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ORIGINAL ARTICLE

# Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial

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**Abstract**
*Background* The aim of this phase II study was to evaluate the feasibility and safety of a carboplatin and gemcitabine combination regimen in the treatment of completely resected non-small cell lung cancer (NSCLC).
*Methods* Patients with completely resected pathologically documented stage IB, II or IIIA NSCLC were treated with carboplatin and gemcitabine. Chemotherapy consisted of 4 cycles of carboplatin at an area under the curve of 5 (level 1) or 4 (level 2) on day 1 combined with gemcitabine 1,000 mg/m$^2$ on days 1 and 8 every 3 weeks. The primary endpoint of this study was the completion rate of 4 cycles.
*Results* Twenty patients were treated, and the patient's demographics were: median age 61 years (range 51–74), gender male ($n = 13$, 65%)/female ($n = 7$, 35%), stage IB ($n = 8$, 40%), IIA ($n = 1$, 5%), IIB ($n = 6$, 30%), IIIA ($n = 5$, 25%). Seventeen patients (85%, 95% confidence interval 64.0–94.8) received the planned 4 cycles of the chemotherapy regimen at level 1 every 3 weeks. Among the 3 patients who failed to complete 4 cycles, the reasons for stopping were refusal ($n = 1$), thrombocytopenia ($n = 1$) and rash ($n = 1$). The main adverse effects were hematological toxicity as well as grade 3/4 neutropenia and thrombocytopenia (which occurred in 65% and 40% of the patients, respectively).
*Conclusions* Adjuvant chemotherapy with a carboplatin and gemcitabine combination regimen has an acceptable toxicity profile, and the majority of patients completed 4 cycles of therapy.

**Keywords** Non-small cell lung cancer · Adjuvant chemotherapy · Carboplatin · Gemcitabine · Phase II study

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## Introduction

Lung cancer is the leading cause of cancer death in Japan as well as in other countries of the Western world. Approximately 80% of all cases of lung cancer are non-small cell lung cancer (NSCLC). Although a complete surgical resection is the optimal treatment for patients with early-stage NSCLC, the 5-year survival rates are no better than 40–60%, even for patients with clinical stage IB/II disease, which therefore cannot be considered a satisfactory result [1].

Recently, adjuvant chemotherapy with cisplatin and vinorelbine has been shown to prolong survival among

patients with completely resected stage II and IIIA NSCLC, as demonstrated in the JBR.10 and ANITA trials [2, 3]. In addition, the recent lung adjuvant cisplatin evaluation (LACE) meta-analysis of the individual patient data from 5 trials revealed a significant improvement in overall survival with the combination of cisplatin-based chemotherapy and surgery in comparison to surgery alone [HR 0.89, 95% confidence interval (CI) 0.82–0.96; $p = 0.004$] [4]. However, about half of the patients could not complete the planned cycles because of adverse events. In other words, treatment compliance has been low in platinum-based adjuvant chemotherapy in the postsurgical setting. Therefore, less toxic and more effective regimens are desired for patients with resected NSCLC.

In a recent meta-analysis, the gemcitabine–platinum combination regimen led to a better survival than other third-generation drug combinations in patients with advanced NSCLC [5]. Carboplatin, an analog of cisplatin, is less nephrotoxic and less emetogenic than cisplatin. In addition, in phase II and III studies in which gemcitabine–cisplatin and gemcitabine–carboplatin were compared, no survival benefit for the cisplatin combination could be demonstrated in advanced NSCLC [6, 7]. In the adjuvant treatment setting, the increase in efficacy must be balanced with the increased toxicity. Considering that higher completion rates could be anticipated with the gemcitabine–carboplatin combination regimen, we planned a phase II trial that was designed to investigate the feasibility of delivering 4 cycles of the gemcitabine–carboplatin combination regimen as postoperative adjuvant chemotherapy for patients with completely resected IB–IIIA NSCLC.

## Patients and methods

### Patient selection

The eligible patients had pathologically documented NSCLC of stage IB, IIA, IIB or IIIA disease and had undergone complete surgical resection. The other inclusion criteria were an age between 20 and 75 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; the absence of preoperative anticancer treatment, previous cancer, and synchronous multiple cancers; a leukocyte count of at least 4,000/μL; a platelet count of at least 100,000/μL; a hemoglobin level of at least 9.5 g/dL; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than 2.5 times the institutional upper limit of normal; and an absence of severe postoperative complications, such as pneumonia or empyema. The patients who fulfilled all of these criteria were enrolled in the study, and the chemotherapy was started at between 4 and 12 weeks following surgery. The study had appropriate institutional ethical review board approval, and all patients provided their written, informed consent according to the institutional guidelines.

### Treatment schedule

Gemcitabine was given at a dose of 1,000 mg/m$^2$ in 100 mL of normal saline solution as a 30-min intravenous infusion on days 1 and 8. Carboplatin was administered at an area under the curve (AUC) of 5 (level 1) in 250 mL of 5% glucose solution as a 60-min intravenous infusion on day 1 only. The Calvert formula was used to calculate the carboplatin dose. The glomerular filtration rate was estimated using the formula described by Gault et al. [8]. The scheduled day-8 gemcitabine was delayed until recovery (no longer than 2 weeks) if the patient had a leukocyte count <2,000/μL, a platelet count <75,000/μL, and/or other nonhematologic toxicities of >grade 2. If these parameters did not improve sufficiently, then the day-8 gemcitabine dose was omitted. The treatments were repeated every 3 weeks for a total of 4 courses.

For dose modification in the subsequent cycle, if, during the previous course, grade 4 leukopenia, chemotherapy-induced neutropenic fever >38°C, thrombocytopenia (<25,000/μL), or nonhematologic toxicity of >grade 2 occurred, then the dose of carboplatin was reduced by 0.5 AUC in level 1.

The toxicities were evaluated according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (CTCAE) v.3.0.

### Statistical methods

The primary endpoint of this study was the completion rate of 4 cycles of chemotherapy, while the secondary endpoint was the safety of carboplatin and gemcitabine as adjuvant chemotherapy agents in patients with completely resected NSCLC.

The study was structured according to the two-step Simon design [9]. We set a completion rate of 80% as the expected rate (P1) and 50% as an acceptable lower rate (P0) with an optimal design for an alpha error of 0.05 and a beta error of 0.2, requiring the accrual of 20 eligible patients. If less than 5 completions were seen in the first 7 patients, the study should proceed to level 2: gemcitabine; 1,000 mg/m$^2$ on days 1 and 8 and carboplatin; AUC of 4 on day 1. At this level, if less than 5 completions had been seen in the first 7 patients, then the study would have been discontinued.

## Results

### Patient characteristics

In the span of a year between March 2006 and March 2007, 20 patients were enrolled in this study (13 males, 7 females; median age 61 years, range 51–74 years). The patient's characteristics are summarized in Table 1.

### Drug delivery

Because 6 of the first 7 patients completed 4 courses of the level 1 chemotherapy, the subsequent 13 patients received the same chemotherapy regimen. The drug delivery schedule is summarized in Table 2. A total of 73 chemotherapy courses were administered, with a median of 4 cycles per patient (range 1–4). The completion rate of 4 cycles was 85% (95% CI 62.1–96.8). On the other hand, the perfect completion rates on schedule with full doses without delay were 75% at 1 cycle, 30% at 2 cycles, 20% at 3 cycles and 20% at 4 cycles, respectively. Three patients did not complete postoperative chemotherapy because of a refusal of chemotherapy in 1 patient, the occurrence of grade 4 thrombocytopenia in 1 patient, and a grade 3 rash in 1 patient (Table 3). At least 1 dose omission of gemcitabine on day 8 was observed for 4 patients, a dose reduction of carboplatin was necessary for 6 patients, and a delay in drug administration for 13 patients. Most dose reductions and/or delays were a result of hematological toxicity. As a consequence of a dose reduction and/or delay of administration, the mean dose intensity of carboplatin was 1.42 AUC per week (85.0% of planned), and that of gemcitabine was 556 mg/m$^2$ per week (83.4% of planned).

**Table 1** Patient characteristics

| | |
|---|---|
| Total number of patients | 20 |
| Median age (years) (range) | 61 (51–74) |
| Sex (%) | |
| Male | 13 (65) |
| Female | 7 (35) |
| pStage (%) | |
| IB | 8 (40) |
| IIA | 1 (5) |
| IIB | 6 (30) |
| IIIA | 5 (25) |
| Histology (%) | |
| Adenocarcinoma | 16 (80) |
| Squamous cell carcinoma | 1 (5) |
| Others | 3 (15) |
| Side of primary tumor (%) | |
| Right | 12 (60) |
| Left | 8 (40) |
| Operative procedure (%) | |
| Lobectomy | 18 (90) |
| Pneumonectomy | 2 (10) |

### Toxicity

The main adverse events and their grades are listed in Table 4. Grade 3 neutropenia occurred in 9 patients (45%), and grade 4 in 4 patients (20%). Two patients had grade 3 febrile neutropenia. Grade 3 thrombocytopenia occurred in 7 patients (35%), and grade 4 in 1 (5%). Only 1 patient required platelet transfusions, but no overt hemorrhage was observed. The nonhematologic toxicity was mild, although the treatment was discontinued at the second cycle for 1 patient with a grade 3 rash.

## Discussion

Concerning the treatment of advanced NSCLC, doublets of platinum and a new-generation anticancer agent, such as

**Table 2** Drug delivery

| | |
|---|---|
| Number of cycles delivered (%) | |
| 1 | 20 (100) |
| 2 | 18 (90) |
| 3 | 18 (90) |
| 4 | 17 (85) |
| Total | 73 |
| Median | 4 |
| Range | 1–4 |
| Number of patients who required dose reduction of carboplatin (%) | 6 (30) |
| Number of patients who required dose omission of day 8 gemcitabine (%) | 4 (20) |
| Number of patients who required delay of administration (%) | 13 (65) |
| Mean dose intensity (% planned) | |
| Carboplatin | 1.42 AUC/week (85.0) |
| Gemcitabine | 556 mg/m$^2$/week (83.4) |

*AUC* area under the curve

**Table 3** Causes of treatment suspension

| | Cycle number at suspension | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Grade 4 thrombocytopenia | 1 | – | – |
| Grade 3 rash | – | 1 | – |
| Refusal by patient | 1 | – | – |

**Table 4** Toxicity profiles

| | Grade 3 (%) | Grade 4 (%) |
|---|---|---|
| Hematological | | |
| Neutropenia | 9 (45) | 4 (20) |
| Thrombocytopenia | 7 (35) | 1 (5) |
| Anemia | 1 (5) | 0 |
| Febrile neutropenia | 2 (10) | 0 |
| Nonhematological | | |
| PS | 1 (5) | 0 |
| Nausea | 1 (5) | 0 |
| Vomiting | 1 (5) | 0 |
| Anorexia | 2 (10) | 0 |
| Rash | 1 (5) | 0 |

*PS* performance status

carboplatin plus paclitaxel, cisplatin plus gemcitabine and cisplatin plus vinorelbine are presently considered to be the standard chemotherapy regimens worldwide [10–14]. In other words, the combination of cisplatin and gemcitabine is one of the most active regimens in the treatment of advanced NSCLC. In addition, in phase II and III studies in which gemcitabine–cisplatin and gemcitabine–carboplatin were compared, no survival benefit for the cisplatin combination could be demonstrated in the treatment of advanced NSCLC [6, 7]. Considering that good efficacy and reduced toxicity could be anticipated with the gemcitabine–carboplatin combination regimen, we planned a phase II trial that was designed to investigate the feasibility of delivering 4 cycles of the gemcitabine–carboplatin combination regimen as postoperative adjuvant chemotherapy for patients with completely resected IB–IIIA NSCLC.

In the present study, the completion rate of 4 cycles was 85%. Although 65% of patients required a delay of administration because of hematological toxicity, the mean dose intensities of carboplatin and gemcitabine were 85.0 and 83.4%, respectively. Based on the completion rates of 45–50% in the JBR.10 [2] and ANITA trials [3] with the cisplatin and vinorelbine regimen, the use of carboplatin and gemcitabine as adjuvant chemotherapy is considered to be more feasible.

Toxicity was limited in the study. The known dose-limiting toxicity of the carboplatin–gemcitabine combination is hematological. In the advanced NSCLC setting of studies using the same regimen as in the current study, it was reported that the incidence of grade 3 or 4 thrombocytopenia was more than 80%; however, most patients did not experience bleeding [15]. In this study, although 2 dose levels of carboplatin were selected because of the possibility of a high frequency of occurrence of severe thrombocytopenia, grade 3 or 4 thrombocytopenia was experienced in 40% of cases, and only 1 patient required platelet transfusions. This incidence was less than expected and was the same as the result obtained by Zatloukal et al. [6]. The difference from the hematological toxicities developed in the WJTOG 0104 study may be associated with the patient's condition during the postoperative state [15].

In regard to the nonhematological toxicities, a few patients complained of nausea and vomiting. Only 1 patient had a grade 3 rash, and the treatment was discontinued at the second cycle. Consequently, the occurrence of severe nonhematological toxicity was uncommon.

Recently, the biweekly administration of chemotherapy has become more widely accepted, because it maintains a similar dose intensity with a better toxicity profile. Lopez-Vivanco et al. [16] reported their experience with the biweekly administration of cisplatin and gemcitabine in the treatment of advanced NSCLC. The overall response rate was 38.8% and the median overall survival was 48 weeks. The dose intensity was 91.6% of the planned dose, although a delay in the cycle was observed in 15% of all cycles. Amazingly, the hematologic toxicity was very low, with grade 3/4 neutropenia occurring in only 6% of patients and grade 3/4 thrombocytopenia in 2%. A dose reduction was observed in only 4% of patients. Tomizawa et al. [17] reported on a phase I dose escalation study of the biweekly administration of gemcitabine and 4-weekly administration of carboplatin in completely resected stage IB–IIIA NSCLC. They showed that the maximum tolerated dose was not reached and the recommended dose was gemcitabine 1,000 mg/m$^2$ on days 1 and 15, and carboplatin AUC 5 on day 1, administered every 4 weeks. In our study, although the delay of the cycles was relatively high, severe toxicity and dose reduction were not observed, and a completion rate of 85% was feasible. In the future, a further investigation of the administration schedule may therefore be desirable.

More recently, Scagliotti et al. [18] reported a phase III noninferiority study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with stage IIIB or IV NSCLC. In this study, a significantly longer survival time was observed in the nonsquamous subgroup treated with cisplatin and pemetrexed versus cisplatin and gemcitabine. The current study population showed that 16 patients (80%) had adenocarcinoma. Based on these results, in the future we may have to perform a prospective study of postoperative adjuvant chemotherapy that is specifically designed to evaluate histology findings.

In conclusion, the combination chemotherapy of carboplatin and gemcitabine was found to have an acceptable toxicity profile in the adjuvant setting. The majority of the patients completed the 4 cycles of therapy. We believe that carboplatin and gemcitabine is a feasible and well-tolerated

regimen for the treatment of patients with completely resected NSCLC in the adjuvant setting. To establish the survival benefit of carboplatin and gemcitabine after the complete resection of NSCLC, a multi-institutional phase III study is needed.

**Conflict of interest** No author has any conflict of interest.

## References


1. Mountain CF (1997) Revisions in the international system for staging lung cancer. Chest 111:1710–1717
2. Winton T, Livingston 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
3. Douillard JY, Rosell R, De Lena 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
4. Pignon JP, Tribodet H, Scagliotti GV et al (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 26:3552–3559
5. Le Chevalier T, Scagliotti G, Natale R et al (2005) Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. Lung Cancer 47:69–80
6. Zatloukal P, Petruzelka L, Zemanova M et al (2003) Gemcitabine plus cisplatin vs gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer 41:321–331
7. Mazzanti P, Massacesi C, Rocchi MB et al (2003) Randomized, multicenter, phase II study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer 41:81–89
8. Gault MH, Longerich LL, Harnett JD et al (1992) Predicting glomerular function from adjusted serum creatinine. Nephron 62:249–256
9. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
10. Kelly K, Crowley J, Bunn PA Jr et al (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
11. Scagliotti GV, De Marinis F, Rinaldi M et al (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 20:4285–4291
12. Schiller JH, Harrington D, Belani CP et al (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
13. Fossella F, Pereira JR, von Pawel J et al (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 21:3016–3024
14. 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
15. Yamamoto N, Nakagawa K, Uejima H et al (2006) Randomized phase II study of carboplatin/gemcitabine versus vinorelbine/gemcitabine in patients with advanced nonsmall cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) 0104. Cancer 107:599–605
16. Lopez-Vivanco G, Viteri A, Barcelo R et al (2005) Biweekly administration of cisplatin/gemcitabine in advanced nonsmall cell lung cancer. Am J Clin Oncol 28:501–507
17. Tomizawa Y, Ishihara S, Iijima H et al (2007) A phase I dose escalation study of biweekly gemcitabine and carboplatin in completely resected stage IB–IIIA nonsmall cell lung cancer. Am J Clin Oncol 30:498–502
18. Scagliotti GV, Parikh P, von Pawel J et al (2008) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26:3543–3551