Cancer Chemother Pharmacol (2007) 60:495–501
DOI 10.1007/s00280-006-0391-6

ORIGINAL ARTICLE

Phase II trial of gemcitabine and docetaxel in patients with completely resected stage IIA–IIIA non-small-cell lung cancer

Masafumi Kawamura · Keisuke Eguchi · Yotaro Izumi · Yasushi Yamato · Teruaki Koike · Hirozo Sakaguchi · Enjo Hada · Koichi Kobayashi

Received: 19 July 2006 / Accepted: 12 November 2006 / Published online: 2 December 2006

Abstract
Background Few clinical phase II studies using non-platinum doublet as adjuvant chemotherapy following complete resection of non-small-cell lung cancer (NSCLC) have been published, so this clinical study was designed to evaluate the toxicity profile and efficacy of the non-platinum doublet of docetaxel (DOC) + gemcitabine (GEM).
Methods Eligibility criteria included completely resected NSCLC, pathological stage II or IIIA, younger than 76 years old, and performance status 0–1. Treatment consisted of DOC 60 mg/m^2 on day 8, and GEM 1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks (4 cycles). The GEM dosage was decreased to 800 mg/m^2 after the initial 21 patients because 3 patients developed interstitial lung disease (ILD).
Results Thirty-five patients (male/female 21/14) were enrolled. The median age was 62 years (range 47–74), with five (14.3%) over the age of 70. Performance status was 0 in 34 patients. The diagnosis was ad in 28 patients, sq in 6, and adsq in 1. The pathological stage was IIA in 5 patients, IIB in 1 and stage IIIA in 29 (82.9%). All patients underwent at least one cycle of chemotherapy, with 29 patients completing three cycles of chemotherapy and 23 (66%) had four cycles. The main grade 3/4 toxicities comprised neutropenia ($n = 21$, 60%), thrombocytopenia ($n = 3$, 8.6%), anorexia ($n = 4$, 11.4%), and ILD ($n = 3$, 8.6%), which responded well to corticosteroids. There were no treatment-related deaths. The 4-year recurrence-free survival rate was 42.9%, and the 4-year survival rate was 65.8%.
Conclusions The non-platinum doublet regimen of DOC + GEM as adjuvant chemotherapy following complete resection of NSCLC is feasible, with good compliance, the only problem being ILD.

Keywords Non-platinum doublet · Adjuvant chemotherapy · Non-small-cell lung cancer · Docetaxel · Gemcitabin · Surgery

M. Kawamura (✉) · K. Eguchi · Y. Izumi · K. Kobayashi
Division of General Thoracic Surgery,
Keio University Hospital, 35 Shinanomachi,
Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: kawamura@sc.itc.keio.ac.jp

Y. Yamato · T. Koike
Niigata Prefectural Cancer Center Hospital,
Niigata, Japan

H. Sakaguchi · E. Hada
Mitsui Memorial Hospital, Tokyo, Japan

Introduction

The 5-year survival rates for patients with fully resected non small cell lung cancer (NSCLC) are around 40%, and no better than 40–60% even for patients with clinical stage IB/II disease, which cannot be considered as satisfactory results [1]. Postoperative chemotherapy is part of the standard therapeutic strategy for breast and colorectal cancers, and randomized clinical trials have been conducted to evaluate the efficacy of it for NSCLC. In the latter part of the 1970s chemotherapy based on cisplatin (CDDP) was shown to be effective in cases of advanced NSCLC, so a number of CDDP-based adjuvant regimens have been trialed and a meta-analysis published by the Non-small Cell Lung Cancer Collaborative Group in 1995 found

that these reduced mortality rates in comparison with surgery alone [2]. Although several large-scale clinical trials have subsequently been conducted and recently three large-scale randomized trials containing platinum-based chemotherapy have reported their positive results [including cisplatin-based chemotherapy (IALT) [3], CDDP ± NVB (JBR.10 [4]), ANITA trial [5])], at the time of commencing the present study the clinical benefits of postoperative adjuvant chemotherapy for patients with NSCLC had not yet been established.

On the other hand, in cases of inoperable NSCLC a doublet chemotherapy regimen including third-generation agent has been shown to significantly increase survival times in comparison with earlier doublet or triplet regimens [6–9]. Similar therapeutic effects have been reported for platinum (Pt)- and non-Pt-based doublet regimens in cases of inoperable NSCLC [10, 11].

Although we can anticipate improved survival rates with postoperative adjuvant chemotherapy regimens including third generation anticancer agents in comparison with surgery alone, we can also expect poor feasibility for a regimen of four courses of chemotherapy administered to postoperative patients. Considering that higher completion rates can be anticipated with non-Pt doublets, we planned a phase II trial of postoperative adjuvant chemotherapy for NSCLC using the new agents docetaxel (DOC) and gemcitabine (GEM).

Methods

We aimed for four courses of postoperative chemotherapy using DOC and GEM in patients with completely resected NSCLC, pathological stage II or IIIA. The primary endpoints were completion rates and adverse events, and the secondary endpoints were the recurrence-free survival rate and survival period.

Patient selection criteria were as follows: (1) pathologically complete resection; (2) histologically confirmed NSCLC; (3) age 75 years or less; (4) no double cancer (metachronous or synchronous); (5) postoperative pathological classification IIA, IIB or IIIA; (6) performance status (PS) of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) criteria; (7) no pretreatment; (8) no postoperative infection or fever suggestive of infection; (9) appropriate blood test results (bone marrow function: WBC $\geq$ 3,000 per mm^3, Hb $\geq$ 10 g/dL, Plt $\geq$ 100,000 per mm^3; renal function: serum Cr $\leq$ 1.5 mg/dL, CCr $\geq$ 40 ml/min; hepatic function: serum AST, ALT $\leq$ 2 $\times$ upper limit normal); (10) no other conditions rendering patient medically unsuitable for treatment with anticancer agents (e.g. cardiac disease, severe diabetes); and (11) informed consent given to participate in this study.

Patients who filled all these criteria were enrolled in the study at between 2 and 4 weeks following surgery, and treatment was commenced before the sixth postoperative week.

Treatment protocol

On days 1, 8 and 15, GEM 1,000 mg/m^2 was administered as a 30-min intravenous (IV) infusion and DOC 60 mg/m^2 as a 1-h IV infusion on day 8. Chemotherapy cycles were repeated every 4 weeks, for a total of four courses. Both gemcitabine and docetaxel were administered by approved dosage and administration in Japan.

Patients received granulocyte-colony-stimulating factor (G-CSF) infusions after each cycle at the discretion of the investigator, but G-CSF was not used routinely.

Patients in whom treatment was interrupted due to grade 3/4 myelosuppression were re-treated with 75% of both the GEM and DOC dosages once the hematological parameters had returned to the levels prescribed in selection criterion 9.

Follow-up investigations

Every 3 months after surgery, patients attended the Outpatients Department for an periodic examination including plain chest radiography. Thoracic CT scanning, abdominal ultrasonography or CT scanning, and bone scintigraphy were examined once a year for at least 3 years following surgery.

Statistical analyses

Recurrence-free survival rates and cumulative survival periods were calculated using the method of Kaplan–Meier.

Results

Patient characteristics

A total of 35 patients (21 males, 14 females) were enrolled from the three institutions between August 2000 and 2002 (average age 62 years (range 47–74), five patients (14.3%) >70 years) (Table 1). The PS was zero in 34 patients, and one in 1. All patients were evaluated

Table 1 Patient characteristics

	All patients ($n = 35$)
Gender, no. (%)	
Male	21 (60%)
Female	14 (40%)
Age (years)	
Median	62
Range	47–74
ECOG PS	
0	34 (97%)
1	1 (3%)
Histology	
Adenocarcinoma	28 (80%)
Squamous cell carcinoma	6 (17%)
Adenosquamous cell carcinoma	1 (3%)
Surgical procedure	
Segmentectomy	1 (3%)
Lobectomy	32 (91%)
Bilobectomy	2 (6%)
Pathological stage	
Stage IIA	5 (14%)
Stage IIB	1 (3%)
Stage IIIA	29 (83%)

ECOG Eastern Cooperative Oncology Group, *PS* performance status

in terms of treatment toxicity and feasibility, and survival.

Treatment summary

The number of cycles of treatments administered to the patients is shown in Table 2. The first 21 patients were administered GEM 1000 mg/m^2, but after three patients developed interstitial lung disease (ILD), the dosage was decreased to 800 mg/m^2 for all subsequent patients. The average total GEM dosage was therefore 8736 mg/m^2, or 76.9% of the planned total dosage (calculations made on the basis of GEM 800 mg/m^2 on days 1, 8 and 15 as the full dosage for patients 22–35). The average total DOC dosage was 198.8 mg/m^2, or 82.9% of the planned total dosage.

Table 2 Treatment summary

	All patients ($n = 35$)
Cycle number	
1	35 (100%)
2	33 (94%)
3	29 (83%)
4	23 (66%)
Average no. of cycles	3.43
Mean total dose administered	
Gemcitabine	8736 mg/m^2 (76.9% planned)
Docetaxel	198.8 mg/m^2 (82.9% planned)

Causes of treatment suspension

The causes of treatment suspension, and the number of cycles completed when treatment was ceased, for the 12 patients who did not complete four courses are shown in Table 3. Cessation was due to adverse events in ten cases, the most common being grade 3/4 neutropenia, followed by pneumonitis, and there was one case each of cancer recurrence and patient refusal.

Adverse events

The main adverse events and their grades are shown in Table 4. Grade 3/4 neutropenia occurred in 21 patients, and grade 4 in two (5.7%). All subsequent chemotherapy was ceased in four patients with grade 3/4 neutropenia on the decision of the treating physician. Grade 3 thrombocytopenia occurred in three patients (8.6%), grade 3 anemia occurred in one patient (2.9%), 17 patients (48.6%) complained of nausea, but there was only one case of grade 3 nausea, 18 patients became anorexic (51.4%), four (11.4%) of whom required fluid supplementation (grade 3), ten patients (28.6%) recorded abnormal liver function tests but only one case was serious (2.9%), peripheral neuropathy occurred in six patients (17.1%), but no grade 3/4 cases, and although six patients (17.1%) complained of dyspnea, the diagnosis of ILD was made in three patients (8.6%) only, on the basis of the physical and radiological findings.

The three patients who developed ILD had all been administered GEM at the dosage of 1,000 mg/m^2, with the onset of symptoms occurring during the second course in one patient, and during the third course in two patients. The initial presentation was of dyspnea on exertion in one case, and fever in the other two cases. Subsequent thoracic CT scans revealed interstitial opacities in all three cases, and the diagnosis of drug-induced interstitial pneumonitis was made. The

Table 3 Causes of treatment suspension

	Cycle number at suspension		
	1	2	3
Grade 3 transaminitis	1	–	–
Grade 3 allergic reaction	1	–	–
Grade 3 pneumonitis	–	1	2
Grade 3 anorexia	–	–	1
Grade 3/4 neutropenia	–	–	3
Infection with grade 4 neutropenia	–	1	–
Recurrence	–	1	–
Refusal by patient	–	1	–

Table 4 Summary of adverse events

Adverse event	All patients[a] ($n = 35$)	Worst toxicity grade[b]				
		0	1	2	3	4
Hematological						
Neutropenia	33	–	2	10	19	2.
Thrombocytopenia	8	–	2	3	3	0.
Anemia	14	–	9	4	1	0.
Nonhematological						
Fever	7	–	3	4	0	0.
Nausea	17	–	11	5	1	0.
Anorexia	18	–	11	3	4	0.
Transaminitis	10	–	7	2	1	0.
Dyspnea	6	–	3	0	3	0.
Pneumonitis	3	–	0	0	3	0.
Peripheral neuropathy	6	–	3	3	0	0

[a] Each patient was counted once for each adverse event and assigned the worst toxicity grade reported for that patient during the study. Treatment related events were assessed as possibly, probably, or definitely related to treatment

[b] Common terminology criteria for adverse events, Version 3.0, were used to grade adverse events

highest recorded C-reactive protein (CRP) value for each of these patients was 1.9, 12.1 and 18.3 mg/dL, respectively. All three patients were given oxygen therapy and methyl-prednisolone (PSL) therapy (500 mg daily for 3 days, then PSL 20 mg daily gradually tapering the dosage for one patient, 80 mg and 50 mg, respectively, then gradually tapering for the other two patients). Symptoms resolved rapidly within 2–3 days of commencing PSL and the radiological signs also cleared relatively rapidly as the PSL dosage was reduced. None of the patients required assisted ventilation. Chemotherapy was ceased in all three patients at the onset of ILD. Following these developments, the GEM dosage was reduced to 800 mg/m^2 for the 22nd patient onwards. There were no chemotherapy-related deaths.

Survival

The median follow-up period was 4 years and 4 months. Using the Kaplan–Meier method, the 4-year recurrence-free survival rate was 42.9%, and the 4-year cumulative survival rate was 65.8% (Fig. 1).

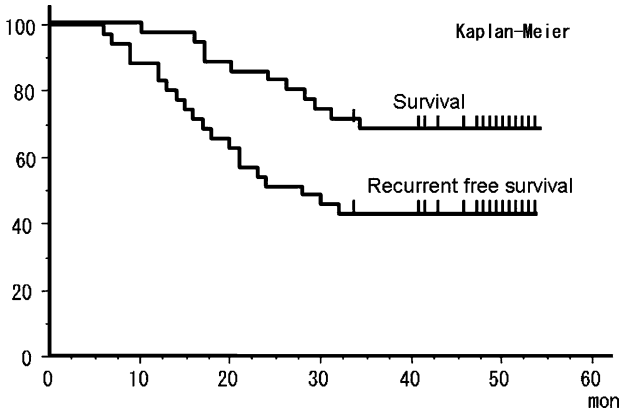

Fig. 1 Postoperative cumulative survival curve and postoperative recurrence-free survival curve (Kaplan–Meier method)

Discussion

The results of the 2003 International Adjuvant Lung Cancer Trial Group (IALT) Phase III comparative trial with patients with completely resected NSCLC showed significantly prolonged survival times for Pt doublet chemotherapy versus surgery alone, including median survival time (MST) (50.8 vs. 44.4 months), recurrence-free survival (40.2 vs. 30.5 months), and 5-year survival rate (44.5 vs. 40.4%) [3, 12]. Winton et al. [4] reported that postoperative CDDP + vinorelbine (VNR) doublet chemotherapy significantly prolonged survival times. In comparison to surgery alone, MST (94 vs. 73 months), 5-year survival rate (69 vs. 54%) and recurrence-free survival rate (61 vs. 48%) were all significantly improved, and feasibility was also relatively favorable. In 2005, the Adjuvant Navelbine International Trialist Association (ANITA) published the final results of their trial of postoperative CDDP + VNR doublet chemotherapy. They reported that both the MST (36.3 vs. 20.7 months) and 5-year survival rate (51.2 vs. 42.6%) were more favorable for the adjuvant chemotherapy group than for the surgery alone group, and suggested that, since prolongation of the MST was particularly marked for stage II/IIIA disease, adjuvant chemotherapy should be considered standard treatment for these patients [5].

Subgroup analysis by stage confirmed that improvement in survival on stage II disease was significant in JBR.10 [4] and ANITA trial [5]. IALT [3] and ANITA trial showed a survival benefit from adjuvant chemotherapy in stage III disease.

Based on these reports, postoperative adjuvant chemotherapy is now becoming standard treatment for completely resected stage II and IIIA NSCLC, with Pt doublet regimens the most commonly used worldwide. However, few comparative trials have been conducted to determine the optimum regimen, and a consensus has not been reached as to what regimen should be used in which patients. We were unable to find any reports of phase II trials of postoperative adjuvant chemotherapy using non-platinum doublets.

Platinum doublet chemotherapy is also considered the standard treatment for advanced NSCLC, although

Georgoulias et al. [13] have reported a comparative trial of the non-Pt-based DOC + GEM regimen and the Pt-based DOC + CDDP regimen. No significant differences were seen between the two regimens in terms of efficacy, MST, or 1-year survival rates, but the lower toxicity for the DOC + GEM regimen suggested it might be more clinically advantageous. Subsequent phase III trials by Pujol et al. [10] and Georgoulias et al. [11] comparing VNR + CDDP and DOC + GEM doublet regimens similarly found no difference between regimens in survival, and superiority toxicity results for DOC + GEM. Matsui et al. [14] conducted a phase I/II study of the DOC + GEM doublet regimen, reporting an efficacy rate of 32.2%, similar to Pt-based regimens, but with less toxicity, suggesting that this regimen is a suitable candidate for future phase III trials. ASCO published the updated 2003 guidelines [15] for treatment of NSCLC. For stage IV NSCLC, non-platinum-containing chemotherapy regimens may be used as alternatives to platinum-based regimen in the first line. The results of those studies in cases of advanced NSCLC indicate that the DOC + GEM doublet regimen shows promise as postoperative adjuvant chemotherapy, and future phase III trials should elucidate its adverse reaction profile in comparison with Pt-based regimens.

In the present study, DOC + GEM doublet postoperative adjuvant chemotherapy was administered for a mean 3.43 courses (85.6%), with actual administered total dosages 76.9% of the planned dosage for GEM and 82.9% for DOC. Completion rates in JRB.10 [4] and ANITA trial [5] with the CDDP ± NVB regimen were 45 and 50%, respectively. Compliance with the protocol in ANITA was 89% for CDDP and 59% for NVB. These results indicate better feasibility than for the CDDP + NVB regimen which may be partially related to the low incidence of nausea and vomiting with DOC + GEM, making it suitable for administration on an outpatient basis.

The incidence of hematological toxicity in the present study was high, with grade 3/4 neutropenia detected in 60% of patients. The incidence of grade 3/4 neutropenia with DOC + GEM chemotherapy in patients with inoperable NSCLC has been reported as 10–19% [11, 16–18], so the present incidence with postoperative DOC + GEM is rather high. In comparison, the reported incidence of grade 3/4 neutropenia with postoperative CDDP + NVB chemotherapy was 73% in the Intergroup JBR.10 [4], and 84.6% in the ANITA report [5]. In two studies in which at least six courses of CDDP + NVB were administered to patients with inoperable NSCLC the reported incidence of grade 3/4 neutropenia was 57 [19] or 58% [20], indicating that this combination also produces a high incidence of grade 3/4 neutropenia postopeatively, similar to the DOC + GEM combination. There are as yet few reports of postoperative adjuvant chemotherapy using third generation anticancer agents, and it is unclear at present whether the present high incidence of grade 3/4 neutropenia is a general trend or not. Future studies with more patients, and possibly the prophylactic administration of G-CSF, might show increased feasibility and eliminate delays in treatment schedules.

Grade 3/4 thrombocytopenia was detected in three of the present patients (8.6%), which is a similar incidence to the 2–8% reported in studies [5, 13, 14, 16] of patients with inoperable NSCLC. All three of the present cases were grade 3 and none required platelet transfusions.

In terms of non-hematological toxicities, few of the present patients complained of severe nausea, and the DOC + GEM regimen could be administered on an outpatient basis. Grade 3 anorexia occurred in four patients (11.4%), although no record of grade 3 anorexia event could be found in reports of DOC + GEM chemotherapy in patients with inoperable NSCLC. Further investigation with more patients required to determine whether this is characteristic of postoperative chemotherapy.

The other important adverse event encountered in this study was interstitial pneumonitis (3 patients, 8.6%). With a reported incidence of the order of 5.2–23% [10, 16, 21, 22], pulmonary events can be considered characteristic complications of the DOC + GEM regimen. In a Japanese trial of DOC + GEM chemotherapy as second-line treatment in cases of advanced NSCLC, 12.3% of patients developed ILD, with three deaths, causing the premature closure of the study [21].

GEM is known to cause ILD, with incidences as high as 8% when it is used as monotherapy [23]. Pavlakis et al. [24] stated, "Unexpected peripheral edema and the noncardiogenic pulmonary edema may be explained by a capillary leak syndrome induced by gemcitabine. In view of structural and metabolic similarities between Ara-C and gemcitabine, perhaps the mechanism of lung injury is common to both these drugs". Referring to DOC, Read et al. [25] stated, "The lung biopsy suggests that docetaxel-induced pneumonitis might be a hypersensitive pneumonitis similar to that described for methotrexate". They added, "Docetaxel-induced pneumonitis is remarkable in its long duration. It is conceivable that docetaxel pneumonitis might result from taxane-induced alterations in leukocytes, with the resulting pulmonary insult lasting for the life span of the leukocyte". As all three of the present cases of ILD responded rapidly to

corticosteroid therapy, we suppose that their ILD might be induced by GEM. Patients undergoing postoperative adjuvant chemotherapy with this combination should be carefully monitored for the development of ILD, and factors contributing to the development of ILD need further eludication.

Conclusions

Although over 80% of the present patients had postoperative pathological stage IIIa NSCLC, favorable results were achieved with DOC + GEM postoperative adjuvant chemotherapy, with a 4 year recurrence-free survival rate of 42.9%, and a 4 year survival rate of 65.8%. Feasibility was relatively favorable for this regimen, despite being 'postoperative' in all cases, and high compliance can be anticipated for postoperative adjuvant chemotherapy. The incidences of neutropenia and anorexia were, however, higher than for the chemotherapy in patients with inoperable NSCLC.

In conclusion, this regimen warrants further study as one arm of postoperative adjuvant chemotherapy for NSCLC. Larger studies are needed to elucidate the adverse effect profile. The next step could be a randomized phase II study comparing DOC + GEM with another combination already used as postoperative chemotherapy for NSCLC, such as CDDP ± NVB.

References

1. Mountain CF (1997) Revisions in the international system for staging lung cancer. Chest 111:1710–1717
2. 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
3. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 350:351–360, 2004
4. Winton TL, Livingston R, Jhonson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F (2005) Vinorelbine plus cisplatin versus observation in resected non-small-cell lung cancer. N Engl J Med 352:2589–2597
5. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, Grodzki T, Pereira JR, Le Groumellec A, Lorusso V, Clarv C, Torres AJ, Dahabreh J, Souquet PJ, Astudillo J, Fournel P, Artal-Cortes A, Jassem J, Koubkova L, His P, Riqqi M, Hurteloup P (2006) ANITA: adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer [Adjuvant Navelbine International Trialist Association (ANITA)]: a randomised controlled trial. Lancet Oncol 7:719–27
6. Chevalier TL, Brisgand D, Douillard JY, Pujor JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S, Gottfried M, Ruffie P, Panizo A, Gaspard MH, Ravaioli A, Besenval M, Bessonval M, Besson F, Martinez A, Berthaud P, Tursz T (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatine versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. J Clin Oncol 12:360–67
7. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama M, Yokota S, Yoneda S, Matsui K, Kudo S, Shibuya M, Isobe T, Segawa Y, Nishiwaki Y, Ohashi Y, Niitani H (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 22:254–61
8. Rudd RM, Gower NH, Spiro SG, Eisen TG, Harper PG, Littler JAH, Hatton M, Johnson PWM, Martin WMC, Rankin EM, James LE, Gregory WM, Qian W, Lee SM (2005) Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol 23:142–53
9. Bonomi P, Kim KM, Fairclough D, Cella D, Kugler J, Rowinsky E, Jiroutek M, Johnson D (2000) Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 18:623–31
10. Pujol JL, Breton JL, Gervais R, Rebattu P, Depierre A, Morère JF, Milleron B, Debieuvre D, Castéra D, Souquet PJ, Moro-Sibilot D, Lemarié E, Kessler R, Janicot H, Braun D, Spaeth D, Quantin X, Clary C (2005) Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 16:602–606
11. Georgoulias V, Alexandros A, Xanthi T, Athina A, Penelope M, Ourania A, Panagiotis Z, Michael T, Kostas S, Nikolaos S, Aris P, Anna C, Stylianos K, Charalambos K, Nikolaos A, George S, Dora C (2005) Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 23:2937–2945
12. Chevalier TL (2003) Results of the randomized international adjuvant lung cancer trial (IALT): cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol (abstr 6)
13. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis D (2002) Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomized multicentre trial. Lancet 357:1478–1484
14. Matsui K, Hirashima T, Nitta T, Kobayashi M, Ogata T, Furukawa M, Kudoh S, Yoshimura N, Mukohara T, Yamauchi S, Shiraishi S, Kamoi H, Negoro S, Takeda K, Nakagawa K, Takada M, Yana T, Fukuoka M (2005) A phase I/II study comparing regimen schedules of gemcitabine and docetaxel in Japanese patients with stage IIIB/IV non-small-cell lung cancer. Jpn J Clin Oncol 35:181–187
15. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR (2004) American Society of Clinical Oncology. American society of clinical oncology treatment of unresec-

table non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22:330–53
16. Popa IE, Stewart K, Smith F, Rizvi NA (2002) A phase II trial of gemcitabine and docetaxel in patients with chemotherapy-naive, advanced nonsmall cell lung cancer. Cancer 95:1714–1719
17. Neubauer MA, Garfield DH, Kuerfler PR, Raju RN, Lindquist DL, Soo EW, Khan M, Boehm KA, Asmar L (2005) Members of the US Oncology Study Group: results of a phase II multicenter trial of weekly docetaxel and gemcitabine as first-line therapy for patients with advanced non-small cell lung cancer. Lung Cancer 47:121–127
18. Castro JD, Lorenzo A, Morales S, Belón J, Dorta J, Lizón J, Madroñal C, Gallurt PM, Casado E, Feliu J, González M (2005) Oncopaz Cooperative Group. Phase II study of a fixed dose-rate infusion of gemcitabine associated with docetaxel in advanced non-small-cell lung carcinoma. Cancer Chemother Pharmacol 55:197–202
19. Yasuda H, Yamaya M, Nakayama K, Sasaki T, Ebihara S, Kanda A, Asada M, Inoue D, Suzuki T, Okazaki T, Takahashi H, Yoshida M, Kaneta T, Ishizawa K, Yamanda S, Tomita N, Yamasaki M, Kikuchi A, Kubo H, Sasaki H (2006) Randomized phase II trial comparing nitroglycerin plus vinorelbine and cisplatin with vinorelbine and cisplatin alone in previously untreated stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 24:688–694
20. Kelly K, Crowley J, Bunn PA, Present CA, Grevstad PK, Mainpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group Trial. J Clin Oncol 19:3210–3218
21. Takeda K, Negora S, Tamura T, Nishiwaki Y, Kudoh S, Fukuda N, Saijo N (2004) Docetaxel versus docetaxel plus gemcitabine for second-line treatment of non-small cell lung cancer: results of a JCOG randomized trial. Proc Am Soc Clin Oncol (abstr 7034)
22. Kouroussis C, Mavroudis D, Kakolyris S, Voloudaki A, Kalbakis K, Souglakos J, Agelaki S, Malas K, Bozionelou V, Georgoulias V (2004) High incidence of pulmonary toxicity of weekly docetaxel and gemcitabine in patients with non-small cell lung cancer: results of a dose-finding study. Lung Cancer 44:363–368
23. Nelson R, Tarassoff P (1995) Dyspnea with gemcitabine is commonly seen. Eur J Cancer 31S:197–198
24. Pavlakis N, Bell DR, Millward MJ, Levi JA (1997) Fatal pulmonary toxicity resulting from treatment with gemicitabine. Cancer 80:286–291
25. Read WL, Mortimer JE, Picue J (2002) Severe interstitial pneumonitis associated with docetaxel administration. Cancer 94:847–853