Gemcitabine and cisplatin treatment of advanced-stage non-small-cell lung cancer in patients given cisplatin on day 8

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ABSTRACT

Aims and background. Gemcitabine and cisplatin treatment were administered to patients with advanced-stage, non-small-cell lung cancer. During phase II studies, the treatment is performed using a 28-day cycle, with gemcitabine administered on days 1, 8, and 15. Although it is advised that cisplatin not be administered on the first day, gemcitabine and cisplatin treatment is usually performed using a 21-day cycle, with gemcitabine administered on days 1 and 8, and cisplatin is given on the first day in most phase III studies. In contrast with previous phase III studies, cisplatin was administered on day 8 in our study. Dose density, drug toxicity, and efficacy were analyzed.

Methods and study design. Chemonaive patients with stage IIIB or stage IV non-small-cell lung cancer received gemcitabine (1250 mg/m²) on days 1 and 8 plus cisplatin (75 mg/m²) on day 8 every 3 weeks (1 cycle contained 2 applications).

Results. Sixty-seven patients received a total of 293 applications. Dose densities were 92.3% for gemcitabine and 93.9% for cisplatin. The types and rates of grade 3 and grade 4 hematologic toxicities were anemia (6%), granulocytopenia (46%), and thrombocytopenia (6%). Complete remission was seen in 2 patients (3%); partial remission was 40%, stable disease was 39%, and progression of disease, 10%. The median overall survival time was 13 months. The median progression-free survival time was 9.5 months. One-year survival rate was 54% and 2-year survival, 10.4%.

Conclusions. In this 21-day treatment regimen, overall survival was longer than 1 year and the 1-year survival rate was more than 50%. Both the severity and rate of observed thrombocytopenia in the study were very low. Other adverse effects in the current study were comparable to those reported in the literature.

Introduction

Chemotherapy treatment in advanced stage (stage IIIB/IV) non-small-cell lung cancer (NSCLC) has favorable effects on patient survival and quality of life. One platinum drug, usually cisplatin or carboplatin, combined with another antineoplastic drug comprises the first-line treatment. Although three-drug combinations have been used in recent trials and most of them demonstrated high response rates, their survival rates were similar to two-drug combinations, and more toxicities have been shown. Therefore, two-drug combinations are usually preferred. However, it should be noted that Paccagnella et al. demonstrated a survival advantage by adding gemcitabine to the paclitaxel/carboplatin combination. A combination of cisplatin plus gemcitabine has been found to be superior to the previous combination of cisplatin plus etoposide. Other two-drug combinations using cisplatin with gemcitabine, vinorelbine, paclitaxel or docetaxel in advanced-stage NSCLC patients have been tried, but all of the combinations demonstrated nearly the same effect on tumor dimensions and patient survival. Some meta-analyses suggested that the gemcitabine

Key words: cisplatin, gemcitabine, non-small-cell lung cancer.

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plus platinum drug combination has a small survival advantage over other combinations. According to one meta-analysis of advanced-stage NSCLC, overall survival was 9 months, median progression-free survival (PFS) was 5.1 months, and the 1-year survival rate was 40% for gemcitabine-based treatments. Usually, a gemcitabine-platinum combination is less expensive than other combinations. Gemcitabine is frequently combined with carboplatin and more recently with oxaliplatin. Consequentially, gemcitabine plus platinum is frequently used as an effective and inexpensive combination as a first-line treatment for NSCLC.

Different schedules of platinum plus gemcitabine combinations have been used to minimize toxic effects without compromising antitumor effects. In phase II trials, cycle lengths have been 28 days with gemcitabine (1000 mg/m²) administered on days 1, 8 and 15. These studies were analyzed in separate publications. suggested that gemcitabine be administered on the first day and that the platinum be administered on another day of the cycle to ensure better survival rates. However, in later phase III studies, the cycle length was 21 days, gemcitabine was administered on days 1 and 8, and the platinum was usually administered on the first day.

In one phase III trial, gemcitabine plus cisplatin was compared with cisplatin plus etoposide; cisplatin (100 mg/m²) was administered on day 1, and gemcitabine (1250 mg/m²) was administered on days 1 and 8. Response rates and PFS were better in the gemcitabine-cisplatin arm. After this trial, cisplatin was administered at a dosage lower than 100 mg/m², and a cycle length of 21 days was used in phase III trials. Some of these trials are summarized in Table 1. Over one Korean study, overall survival ranged from 8.7 to 11 months, and 1-year survival rates were 32%-44%.

Additional studies were found in which gemcitabine and a platinum drug were administered on day 8 but combined with carboplatin instead of cisplatin. In one of these studies, gemcitabine (1100 mg/m²) was administered on days 1 and 8, and carboplatin was administered at an AUC of 5 on day 8. In another study, gemcitabine (1000 mg/m²) was administered on days 1 and 8, and carboplatin was administered at an AUC of 5 on day 8. The response rates were similar in these two studies, but the reported severity of thrombocytopenia was lower than with the previous gemcitabine plus carboplatin studies.

In our study, for advanced-stage NSCLC patients, we followed the advice of Shepherd et al. and did not administer cisplatin in combination with gemcitabine on day 1. Instead, we administered cisplatin (75 mg/m²) on day 8 and gemcitabine (1250 mg/m²) on days 1 and 8, every 21 days. We thought that this application was the best replacement for the schedule that Abratt et al. published in 1997, which was every 28 days. Abratt et al. combined gemcitabine (1000 mg/m²) on days 1, 8 and 15 with cisplatin on day 15, and the phase II study demonstrated some of the best survival and tumor response rates. Both the study of Abratt et al. and ours used gemcitabine alone for 1 week prior to cisplatin; patients received no treatment for 14 days between the second cycle and cisplatin administration.

### Patients and methods

#### Patients

Histologically or cytologically confirmed NSCLC patients, whose disease was staged as IIIB or IV according to the American Joint Committee on Cancer staging system (AJCC, 1997), whose performance status was between 0 and 1.

### Table 1 - Cisplatin + gemcitabine schedules and results of phase III studies

<table>
<thead>
<tr>
<th>Gemcitabine</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/m²) Day</td>
<td>Dose (mg/m²) Day</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1200</td>
<td>1+8</td>
</tr>
<tr>
<td>1200</td>
<td>1+8</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1000</td>
<td>1+4</td>
</tr>
<tr>
<td>1250</td>
<td>1+8</td>
</tr>
<tr>
<td>1200</td>
<td>1+8</td>
</tr>
</tbody>
</table>

*Combined result with both gemcitabine-cisplatin and cisplatin-vinorelbine arm.
1Includes only stage IIIA and IIIB patients.
2Grn and Plt rate is calculated per cycle, according to WHO criteria.
Treatments schedule was approved by the local research and ethics committees. Patients with active infection, serious concomitant systemic disorders, second primary malignancies (except in patients with active infection, serious concomitant systemic disorders, second primary malignancies except in patients with active infection, serious concomitant systemic disorders, second primary malignancies), or pregnancy were excluded from the study. Written informed consent was obtained from each patient. Patients with bidimensionally measurable masses. These masses were assessed in all patients. Adverse events were scored between 0 and 5 (5 meaning death due to toxicity) according to the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 3 (CTCAE V3).

Response evaluation and follow-up

Medical history, physical examination, complete blood count, electrocardiography, chest radiograph, blood chemistries, and calculated creatinine clearance were assessed in all patients. Additional assessments included computed tomography (CT) of the chest, bone scintigraphy, and abdominal ultrasonography or CT to detect liver and suprarenal metastases. CT or magnetic resonance imaging of the brain was obtained if brain metastases were suspected. Tumor responses were defined as complete response (CR; complete disappearance of all clinically detectable malignant disease on 2 occasions at least 4 weeks apart), partial response (PR; a reduction of at least 50% of the tumor size as determined on 2 occasions at least 4 weeks apart with no appearance of new lesions or progression of any lesion), progressive disease (PD; an increase in the size of 1 or more lesions of 25% or more or the appearance of a new lesion), and stable disease (SD; no response or progressive disease demonstrated during the first 8 weeks of treatment). Response durations were measured from the date of diagnosis to progression date if the response was SD, and from the observation of response to progression date if the response was a PR or a CR. Overall survival was calculated as the interval between date of diagnosis and death. PFS was measured from the date of diagnosis until observation of PD. Toxicities were scored between 0 and 5 (5 meaning death due to toxicity) according to the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 3 (CTCAE V3). Complete blood count, blood urea nitrogen and creatinine levels were measured before every application. Complete biochemistry profiles were assessed prior to chemotherapy administration during every cycle. Chest radiographs were obtained and assessed every 2 cycles if there were no lung symptoms. Chest CT was performed after cycle 3 and cycle 6, or prior to radiotherapy or curative surgery.

Statistics

There was no control group; all patients were given the same treatment. Patient and disease characteristics, response rates, survival rates, and toxic effects are presented as percentages. Age and survival times are presented as median values with lower and upper limits.
Survival curves were plotted according to the Kaplan-Meier method using SSPS software (Statistical Package for the Social Sciences, version 11.5, SSPS Inc, Chicago, Ill, USA). Ninety-five percent confidence intervals (CI) are given where appropriate.

Results

Patient and disease characteristics

From December 2000 to February 2006, 67 patients were treated and evaluated. Patient characteristics are summarized in Table 2. The median follow-up was 13 months (range, 1.5-48; 95% CI, 11.42-14.58). Fifty-eight patients (86.5%) died, and 9 (13.5%) were alive at the time of this writing. Thirteen bone, 10 brain, 2 suprarenal gland, 1 pericardial, and 1 leptomeningeal metastases occurred during follow-up. Median age was 62 years (range, 44-78).

Treatment administration

The mean dose for gemcitabine was 1154 mg/m² (92.3% of the planned dose). The mean dose for cisplatin was 70 mg/m² (93.9% of the planned dose). Six cycles were planned for 49 patients (73%), 4 cycles were planned for 14 patients (21%), and 3 cycles were planned for 4 patients (6%). A median of 4 chemotherapy cycles was given (mean, 4.3; 95% CI, 0.5-6) at a median of 13.5 weeks. A total of 288 cycles was performed in 67 patients. Drugs were given to 25 patients without any delay. Treatment was delayed 1 time in 16, 2 times in 15, 3 times in 4, and 4 or more times in 7 patients.

Fourteen stage IIIB patients (53%) received radiotherapy for a primary lung mass, one (3.5%) stage IIIB patient was operated with a curative intent, and one patient was treated with both radiotherapy and surgery. Responses to gemcitabine plus cisplatin were assessed and reported before radiotherapy in these patients. These 16 patients were excluded from PFS analysis.

Forty patients (60%) received second-line chemotherapy after the disease had progressed. These schedules were cisplatin plus docetaxel in 18 (27%), docetaxel only in 15 (22%), cisplatin plus vinorelbine in 3 (4.5%), and other schedules in 4 (6%) patients. Five patients (7%) received third-line chemotherapy. Twenty-two patients received cisplatin-containing salvage regimens. Four of them were not responsive to gemcitabine-cisplatin, 16 of them had SD or PR duration of at least 3 months. Overall survival of 4 unresponsive stage IV patients was 5, 6, 14 and 17 months.

Responses

Two (2%) radiological CR and 27 (40%) PR were obtained. Responses were SD in 26 patients (39%) and PD in 7 (10%). Five patients (7.5%) could not be assessed for the responses – 4 owing to toxicity and 1 because of death at home for unknown reasons prior to the second cycle. Responses according to stages are given in Table 3.

Toxicity

Treatments were terminated in 9 patients (13.4%) owing to toxicity. Three of these patients (4.5%) died. The reasons for death were neutropenic infection, nonneutropenic sepsis, and cerebral infarction after orthopedic surgery for a traumatic (nonmetastatic) bone fraction. Hematologic toxicities are shown in Table 4. Only 1 pa-
tient experienced long-term hematologic toxicity requiring 4 units of platelets and 6 units of erythrocytes. Nonhematologic toxicities are shown in Table 5. Additionally, nausea and vomiting occurred: grade 2 in 6 (9%), grade 3 in 5 (7.5%), and grade 4 in 3 (4%) patients.

Table 5 - Nonhematologic toxicity (according to CTC V3)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5 (death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>5 (7.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2 (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>6 (9)</td>
<td>-</td>
<td>-</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (10)</td>
<td>3 (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9 (13)</td>
<td>3 (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1 (1.5)</td>
<td>3 (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In parenthesis, percentage.

**PFS and response duration**

Median PFS for 46 patients who had known responses (5 patients were not assessed for the response) and who were treated with chemotherapy only (16 patients were also treated with radiotherapy or surgery) was 8.0 months (95% CI, 7.11-8.89). Median response duration was 6.0 months (mean, 6.4; 95% CI, 7.3-10.3). According to the responses, median response duration was 7.0 months for CR (1 patient), 6.5 months (mean, 7.8; 95% CI, 5.5-10.2) for PR (20 patients), and 6.5 months (mean, 7.3; 95% CI, 4.9-9.9) for SD (18 patients).

**Survival time**

The median overall survival was 13 months (95% CI, 11.5-14.5). For 51 patients treated with chemotherapy only, the median overall survival was 12.0 months (95% CI, 10.2-13.7) (Figure 1). When ranked according to stages, the median overall survival was 15 months (95% CI, 9-21) for stage IIIB and 12.0 months (95% CI, 10.0-14.0) for stage IV patients (Figure 2). The 1-year survival rate was 54% for all patients (36 patients). When ranked according to stages, the 1-year survival rate was 61% (17 patients) for stage IIIB and 49% (19 patients) for stage IV patients. The 2-year survival rate was 10.4% (a total of 7: 4 stage IIIB and 3 stage IV patients) for all patients.

**Discussion**

Our survival rates – more than 1-year overall survival and more than 50% 1-year survival rates – indicate a highly effective schedule. Docetaxel-containing second- and even third-line antineoplastic drugs may have contributed to these survival results. A long PFS of 8.0 months independent of second- and third-line drugs also shows the effectiveness of this schedule. There are few publications demonstrating activity of platinum-containing regimens in a second-line setting. Platinum sensitivity was required in the study of Song et al.25 but not required in that of Hamada et al.26 Two of 4 patients who were unresponsive to gemcitabine-cisplatin but who received platinum-containing second-line treatments lived longer than 1 year in our study. Grade 3 or 4 thrombocytopenia reached 50% in other gemcitabine-cisplatin studies; our rate of 6% is lower. Thrombocytopenia also was not clinically important, because our patients did not experience bleeding or petechiae. We de-
layed administration when the platelet count was below 100×10^9/L, but some authors have administered gemcitabine with or without reduced doses when the platelet count was above 75×10^9/L. If we had done this, our delay rates would have been much lower. Our grade 3 and 4 granulocytopenia rates are consistent with those of other studies. Only 1 patient died for a neutropenic infection. One patient died because of a nongranulocytic infection. One patient had a nonmetastatic femur fracture during chemotherapy administration and then died after experiencing a deep vein thrombosis and cerebral infarction. It is unlikely that this patient died owing to the direct toxic effects of chemotherapy. Drug-related mortality was thus 3% and was comparable with other studies (Table 1).

Cycle lengths were 28 days in the first gemcitabine-cisplatin combination studies, and gemcitabine was administered on days 1, 8, and 15. When cisplatin was administered on day 1, gemcitabine was frequently omitted on day 8 or 15 because of hematologic (mainly thrombocytopenia) toxicity. The best survival results were obtained if cisplatin was administered on day 2 or day 15 in these phase II studies. Shepherd et al. and Abratt et al. believed that the optimal way to administer these two agents was with a loading course of gemcitabine followed later in the treatment cycle by cisplatin. Unfortunately, most randomized trials of gemcitabine and cisplatin using either a 28- or 21-day cycle administered gemcitabine and cisplatin together on day 1. Practically, it was difficult to administer cisplatin on day 2, but there are no published data about administering the two drugs together on day 8.

Gemcitabine pretreatment negatively affects the intracellular pharmacokinetics of cisplatin when administered 4 hr before cisplatin. Moreover, treatment of cancer patients with cisplatin 24 hr before gemcitabine led to the highest active gemcitabine accumulation in WBC and total platinum in plasma. The schedule may increase tumor response but also worsens side effects. There is no consensus on the sequence of the drugs, and some authors also administered gemcitabine first, similar to our study (Table 1).

References


