA, Kirshner J, Newman N, Graziano SL: Phase I study of gemcitabine and carboplatin in advanced non-small cell lung carcinoma. Lung Cancer, 32: 189–196, 2001.
8) Thomas P, Robinet G, Ferri-Dessens RM, Lena H, Gouva S, *et al.*: Phase I trial of gemcitabine and carboplatin in metastatic non-small-cell lung cancer: a Groupe Francais de Pneumo-Cancerologie Study. Lung Cancer, 36: 191–198, 2002.
9) Kortsik C, Albrecht P, Elmer A: Gemcitabine and carboplatin in patients with locally advanced or metastatic non-small cell lung cancer: a prospective phase II study. Lung Cancer, 40: 85–90, 2003.
10) Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, *et al.*: Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer, 41: 321–331, 2003.
11) Sederholm C, Hillerdal G, Lamberg K, Kolbeck K, Dufmats M, *et al.*: Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: The Swedish Lung Cancer Study Group. J Clin Oncol, 23: 8380–8388, 2005.
12) Yamamoto N, Nakagawa K, Uejima H, Sugiura T, Takada Y, *et al.*: Randomized phase II study of carboplatin/gemcitabine versus vinorelbine/gemcitabine in patients with advanced nonsmall cell lung cancer. Cancer, 107: 599–605, 2006.
13) Iaffaioli RV, Tortoriello A, Facchini G, Caponigro F, Gentile M, *et al.*: Phase I-II study of gemcitabine and carboplatin in stage IIIB-IV non-small-cell lung cancer. J Clin Oncol, 17: 921–926, 1999.
14) Mott FE, Cable CT, Sharma N: Phase II study of an alternate carboplatin and gemcitabine dosing schedule in advanced non-small-cell lung cancer. Clin Lung Cancer, 5: 174–176, 2003.
15) Abratt RP, Bezwada WR, Falkson G, Goedhals L, Hacking D, *et al.*: Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. J Clin Oncol, 12: 1535–1540, 1994.
16) Anderson H, Lund B, Bach F, Thatcher N, Walling J, *et al.*: Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a phase II study. J Clin Oncol, 12: 1821–1826, 1994.
17) Crino L, Scagliotti G, Marangolo M, Figoli F, Clerici M, *et al.*: Cisplatin-gemcitabine combination in advanced non-small-cell lung cancer: a phase II study. J Clin Oncol, 15: 297–303, 1997.
18) Abratt RP, Bezwasda WR, Goedhals L, Hacking DJ: Weekly gemcitabine with monthly cisplatin: effective chemotherapy for advanced non-small-cell lung cancer. J Clin Oncol, 15: 744–749, 1997.
19) Anton A, Diaz-Fernandez N, Gonzalez Larriba JL, Vadell C, Masutti B, *et al.*: Phase II trial assessing the combination of gemcitabine and cisplatin in advanced non-small cell lung cancer (NSCLC). Lung Cancer, 22: 139–148, 1998.
20) Soto Parra H, Cavina R, Latteri F, Sala A, Dambrosio M, *et al.*: Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. Ann Oncol, 13: 1080–1086, 2002.
21) Yoshimura M, Imamura F, Ueno K, Uchida J: Gemcitabine/carboplatin in a modified 21-day administration schedule for advanced-stage non-small-cell lung cancer. Clin Lung Cancer, 8: 208–213, 2006.
22) Crombie C, Burns WI, Karapetis C, Lowenthal RM, Kirsten F, *et al.*: Randomized phase II trial of gemcitabine and either day1 or day 8 carboplatin for advanced non-small-cell lung cancer: Is thrombocytopenia predictable? Asia-Pac J Clin Oncol, 5: 24–31, 2009.
23) Surmont V, Aerts JGJV, van Klaveren RJ, Tournoy K, Tan KY, *et al.*: A randomized phase II study comparing two schedules of the 21-day regimen of gemcitabine and carboplatin in advanced non-small cell lung cancer. Oncology, 78:

267–270, 2010.
24) Obasaju CK, Ye Z, Bloss LP, Monberg MJ, Curiel RF: Gemcitabine/carboplatin in patients with metastatic non-small-cell lung cancer: phase II study of 28-day and 21-day schedules. Clin Lung Cancer, 7: 202–207, 2005.
25) Masters GA, Argiris AE, Hahn EA, Beck JT, Rausch PG, *et al.*: A randomized phase II trial using two different treatment schedules of gemcitabine and carboplatin in patients with advanced non-small-cell lung cancer. J Thorac Oncol, 1: 19–24, 2006.
26) Davis AM, Ruel C, Lara PN, Lau DH, Gumerlock PH, *et al.*: The proteasome inhibitor bortezomib in combination with gemcitabine and carboplatin in advanced non-small cell lung cancer: a California Cancer Consortium phase I study. J Thorac Oncol, 3: 68–74, 2008.
27) Davis AM, Chansky K, Lara PN Jr, Gumerlock PH, Crowley J, *et al.*: Bortezomib plus gemcitabine/carboplatin as first-line treatment of advanced non-small cell lung cancer: A phase II Southwest Oncology Group Study (S0339). J Thorac Oncol, 4: 87–92, 2009.
28) Clement-Duchene C, Krupitskaya Y, Ganjoo K, Lavori P, McMillan A, *et al.*: A phase II first-line study of gemcitabine, carboplatin, and bevacizumab in advanced stage nonsquamous non-small cell lung cancer. J Thorac Oncol, 5: 1821–1825, 2010.
29) Sandler A, Gary R, Perry MC, Brahmer J, Schiller JH, *et al.*: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med, 355: 2542–2550, 2006.