A Phase II Study with Gemcitabine and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer

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Purpose: To evaluate the efficacy and safety of gemcitabine and carboplatin (GC) in the treatment of advanced non-small-cell lung cancer (NSCLC).

Materials and Methods: Between November 1999 and April 2001, 34 patients were enrolled in this study. The median age was 66 (range: 52–74) years old and all were male. Sixteen patients demonstrated stage IIIb, 15 stage IV, and 3 recurrence of disease after surgery. Twenty-two patients showed a ECOG performance status of 0 or 1 and 12 had 2. Twenty patients presented with squamous cell carcinoma, 11 adenocarcinoma and 3 unclassified NSCLC. The treatment regimen consisted of intravenous carboplatin AUC of 6 on day 1 and gemcitabine 1,250 mg/m² on day 1 and 8. The treatment was repeated every 28 days. Toxicities were evaluated according to WHO toxicity criteria.

Results: All thirty-four patients were evaluable. Partial responses were observed in 15 patients. The overall response rate was 44% (95% confidence interval: 27–61%) and the median response duration was 26 (range 8–60+) weeks. The median survival of all patients was 50 (range 8–70+) weeks. During a total of 144 cycles, granulocytopenia greater than WHO grade 2 occurred in 2%, thrombocytopenia in 2%, and anemia in 3%, respectively. Non-hematologic toxicities were minor and easily controlled.

Conclusion: A combination chemotherapy of intravenous gemcitabine and carboplatin has a relatively high activity with acceptable toxicities in patients with advanced NSCLC. (Cancer Research and Treatment 2002; 34:23-27)

Key Words: Non-small cell lung cancer, Combination chemotherapy, Gemcitabine, Carboplatin

INTRODUCTION

Lung cancer is the second most common malignant tumor in Korea, preceded by gastric cancer (1). Additionally, lung cancer is currently the leading cause of death in men and the second greatest cause of death in women from malignant disease in Korea (2). Non-small cell lung cancer (NSCLC) constitutes 70–80% of primary malignant lung tumors and is unresectable in over 70% of cases because the majority of patients are in the progressive stage at the time of diagnosis (3,4). The issue of the benefits of chemotherapy has been addressed by several randomized trials. Three meta-analyses of these studies have demonstrated a small but significant (p < 0.05) survival benefit for chemotherapy with concurrent improvement in quality of life (5–7). In the last few years, a promising number of new agents with differing mechanisms of action and encouraging toxicity profiles have demonstrated significant activity in advanced NSCLC, with response rates that range from 14% to 33% (8).

Among these new compounds, gemcitabine (2′-2′ difluorodeoxycytidine) is an analog of deoxycytidine with two fluorine substitutes for the two hydrogen atoms in the 2′ position of deoxyribose sugar. Although similar to the antimetabolite cytarabine, gemcitabine is substantially different in its pharmacokinetic and antitumor activity (9). Several phase II trials have been performed in advanced NSCLC in a large number of cases, with a consistent, reproducible response rate in seven trials in the range of 20% to 23%. The toxicity profile in all of these studies, which used the same gemcitabine weekly schedule at doses that ranged from 800 to 1,250 mg/m², was modest and confirms the safety of this treatment modality (10). Moreover, in a phase II multi-center clinical study in Korea, 7 out of 35 (20%) patients showed a partial response (11). In a recent phase II study of combination chemotherapy of gemcitabine and cisplatin in advanced NSCLC, the response rate was 42% to 54% and the median survival duration was 9 to 13 months with modest side effects and few dose modifications during its administration (12–14).

Carboplatin has several advantages over cisplatin. With the exception of hematologic toxicity, it is tolerated much better, with diminished renal, neurologic, and gastrointestinal side effects. Moreover, it does not require the aggressive hydration
and antiemetics necessitated by cisplatin therapy. In an ECOG trial of cisplatin analogs and combinations, the initial therapy with carboplatin, despite a lower response rate (9%), yielded the best median survival (15). In addition, a European Organization for Research and Treatment of Cancer study comparing cisplatin/etoposide with carboplatin/etoposide demonstrated equivalent median survival, with less toxicity for the carboplatin-containing regimen (16).

In view of the mild toxicity profile of gemcitabine, its efficacy when combined with cisplatin, and the reduced toxicity of carboplatin as compared with cisplatin, we initiated a phase II study of gemcitabine and carboplatin in advanced, inoperable NSCLC with the aim being to assess the response to therapy and to evaluate the toxicity.

**MATERIALS AND METHODS**

1) Patient selection

Eligibility criteria for study entry included 1) histologically confirmed stage IIIB or IV NSCLC, 2) age 18–75 years, 3) no prior chemotherapy, 4) an ECOG performance status of 0 to 2, 5) one or more lesions that could be measured from each side, and 6) adequate baseline organ function, defined as a WBC count of at least 4,000/mL, a platelet count of at least 100,000/mL, a total bilirubin level of less than 3.0 mg/dL, serum transaminases levels of less than 3 times the upper limit of normal, and a serum creatinine value of less than 1.5 mg/dL or a creatinine clearance more than 50 mL/min.

However, patients with symptomatic brain metastases or other severe illnesses were excluded from study entry. Additionally, written informed consent was required from each patient.

2) Patient evaluation

A complete history, physical examination, recording of performance status according to ECOG criteria, complete blood cell count with differential, serum biochemistry, urinalysis, and ECG were obtained at baseline for each patient. Chest radiographs and CT scans were routinely performed in all patients. Other radiographic examinations, e.g., isotope bone scans, brain CT scan, abdominal ultrasonography, abdominal CT scan were performed if clinically indicated. If biopsy was impossible to perform with flexible bronchial endoscopy, a pathologic test was performed with fine-needle aspiration biopsy.

3) Treatment

GC combination chemotherapy consisted of gemcitabine 1,250 mg/m², intravenously on days 1 and 8 and carboplatin AUC of 6 on day 1. Carvert formula for AUC dosing was used. The glomerular filtration rate was approximated using Chaterut formula (Cr=0.134×weight (kg)×[218×weight (kg)×(1-0.00457×age (years))]/[serum creatinine mg/dL]×89.4) (17). Full doses of chemotherapy were given on days 1 and 8 if WBC and platelet counts were at least 4,000/mL and 100,000/mL on day 0, respectively. In the case of WHO grade 1 leukena or thrombocytopenia, treatment was given at doses reduced by 25% on both day 1 and day 8. In patients with grade 2 or higher leukena or thrombocytopenia, treatment was delayed 1 week. Cycles were repeated every 28 days until evidence of progressive disease or unacceptable toxicity was seen. Prophylactic antiemetics were routinely administered on the day of chemotherapy with 5-HT3 receptor antagonists.

4) Response and toxicity assessment

Physical examinations, complete blood counts, and biochemistry profiles were repeated every 4 weeks. Toxicities were graded according to WHO toxicity criteria. Radiographic evaluations for tumor response including isotopic bone scan and CT scan were performed every two courses of chemotherapy. Responses were defined as follows: a complete response was indicated by the disappearance of all clinical and radiographic signs of tumor for at least 4 weeks; a partial response was seen as a greater than 50% reduction in the sum of products of the biperpendicular diameters of all measurable lesions with no increase in size of any lesion and no new lesions; stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the product of the longest perpendicular diameters of measurable lesions and no new lesion; and disease progression was equated with a 25% or greater increase in size of any lesion or the appearance of any new lesion.

The response duration was measured from the date of confirmation of at least partial tumor response to the date of disease progression. Survival was measured from the date of therapy initiations until the date of death or last follow-up evaluation.

5) Method of analysis

Statistical analysis was performed with SPSS (version 10.0) statistical program for a personal computer. Response rates according to the prognostic factors were compared by the Fisher’s exact test. Survival curves were estimated by the Kaplan-Meier method, and the log-rank test was used to compare the difference in survival and duration of response. A logistic regression analysis was used in a multivariate model.

**RESULTS**

1) Patient characteristics

From November 1999 to April 2001, a total of 34 patients were enrolled into the study. All patients were male. Their median age was 66 years (range, 52 to 74 years), and 28 (82%) patients were older than 60 years. The ECOG performance status was 0 to 1 in 22 (65%) patients and 2 in 12 (35%) patients. Pathologically, the majority of patients had squamous cell carcinoma (59%) and adenocarcinoma (32%). Sixteen patients demonstrated stage IIIB disease, fifteen patients were stage IV disease, and three patients showed recurrent disease after surgical resection. None of the patients had previously received radiation therapy. Sites of metastasis included the contralateral lung (8 patients), bone (4 patients), liver (1 patient), subcutaneous tissue (1 patient), and intraabdominal lymph nodes (1 patient). Among all patients, the serum carcinoembryonic antigen (CEA) was 2–2,780 ng/mL (normal range, <2.5 ng/mL), and 31 (91%) patients were greater than normal. A total of 144 courses of treatment were given, for a median of four courses per patients (range, 2 to 12 courses).
2) Response and survival

All of the patients completed at least two cycles and were evaluated for response. After a median four cycles of chemotherapy, there were no complete response and 15 partial responses, for an overall response rate of 44% (95% CI, 27% to 61%). Four patients demonstrated stable disease and 18 showed progressive disease. Objective responses were observed in nine of 16 stage IIIb patients and six of 18 stage IV patients. The median response duration was 26 weeks (range, 8 to 60+ weeks).

The median follow-up period was 49 weeks. At the time of this analysis, 16 patients were reported dead. The median progression-free survival was 45 weeks (range, 8 to 62+ weeks). The median survival time was 50 weeks (range, 8 to

The median survival duration was not reached in responding patients and was 17 weeks in nonresponding patients, however the difference between the two groups was not statistically significant (p=0.06).

4) Prognostic factor analysis

A prognostic factor analysis was performed for response and survival as shown in Table 1. There were no statistically significant parameters for response. For survival, only performance status was found to be of prognostic significance: did not reach median survival for ECOG 0 to 1 vs. 18 weeks for ECOG 2 (p=0.02). A multivariate analysis for survival showed no parameter as a significant prognostic factor.

5) Toxicities

Hematologic and non-hematologic toxicities are listed in Table 2. Hematologic toxicity grading was based on complete blood count done just prior to the next cycle. Hematologic toxicity was mild. WHO grade 3 or 4 toxicity was rarely seen, with leukopenia in three of 144, thrombocytopenia in three of 144, and anemia in five of 144 courses, respectively.

All thirty-four patients are assessable for symptomatic toxicity. Non-hematologic toxicity was also mild. There were no cases of grade 3 or 4 non-hematologic toxicity. Nausea and vomiting were documented in the majority of patients (80%). However, the majority of patients (65%) had WHO grade 1 vomiting. Only one patient displayed WHO grade 1 diarrhea. Stomatitis was common, occurring in 11 of 34 patients. The majority (9 patients) had WHO grade 1 toxicity.

Alopecia was common, occurring in 30 of 34 patients. Neuropathy was also common, occurring in 26 of 34 patients. Renal toxicity did not develop in any of the patients. Eighteen of 34 patients reported transient skin rashes (WHO grade 1 in 3, grade 2 in 15) during gemcitabine therapy. These rashes

![Fig. 1. Time to progression and overall survival curves of total patients](image)

Table 1. Analysis of prognostic factors

<table>
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<tr>
<th>Response</th>
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<th>OS†</th>
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<td></td>
<td>n</td>
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<tr>
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<tr>
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<td>20</td>
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<td>&gt;60</td>
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<td>56</td>
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<td>Performance status (ECOG)</td>
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<tr>
<td>2</td>
<td>12</td>
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<tr>
<td>Others⁴</td>
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<tr>
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<td>63</td>
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<td>IV/rec⁵</td>
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<td>CEA (ng/mL)</td>
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<tr>
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<td>&gt;2.5</td>
<td>31</td>
<td>48</td>
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*time to progression, †overall survival, ‡not reached, §squamous cell carcinoma, †adenocarcinoma+others, ‡recurrent disease 70+ weeks) and the 1-year survival rate was 52.5% (Fig. 1). tended to be macular and were associated with an itching
sensation. The rashes subsided spontaneously or by symptomatic management.

**DISCUSSION**

In the last few years, there has been a surge of interest in a number of new agents such as vinorelbine, gemcitabine, irinotecan, topotecan, paclitaxel, and docetaxel. Among these, gemcitabine is one of the most promising. Although structurally similar to cytarabine, gemcitabine differs pharmacokinetically and pharmacologically. Gemcitabine also has a different spectrum of antitumor activity. Gemcitabine is a prodrug with greater membrane permeability and a higher affinity for deoxycytidine kinase than the parent compound. This leads to the intracellular synthesis of the active metabolite, gemcitabine triphosphate, which achieves a higher concentration and is retained significantly longer than other pyrimidine analogs (18). There is evidence of a possible synergistic effect between gemcitabine and alkylating agents: the molecular basis of this synergism probably lies in gemcitabine’s inhibition of the excision repair mechanism, through which tumor cells can overcome platinum-induced cytotoxicity (DNA-DNA cross-links) (19). A few phase II trials of gemcitabine and cisplatin have been completed, and a consistent objective response rate averaging 50% has been reported (12–14).

Carboplatin is a platinum analog that, although retaining antitumor activity, has significantly less neurotoxicity and nephrotoxicity than cisplatin. The lack of severe myelosuppression with carboplatin suggests that gemcitabine may be safely added to carboplatin.

In our study, the combination of carboplatin and gemcitabine proved feasible and well tolerated. There were neither treatment-related mortalities nor overwhelming infections. We decided to recycle treatment every 28 days instead of every 21 days, which is the most common treatment interval when gemcitabine is used on days 1 and 8. In addition we escalated the dose of gemcitabine to 1,250 mg/m² instead of 1,000 mg/m². This treatment schedule was chosen because in several phase II studies using a 28-day schedule with gemcitabine on days 1, 8 and 15 and carboplatin on D1 for NSCLC, hemato-

tologic toxicities, particularly severe thrombocytopenia, were problematic (20,22).

Carmichael et al reported 50% grade 3 or 4 neutropenia and more than 40% grade 3 or 4 thrombocytopenia in nineteen assessable patients treated with gemcitabine at a dose of 1,000 mg/m²/week (days 1, 8, and 15), followed by carboplatin at a dose of area under the curve 5.2 mg/mL/min on day 1 of each 28-day cycle (20). Ng and his colleague have reported severe thrombocytopenia, which has led to premature discontinuation of a phase II study in which gemcitabine was administered at 1,000 mg/m² on days 1, 8, and 15 every 4 weeks, and carboplatin at an AUC dose of 5 mg/mL/min on day 1 of the 28-day cycle (22). Therefore they did not recommend the two-drug combination in the dose and schedule used in this study.

In a phase I–II study reported by Iaffaioli et al, chemotherapy-naïve patients with stage IIIB-IV non-small-cell lung cancer received carboplatin at area under the concentration-time curve 5 mg/mL/min and gemcitabine was given at an initial dose of 800 mg/m², and subsequently escalated by 100 mg/m² per step. Gemcitabine was administered on days 1 and 8 and carboplatin on day 8 of the 28-day schedule. The dose-limiting toxicity was neutropenia but not thrombocytopenia. Non-hematologic toxicities were mild. An objective response was observed in 13 (50%) of 26 patients, including four complete responses. The median duration of response was 13 months. The median overall survival was 16 months (21).

In the present study, the objective response rate was 44% and the median duration of overall survival was 50 weeks, with a one-year survival rate of 52.5%. In hematologic toxicity, grade 3 or 4 leukopenia and thrombocytopenia occurred in less than 5% of treatment courses. Non-hematological side effects were mild and well tolerated. There were no cases of treatment-related severe bleeding or mortality.

In the prognostic factor analysis, there was no statistically significant parameter for response. Performance status was found to be the only significant prognostic factor for survival. In a multivariate analysis, no significant prognostic factor was detected.

<table>
<thead>
<tr>
<th>WHO grade</th>
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<tr>
<td>Hematologic toxicities* (% of total 144 cycles)</td>
<td>Leukopenia 22 (16) 16 (12) 3 (2) 0</td>
<td>Thrombocytopenia 1 (1) 1 (1) 0 3 (2)</td>
<td>Anemia 34 (24) 25 (17) 5 (3) 0</td>
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<tr>
<td>Non-hematologic toxicities (% of total 34 patients)</td>
<td>Nausea/vomiting 22 (65) 5 (15) 0 0</td>
<td>Diarrhea 1 (3) 0 0 0</td>
<td>Stomatitis 9 (26) 2 (6) 0 0</td>
<td>Alopecia 26 (76) 4 (5) 0 0</td>
</tr>
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</table>

*Based on CBC done just prior to next cycle

**Table 2. Toxicities of GC chemotherapy**
CONCLUSIONS

The combination of gemcitabine administered at a dose 1,250 mg/m² on days 1 and 8 and carboplatin at AUC 6 on day 1, every 28 days, was well tolerated, and effective in patients with NSCLC.

REFERENCES