Cancer Chemother Pharmacol (2010) 66:107–112
DOI 10.1007/s00280-009-1139-x

ORIGINAL ARTICLE

Feasibility study for biweekly administration of cisplatin plus gemcitabine as adjuvant-chemotherapy for completely resected non-small cell lung cancer

Masafumi Yamaguchi · Sadanori Takeo · Ryuichi Suemitsu · Hironori Matsuzawa

Received: 13 July 2009 / Accepted: 8 September 2009 / Published online: 7 October 2009

Abstract
Purpose To evaluate the feasibility of biweekly administration of cisplatin and gemcitabine as adjuvant chemotherapy for patients with completely resected non-small cell lung cancer (NSCLC).
Patients and methods This was a single-arm, single-institutional study. Patients with completely resected NSCLC (p-Stages IB–IIIA) with no previous chemotherapy or radiotherapy were eligible. Simon's optimal two-stage design was applied. Both cisplatin (50 mg/m^2) and gemcitabine (1,000 mg/m^2) were given on days 1 and 15, every 28 days. The primary endpoint of this study was the feasibility of this combination in the four cycles of treatment.
Results Twenty patients (19 lobectomies and 1 pneumonectomy) were enrolled in this study. Nine (45%) of patients had grade 3/4 neutropenia, and 6 (30%) had grade 3/4 anemia. Severe non-hematologic toxicities were uncommon in this series. No treatment-related death was encountered. Thirteen (65%) patients completed the planned 4 cycles of chemotherapy. The median intensity was 24 (range 21–25) mg/(m^2 week) with an average of 24.0 (21–25) mg/(m^2 week) cisplatin and 483 (range 412–500) mg/(m^2 week) with an average of 481.0 (412–500) mg/(m^2 week) gemcitabine. The median relative dose intensity of cisplatin was 100 (range 25–100) % with an average of 87.4 (25–100) % and that of gemcitabine was 100 (range 25–100) % with an average of 86.8 (25–100) %.
Conclusion This regimen is feasible in the treatment of patients with completely resected NSCLC. A multicenter phase III trial is warranted to assess the efficacy of this regimen at promoting survival and preventing recurrence.

Keywords NSCLC · Adjuvant chemotherapy · Cisplatin · Gemcitabine · Biweekly

M. Yamaguchi · S. Takeo (✉) · R. Suemitsu · H. Matsuzawa
Division of General Thoracic Surgery,
Respiratory Center and Clinical Institute,
National Hospital Organization Kyushu Medical Center,
Jigyouhama 1-8-1, Chuou-ku, Fukuoka 810-8563, Japan
e-mail: sada@kyumed.jp

M. Yamaguchi
e-mail: masafumiyamaguchi@yahoo.co.jp

R. Suemitsu
e-mail: suemitsu@qmed.hosp.go.jp

H. Matsuzawa
e-mail: hmatsu@juntendo-urayasu.jp

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers [1, 2]. Despite progress in imaging and diagnostic procedures, patients with NSCLC are still found in advanced conditions, such as locally invaded, disseminated, or metastasized, and only around 30% show an early resectable stage at the time of diagnosis [2]. Surgical resection is the only possible choice for a cure in NSCLC patients with c-Stage I, II, and a subset of IIIA disease; however, recent data from 13,010 Japanese lung cancer patients, including surgically resected 12,610 NSCLC showed 5-year survival rates of 83.9% for p-Stage IA, 66.3% for p-Stage IB, 61.0% for p-Stage IIA, 47.4% for p-Stage IIB, and 32.8% for p-Stage IIIA [3] and recurrence has been reported in 36–71% of patients [4–7], which indicates the need for improvements in post-operative survival.

A recently updated meta-analysis of more than 2,000 patients showed that radiotherapy does not add any benefit over surgery alone, and should not be considered as standard

treatment [8, 9]. The absence of a local control strategy and the extra-thoracic relapse may suggest a possible role for adjuvant chemotherapy in NSCLC [2]. To improve the post-operative survival of NSCLC patients, several randomized phase III trials have been conducted to determine the benefit of adjuvant chemotherapy over surgery alone [10–13], and these positive results have changed the therapeutic strategy for resectable NSCLC. The Lung Adjuvant Cisplatin Evaluation (LACE) study, which was based on a pooled meta-analysis [14], indicated that adjuvant cisplatin-based chemotherapy could improve survival in patients with completely resected NSCLC, especially in p-Stages II and III.

The combination of cisplatin plus gemcitabine is a standard drug regimen for the treatment of NSCLC [15, 16]. In addition, two prospective randomized Phase III studies that compared four platinum-based combined regimens, including cisplatin plus gemcitabine for unresectable NSCLC showed the survival benefit of the regimen [17, 18].

Cisplatin plus gemcitabine has also been reported to be safe in patients more than 70 years of age [19]. However, especially for post-operative patients, the tolerability and adverse effects of chemotherapy, including myelotoxicity, should be considered. The biweekly administration of chemotherapy is becoming more accepted, since it makes it possible to maintain a similar dose intensity with a better toxic profile, especially with regard to hematologic toxicity, compared to a conventional administration schedule, such as on days 1, 8, and/or 15 every 3 or 4 weeks [20].

Hence, the safety and tolerability of this regimen for adjuvant chemotherapy need to be demonstrated in a prospective trial.

Patients and methods

This was a single-arm, single-institutional study. The primary endpoint of this study was the feasibility of biweekly administration of cisplatin plus gemcitabine as adjuvant chemotherapy in Japanese patients with curatively resected NSCLC, defined as the ratio of achieving treatment without unacceptable toxicity in the first four cycles of treatment. The secondary endpoint was the safety, which was assessed in terms of the frequency and degree of adverse events with this treatment.

Patient eligibility

Patients who were completely resected with pathologically documented Stage IB–IIIA NSCLC were enrolled in this study. The eligibility criteria were no previous chemotherapy, radiotherapy, or immunotherapy, ECOG performance status 0–1, age between 20 and 75 years, adequate bone marrow functions (leukocyte cell count $\geq$4,000 per mm^3, neutrophil count $\geq$2,000 per mm^3, platelet count $\geq$10,000 per mm^3, and hemoglobin $\geq$9.5 g/dl), and preserved liver function [total bilirubin $\leq$1.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$2.5 times of normal value], renal function (serum creatinine $\leq$1.5 mg/dl), and pulmonary function ($PaO_2 \geq 60$ Torr or $SpO_2 \geq 90\%$ in atmosphere pressure). Patients with concomitant malignancy, active infection or other serious medical problems were excluded. All patients were required to enroll in this study within 4–12 weeks after surgery. The local ethics committee approved this study, and written informed consent was obtained from all patients.

Study design

In this study, gemcitabine was given at 1,000 mg/m^2 by infusion over 30 min, and followed by cisplatin, which was given at doses of 50 mg/m^2 by continuous infusion over 2 h on days 1 and 15 (level 1) every 4 weeks. Patients were evaluated as follows. Toxicity was assessed before and at the middle of each cycle of chemotherapy, according to version 2.0 of the National Cancer Institute Common Toxicity Criteria. The minimum requirements to receive chemotherapy during the four cycles were as follows: absolute neutrophil count $\geq$2,000/l, platelets $\geq$100,000/l, hemoglobin $\geq$8 g/dl and no grade $\geq$2 non-hematologic toxicity (excluding nausea, vomiting, anorexia, fatigue, and alopecia). If these conditions were not met on days 1 and 15, chemotherapy was postponed or omitted, respectively, and dose reductions were planned: cisplatin 45 mg/m^2 and gemcitabine 1,000 mg/m^2 for the first stage, and cisplatin 45 mg/m^2 and gemcitabine 800 mg/m^2 for the second stage. If toxicity persisted after a 2-week delay, treatment was stopped.

Antiemetic therapy consisted of 5-HT antagonist from days 1 to 3 and betamethasone 3 mg orally from days 1 to 5. G-CSF was administered if the patients showed first grade 4 and subsequent grade 3 neutropenia.

If five of the initial seven patients who entered the protocol could not complete the planned treatment, the dose-levels were to be modified as follows: cisplatin 50 mg/m^2 and gemcitabine 800 on days 1 and 15, 4qW (level 2). If another seven patients in level 2 could not complete treatment, this protocol would be considered inadequate and terminated.

For toxicity analysis, the worst data for each patient across all cycles of chemotherapy were used. Unacceptable toxicities included febrile neutropenia, grade $\geq$3 neutropenia, thrombocytopenia and anemia, grade 4 emesis, grade $\geq$3 non-hematologic toxicity (other than hair loss), and any toxicity that worsened the general condition and made restaging impossible after four cycles.

Statistical considerations

The primary outcome of this study was the feasibility of the combination, defined as the completion rate of four cycles of treatment without unacceptable toxicity. According to the minimax two-stage phase II study design by Simon [21], the null hypothesis for completion rates was 55%, with an alternative hypothesis of 85% at a significance level of 0.05 and a statistical power of 80%. This required 15 evaluable patients. The upper limit for first-stage drug rejection was 4 patients who completed the treatment among 7 evaluable patients; the upper limit of second-stage rejection was 11 patients who completed the treatment among 15 evaluable patients. The relative dose intensity (RDI) was defined as the percentage of the expected dose administered to the patient [per unit of time expressed in mg/(m^2 week)].

Results

Patient characteristics

From September 2006 to December 2007, 20 patients were enrolled in this trial. The baseline characteristics of the patients are summarized in Table 1. The median age of the patients was 63.5 (range 41–75) years; 14 males and 6 females, and 18 were ECOG PS 0 and 2 were PS 1 upon entry. Nineteen (95%) patients underwent lobectomy and 1 (5%) underwent pneumonectomy. Seven patients (35%) were p-Stage IB, 5 (25%) were p-Stage IIA, 3 (15%) were p-Stage IIB and 5 (25%) were p-Stage IIIA. Patients were enrolled in this trial between 28 and 71 (median 46) days after surgery.

Table 1 Baseline patient characteristics

Characteristics	Number	%
Age, years		
Median	63.5	–
Range	41–75	–
Gender		
Male	14	70
Female	6	30
ECOG performance status at baseline		
0	18	90
1	2	10
Type of surgery		
Lobectomy	19	95
Pneumonectomy	1	5
Pathological stage		
IB	7	35
IIA	5	25
IIB	3	15
IIIA	5	25
Histologic type		
Adenocarcinoma	15	75
Squamous cell carcinoma	4	20
Large cell carcinoma	1	5

Toxicity

Both hematologic and non-hematologic toxicities are shown in Table 2. Neutropenia and anemia were the most common severe toxic effects of chemotherapy; 9 (45%) patients had grade 3 or 4 neutropenia, and 6 (30%) had grade 3 or 4 anemia. Febrile neutropenia was not encountered and none of the patients required blood transfusion. No grade 3 or 4 thrombocytopenia was observed. Colony-stimulating factors were administered to 1 (5%) patient. Severe non-hematologic toxicity from chemotherapy was uncommon in this series. Three patients with elevated grade 3 AST and two patients with grade 3 total bilirubinemia and

Table 2 Worst toxicity according to NCI-CTC grade

Grade	0–1	2	3	4
Hematologic				
Leukopenia	11	7	2	0
Neutropenia	8	3	8	1
Anemia	2	12	3	3
Thrombocytopenia	18	2	0	0
Non-hematologic				
Alb	18	2	0	0
AST	17	0	3	0
ALT	16	4	0	0
T-bil	18	1	1	0
Serum creatinine	18	2	0	0
Hyponatremia	19	0	1	0
Hyperkalemia	20	0	0	0
Hypercalcemia	20	0	0	0
GGT	19	1	0	0
Nausea	18	2	0	0
Vomiting	20	0	0	0
Anorexia	19	1	0	0
Fatigue	20	0	0	0
Diarrhea	20	0	0	0
Constipation	19	1	0	0
Neuropathy: sensory	19	1	0	0
Phlebitis	20	0	0	0
Infection	19	1	0	0

Data represent the number of patients

T-bil total bilirubin, *AST* aspartate amino transferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyltranspeptidase

hyponatremia (one each) were encountered; however, no additional treatment was required for these adverse effects. Other toxicities were treated without events and did not disturb the planned treatment. No treatment-related fatal toxic effect was encountered.

Compliance

A median number of 4 cycles were delivered (range 1–4), and 13 (65%) patients completed the planned four cycles of chemotherapy (Table 3). Five patients (25%) discontinued chemotherapy. One patient had one-stage dose reduction related to grade 2 serum creatinine elevation in the second cycle. The reasons for discontinuation were prolonged grade 4 anemia in 3, physician's decision in 1, patient's refusal in 2 and disease recurrence in 1.

Seventeen (85%) patients received at least 300 mg/m^2 of cisplatin and 6,000 mg/m^2 of gemcitabine. The actuarial dose of cisplatin was a median of 400 (range 100–400) mg/m^2 with an average of 349.5 (range 100–400) mg/m^2, and that of gemcitabine was 8,000 (range 2,000–8,000) mg/m^2 with an average of 7,000 (range 2,000–8,000) mg/m^2; the dose intensity for cisplatin was 24 (range 21–25) mg/(m^2 week) (both median and average) and that for gemcitabine was 483 (range 412–500) mg/(m^2 week) (median) with an average of 481.0 (range 412–500) mg/(m^2 week). The median RDI of cisplatin was 100 (range 25–100) % with an average of 87.4 (25–100) %, and that of gemcitabine was 100 (range 25–100) % with an average of 86.8 (25–100) %.

Table 3 Chemotherapy compliance

Patients who completed cycles (% of treated patients)		
Cycle 1		20 (100)
Cycle 2		19 (95)
Cycle 3		17 (85)
Cycle 4		13 (65)
	CDDP	Gemcitabine
Planned cumulative dose (mg/m^2)	400	8,000
Actuarial cumulative dose (mg/m^2)		
Median	400 (100–400)	8,000 (2,000–8,000)
Average	349.5 (100–400)	7,000 (2,000–8,000)
Dose intensity [mg/(m^2 week)]		
Median	24.0 (21–25)	483.0 (412–500)
Average	24.0 (21–25)	481.0 (412–500)
Relative dose intensity (%)		
Median	100 (25–100)	100 (25–100)
Average	87.4 (25–100)	86.8 (25–100)

Data represent the number of patients (%). Ranges are shown in parentheses

Discussion

To the best of our knowledge, this is the first report of a study designed to determine the feasibility of biweekly administration of cisplatin plus gemcitabine for adjuvant chemotherapy in completely resected patients with p-Stages IB, II, and IIIA NSCLC.

Based on the information of The Non-small Cell Lung Cancer Collaborative Group that reported a 5% survival advantage at 5 years for patients with surgical resection of NSCLC followed by treatment with cisplatin-based chemotherapy, compared to patients who were only followed-up after resection [22], several large phase III trials have been conducted, and four of them showed that cisplatin-based adjuvant chemotherapy improves survival among patients who have undergone complete resection of NSCLC, and thus adjuvant chemotherapy after complete resection of p-Stages IB–IIIA NSCLC is now the standard of care [10–14]. The Adjuvant Lung Cancer Trial Collaborative Group (IALT) reported that 74% of the patients in their trial received at least 240 mg/m^2 of cisplatin combined with etoposide (56.5%) or vinorelbine (26.8%), among 1,867 patients who were randomized after complete resection of p-Stage I-IIIA of NSCLC. There was a statistically significant advantage in overall survival of 4.1% at 5 years in favor of adjuvant chemotherapy [10]. The National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators (JBR 10) reported a 15% improvement in 5-year survival in the adjuvant chemotherapy arm in a total of 482 patients who were randomized to compare four cycles of vinorelbine and cisplatin to an observation after complete resection of NSCLC [11]. The Adjuvant Navelbine International Trialist Association (ANITA) showed a 9% survival advantage at 5 years in an adjuvant chemotherapy group in a total of 840 patients who were randomized either to receive only observation or four cycles of chemotherapy with vinorelbine and cisplatin [12]. In a Japanese phase III adjuvant trial with the oral administration of uracil–tegafur for 979 patients with completely resected p-Stage I adenocarcinoma of the lung [13], a significant survival benefit was observed with adjuvant chemotherapy ($P = 0.04$) in the subgroup with p-Stage IB. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group [14] reported a meta-analysis based on pooled individual patient data from the five largest randomized trials of adjuvant chemotherapy for NSCLC [10–12, 23, 24]. This meta-analysis revealed that the hazard ratio of death was 0.89 (95% CI 0.82–0.96, $P < 0.005$), which corresponds to

an absolute benefit in 5-year survival of 4.2% with chemotherapy, indicated that adjuvant cisplatin-based chemotherapy may improve survival in patients with completely resected p-Stages II and III NSCLC. In addition, two recent meta-analyses based on trials published since 1995 showed that cisplatin-based chemotherapy could reduce the relative risk of 5-year mortality by 11% [25, 26].

The combination of cisplatin plus gemcitabine has been reported to be an effective regimen for c-Stage IIIB-IV NSCLC in some phase III studies. Eastern Cooperative Oncology Group reported the better 1- and 2-year survival rates and time-to-progression in the cisplatin plus gemcitabine arm in comparison of four combined regimen, including cisplatin plus paclitaxel as a reference regimen, cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel [17]. The Four-Arm Cooperative Study in Japan also reported similar results with a comparison of cisplatin plus irinotecan as a reference arm to cisplatin plus gemcitabine, carboplatin plus paclitaxel, and cisplatin plus vinorelbine. In this trial, cisplatin plus gemcitabine showed a 2-year survival rate of 31.5% compared to 26.5% with cisplatin plus irinotecan, and this difference was not statistically significant [18].

Although the optimal dose of cisplatin has been controversial, LACE [14] reported a favorable prognosis in a subset analysis in their study with patients who received more than 300 mg of cisplatin. IALT [10] settled on a range between 80 and 120 mg/m^2 per cycle, for a total dose of 300–400 mg/m^2 of cisplatin, and 73.8% of patients received at least 240 mg/m^2 of cisplatin in combination with vinblastine, vinorelbine, or etoposide. In JBR 10, the planned total dose was 100 mg/m^2 per cycle for cisplatin and 100 mg/m^2 per cycle for vinorelbine, for 4 cycles, with a median dose of 336 mg for cisplatin, and 58% of patients in this series received more than 3 cycles of treatment [11, 27]. In a series of patients in ANITA [12], the planned doses of cisplatin and vinorelbine were 100 mg/m^2 per cycle and 120 mg/m^2 per cycle for a total of 4 cycles, respectively, and the dose intensity was 22 (range 4–27) mg/m^2 per week for cisplatin and 18 (range 5–30) mg/m^2 per week for vinorelbine, with RDI of 89 (range 17–108) % for cisplatin and 59 (range 17–100) % for vinorelbine, and the median dose of cisplatin was 304 (range 50–418) mg; 49% of patients in this series received four complete cycles of cisplatin.

In our series of patients, the planned dose was 100 mg/m^2 for cisplatin and 2,000 mg/m^2 for gemcitabine in 1 cycle for 4 cycles; 17 (85%) patients received at least 300 mg/m^2 of cisplatin and 6,000 mg/m^2 of gemcitabine. Both the median and average dose intensity was 24 (range 21–25) mg/(m^2 week) for cisplatin, and the median dose intensity for gemcitabine was 483 (range 412–500) mg/(m^2 week), with an average of 481.0 (range 412–500) mg/(m^2 week). The median dose intensity of cisplatin was 100 (range 25–100) % with an average of 87.4 (25–100) % and that of gemcitabine was 100 (range 25–100) % with an average of 86.8 (25–100) %, and 65% of the patients in this series received four cycles of treatment. Our treatment schedule could provide equal or higher doses of cisplatin compared to trials that showed a survival advantage with adjuvant chemotherapy for completely resected NSCLC.

The combination of cisplatin plus gemcitabine has also been reported to be safe even for elderly patients. The MILES-2P studies showed the feasibility of cisplatin plus gemcitabine in a series of patients older than 70 years with unresectable c-Stage IIIB–IV NSCLC with a dose of 60 mg/m^2 of cisplatin on day 1 and 1,000 mg/m^2 of gemcitabine on days 1 and 8, every 21 days for 3 cycles [28]. This trial concluded that cisplatin plus gemcitabine provided a higher dose of cisplatin than cisplatin plus vinorelbine.

Biweekly administration of cisplatin plus gemcitabine has been reported in various cancers. Bozas et al. reported paclitaxel-pretreated ovarian and peritoneal cancer patients with six cycles (median 4 cycles) of cisplatin 40 mg/m^2 plus gemcitabine 1,000 mg/m^2 on days 1 and 15, repeated every 4 weeks. In this series of patients, the grade 3–4 toxicity was mainly hematologic; neutropenia in 20%, thrombocytopenia in 6%, anemia 8% [29]. Tas et al. reported the biweekly administration of four cycles (median 4 cycles) of cisplatin 50 mg/m^2 plus gemcitabine 2,000 mg/m^2 on days 1 and 15, repeated every 4 weeks, to breast cancer patients who had been pretreated with anthracycline and taxane. In their series of patients, there was no principal dose-limiting grade 3–4 toxicity [30]. No treatment-related death was encountered in the two trials described above. This regimen has also been reported to be safe and effective in c-Stage IIIB-IV NSCLC patients [31]. Six cycles (median 4 cycles) of 50 mg/m^2 cisplatin plus 2,500 mg/m^2 gemcitabine were given on days 1 and 15 every 28 days. In that trial, 4.1% of patients required 25% reduction in the dose of both drugs. Grade 3–4 toxicities were neutropenia in 6.1%, thrombocytopenia in 2%, anemia 4.1%, both nausea and vomiting in 10.2%, esophagitis in 2% and peripheral arterial ischemia in 4%. There was one treatment-related death due to grade 4 thrombocytopenia and esophagitis.

In our study, the most common grade 3–4 toxicities were in 9 (45%) cases and anemia in 6 (30%). Grade 3–4 anemia was more frequent than in the trials mentioned above that included the biweekly administration of cisplatin plus gemcitabine. There were three cases (15%) of grade 3 AST elevation, and one case each (5%) of grade 3 total bilirubinemia and hyponatremia, but this did not affect the treatment schedule. There was no treatment-related death. The proportion of treatment-related deaths is generally considered to be below 1.0%. Even if this proportion is low, the importance of treatment-related toxicity should be considered

in the indications for adjuvant chemotherapy and in the discussion of adjuvant chemotherapy for patients with completely resected NSCLC.

In conclusion, our biweekly administration of cisplatin plus gemcitabine as adjuvant chemotherapy for completely resected p-Stage IB–IIIA NSCLC is feasible. Anemia should be carefully monitored. A multicenter phase III trial to assess the beneficial effects of this regimen on survival and the prevention of disease recurrence should be warranted.

Acknowledgments We thank the study participants; Sawako Tanaka for data management.

References

1. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics. CA Cancer J Clin 58:71–96
2. Spira A, Ettinger DS (2004) Multidisciplinary management of lung cancer. N Engl J Med 350:379–392
3. Asamura H, Goya T, Kobishi Y et al (2008) Japanese Joint Committee of Lung Cancer Registry: A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol 3:46–52
4. Williams BA, Sugimura H, Endo C et al (2006) Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. Ann Thorac Surg 81:1021–1027
5. Westeel V, Choma D, Clément F et al (2000) Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. Ann Thorac Surg 70:1185–1190
6. Baldini EH, DeCamp MM Jr, Katz MS et al (1999) Patterns of recurrence and outcome for patients with clinical stage II non-small-cell lung cancer. Am J Clin Oncol 22:8–14
7. Choi YS, Shim YM, Kim K et al (2004) Pattern of recurrence after curative resection of local (stage I and II) non-small cell lung cancer: difference according to the histologic type. J Korean Med Sci 19:674–676
8. PORT Meta-analysis Trialists Group (1998) Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet 352:257–263
9. Burdett S, Stewart L (2005) PORT Meta-analysis Group: postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. Lung Cancer 47:81–83
10. Arriagada R, Bergman B, Dunant A et al (2004) 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
11. Winton TL, Livingstan R, Johnson D et al (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 352:2589–2597
12. Douillard J, Rosell R, Delena M et al (2006) 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 7:719–727
13. Kato H, Ichinose Y, Ohta M et al (2004) A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med 350:1713–1721
14. Pignon JP, Tribodet H, Scagliotti GV et al (2008) Lung Adjuvant Cisplatin Evaluation: a pooled analysis by the LACE Collaborative Group. Clin Oncol 26:3552–3559
15. Rosell R, Tonanto M, Sandler A (1998) The activity of gemcitabine plus cisplatin in randomized trials in untreated patients with advanced non-small cell lung cancer. Semin Oncol 25:S27–S34
16. Edelman MJ (2002) Past, present and future of gemcitabin and cisplatin regimen in advanced non-small cell lung cancer. Lung Cancer 38:S37–S43
17. Schiller JH, Harrington D, Belani CP et al (2002) Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
18. Ohe Y, Ohashi Y, Kubota K et al (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 18:317–323
19. Gridelli C, Maione P, Illiano A et al (2007) Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non small-cell lung cancer: the MILES-2P studies. J Clin Oncol 25:4663–4669
20. López-Vivanco G, Viteri A, Barceló R et al (2005) Biweekly administration of cisplatin/gemcitabine in advanced nonsmall cell lung cancer. Am J Clin Oncol 28:501–507
21. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
22. 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 randomised clinical trials. BMJ 311:899–909
23. Scagliotti GV, Fossati R, Torri V et al (2003) Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. J Natl Cancer Inst 95:1453–1461
24. Waller D, Peake MD, Stephens RJ et al (2004) Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the big lung trial. Eur J Cardiothorac Surg 26:173–182
25. Hotta K, Matsuo K, Ueoka H et al (2004) Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. J Clin Oncol 22:3860–3867
26. Sedrakyan A, van Der Meulen J, O'Byrne K et al (2004) Postoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 128:414–419
27. Alam N, Shepherd FA, Winton T et al (2005) Compliance with post-operative adjuvant chemotherapy in non-small lung cancer: an analysis of National Cancer Institute of Canada and Intergroup trial JBR. 10 and a review of the literature. Lung Cancer 47:385–394
28. Gridelli C, Maione P, Illiano A et al (2007) Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non-small-cell lung cancer: The MILES-2P studies. J Clin Oncol 25:4663–4669
29. Bozas G, Bamias A, Koutsoukou V et al (2007) Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma. Gynecol Oncol 104:580–585
30. Tas F, Guney N, Derin D et al (2008) Biweekly administration of gemcitabine and cisplatin chemotherapy in patients with anthracycline and taxane-pretreated metastatic breast cancer. Invest New Drugs 26:363–368
31. López-Vivanco G, Viteri A, Barceló R et al (2005) Biweekly administration of cisplatin/gemcitabine in advanced nonsmall cell lung cancer. Am J Clin Oncol 28:501–507