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ORIGINAL ARTICLE

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The combination of cisplatin and vinorelbine with concurrent thoracic radiation therapy for locally advanced stage IIIA or IIIB non-small-cell lung cancer

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Abstract *Aims*: The aims of this study were to assess the efficacy and toxicity of concurrent chemoradiotherapy with divided schedule of cisplatin and vinorelbine in patients with locally advanced non-small-cell lung cancer (NSCLC). *Methods*: Patients with previously untreated, unresectable, and stage IIIA or IIIB NSCLC were eligible if they had a performance status of 0 or 1, were 75 years or younger, and had adequate organ function. Twenty-six patients (24 men and 2 women; median age, 66 years; age range, 42–75 years) were enrolled. Both cisplatin (40 mg/m^2) and vinorelbine (20 mg/m^2) were given on days 1 and 8 every 3 weeks. Beginning on day 2 of chemotherapy, thoracic radiotherapy was given for approximately 6 weeks (2 Gy per fraction; total dose, 60 Gy). *Results*: Five of the 26 patients achieved a complete response, and 16 achieved a partial response for an overall response rate of 80.8% (95% confidence interval, 60.6–93.4%). The median survival time was 23 months (range, 4–43 months). Overall survival rates at 1 and 2 years were 80 and 56%, respectively. Hematologic toxicities included grade 3–4 neutropenia in 84.6% of patients, grade 3–4 thrombocytopenia in 3.8%, and grade 3–4 anemia in 61.5%. Two patients (7.7%) had grade 3 radiation esophagitis that resolved completely without dilation. Grade 3–4 radiation pneumonitis occurred in two patients (7.7%) and was treated with corticosteroids. Both patients had a good partial resolution of symptoms and radiographic abnormalities. There were no treatment-related deaths. The actual delivered dose intensities for both cisplatin and vinorelbine were 79.5%. Radiotherapy was completed in 96% of patients. *Conclusion*: Concurrent chemoradiotherapy with cisplatin and vinorelbine administered on a divided schedule is effective and well tolerated in patients with locally advanced NSCLC.

Keywords Locally advanced non-small-cell lung cancer · Cisplatin · Vinorelbine · Concurrent thoracic radiotherapy

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Introduction

Approximately one in three patients with non-small-cell lung cancer (NSCLC) have locally advanced stage III disease at the time of diagnosis. Thoracic radiotherapy has been the mainstay of treatment for patients with localized NSCLC, but outcomes remain poor, with median survival times (MSTs) of 9–13 months and 5-year survival rates of 5–9% [17]. In patients with locally advanced NSCLC, chemoradiotherapy achieves both higher response rates and survival rates than does radiotherapy, with reported MSTs of 13–14 months and 5-year survival rates of 15–20% [6, 20]. Meta-analyses of randomized trials have shown that the addition of chemotherapy to radiotherapy improves survival, although the absolute survival advantage is modest [16, 18]. Moreover, Furuse et al. have reported that concurrent radiotherapy, when administered with cisplatin and vindesine, with or without mitomycin, results in significantly greater response rate and longer MST than does sequential radiotherapy but is also associated with more severe acute toxicity [9]. However, these trials were designed and performed before the availability of newer chemotherapeutic agents, such as vinorelbine, gemcita-

bine, docetaxel, and paclitaxel, with greater activity against NSCLC [7].

Vinorelbine is a semisynthetic vinca alkaloid that binds to tubulin and is a potent inhibitor of mitotic microtubule polymerization. Vinorelbine blocks the progression of cells at the G2/M stage of the cell cycle and produces apoptosis in NSCLC cell lines [10]. In preclinical studies vinorelbine has shown a high level of activity against experimental tumors than have other vinca alkaloids [2]. In a phase II trial, vinorelbine achieved a 29% overall objective response rate with an MST of 33 weeks [4]. In addition, synergy has been observed between vinorelbine and cisplatin. The combination of cisplatin and vinorelbine has proven to be one of new standard regimens for metastatic NSCLC, with objective responses ranging from 25 to 44% and MSTs of 8.0–9.5 months [11, 14, 21]. In a large randomized study, cisplatin and vinorelbine showed a clear survival advantage over cisplatin and vindesine [14]. Therefore, incorporation of vinorelbine rather than vindesine in concurrent chemoradiotherapy is an important strategy for the treatment of locally advanced NSCLC.

Preclinical studies have shown that both cisplatin and vinorelbine act as radiation enhancers. Cisplatin enhances the cytotoxic effects of radiation against tumor cells both in vitro and in vivo [5]. In addition, recent studies have shown that vinorelbine enhances the antitumor effects of radiation in vitro in a cell-cycle-dependent manner, with maximal effects when the cells are in the G2/M phase [8].

Masters et al. have recommended a regimen in which 80 mg/m^2 cisplatin is given once and 15 mg/m^2 vinorelbine is given on days 1 and 8 every 3 weeks with concurrent radiotherapy [15]. The dose-limiting toxicities of this regimen were acute myelosuppression and cumulative esophagitis. When vinorelbine was administered in combination with cisplatin and radiotherapy in this regimen, its dose was significantly lower than in trials without concurrent radiotherapy [11, 14, 21]. Therefore, to reduce toxicity we administered cisplatin on a divided schedule on days 1 and 8. Although no phase I data were available for the divided schedule of cisplatin and vinorelbine with concurrent radiotherapy, we increased the vinorelbine dose from 15 to 20 mg/m^2 based on a previous report that by dividing administration the toxicity of cisplatin could be reduced [22]. To counteract neutropenia and facilitate the administration of radiation according to schedule, we routinely used granulocyte colony-stimulating factor (G-CSF) in patients with grade 4 neutropenia following the guidelines of the Japanese Ministry of Health, Labor and Welfare.

We performed a phase II study of the combination of 40 mg/m^2 cisplatin and 20 mg/m^2 vinorelbine with concurrent radiotherapy in previously untreated patients with stage IIIA or IIIB NSCLC. The primary endpoint of this study was to determine the response rate. The secondary endpoints of this study were to investigate survival and toxicity.

Patients and methods

Eligibility criteria

Patients with histologically or cytologically proven unresectable stage IIIA or IIIB NSCLC who had not previously received chemotherapy or radiotherapy were eligible for this study. Other eligibility criteria were: (1) age 20–75 years; (2) Eastern Cooperative Oncology Group performance status of 0 or 1; (3) a tumor within an estimated irradiation field no larger than half the hemithorax; (4) a measurable lesion; (5) life expectancy of 3 months or more; and (6) adequate bone marrow function [white blood cell (WBC) count of 4,000/μl or more and 12,000/μl or less, neutrophil count of 2,000/μl or more, platelet count of 100,000/μl or more, and hemoglobin level of 9.0 g/dl or more], renal function (serum creatinine levels less than 1.5 mg/dl and creatinine clearance level 60 ml/min or more) and hepatic function (total serum bilirubin level within the upper limit of the normal range, levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges), and PaO_2 of 70 mmHg or more. Patients with malignant pleural effusion, pericardial effusion, or pleural dissemination were excluded. Patients were also excluded if they had active infections, severe heart disease, interstitial pneumonia, peripheral neuropathy, or active second malignancy. Written informed consent was obtained from all patients.

Treatment protocol

Therapy consisted of cisplatin and vinorelbine with concurrent thoracic radiation therapy. Both cisplatin and vinorelbine were administered on days 1 and 8. Vinorelbine, 20 mg/m^2, was diluted in 20 ml of normal saline and given as an intravenous infusion over 6 min. Cisplatin, 40 mg/m^2, was then diluted in 500 ml of normal saline and given immediately as an intravenous drip infusion over 60 min. Prophylactic antiemetic therapy with ondansetron and dexamethasone was routinely given before cisplatin in all patients. This chemotherapy regimen was repeated every 3 weeks for a total of two to four cycles. Chemotherapy was discontinued if the treatment outcome was progressive disease or if intolerable toxicity developed at any time.

Cisplatin and vinorelbine were not given on day 8 of treatment if the WBC count was less than 2,000/μl or if the platelet count was less than 75,000/μl. Full doses of cisplatin and vinorelbine were then given on day 15 of treatment. If the WBC count was less than 3,000/μl or if the platelet count was less than 100,000/μl on day 22, the

next chemotherapy administration was withheld until the count recovered. Cisplatin was permanently discontinued at any time when the serum creatinine level was greater than 2.0 mg/dl. If the serum creatinine level was 1.5–2.0 mg/dl, cisplatin administration was withheld for 2 weeks. If the WBC or neutrophil count decreased to grade 4 after chemotherapy, G-CSF was administered until the count returned to the normal range. The doses of both cisplatin and vinorelbine were reduced by 25% for grade 4 leukopenia or neutropenia lasting 3 days or longer, neutropenic fever during grade 4 neutropenia, or grade 4 thrombocytopenia. Chemotherapy was discontinued for grade 3 or higher nonhematologoic toxicity, except for alopecia, nausea/vomiting, fever, and esophagitis. Radiotherapy was suspended for grade 3–4 esophagitis, fever higher than 38°C, during administration of G-CSF, or thrombocytopenia less than 20,000/μl and was resumed when those toxicities had decreased to grade 2 or less. Radiotherapy was discontinued for grade 3–4 radiation pneumonitis.

Radiotherapy was administered from day 2 of the first course of chemotherapy. According to Japanese guideline, radiotherapy consisted of standard chest irradiation in single daily fractions of 2 Gy for 6 weeks, for a total dose of approximately 60 Gy. The planned initial radiation field was not to exceed 50% of one lung. The initial dose (until 40 Gy) was administered to the original volume that was determined by the size and location of the primary tumor and the draining lymphatic vessels and included a 2 cm margin around the pretreatment primary tumor and the ipsilateral hilum. The entire width of the mediastinum was included, with a 2 cm margin around the radiographically visible area of involvement. The inferior margin extended 3 cm below the carina or 2 cm below the radiographically visible tumor mass. When no tumor in the area was detected with a physical or radiographic examination, the supraclavicular fossa was not irradiated. Subsequently, an additional 20 Gy dose was administered to the boost volume, including the entire primary tumor and clinically involved regional hilar and mediastinal lymph nodes, as determined with computed tomography (CT). The original volume was treated with an anterior–posterior parallel–opposed pair of portals, and the boost volume was treated with the same pair or with a pair of oblique fields if the cumulative radiation dose to the spinal cord exceeded 40 Gy. We did not plan any recalculation and additional radiation dose, when radiation doses were delayed.

Toxicity and evaluation of response

Pretreatment evaluation included a baseline history and physical examination, complete blood cell count with differential and routine chemistry profiles, urinalysis, chest radiography, chest and abdominal CT, magnetic resonance imaging or CT of the brain, and radionucleotide bone scan. Mediastinoscopy was not included in the staging workup. Metastatic lymph nodes were defined as mediastinal lymph nodes larger than 10 mm along the short axis on CT scan. Complete blood counts with differential and routine chemistry profiles were determined at least twice a week during chemotherapy. Chest radiography was performed once per week during chemotherapy. Electrocardiograms were obtained before and after chemotherapy.

Acute toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, and late toxicity associated with thoracic radiotherapy, occurring more than 90 days after the start of radiotherapy, was graded according to Radiation Therapy Oncology Group (RTOG) late-toxicity criteria. Tumor response was classified according to World Health Organization criteria. All patients who received at least two cycles of chemotherapy were assessable for response, and all patients who received at least one cycle of chemotherapy were assessable for toxicity and survival.

Statistical considerations

The trial was designed as a phase II study, with response rate as the primary endpoint. According to the Simons minimax design, our study, with a sample size of 26, had 80% power to accept the hypothesis that the true response rate was greater than 75% and had 5% significance to reject the hypothesis that the true response rate was less than 50%.

Duration of response was measured from the documentation of response to the date of disease progression. Time to progression was defined as the period from the start of this treatment to the date of disease progression or death. Survival time was measured from the start of the present treatment until death or last follow-up. The Kaplan–Meier method was used to calculate survival curves.

Results

Patient characteristics

From August 2001 through January 2005, 26 patients were enrolled and all patients were eligible (Table 1). Toxicity, response, and survival could be assessed in all the 26 eligible patients. Among the patients were 24 men and 2 women with a median age of 66 years (range, 42–75 years). Eleven patients had stage IIIA disease, and 15 patients had stage IIIB disease.

Treatment response and survival

Five (19.2%) of the 26 patients achieved a complete response, 16 (61.5%) achieved a partial response, 2 (7.6%) had no change, and 3 (11.5%) had progressive

Table 1 Patient characteristics and response rates

Total no. of patients	26
Sex (M/F)	24/2
Mean age (range), years	66 (40–75)
Performance status (0/1)	5/21
Histologic type	
Adenocarcinoma	16
Squamous	9
Unclassified	1
Stage (IIIA/IIIB)	11/15
Response rates	
Complete response	5
Partial response	16
No change	2
Progressive disease	3

disease, for an overall response rate of 80.8% (95% confidence interval, 60.6–93.4%; Table 1). Survival analysis was performed when the median follow-up time of all assessable patients was 14.0 months. At the time of analysis, 13 patients (50%) were alive and none had been lost to follow-up. One patient died of bacterial pneumonia without disease recurrence 18 months after the completion of treatment. The median duration of response for all responders was 12 months (range, 3–42 months). The median time to progression was 11 months (range, 2–42 months). The MST from the start of this regimen was 23 months (range, 4–43 months; Fig. 1). Overall survival rates at 1 and 2 years were 80 and 56%, respectively.

Toxicity

A total of 87 courses of chemotherapy were given. The median number of courses given per patient was 4 (range, 2–4). The most frequent toxicity was myelosuppression. Table 2 lists the maximum hematological toxicities experienced during treatment. All 26 patients (100%) had grade 3–4 leukopenia, and 22 of 26 patients (84.6%) had grade 3–4 neutropenia. G-CSF was given during 66.7% of courses (58 of 87 courses; median duration of administration, 5 days; range, 2–9 days). Only one patient had grade 3 thrombocytopenia, and no patients had grade 4 thrombocytopenia. No patients had hemorrhage or required prophylactic platelet transfusion during any course of treatment. Grade 3–4 anemia occurred in 61.5% (16–26 patients) of patients during all courses of treatment. Seven patients received transfusions of erythrocytes, but none had severe complications related to anemia.

Table 2 shows the most severe nonhematologic toxicities experienced during treatment. Although 19 patients (73.1%) had grade 1 or 2 radiation esophagitis, only 2 patients (7.7%) had grade 3 radiation esophagitis that resolved completely without requiring dilation. No patients had grade 4 radiation esophagitis. Grade 3–4 radiation pneumonitis requiring treatment with corticosteroids developed in 7.7% of patients (2 of 26 patients). Two patients who received corticosteroids had a good partial resolution of symptoms and radiographic abnormalities. Nausea and vomiting of grade 3 or worse did not occur in any course despite the administration of cisplatin. Although grade 3 febrile neutropenia occurred in 26.9% of patients (7 of 26 patients), all patients recovered rapidly after receiving antibiotics. One patient had grade 3 gastric ulcers during the second cycle of chemotherapy but recovered after treatment with a proton pump inhibitor. There were no treatment-related deaths.

Dose intensity

Doses of both cisplatin and vinorelbine were reduced in four patients, because of grade 4 neutropenia lasting 3 days in two patients and neutropenic fever during grade 4 neutropenia in two patients. During the 87 courses of chemotherapy, seven (8%) doses of vinorelbine or cisplatin were skipped on day 8, usually because of neutropenia. However, three of the seven skipped

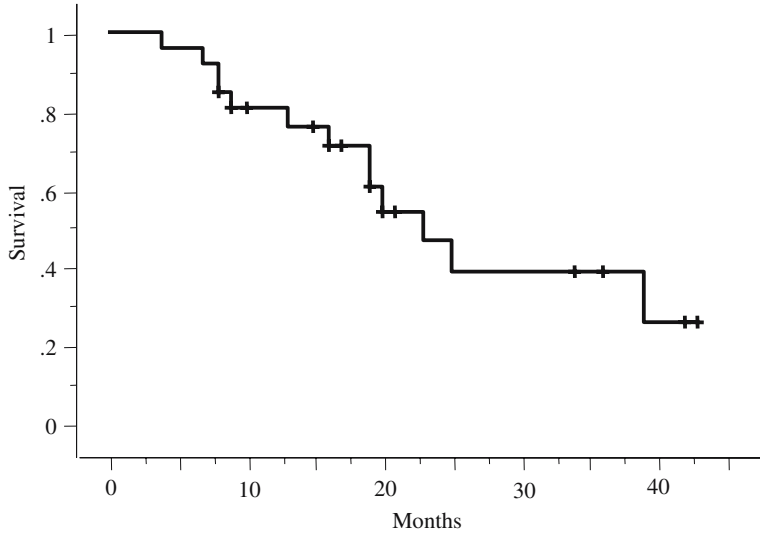

Fig. 1 Overall survival time from the start of treatment

Table 2 Toxicity

Toxicity	National Cancer Institute—Common Toxicity Criteria grade				
	1	2	3	4	3 or 4 (%)
Leukopenia	0	0	16	10	100
Neutropenia	0	4	7	15	84.6
Thrombocytopenia	11	3	1	0	3.8
Anemia	1	9	13	3	61.5
Nausea	12	3	0	0	0
Vomiting	2	1	0	0	0
Diarrhea	5	3	1	0	3.8
Infection	0	3	7	0	26.9
Esophagitis	15	4	2	0	7.7
Pneumonitis	1	2	1	1	7.7
Gastric ulcer	0	0	1	0	3.8
Elevation of serum creatinine	3	1	0	0	0
Elevation of transaminase	0	3	0	0	0
Neurologic peripheral	2	0	0	0	0

doses could be administered on day 15. Chemotherapy was delayed in 19 courses (21.8%), because of neutropenia in 16 courses, infection in 2 courses, and gastric ulcer in 1 course. The actual delivered dose intensities for both vinorelbine and cisplatin were 79.5%.

Twenty-five patients (96%) could complete radiation therapy according to dose and schedule modification of the protocol. The median total radiation dose was 60 Gy. Only one patient could not complete radiation therapy, because grade 4 radiation pneumonitis occurred after the second course of chemotherapy and 30 Gy of radiation had been given. Eighteen (69.2%) patients required a rest from radiation (median, 5 days; range, 2–16 days) because of grade 4 neutropenia in 12 patients, neutropenic fever in 4, and infection in 2 patients.

Discussion

The standard chemoradiotherapy regimen, including radiation dose and schedule, choice of chemotherapeutic agents, and sequence of chemotherapy and radiotherapy has not been determined. Thus, research is needed to develop chemoradiotherapy regimens that are less toxic and more effective. Furuse et al. have evaluated chemoradiotherapy with cisplatin and vindesine (with or without mitomycin) and have found that the MST with concurrent radiotherapy (16.5 months) was longer than with sequential radiotherapy (13.3 months, $P = 0.04$) and that the 5-year survival rate was nearly doubled (16 vs. 9%) [9]. Similar results have been obtained in a RTOG trial [3]: both the MST and 4-year survival rate were higher in the concurrent arm than in the sequential arm. In addition, a randomized study of cisplatin and vinorelbine found higher rates of response and overall survival with concurrent chemoradiotherapy than with sequential chemoradiotherapy [13]. However, in these trials, rates of acute toxicities, such as myelosuppression and esophagitis, were higher in the concurrent arm. These trials suggest that concurrent chemoradiotherapy results in better survival than does sequential chemoradiotherapy.

Several phase I or II studies have been conducted with vinorelbine, paclitaxel, docetaxel, or gemcitabine combined with a platinum agent and radiation to examine optimal doses and drug toxicity in patients with locally advanced NSCLC [1, 12, 13, 19, 23, 25, 26]. Results of some of these studies suggest that concurrent radiotherapy results in better response rates and longer survival times than do earlier combination chemotherapy regimens. In these studies, overall response rates have ranged from 64 to 84%, MSTs have ranged from 16.5 to 30.4 months, and 2-year survival rates have ranged from 38 to 61% [1, 12, 13, 19, 23, 24, 26]. Vokes et al. have reported on a randomized phase II study of two cycles of induction chemotherapy—cisplatin and gemcitabine, cisplatin and vinorelbine, and cisplatin and paclitaxel—followed by two additional cycles of the same drugs with concurrent radiotherapy in patients with locally advanced NSCLC. Three new agents, when combined with cisplatin and radiotherapy, had similar activity, with response rates of 67–74% and MSTs of 14.8–18.3 months [25]. In the present study, the overall response rate was 80.8% with an MST of 23 months, and 1- and 2-year survival rates of 80 and 56%, although survival data are preliminary because of very short follow-up time.

The principal disadvantage of concurrent chemoradiotherapy is heightened normal-tissue toxicity, especially hematologic, esophageal, and pulmonary toxicities. The most frequent toxicity in the present study was myelosuppression. In our trial, grade 3–4 hematologic toxicities included neutropenia in 84.6% of patients, thrombocytopenia in 3.8%, and anemia in 61.5%. In recent combined-modality trials with new chemotherapeutic agents, rates of grade 3–4 neutropenia, thrombocytopenia, and anemia have ranged from 12 to 77%, 0 to 56%, and 0 to 32%, respectively [1, 12, 13, 19, 23–26]. Although the rate of grade 3–4 neutropenia was slightly higher in our study than in other recent trials, no patients had severe infections due to neutropenia. The rate of grade 3–4 anemia was also higher than in other recent trials, but no patients had severe complications related to anemia.

Severe esophagitis has been reported in many trials. The rate of grade 3–4 esophagitis in recent trials has ranged from 0 to 52% [1, 12, 13, 19, 23–26]. In our study, only two patients (7.7%) had grade 3 radiation esophagitis and no patients had grade 4 esophagitis. Furthermore, the rate of pulmonary toxicity compare favorably with those in most recently published combined-modality trials with new chemotherapeutic agents in patients with locally advanced NSCLC. Grade 3–4 radiation pneumonitis occurred in 7.7% of patients in the present study. Rates of grade 3–4 radiation pneumonitis were 0 to 24% in recent trials [1, 12, 13, 19, 23–26].

Some clinical trials are now assessing combinations of vinorelbine and cisplatin with concurrent radiotherapy for patients with locally advanced NSCLC. For phase II studies Masters et al. have recommended 80 mg/m^2 cisplatin given once and 15 mg/m^2 vinorelbine given on days 1 and 8 every 3 weeks [15]. Sekine et al. have recommended 80 mg/m^2 cisplatin given once with 20 mg/m^2 vinorelbine given on days 1 and 8 every 4 weeks [23]. Zatloukal et al. have recommended 80 mg/m^2 cisplatin given once with 12.5 mg/m^2 vinorelbine given on days 1, 8, and 15 every 4 weeks [26]. The doses of vinorelbine in these trials were significantly lower than those in earlier studies in which vinorelbine was administered with cisplatin without concurrent radiotherapy [11, 14]. Therefore, we attempted to increase the dose intensities of vinorelbine and cisplatin by dividing the dose of cisplatin on days 1 and 8. The planned dose intensities in the present study, in which both 40 mg/m^2 of cisplatin and 20 mg/m^2 of vinorelbine were given on days 1 and 8 every 3 weeks, were 1.3 times higher than those in previous studies. However, the actual delivered dose intensities for both vinorelbine and cisplatin were 79.5%.

In conclusion, we found that the combination of a divided schedule of cisplatin and vinorelbine with concurrent radiotherapy is effective and feasible. Although survival data are preliminary because of very short follow-up time, the overall response rate was 80.8% with an MST of 23 months. Furthermore, grade 3–4 radiation esophagitis and pneumonitis both occurred in only 7.7% of patients. Therefore, the combination of a divided schedule of cisplatin and vinorelbine with concurrent radiotherapy could be an acceptable option for patients with locally advanced NSCLC. In the future, the search for even more active regimens including new cytotoxic and target-specific agents should be continued.

References

1. Choy H, Akerley W, Safran H, Graziano S, Chung C, Williams T, Cole B, Kennedy T (1998) Multiinstitutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. J Clin Oncol 16:3316–3322
2. Cros S, Wright M, Morimoto M, Lataste H, Couzinier JP, Krikorian A (1989) Experimental antitumor activity of navelbine. Semin Oncol 16(suppl 4):15–20
3. Curren WJ, Scott CB, Langer CL, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Sause W, Cox JD (2003) Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 22:621
4. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC (1991) A phase II study of navelbine (vinorelbine) in the treatment of non-small cell lung cancer. Am J Clin Oncol 14:115–119
5. Dewit L (1987) Combined treatment of radiation and cis-diammine-dichloroplatinum II: A review of experimental and clinical data. Int J Radiat Oncol Bio Phys 13:403–426
6. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR (1996) Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) trial. J Natl Cancer Inst 88:1210–1215
7. Edelman MJ, Gandara DR (1996) Promising new agents in the treatment of non-small cell lung cancer. Cancer Chemother Pharmacol 37:385–393
8. Edelstein MP, Wolfe LA III, Duch DS (1996) Potentiation of radiation therapy by vinorelbine (Navelbine) in non-small cell lung cancer. Semin Oncol 23:41–47
9. Furuse K, Fukuoka M, Kawahara M, Nishiwaki H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692–2699
10. Goa KL, Faulds D (1994) Vinorelbine-a review of its pharmacological properties and clinical use in cancer chemotherapy. Drugs Aging Adis Int 5:200–234
11. Kelly K, Crowley J, Burn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara D (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
12. Kiura K, Ueoka H, Segawa Y, Tabata M, Kamei H, Takigawa N, Hiraki S, Watanabe Y, Bessho A, Eguchi K, Okimoto N, Harita S, Takemoto M, Hiraki Y, Harada M, Tanimoto M (2003) Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 89:795–802
13. Lau D, Leigh B, Gandara D, Edelman M, Morgan R, Israel V, Lara P, Wilder R, Ryu J, Doroshow J (2001) Twice-weekly paclitaxel and weekly carboplatin with concurrent thoracic radiation followed by carboplatin/paclitaxel consolidation for stage III non-small-cell lung cancer: a California cancer consortium phase II trial. J Clin Oncol 19:442–447
14. Le Chevalier T, Brisgand D, Douilland JY, Pujol 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, Besson F, Martinez A, Berthaud P, Tursz T (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbin alone in advanced non-small cell lung cancer: results of a European multicentre trial including 612 patients. J Clin Oncol 12:360–367
15. Masters GA, Haraf DJ, Hoffman PC, Drinkard LC, Krauss SA, Ferguson MK, Oiak J, Samuels BL, Golomb HM, Vokes EE (1998) Phase I study of vinorelbine, cisplatin, and concomitant thoracic radiation in the treatment of advanced chest malignancies. J Clin Oncol 16:2157–2163
16. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trails. BMJ 311:899–909

17. Perez CA, Stanley K, Grundy G, Hanson W, Rubin P, Kramer S, Brady LW, Marks JE, Perez-Tamayo R, Brown GS, Concannon JP, Rotman M (1982) Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung. Cancer 50:1091–1099
18. Pritchard RS, Anthony SP (1996) Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. Ann Intern Med 125:723–729
19. Robert F, Spencer SA, Childs HA III, Zhang R, Meredith RF, Wheeler RH, Hawkins MH, Carey D (2002) Concurrent chemoradiation therapy with cisplatin and paclitaxel for locally advanced non-small cell lung cancer: long-term follow-up of a phase I trial. Lung Cancer 37:189–199
20. Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT, Dar AR, Cox JD (1995) Radiation therapy oncology group (RTOG) 88–08 and Eastern cooperative oncology group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced unresectable non-small-cell lung cancer. J Natl Cancer Inst 87:198–205
21. Scagliotti GV, Marinis FD, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Costanzo FD, Frontini L, Tonato M (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 20:4285–4291
22. Segawa Y, Ueoka H, Kiura K Kamei H, Tabata M, Sakae K, Hiraki Y, Kawahara S, Eguchi K, Hiraki S, Harada M (2000) A phase II study of cisplatin and 5-fluorouracil with concurrent hyperfactionated thoracic radiation for locally advanced non-small-cell lung cancer: a preliminary report from the Okayama lung cancer study group. Br J Cancer 82:104–111
23. Sekine I, Noda L, Oshita F, Yamada K, Tanaka M, Yamashita K, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, Sumi M, Saijo N (2004) Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. Cancer Sci 95: 691–695
24. Solomon B, Ball DL, Richardson G, Smith JG, Millward M, Macmanus M, Michael M, Wirth A, Okane C, Muceniekas L, Ryan G, Rischin D (2003) Phase I/II study of concurrent twice-weekly paclitaxel and weekly cisplatin with radiation therapy for stage III non-small cell lung cancer. Lung Cancer 41:353–361
25. Vokes EE, Herndon JE II, Crawford J, Leopold KA, Perry MC, Miller AA, Green MR (2002) Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. J Clin Oncol 20:4191–4198
26. Zatloukal PV, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, Kubik A, Krepela E, Fiala P, Pecen L (2004) Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 46:87–98