Original Article

Nedaplatin/Gemcitabine Versus Carboplatin/Gemcitabine in Treatment of Advanced Non-small Cell Lung Cancer: A Randomized Clinical Trial

Jin-ji Yang, Qing Zhou, Ri-qiang Liao, Yi-sheng Huang, Chong-rui Xu, Zhen Wang, Bin-chao Wang Hua-jun Chen, Yi-long Wu*

Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Cancer Center, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, China

DOI: 10.1007/s11670-012-0097-8

ABSTRACT

Objective: To evaluate the efficacy and safety of nedaplatin/gemcitabine (NG) and carboplatin/gemcitabine (CG) in the management of untreated advanced non-small cell lung cancer (NSCLC).

Methods: Sixty-two patients with previously untreated advanced NSCLC were recruited between June 2006 and November 2007. Subjects were randomly assigned to the NG arm (n=30) and the CG arm (n=32). Only patients (24 and 25 in the NG and CG arms, respectively) who completed ≥2 chemotherapy cycles were included in the data analysis. The primary outcome measure was the objective response rate (ORR). The secondary outcome measures included progression-free survival (PFS), overall survival (OS) and adverse events.

Results: There were no statistically significant differences in the efficacy measures (ORR, *P*=0.305; median PFS, *P*=0.198; median OS, *P*=0.961) or in the major adverse events (grade 3/4 neutropenia, *P*=0.666; grade 3/4 anemia, *P*=0.263; grade 3/4 thrombocytopenia, *P*=0.212) between the two treatment arms. However, there was a trend towards higher ORR (37.5% vs. 24.0%), longer PFS (6.0 vs. 5.0 months), and less adverse events in the NG arm.

Conclusion: NG regimen seems to be superior over CG regimen for advance NSCLS, but further investigation is needed to validate this superiority.

Key words: Non-small cell lung cancer; Chemotherapy; Nedaplatin; Carboplatin; Gemcitabine; Squamous cell carcinoma

INTRODUCTION

Non-small cell lung cancer (NSCLC) poses a significant health problem worldwide. At the early stage, NSCLC is potentially curable with surgical resection. However, in most cases, the disease has progressed to an advanced stage upon diagnosis[1]. For advanced NSCLC, platinum-based combination chemotherapy is the mainstay of the treatment[2-4].

Since the approval of cisplatin (the protypic platinum coordination compound) as a chemotherapeutic agent for testicular and ovarian cancers in the late 1970s, cisplatin-based combination chemotherapy has become the cornerstone of treatment of advanced NSCLC[5]. One of the major limitations with cisplatin is its severe and sometimes dose-limiting side effects, including but not limited to nausea/vomiting, renotoxicity and thrombocytopenia. As a result, many cisplatin derivatives have been developed, among which nedaplatin and carboplatin are of particular importance.

Nedaplatin is believed to have anti-tumor activities that are equivalent to cisplatin but with less toxicity[6,7]. Nedaplatin-based combination regimens have been evaluated in several clinical trials. In a phase I study of nedaplatin/gemcitabine (NG) that included both previously treated and untreated advanced NSCLC[8], nedaplatin was well tolerated (maximum tolerated dose up to 100 mg/m^2) and active; an overall response rate of 16.7% was observed; a median survival time of 9.1 months and a 1-year survival rate of 34.1% were achieved. In a phase II study of NG in patients with untreated NSCLC, a response rate of 30.3% [95%

Received 2011–07–12; **Accepted** 2011–12–22
*Corresponding author.
E-mail: syylwu@live.cn

confidence interval (95% CI), 15.6%–48.7%] and a median survival time of 9.0 (range, 1–17) months were demonstrated[9]. Two additional phase II studies of nedaplatin in patients with NSCLC conducted in Japan achieved an objective response rate of 14.7% and 20.5%, respectively[10,11]. In a phase III study of previously untreated patients with NSCLC, a combination of nedaplatin and vindesine yielded response rate and overall survival rate similar to that obtained with cisplatin or vindesine alone[11]. Taken together, these studies suggest that nedaplatin-based combination chemotherapy may offer a promising and effective chemotherapeutic strategy for previously untreated advanced NSCLC.

Carboplatin-based combination regimens have also been evaluated. A phase III study showed that the overall response rate, median progression-free survival (mPFS), median overall survival (mOS) and 1-year survival rate were 27%–42%, 4.8–7.3 months, 7.9–11.6 months and 13%–40%, respectively, in patients with advanced NSCLC following the treatment with carboplatin/ gemcitabine (CG)[12]. An acceptable toxicity profile was demonstrated for CG in patients with advanced NSCLC[13].

NG has been demonstrated to be superior to CG in an animal model of NSCLC[14]. However, to our knowledge, NG and CG have not been evaluated head-to-head in human trials. This randomized clinical trial compared the efficacy and safety profile of NG and CG as chemotherapeutic regimens for patients with previously untreated advanced NSCLC.

MATERIALS AND METHODS

Ethical Considerations

The study was approved by the Institutional Ethics Committee of Guangdong General Hospital & Guangdong Academy of Medical Sciences and conducted in compliance with the Helsinki Declaration. Written informed consent was obtained from all study subjects.

Subject Recruitment

A total of 62 subjects were recruited between June 2006 and November 2007. The inclusion criteria included: 1) wet stage III B (including malignant pleural or/and pericardial effusion) or stage IV NSCLC as categorized based on the International Union Against Cancer (UICC) 1997 International System for Staging Lung Cancer[15] and confirmed by radiographic imaging, magnetic resonance imaging (MRI), computer tomography (CT) scan, and histological and cytological assessments; 2) no prior chemotherapy; 3) responsive lesions as assessed according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.0[16]; 4) East Cooperation Oncology Group (ECOG) score at 0–2; 5) estimated life expectance at ≥12 weeks; 6) adequate bone marrow reserve (white blood cell at 3,500–12,000/μl, neutrophil count ≥1,500/μl, platelet ≥100,000/μl, and hemoglobin ≥9.0 g/dl); 7) normal renal function (serum creatinine <1.5 mg/dl and creatinine clearance rate ≥50 ml/min); and 8) aspartate aminotransferase and alanine aminotransferase levels at or less than twice the upper limit of the normal range and no juandice. The exclusion criteria included: 1) metastasis to the brain; 2) active secondary malignancy; 3) evident infection; and 4) co-morbid severe heart diseases or other uncontrolled systemic disease.

Treatment Allocation and Regimens

Subjects were randomized to the NG (n=30) or CG (n=32) arm based on the last digit of the admission number (even: NG; odd: CG). The NG regimen consisted of nedaplatin [Jiangsu Aosaikang Pharmaceutical Co., Ltd; 80 mg/m^2, 60 min, d1, every 3 weeks (q3w)] and gemcitabine (1,250 mg/m^2, 30 min, d1, d8, q3w). The CG regimen included: carboplatin at area under the curve (AUC)=5, 20 min, d1, q3w; and gemcitabine 1,250 mg/m^2, 30 min, d1, d8, q3w. All chemotherapeutic agents were administration as an intravenous (iv) drip. No prophylactic granulocyte colony-stimulating factor and prophylactic antibiotics were used. Toxicity profile was evaluated based on the criteria set in the US National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTC) Version 3.0[17]. Whenever grade 4 toxicity developed, a dose reduction of 20% was applied. Patients requiring more than two dosage adjustments were withdrawn from the study. A rest period of up to 42 d was allowed between the cycles to minimize the therapy-related toxicities.

Outcome Assessment

Objective response was assessed every 2 cycles of the chemotherapy based on the criteria stated in RECIST 1.0[16]. Complete response (CR) was defined as disappearance of all target lesions, partial response (PR) as at least 30% decrease in the sum of diameters of target lesions relative to the baseline prior to the treatment, progressive disease (PD) as at least 20% increase in the sum of diameters of target lesions, relative to the smallest sum of diameters during the study or as the appearance of one or more new lesions, and stable disease (SD) as either insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD. CR and PR were established based on at least 4-week response, and SD based on at least 6-week observations.

Patients with SD after 2 cycles underwent one or two additional treatment cycles. Those achieving PR or CR after 2 cycles continued the same regimen for additional 2–4 cycles. Those developing PD were

switched to second-line therapy with or without radiotherapy. The second-line therapy utilized a single chemotherapeutic agent (docetaxel or pemetrexed), epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), gefitinib or erlotinib.

Follow-up examinations were conducted every 6 weeks, and included a physical checkup by an oncologist and a routine laboratory test. In case of evident deteriorating symptom(s) suggestive of PD, additional imaging assessment was performed. Progression-free survival (PFS) was defined as the period from the first day of the treatment to PD. Overall survival (OS) was defined as the period from the first day of the treatment to death due to any cause.

Statistical Analyses

Only those subjects who had completed at least 2 cycles of chemotherapy were included in the final statistical analysis. Demographic data were analyzed with either χ^2 test or Student's *t*-test. The objective response rate (ORR) and adverse events were analyzed by χ^2 test (two-sided). PFS and OS were analyzed using the Kaplan-Meier method (Log Rank test). The difference was considered significant at $P<0.05$. Statistical computations were performed with the SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Demographics

In the NG group, six patients received only one cycle of chemotherapy (2 due to financial problems and 4 switched to traditional Chinese medicine). In the CG group, three patients received only one cycle of chemotherapy (2 due to ECOG score at 3 or 4 after one cycle, and 1 switched to traditional Chinese medicine). No CT or MRI images were carried out in the four patients although they completed more than two cycles of chemotherapy at local hospitals. The final analysis included 24 patients in the NG group and 25 in the CG group. The base-line demographics and clinical characteristics of the study subjects are presented in Table 1. There was no significant difference between the two treatment arms in any of the variables, including gender (i.e., male to female ratio), age, history of smoking, ECOG performance status, lesion classification and stage, and the number of chemotherapy cycles applied.

Table 1. Baseline demographics and clinical characteristics of patients in NG and CG arms.

Variable	NG (*n*=24)	CG (*n*=25)	χ^2/t	*P*
Male/female ratio	16/8	19/6	0.523	0.470
Age (year)	56.8 (36–75)	57.5 (33–72)	1.565	0.788
Smoking	54.17% (13)	68% (17)	0.987	0.320
ECOG 1	95.83% (23)	96% (24)	0.001	0.976
ECOG 2	4.17% (1)	4% (1)		
BW loss <5%	91.67% (22)	96% (24)	0.400	0.527
BW loss ≥5%	8.33% (2)	4% (1)		
Adenocarcinoma	83.33% (20)	76% (19)		
Squamous cell carcinoma	12.5% (3)	12% (3)	0.405	0.524
Other	4.17% (1)	12% (3)		
Wet stage III B	16.67% (4)	4% (1)		
Stage IV	83.33% (20)	96% (24)	2.144	0.143
Brain metastasis	33.33% (8)	24% (6)		
Chemo cycles	3.8 (2–6)	3.5 (2–4)	1.273	0.209

BW: body weight; Chemo: chemotherapy

Response and Survival

Twenty-four and 25 participants completed ≥2 chemotherapy cycles in the NG and CG arms, respectively, and were included in the final assessment. The last follow-up examination was performed on September 23, 2009. Median follow-up time was 33.2 (range, 22.1–39.7) months. No patient achieved CR in either treatment arm (Table 2). The NG treatment regimen resulted in a seemingly higher PR than the NG regimen (37.5% vs. 24.0%) (Table 2), but the difference did not reach the statistically significant level ($\chi^2=1.051$, $P=0.305$). Three patients in each of the two treatment arms had squamous cell carcinoma (Table 1). Two patients with squamous cell carcinoma achieved PR (Figures 1 and 2) after the NG treatment; the remaining one attained SD. Only one patient with squamous cell carcinoma achieved PR after the CG treatment; the remaining two patients had SD and PD, respectively.

Table 2. Response in patients who completed ≥2 chemotherapy cycles.

	NG (*n*=24)	CG (*n*=25)
Complete response (CR)	0	0
Partial response (PR)	37.5% (9)	24.0% (6)
Stable disease (SD)	54.2% (13)	60.0% (15)
Progressive disease (PD)	8.3% (2)	16.0% (4)
Objective response rate (ORR)	37.5%	24.0%
Disease control rate (DCR)	91.7%	84.0%

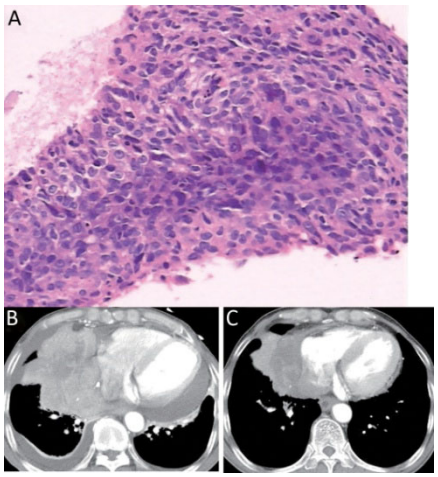

Figure 1. PR (target lesions reduction by 32%) achieved by the patient diagnosed with cT4N3M0 stage III B squamous cell carcinoma (SCC) of the right lower lung lobe after completing first-line NG. **A:** CT-guided biopsy of the primary lesion showed SCC (HE ×200); **B:** Baseline primary lesion in the right lower lung lobe and malignant pleural and pericardial effusion; **C:** Tumor shrinkage and disappearance of malignant pleural and pericardial effusion after 4 cycles of NG.

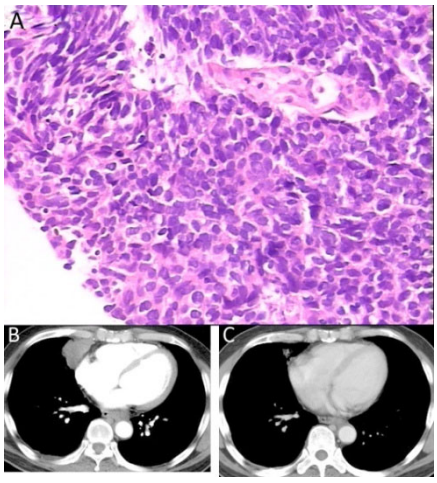

Figure 2. PR (target lesions reduction by 45%) attained by the patient diagnosed with cT4N2M1 (liver) stage IV squamous cell carcinoma (SCC) of the right middle lung lobe after completing first-line NG. **A:** Bronchoscopy revealed SCC (HE ×200); **B:** Baseline primary lesion in the right middle lung lobe; **C:** Tumor shrinkage after 2 cycles of NG.

The follow-up rate was 83.3% (25/30) in NG group and 75.0% (24/32) in CG group (χ^2=0.649, P=0.421). mPFS was seemingly longer in the NG arm (6.0 months, 95% CI: 5.5–6.5 months vs. 5.0 months, 95% CI: 4.9–5.1 months in the CG arm), but the difference was not significantly different (Log Rank χ^2=1.654, P=0.198). After the emergence of resistance to platinum-based chemotherapy, 58.3% (14/24) of patients received standard second-line therapy in the NG group and 52.0% (13/25) in the CG group (χ^2=0.199, P=0.656), and 33.3% (8/24) in the NG group and 32.0% (8/25) in CG group received EGFR TKIs (χ^2=0.01, P=0.921). mOS did not differ between the two treatment arms (17.5 months, 95% CI: 10.8–24.2 months in the NG group vs. 17.0 months, 95% CI: 12.1–21.9 months in the CG group; Log Rank χ^2=0.002, P=0.961). The Kaplan-Meier survival curves of PFS and OS are presented in Figure 3. mOS was 8.8 months for the 9 patients in both arms who completed only one cycle of chemotherapy.

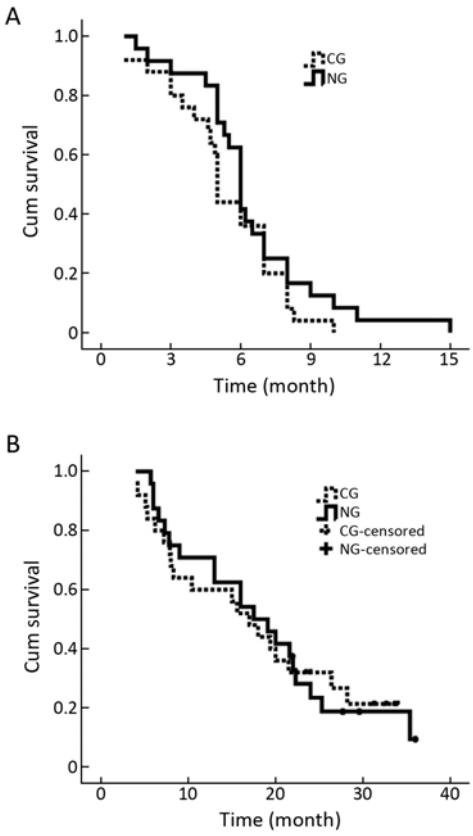

Figure 3. Kaplan-Meier survival curves of PFS and OS. **A:** Survival curves of PFS between NG and CG arms; **B:** Survival curves of OS between NG and CG arms.

Adverse Events

Neutropenia was the most common hematological toxicity but did not differ between the two treatment arms (Table 3). Grade 3/4 neutropenia was observed in 54.2% and 48.0% of the patients in the NG and CG groups, respectively (χ^2=0.186, P=0.666). Anemia was the second most common adverse event; grade 3/4 anemia occurred in 25.0% and 40.0% of patients in the NG and CG groups, respectively (χ^2=1.253, P=0.263). The third most common event was thrombocytopenia; grade 3/4 thrombocytopenia was observed in 16.7%

and 32.0% of patients in the NG and CG groups, respectively (χ^2 =1.557, P=0.212).

Minor adverse events included febrile neutropenia (4.2% and 0.0% in the NG and CG groups, respectively, χ^2=1.063, P=0.302), grade 3/4 nausea/vomiting (12.5% and 0.0%, χ^2=3.329, P=0.068), and grade 2 allopecia (20.8% and 8.0%, χ^2=1.647, P=0.199). Other non-hematological toxicities were also observed but were moderate and manageable. No cytotoxicity-related death occurred in either treatment arm.

Table 3. Number of patients who developed the indicated adverse event (≥grade 2) following ≥2 cycles of chemotherapy with the NG or CG regimen.

Variable	NG (*n*=24)				CG (*n*=25)			
	G 2	G 3	G 4	≥G 3 (%)	G 2	G 3	G 4	≥G 3 (%)
Neutropenia	7	12	1	54.2	5	8	4	48.0
Thrombocytopenia	4	4	0	16.7	2	5	3	32.0
Anemia	9	4	2	25.0	10	9	1	40.0
Febrile neutropenia	1	0	0	0	0	0	0	0
Nausea/vomiting	5	3	0	12.0	4	0	0	0
Elevated ALT	3	0	0	0	3	0	0	0
Elevated AST	2	0	0	0	0	0	0	0
Elevated creatinine	0	0	0	0	0	0	0	0
Allopecia	5				2			
Subcutaneous bleeding	0	0	0	0	1	0	0	0
Pulmonary fibrosis	0	0	0	0	1	0	0	0
Anorexia	3	0	0	0	4	0	0	0
Rash	2	0	0	0	3	0	0	0
Fatigue	4	0	0	0	2	0	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

DISCUSSION

We observed an ORR of 37.5% in patients receiving the NG regimen. Such a finding is compatible to the ORR (30.3% and 35.0%) reported previously for NG regimen in chemotherapy-naive advanced NSCLC [9,18], despite of the lower doses of nedaplatin (80 mg/m^2) and gemcitabine (1,250 mg/m^2) in the current study. The NG regimen seemed to be superior to the CG regimen in terms of treatment response and patient survival (ORR: 37.5% vs. 24.0%; PFS: 6.0 vs. 5.0 months). The differences failed to reach statistically significant level (Table 2), probably due to the relatively small sample size. mOS in Chinese patients with previously untreated advanced NSCLC is apparently longer than that in Caucasian populations, probably due to higher frequency of EGFR mutation in Chinese NSCLC patients[19]. Also, more than 1/3 of patients in both arms in our study received second-line EGFR TKIs. Nevertheless, these findings encourage further head-to-head studies.

In the present study, NG regimen was well tolerated without any severe complications or deaths when nedaplatin was used at 80 mg/m^2 and gemcitabine at 1,250 mg/m^2. This cytotoxic profile of the NG regimen was similar to that previously reported in a phase II study where the use of nedaplatin at 100 mg/m^2 and gemcitabine at 1,000 mg/m^2 did not lead to the development of any severe complications related to myelosuppression, even in patients over 70 years or with a Performance Status of 2[9]. These observations suggest that the NG combination regimen has an acceptable safety profile for previously untreated patients with advanced NSCLC. The adverse events observed in our study included neutropenia, anemia and thrombocytopenia. Grade 3/4 neutropenia occurred in 54.2% of patients in the NG arm, similar to that reported previously in phase I (44.4%) and phase II (62.0%) studies[8,9]. In compared to the CG arm, neutropenia seemed to be more frequent in the NG arm; less patients receiving the NG regimen developed anemia or thrombocytopenia (Table 3).

Numerous studies have demonstrated a cancer subtype-associated efficacy and cytotoxicity of nedaplatin-based therapy. A preclinical study demonstrated higher intracellular concentration of nedaplatin in squamous carcinoma cells (SCCs) than in adenocarcinoma cells[20]. In phase II trials of mono-chemotherapy, SCCs of the lung were more sensitive than adenocarcinoma cells[5,6]. In a phase II study of nedaplatin/docetaxel regimen in patients with advanced squamous carcinoma of the lung, the ORR, mPFS and mOS were 62%, 7.4 months and 16.1 months, respectively[21]. In a meta-analysis of four trials comparing nedaplatin and irinotecan, better response and survival rate were observed in patients with

squamous carcinoma than in those with non-squamous carcinoma of the lung (ORR: 51.9% vs. 35.1%; median survival time: 14.5 months vs. 9.1 months; 1-year survival rate: 63.0% vs. 39.4%; and 2-year survival rate: 29.6% and 19.1%)[22]. In the present study, there were 3 patients with squamous carcinoma in each of the two treatment arms. Of these patients, two (66.7%) achieved PR in the NG arm; one (33.3%) achieved PR in the CG arm. The PR rate for the NG regimen was similar to that of nedaplatin and docetaxel or nedaplatin and irinotecan[21,22]. Although our findings seem to suggest that the NG regimen has response and survival benefits than CG in patients with squamous carcinoma of the lung, only 3 patients for each treatment regimen were assessed and the superiority of the NG regimen in managing squamous carcinoma has to be further established in more clinical trials of large sample size.

In summary, the results from the current study suggested the NG combination regimen may be superior to the CG regimen for naive advanced NSCLC and squamous carcinoma in particular. The slightly better response rate and less cytotoxicity are not statistically significant, but may be clinically relevant in our opinion, and worthy of further investigation in our opinion.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

REFERENCES

1. Wagner TD, Yang GY. The role of chemotherapy and radiation in the treatment of locally advanced non-small cell lung cancer (NSCLC). Curr Drug Targets 2010; 11:67–73.
2. Ramalingam S, Belani CP. Carboplatin/gemcitabine combination in advanced NSCLC. Oncology (Williston Park) 2004; 18:21–6.
3. Maione P, Rossi A, Bareschino MA, et al. "Factors driving the choice of the best second-line treatment of advanced NSCLC." Rev Recent Clin Trials 2011; 6:44–51.
4. Belvedere O, Grossi F. Lung Cancer Highlights from ASCO 2005. Oncologist 2006; 11: 39–50.
5. Rinaldi M, Cauchi C, Gridelli C, et al. First line chemotherapy in advanced or metastatic NSCLC. Ann Oncol 2006; 17:64–7.
6. Kameyama Y, Okazaki N, Nakagawa M, et al. Nephrotoxicity of a new platinum compound, 254-S, evaluated with rat kidney cortical slices. Toxicol Lett 1990; 52:15–24.
7. Ota K, Wakui A, Majima H, et al. Phase I study of a new platinum complex 254-S, cis-diammine (glycolato)-platinum (II). Gan To Kagaku Ryoho (in Japanese) 1992; 19:855–61.
8. Kurata T, Tamura K, Yamamoto N, et al. Combination phase I study of nedaplatin and gemcitabine for advanced non-small-cell lung cancer. Br J Cancer 2004; 90:2092–6.
9. Shirai T, Hirose T, Noda M, et al. Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small-cell lung cancer. Lung Cancer 2006; 52:181–7.
10. Fukuda M, Shinkai T, Eguchi K, et al. 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 1990; 26:393–6.
11. Furuse K, Fukuoka M, Asamoto H, et al. A randomized comparative study of 254-S plus vindesine (VDS) vs. cisplatin (CDDP) plus VDS in patients with advanced non-small cell lung cancer (NSCLC). Gan To Kagaku Ryoho (in Japanese) 1992; 19:1019–26.
12. Sederholm C, Hillerdal G, Lamberg K, 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 2005; 23:8380–8.
13. Ramalingam S, Belani CP. Carboplatin/gemcitabine combination in advanced NSCLC. Oncology (Williston Park) 2004; 18 (8 Suppl 5):21–6.
14. Matsumoto M, Takeda Y, Naki H, et al. Preclinical in vivo antitumor efficacy of nedaplatin with gemcitabine against human lung cancer. Jpn J Cancer Res 2001; 92:51–8.
15. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997; 111:1710–7.
16. Padhani AR, Ollivier L. The RECIST (Response Evaluation Criteria in Solid Tumors) criteria: implications for diagnostic radiologists. Brit J Radiol 2001; 74:983–6.
17. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE). Version 3.0, DCTD, NCI, NIH, DHHS. August 9, 2006. http://ctep.cancer.gov/forms/ CTCAEv3.pdf. Accessed July 16, 2007.
18. Hirose T, Horichi N, Chmori T, et al. Phase I study of the combination of gemcitabine and nedaplatin for treatment of previously untreated advanced non-small cell lung cancer. Lung Cancer 2003; 39: 91–7.
19. Wu YL, Zhong WZ, Li LY, et al. Epidermal growth factor receptor mutations and their correlation with Gefitinib therapy in patients with non-small cell lung cancer: A meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol 2007; 2:430–9.
20. Nakajima O, Inoue S, Kobayashi K. Differences in intracellular uptake of cisplatin, carboplatin and 254-S among human lung cancer cell lines. Japan J Lung Cancer 1994; 34: 313–9.
21. Naito Y, Kubota K, Ohmatsu H, et al. Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung. Ann Oncol 2011; 781:1–5.
22. Oshita F, Honda T, Murakami S, et al. Comparison of nedaplatin and irinotecan for patients with squamous and non-squamous cell carcinoma of the lung: meta-analysis of four trials. J Thorac Oncol 2011; 6:128–31.