Abstract. Background: The aim of this study was to evaluate the effectiveness of cisplatin- (CDDP) combined chemotherapy in non-cisplatin pretreated patients with non-small-cell lung cancer (NSCLC). The second cytotoxic drug administered was either etoposide or gemcitabine. First-line treatment was based on paclitaxel combined with either carboplatin or vinorelbine. Patients and Methods: Seventy-eight patients with histologically- or cytologically- confirmed NSCLC, having failed front-line treatment, were enrolled. All patients received 80 mg/m² of cisplatin as second-line treatment, on day 1, repeated every 3 weeks; in 48 patients the second agent was etoposide (120 mg/m²) on days 1, 2 and 3, repeated every 3 weeks and in 30 patients 1 g/m² of gemcitabine on day 1, repeated every 3 weeks. Results: All patients were evaluable for response and toxicity. No complete responses were observed. Thirteen (16.67%) patients achieved partial response, 42 (53.85%) stable disease and 23 (29.49%) had disease progression. The median duration of response was 4 months (range 2-8+ months), median time to tumor progression (TTP) 5 months (range 2-9 months) and median survival time after starting second-line chemotherapy, 6 months (range 2-9+ months). Toxicity was acceptable: 9 patients presented with nephrotoxicity (11.54%) and 13 (16.67%) with grade 3-4 neutropenia. Conclusion: The cisplatin combination as second-line treatment in patients with NSCLC exhibited a notable degree of activity and tumor growth control was evidenced by the 16.67% partial response and 53.85% disease stability.

Treatment of advanced non-small cell lung cancer (NSCLC) with newer cytotoxic agents, versus previous cytotoxic combinations including cisplatin, does not appear to have increased response rate and survival. Chemotherapy has rendered an improvement in survival in metastatic NSCLC, as reported in a meta-analysis of relevant studies (1). Large randomized trials related to the treatment of stages IIIB and IV are indicative of this (2, 3). There is a high percentage of non-responders and also of responders who relapse within a short time period. After first-line chemotherapy, patients may still have a reasonably good performance status, thus inspiring the need for further management in order to increase survival and improve the quality of life. Second-line chemotherapy treatment trials, chiefly with the recent pool of cytotoxic agents, have been carried out. Older agents such as etoposide, vindesine, epirubicin or even cisplatin have not shown a response rate of over 10% (4). Similar or higher responses have been produced by agents such as gemcitabine, vinorelbine and paclitaxel (5-11) and by docetaxel, as single-agent therapy (12-14). Cisplatin has only infrequently been applied as second-line treatment in pretreated patients with NSCLC. The existing cisplatin trials mainly utilize new agents (15). The majority of second-line chemotherapy schedules are related either to combinations of newer agents (10, 16-22) or single-agent chemotherapy (23-26) in patients pretreated with cisplatin-combined schedules.

In the present trial, cisplatin-based second-line chemotherapy was administered in combination with other agents considered to be first-line cytotoxic drugs for NSCLC, to patients who had had a non-cisplatin front-line combination. Our main objective was to determine the response rate and, secondly, to evaluate tolerance and survival.

Patients and Methods

Statistical design. In this two-step phase II study, 30 patients were to be initially enrolled and, if an objective response rate of <10% were observed, the treatment would have been abandoned; otherwise at least 20 more patients were to be enrolled. The primary end-point was the efficacy of the regimen and the secondary end-point was duration of response calculated from the...
Table I. Second-line chemotherapy schedules.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Drug</th>
<th>Dosage</th>
<th>Day</th>
<th>Every 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>Cisplatin</td>
<td>80 mg/m²</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>120 mg/m²</td>
<td>Days 1,2,3</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>30</td>
<td>Cisplatin</td>
<td>80 mg/m²</td>
<td>Day 1</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>1 g/m²</td>
<td>Day 1</td>
<td>Every 3 weeks</td>
</tr>
</tbody>
</table>

Table II. Patients’ characteristics at start of second-line chemotherapy*.

| No. of patients enrolled | 78 | 100 |
| No. of patients evaluable | 78 | 100 |

Gender

- Male: 69 (88.46)
- Female: 9 (11.54)

Age (yr)

- Median: 62
- Range: 42-75

Performance status (WHO)

- 0: 2 (2.56)
- 1: 31 (39.74)
- 2: 45 (57.69)

Histology

- Adenocarcinoma: 43 (55.13)
- Squamous cell: 24 (30.77)
- Undifferentiated: 9 (11.54)
- Large cell: 2 (2.56)

Stage

- IIIA: 9 (11.54)
- IIIB: 30 (38.46)
- IV: 39 (50.00)

*Prior treatment: paclitaxel with carboplatin or vinorelbine

Evaluation of patients. Baseline evaluation included medical history, physical examination, tumor measurement or evaluation, WHO performance status, ECG, full blood count, liver and renal function tests, urinalysis, chest and abdominal computed tomography, bone scan and occasional magnetic resonance imaging. Blood count, blood urea and serum creatine were examined before each treatment administration and 7 days after each course. Radiological tests were conducted after 2 courses of treatment or if the clinical signs were indicative of disease progression. Response and toxicity were assessed using standard WHO criteria, as follows: complete response (CR), the disappearance of any sign of demonstrable disease; partial response (PR), ≥50% reduction of measurable disease; and stable disease (SD) <50% decrease of measurable disease or up to 25% increase. The duration of response was measured from the time of documentation of response (CR or PR) to progressive disease. Time to disease progression was measured from the time of the first dose administration to disease progression. The determination of objective response on computed tomography was performed by two independent radiologists and two experienced oncologists.

Results

Demographics. From January 2002 until April 2004, 78 patients were enrolled in the study (Table II). All patients...
had previously undergone paclitaxel-based front-line chemotherapy.

Response. No CR was achieved. All responders had partial tumor regression: 13 (16.67%) patients showed PR, 42 (53.85%) SD and 23 (29.49%) had disease progression (Table III). The median response duration was 4 months (range 2-8+ months), the TTP was 5 months (range 2-8 months) and the median survival from the beginning of second-line chemotherapy was 6 months (range 2-9+ months). There was no difference in the response rate of those treated with cisplatin-etoposide and those with cisplatin-gemcitabine ($p=0.85$).

Toxicity. The main adverse reactions were nausea/vomiting, myelotoxicity and nephrotoxicity. Generally, toxicity was acceptable; a small percentage (11.7%) had to refrain from treatment due to blood urea and serum creatine increase after the second or third course. Hematological and non-hematological toxicities are shown in Table IV. There was no difference in the toxicity of cisplatin-etoposide versus cisplatin-gemcitabine.

Discussion

Many studies related to second-line chemotherapy in NSCLC have been published. This is a justified effort since chemotherapy treatment failure in advanced NSCLC is common, either due to the ineffectiveness of first-line chemotherapy or to recurrence after the initial response. Reviewing the existing data, the great majority of second-line treatments consist of combinations or single-agent chemotherapy of the newer, recent cytotoxic drugs, following first-line therapy with cisplatin combinations. Insistence on treating patients with advanced-stage NSCLC is based on studies indicating that chemotherapy (versus supportive care) produces a significant prolongation of survival (27). In a review article (28), some recent agents were considered to be effective when used alone or in combination as second-line treatment. These agents, vinorelbine, paclitaxel, docetaxel, gemcitabine and irinotecan, have also been administered as first-line therapy with effectiveness. The data related to these agents are controversial, rendering either a very low ‘negligible’ response rate or over 20% in patients pretreated with a cisplatin-combined chemotherapy. In one study, single gemcitabine second-line treatment showed a 6% response rate, which is very low, but the therapy was well-tolerated (8), whereas in another study, the same agent produced a 19% objective response rate (29). This difference in response might have been due to the patients’ characteristics: in the latter study, there were more stage III than stage IV patients. Docetaxel, vinorelbine and ifosfamide have been tested, each as single-agent second-line therapy following a cisplatin front-line combination. The objective response rates were quite low: docetaxel at 100 mg/m$^2$ (10.8%) was the most advantageous versus docetaxel at 75 mg/m$^2$ (6.7%) and versus vinorelbine-ifosfamide (0.8%). These researchers concluded that docetaxel does deliver meaningful benefit (24). In another trial with a small number of patients, the response to vinorelbine was 6.5% (19).

In a review related to second-line chemotherapy, such conflicting results were criticized (30). The authors pointed

| Table III. Response. |  |  |  |  |  |  |
|----------------------|------------|------|------|------|------|
| No. of patients | % |  |  |  |  |
| Complete response | - | - |  |  |  |
| Partial response | 13 | 16.67 |  |  |  |
| Stable disease | 42 | 53.85 |  |  |  |
| Disease progression | 23 | 29.49 |  |  |  |

<table>
<thead>
<tr>
<th>Table IV. Hematological and non-hematological toxicities.</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6 (7.69)</td>
<td>5 (6.41)</td>
<td>9 (11.54)</td>
<td>4 (5.13)</td>
<td>24 (30.77)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (10.26)</td>
<td>15 (19.23)</td>
<td>-</td>
<td>-</td>
<td>23 (29.49)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (3.85)</td>
<td>1 (1.28)</td>
<td>-</td>
<td>-</td>
<td>4 (5.13)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>23 (29.49)</td>
<td>2 (2.56)</td>
<td>-</td>
<td>-</td>
<td>25 (32.05)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (2.56)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (2.56)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.56)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (2.56)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>20 (25.64)</td>
<td>6 (7.69)</td>
<td>-</td>
<td>-</td>
<td>26 (33.33)</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>6 (7.69)</td>
<td>3 (3.85)</td>
<td>-</td>
<td>-</td>
<td>9 (11.54)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (5.13)</td>
<td>6 (7.69)</td>
<td>-</td>
<td>-</td>
<td>10 (12.82)</td>
</tr>
<tr>
<td>Allergy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
out: that a more general definition of drug resistance would be appropriate versus resistance to platinum only, that selection criteria for second-line treatment for NSCLC patients have not yet been defined, that guidelines for second-line NSCLC treatment based on clinical information on drug sensitivity to first-line therapy need to be developed and that more direct comparisons between well-defined groups of patients should be made (30). The same critical comments might be made with regard to several other studies. The combination of docetaxel with gemcitabine after cisplatin-related treatment was administered in NSCLC patients and the partial response rate was 15.6% with stable disease at 34.4% (31). Another second-line combination of docetaxel, this time with vinorelbine, showed a similar response rate (18%) with stable disease at 41% (22). A low response rate was observed in the application of paclitaxel as a single agent in second-line therapy in NSCLC: only 2 out of 64 patients (3%) had a partial response (9). Another trial, again using paclitaxel on a weekly basis, produced a higher second-line treatment response rate of 21% (32). From all of the different studies related to second-line chemotherapy after cisplatin, the dominating assumption is that docetaxel is the preferable treatment (10,33-35); some authors suggest that docetaxel may be the gold standard in second-line chemotherapy (11, 36).

Very few studies related to non-cisplatin front-line chemotherapy and a cisplatin combination second-line treatment have been reported. Two studies by Kakolyris et al. combined cisplatin with irinotecan as second-line chemotherapy in patients with NSCLC who had undergone previous treatment with a docetaxel-based therapy (with either carboplatin or gemcitabine as the second drug) (15,37). The cisplatin fixed dose was 80 mg/m² and that of irinotecan 100 mg/m² on day 1 and 110 mg/m² on day 8 repeated every 3 weeks. The partial response rate was 20% with a median response duration of 4 months and 20% disease stability, but disease progression was 58%. The authors interpreted the rather high response rate as being due to the lack of complete cross-resistance between the drug combinations. Another study tested second-line chemotherapy with cisplatin and vinorelbine in patients with NSCLC pretreated with paclitaxel and gemcitabine. The dose of CDDP was 80 mg/m² on day 1 and that of vinorelbine 25 mg/m² on days 1 and 8, both drugs repeated every 3 weeks; the number of patients was small (seventeen) and the responders were 3 (18%) (38). In another trial (39), second-line therapy included carboplatin instead of CDDP, combined with vinorelbine in patients who had failed a taxane-based treatment. Of the 37 treated patients, a 16% response rate was observed. These authors commented on a statistically significant benefit in patients with response and with disease stability over patients with disease progression. The present study, with cisplatin at 80 mg/m² combined with etoposide or gemcitabine, showed a PR rate of 16.67% with a median response duration of 4 months; stable disease was observed in 53.85% and 29.49% had disease progression. Minor differences between the previous study and ours might be due to the other cytotoxic drug which was used in combination with cisplatin.

The use of well-established agents (used over a long period of time in combination with cisplatin in front-line therapy) in our second-line chemotherapy trial rendered acceptable toxicity with the main adverse reactions being nausea/vomiting and nephrotoxicity to a mild degree.

Cisplatin combinations as second-line treatment do offer benefit to a minority of patients and the responses are at a similar level to that of non-cisplatin combinations when the latter are also used as second-line treatment.

In conclusion, the use of cisplatin combinations as second-line chemotherapy seems to have a place in the management of patients with advanced NSCLC. Although partial responses are not high, when taking into account the high percentage of disease stability (and since non-cisplatin combinations are generally preferable as front-line treatment), the cisplatin-based chemotherapy could be used in patients with normal renal function.

References


