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ORIGINAL ARTICLE

Fixed-dose rate infusion of gemcitabine and weekly cisplatin in elderly or poor performance status patients with unresectable non-small cell lung cancer

Gyeong-Won Lee · Myung-Hee Kang · Hoon-Gu Kim · Jung Hun Kang · Seok Hyun Kim · Yu Ji Cho · Yi Yeong Jeong · Ho-Cheol Kim · Jong Duk Lee · Young Sil Hwang · Hye Jung Kim · Jong-Seok Lee

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Abstract
Purpose We investigated the efficacy and toxicity of a 4-week schedule of a fixed dose rate infusion of gemcitabine and weekly cisplatin in elderly or poor performance status patients with unresectable non-small cell lung cancer (NSCLC).
Methods In this study, 48 patients with previously untreated NSCLC were given combination chemotherapy that consisted of gemcitabine 1,000 mg/m^2 (10 mg/m^2/min fixed dose rate infusion) and cisplatin 25 mg/m^2, and both drugs were given weekly on days 1, 8 and 15.
Results A partial response and stable disease were observed in 20 patients (41.7%, 95% CI; 27.8–55.6%) and 12 patients (25.0%), respectively. The overall median survival was 10.30 months (range: 7.85–12.74 months). Major toxicities included neutropenia (grade 3 to 4, 29.2%) and infection (grade 3 to 4, 27.1%).
Conclusions Our results indicate that this regimen is a feasible treatment for elderly or poor performance status patients with unresectable NSCLC. Nevertheless, the morbidity due to myelosuppression and infection following this treatment should be carefully considered.

Keywords Gemcitabine · Cisplatin · Non-small cell lung cancer · Fixed dose rate · Weekly administration

G.-W. Lee and M.-H. Kang contributed equally to this work.

G.-W. Lee · M.-H. Kang · H.-G. Kim · J. H. Kang · S. H. Kim · Y. J. Cho · Y. Y. Jeong · H.-C. Kim · J. D. Lee · Y. S. Hwang
Department of Internal Medicine,
Gyeongsang National University College of Medicine,
Gyeongsang National University Hospital, Jinju, South Korea

G.-W. Lee · M.-H. Kang · H.-G. Kim · J. H. Kang · Y. J. Cho · Y. Y. Jeong · H.-C. Kim · J. D. Lee · Y. S. Hwang · H. J. Kim
Gyeongsang Institute of Health Science, Jinju, South Korea

G.-W. Lee · M.-H. Kang · H.-G. Kim · J. H. Kang · Y. J. Cho · Y. Y. Jeong · H.-C. Kim · J. D. Lee · Y. S. Hwang
Gyeongnam Regional Cancer Center, Jinju, South Korea

J.-S. Lee (✉)
Department of Internal Medicine Seoul National University College of Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi 463-707, South Korea
e-mail: jslee@snubh.org

H. J. Kim
Department of Pharmacology, School of Medicine, Gyeongsang National University, Jinju, South Korea

Introduction

Platinum-based combination chemotherapy improves the survival of patients with advanced non-small cell lung cancer (NSCLC) and who have a good performance status, and platinum-based combination chemotherapy is now considered as the standard treatment for relatively young patients who have a good performance status [1–4].

However, the optimal treatment for patients who are elderly or who have a poor performance status still remains controversial. Platinum-based regimens have consistently produced more toxicities and especially diarrhea, mucositis and myelosuppression in these patient groups when compared with the young patients or the patients with a good performance status [5–7].

Although some previous studies have revealed that platinum-based chemotherapy may be feasible and safe in elderly patients or poor performance status patients with unresectable NSCLC [8–10], medical oncologists are still

reluctant to use standard platinum-based chemotherapy in elderly patients or patients with a poor performance status.

Combination chemotherapy with gemcitabine and cisplatin is one of the standard platinum-based regimens for treating NSCLC [11–14]. However, the optimal dose and schedule for administration of the two drugs has not yet been determined, and especially for elderly patients or patients with a poor performance status.

Several clinical trials of weekly cisplatin combined with gemcitabine have shown feasible activities and acceptable toxicities in patients suffering with NSCLC [15, 16], ovarian cancer [17], breast cancer [18], and bladder cancer [19].

In addition, we modified the infusion rate of gemcitabine to improve the efficacy of this regimen instead of using the standard infusion rate (800–1,200 mg/m^2 over 30 min).

A fixed-dose rate infusion (10 mg/m^2/min) of gemcitabine has previously shown a twofold increase of the intracellular gemcitabine triphosphate concentration, as compared with the standard infusion rate, and improved efficacy in patients with advanced pancreatic cancer [20] and NSCLC [21].

Therefore, we conducted this phase II study to evaluate the efficacy and toxicity of a 4-week schedule of a fixed dose-rate infusion of gemcitabine and weekly cisplatin in elderly patients or poor performance status patients with unresectable NSCLC.

Patients and methods

Patients eligibility

Patients with previously untreated NSCLC were enrolled in this study. The eligibility criteria included: (1) patients who were ≥65 years of age and they had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, or the patients who were <65 years of age and they had a ECOG PS 2, (2) histologically confirmed non-small cell carcinoma, (3) stage IV or stage IIIB disease with malignant pleural effusion; (4) adequate haematologic parameters (a hemoglobin concentration of at least 9.0 g/dL, an absolute neutrophil count ≥1,500/mm^3 and a platelet count ≥100,000/mm^3), renal function (serum creatinine ≤1.5 mg/dl), and liver function (total bilirubin ≤1.5 mg/dl and a level of serum transaminase twice the upper limits of normal or less) and (5) they had at least one bi-dimensionally measurable lesion according to the RECIST criteria [22].

The patients were ineligible if they had the following criteria: active infection, prior chemotherapy, radiotherapy or surgery for their disease, a history of myocardial infarction in the last 3 months before entry to the study, uncontrolled congestive heart failure or hypertension, uncontrolled diabetes mellitus, pregnancy, lactation or a prior second primary cancer except for cervix cancer in situ or skin cancer. All the patients provided written informed consent before they entered the study.

Treatment schedule and dose modification

The combination chemotherapy consisted of gemcitabine of 1,000 mg/m^2, which was administered intravenously at 10 mg/m^2/min [A fixed-dose rate (FDR) infusion] followed by cisplatin 25 mg/m^2 without pre- and post-hydration, and both drugs were given on days 1, 8 and 15 in an outpatient setting. All the patients received antiemetic therapy that consisted of intravenous 5-HT$_3$ antagonist and dexamethasone before drug administration. The treatment cycles were repeated every 4 weeks until the maximum six cycles.

The patients whose absolute neutrophil count and platelet count were greater than or equal to 1,500 and 100,000/mm^3, respectively, and who had lower than or equal to grade 1 non-hematologic toxicity (excluding alopecia) received chemotherapy on day 1 of each cycle.

On days 8 and 15 of each cycle, the minimum requirements to receive chemotherapy were an absolute neutrophil count between 1,000 and 1,500/mm^3, a platelet count ≥75,000/mm^3 and no grade ≥2 nonhematologic toxicity (excluding alopecia).

If these conditions were not met on days 1, 8 or 15, then chemotherapy was postponed for 1 week. A delay of more than 3 weeks resulted in withdrawal from the study.

If there were any grade 3 to 4 hematologic toxicities at the nadir of the previous cycle, or febrile neutropenia with or without documented infection, then administration of both drugs in the subsequent cycles was reduced by 20% from the planned dose.

The administration of granulocyte-colony stimulating factor (G-CSF) was allowed in the presence of febrile neutropenia, and grade 3 or 4 neutropenia.

In the presence of grade 3 or 4 non-hematologic toxicity (except nausea, vomiting and alopecia), the treatment was postponed until resolution of the toxicity and then both drug doses were reduced by 20% for the next cycle.

Treatment was stopped at any time for documented disease progression, unacceptable toxicity or according to the patient's own refusal.

Assessment of efficacy and toxicity

The pretreatment baseline evaluation included a complete medical history and physical examination, a complete blood cell count (CBC) with the differentials, chemistry profiles and performance status. Chest X-rays, chest and upper abdominal computed tomography (CT) scans, brain CT scan or magnetic resonance imaging, a radionuclide

bone scan and other diagnostic procedures were performed as clinically indicated.

During treatment, a limited history taking, physical examination, assessment of toxicity, a CBC count with the differentials and blood chemistry tests were repeated weekly. A chest X-ray was performed every 4 weeks before each cycle.

Appropriate imaging studies, including CT scans of the chest and upper abdomen, were performed every two cycles to assess the treatment response, and sooner if needed for documenting disease progression. The objective tumor responses were assessed according to the RECIST criteria [22].

The response rate was calculated as the ratio of the number of patients who achieved a complete or partial response to the number of enrolled patients. Overall survival (OS) and time to progression (TTP) were calculated from the start of therapy until death and progression, respectively, or until the last follow-up. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale version 3.0.

Statistical consideration

The sample size was calculated according to Simon's two stage optimal design [23].

Assuming a response rate of 40%, a probability of error of 5% and a power of 80%, a total of 48 patients (43 patients plus 5 patients to compensate a 10% drop-out rate) were enrolled. In the initial stage, 13 evaluable patients were to be entered into the study and evaluated for their response. If $\geq$3 responses were observed during the first stage, then 30 additional patients were to be entered in the second stage. The statistical evaluation was performed based on the intention to-treat analysis.

The descriptive statistics are reported as proportions and medians. OS and PFS were assessed by the Kaplan–Meier method and the 95% confidence interval (95% CI) for the median time to events was computed.

Results

Patients' characteristics

Between August 2005 and July 2007, 48 patients were enrolled, and the patients' characteristics are shown in Table 1. The median age was 67 years (range: 38–76). Thirty-three patients (68.8%) were over 65 years old and 38 patients (79.2%) had an ECOG PS of 2.

Treatment administration

A total of 166 cycles were given, with a median of 3 cycles per patient (range: 1–6 cycles). Among the cycles, administration was delayed for a median of 2 weeks in 22 cycles (13.3%). Three patients received only 1 cycle of treatment because the treatment was stopped owing to treatment-related mortality (neutropenic sepsis in 1 and necrotizing pneumonia in 2). Dose reduction was carried out in 23 cycles, and in 11 cycles (6.7%), administration of gemcitabine and cisplatin was omitted on the day 8 or 15. The major causes for the delay of drug administration and the dose reduction were neutropenia, thrombocytopenia and infection. The dose-intensities are shown in Table 2.

Table 1 Baseline patient characteristics ($N = 48$)

Median age (range)	67 (38–76)
Gender	
Male	37 (77.1%)
Female	11 (22.9%)
ECOG PS	
0–1	10 (20.8%)
2	38 (79.2%)
Histology	
Squamous cell carcinoma	17 (35.4%)
Adenocarcinoma	27 (56.3%)
Others	4 (8.3%)
Stage	
IIIB (wet T4)	5 (10.4%)
IV	43 (89.6%)
Metastatic Site	
Adrenal gland	5 (10.4%)
Bone	17 (35.4%)
Lung to lung	23 (47.9%)
Liver	3 (6.2%)
Distant lymph node	28 (58.3%)
Pleura	11 (22.9%)
Peritoneum	2 (4.2%)

Table 2 Dose-intensity ($N = 48$)

	Actual dose intensity [mg/(m^2 week)]	Relative dose intensity (%)
Gemcitabine	638.8	85.2
Cisplatin	16.2	86.4

Response and survival

Forty-five patients were evaluable for their response and all 48 patients were evaluable for survival analysis on an intention-to-treat basis. The number of overall responses was 20 for an overall response rate of 41.7% (95% CI: 27.8–55.6%). 12 patients were confirmed to have stable disease (Table 3).

Table 3 Objective response rate ($N = 48$) (95% CI: 27.8–55.6%)

Partial response	20 (41.7%)
Stable disease	12 (25.0%)
Progressive disease	13 (27.1%)
Not evaluable	3 (6.2%)

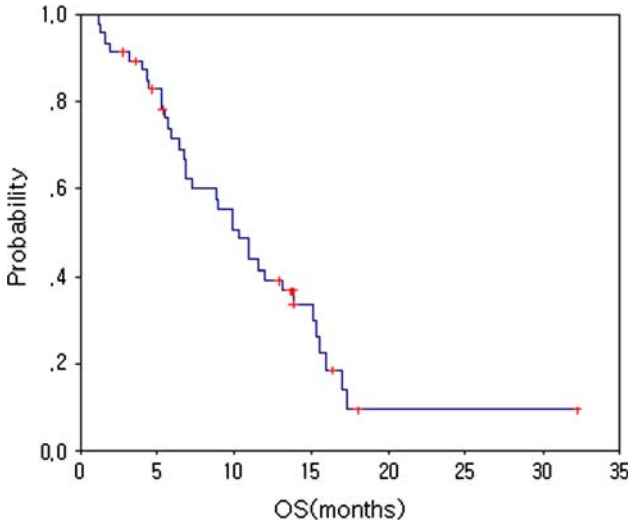

Fig. 1 Kaplan–Meier survival curve for the overall survival

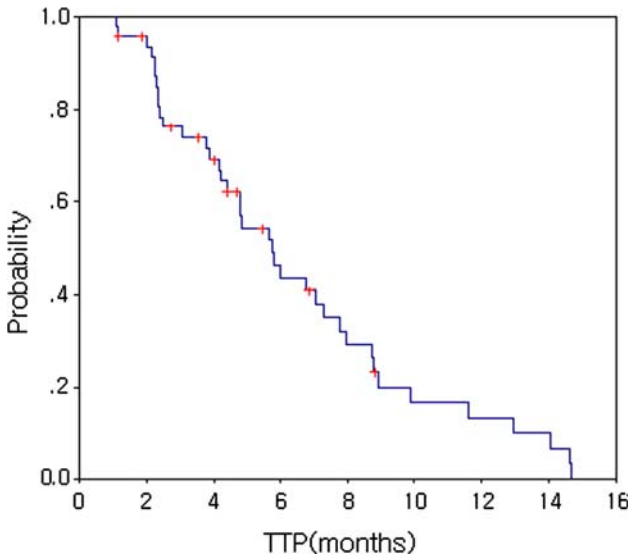

Fig. 2 Kaplan–Meier survival curve for the time to progression

After a median follow-up duration of 18 months, the median OS was 10.30 months (range: 7.85–12.74 months) (Fig. 1). The 1- and 2-year survival rates were 36.8 and 9%, respectively. The median TTP was 5.75 months (range: 4.40–7.11 months) (Fig. 2).

Table 4 Major toxicities of treatment ($N = 48$)

Adverse event	Grade 3 (No. of patients, %)	Grade 4 (No. of patient, %)
Hematologic		
Leukopenia	6 (12.5)	5 (10.4)
Neutropenia	8 (16.7)	6 (12.5)
Anemia	7 (14.6)	0 (0)
Thrombocytopenia	8 (16.7)	2 (4.2)
Nonhematologic		
Diarrhea	1 (2.1)	0 (0)
Mucositis	2 (4.2)	0 (0)
Asthenia	5 (10.4)	0 (0)
Neuropathy	4 (8.3)	0 (0)
Infection	7 (14.6)	6 (12.5)

Toxicities

All the patients were evaluable for toxicities. Table 4 shows the major hematologic and non-hematologic toxicities. Grade 3 or 4 neutropenia, anemia and thrombocytopenia occurred in 14 (29.2%), 7 (14.6%) and 10 (20.9%) patients, respectively. Among the non-hematologic toxicities, grade 3 or 4 infection, grade 3 asthenia and grade 3 neuropathy occurred in 13 (27.1%), 5 (10.4%), and 4 (8.3%) of patients, respectively. The other non-hematologic toxicities were mild and manageable. There were three treatment-related deaths: one was caused by neutropenic sepsis and two were caused by necrotizing pneumonia.

Discussion

In this phase II study, we evaluated the efficacy and safety of a FDR of gemcitabine and weekly cisplatin in elderly patients or poor performance status patients with NSCLC. Our results, with a response rate of 41.7%, a median TTP of 5.75 months and a median survival of 10.30 months, are comparable to the data of the previous studies that used standard combination chemotherapy with gemcitabine and cisplatin in non-elderly or good performance status patients with NSCLC [12–16, 24].

However, relatively high response rates and OS in this study could be related with the followings. First, the ethnic and pharmacogenomic differences between Korean patients and western patients may cause the difference in efficacy and survival. Second, the lower proportions of extrathoracic disease may lead to favorable outcomes in this study. Nonetheless, presently, further studies will be needed to validate the hypothesis.

In this study, we postulated that weekly administration of low dose cisplatin may reduce these toxicities and the

inconvenience of hospitalization for vigorous hydration and so this would improve the compliance of patients. As expected, no grade 3/4 nephrotoxicity, nausea and vomiting were observed in this study. However, the incidence of grade 3/4 neutropenia, thrombocytopenia and infection were more frequently observed in this study, as compared with the previous trials of gemcitabine and cisplatin. This incidence of grade 3/4 neutropenia, thrombocytopenia and infection in our study could be explained by the FDR infusion of gemcitabine and the characteristics of the elderly or poor performance status patients. These factors may be negatively involved in hematologic toxicity profiles of this study, as compared with the other previous trials that used conventional infusion of gemcitabine and cisplatin.

To date, several clinical trials have reported that monotherapy using gemcitabine, vinorelbine or taxane drugs showed a lower incidence of toxicities with inferior efficacy in elderly or poor performance status patients, as compared with the previous combination chemotherapy [5–8, 25, 26].

To maximize the chemotherapeutic efficacy, a FDR infusion of gemcitabine has been reported to increase the intracellular concentration of gemcitabine, as compared to the standard infusion rate (800–1,200 mg/m^2 over 30 min); thus, this enhances its cytotoxic effect and patient survival [20, 21, 27].

The previous three randomized II trials that combined platinum with FDR infusion versus a standard infusion of gemcitabine for treating NSCLC patients have shown inconsistent results. The first Italian randomized phase II study showed higher response rates for the FDR infusion arm [21], whereas the second Italian trial showed no differences between the standard infusion arm and the FDR infusion arm in terms of efficacy, but the FDR arm showed inferior hematologic toxicities [28].

A Brazilian trial also showed no significant differences for the response rate and patient survival, but unfavorable hematologic toxicities occurred in the FDR infusion arm of this trail [29].

According to the Korean phase II study that used conventional infusion of gemcitabine plus split-dose cisplatin in patients with unresectable NSCLC, the overall response rate was 51% and the median TTP and OS were 6 months and 13.1 months, respectively [16]. This study reported that grade 3/4 neutropenia was observed in eight patients (18%) and there was only one patient (2%) that suffered grade 3 vomiting. Yet this study showed a relatively good ECOG performance status (0 or 1) in most of the enrolled patients (82%). According to the Korean phase II trials that used a FDR infusion of gemcitabine combined with cisplatin, grade 3/4 neutropenia was observed in 14 patients (37%) and febrile neutropenia was observed in four (11%) [27]. This phase II study reported an overall response rate of 48.6%, a median OS of 14.7 months and a median TTP of 5.4 months. Of the 37 total patients, 34 (92%) patients had a good ECOG performance status (0 or 1) [27].

In a previous trial of 3-week scheduled combination chemotherapy of gemcitabine and cisplatin in 46 elderly patients who were aged 65 years or older, the overall response rate was 45.6% (95% CI: 31.3–60) and the TTP was approximately 8 months [30]. In regards to the hematologic toxicity, grade 3/4 neutropenia was observed in 22% of the patients with manageable minimal non-hematologic toxicities. However, in that previous study, there were 35 patients (76%) with an ECOG 0–1 performance status, whereas 38 patients (79.2%) had an ECOG 2 performance status in our study.

In conclusion, fixed dose rate infusion of gemcitabine and weekly cisplatin is effective in an outpatient setting for elderly or poor performance status patients with unresectable NSCLC. Nevertheless, physicians should carefully consider the higher incidence of neutropenia and infection, as compared with the previous studies that used a standard infusion of gemcitabine combined with cisplatin or the studies that enrolled good performance status patients [12–14, 31].

Further randomized phase II and III studies need to be performed to weigh the risks and benefits of weekly cisplatin combined with a FDR infusion of gemcitabine, and especially for elderly patients or poor performance status patients with NSCLC.

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