Abstract. This study evaluated the activity and toxicity of a weekly paclitaxel plus gemcitabine combination as second-line treatment in patients with advanced non-small cell lung cancer (NSCLC). Paclitaxel 80 mg/m² on days 1, 8 and 15 and gemcitabine 1000 mg/m² on days 1 and 8 every 3 weeks were administered to 34 consecutive, advanced NSCLC patients uniformly pretreated with cisplatin or carboplatin and vinorelbine. The median time interval from first- to second-line treatment was 8 weeks (range 1-72). A total of 124 cycles with a median of 3 cycles per patient were administered (range 1-6). Four patients (12%) achieved a partial response (95% confidence interval: 1-23%), 17 had stable disease (50%) and 12 progressed (37%). Three responses were observed in 14 patients showing disease response or stabilization to previous platinum therapy. The median survival was 28 weeks (range 3-91), the median progression-free survival was 12 weeks (range 3-50) and the 1-year survival rate was 23%. The toxicity profile was favorable. In conclusion, a weekly schedule of paclitaxel plus gemcitabine as a second-line regimen has moderate activity and good tolerability in NSCLC patients not refractory to previous platinum-vinorelbine treatment.

Non-small cell lung cancer (NSCLC) represents a major health problem in Western countries (1). Currently, cisplatin- or carboplatin-based therapy is considered the standard treatment for patients with advanced disease (2). Randomized clinical trials and a meta-analysis have shown that, when compared with supportive care, platinum-based regimens significantly prolong survival and provide relief of symptoms and improved quality of life (3,4). However, the benefit from combination chemotherapy still remains modest, since an important proportion of advanced NSCLC patients fail to respond to front-line treatment, while the remaining patients are likely to relapse after an initial response. Until recently, few patients who progressed on first-line therapy went on to receive subsequent chemotherapy. However, as newer and more effective chemotherapy agents become available, this situation is changing. Of the second generation agents that have been tested in previously treated NSCLC, docetaxel appears the most promising. It is the only agent to have been studied in randomised phase III trials (5,6) and it is the only currently approved therapy for treatment-refractory NSCLC patients in Europe.

Paclitaxel as a single agent or in combination has been repeatedly found to be active in previously untreated NSCLC patients, with response rates ranging from 10% to 38% and median survival ranging from 6 to 11 months (7). This drug has not been systematically studied in a second-line setting and the available data are conflicting (8). An important clinical issue regarding paclitaxel is the optimal schedule. Preclinical evaluation has shown that frequent administration of paclitaxel provides better therapeutic effects than delayed schedules (9,10). This dose-dense approach may inhibit tumor re-growth between cycles and enhance the apoptotic and antiangiogenetic effects of the drug (11,12). Preliminary experience of weekly paclitaxel administered to NSCLC patients suggests that this schedule is not only effective and well-tolerated, but is also able to maintain the planned dose intensity (13). In a recently published prospective randomized phase II trial involving NSCLC patients previously treated with platinum-based
chemotherapy, weekly paclitaxel showed similar activity but lower non-hematological toxicity than weekly docetaxel (14). This result suggests that, in studies testing the activity of taxanes administered on a weekly schedule, paclitaxel may be preferable to docetaxel.

Gemcitabine is notoriously active against NSCLC both as first- and second-line treatment (15,16). Paclitaxel and gemcitabine exert their cytotoxic effects through different mechanisms and display different toxicity profiles, providing a rationale for the combination of the two drugs. In two phase III trials (17,18), the paclitaxel and gemcitabine doublet was demonstrated to have an efficacy similar to standard platinum-based combinations. The low toxicity profile makes this association also applicable in pretreated patients. Cisplatin (or carboplatin) and vinorelbine is a widely employed first-line treatment for advanced NSCLC (19). In patients refractory to this regimen, or who relapse, the association of paclitaxel and gemcitabine appears to offer a reasonable treatment option. Some activity was reported for the combination of paclitaxel and gemcitabine as tested in two phase I-II studies involving cisplatin-pretreated NSCLC. In both studies, paclitaxel was administered every 3 weeks and gemcitabine every week (20,21). In a prospective phase II trial involving chemotherapy-naive metastatic NSCLC (22), weekly paclitaxel and gemcitabine was found to be extremely active, leading to a 55% overall response rate. These findings are consistent with the notion that the schedule of paclitaxel administration, and dose-dense delivery in particular, may have a significant influence on the activity of the combination regimen.

In this study the activity and toxicity of weekly paclitaxel associated with gemcitabine were tested in a single institution phase II trial as a second-line approach in a consecutive series of NSCLC uniformly pretreated with cisplatin and vinorelbine.

Patients and Methods

Eligibility criteria. Patients were required to have histological or cytological evidence of NSCLC, locally advanced or metastatic disease and progressive lesions after first-line platinum-based chemotherapy. Other eligibility criteria were: presence of at least one bi-dimensionally measurable tumor site (target lesions) outside of a previously irradiated area; age between 18 and 75 years; an ECOG Performance Status (PS) of 0 to 2; life expectancy of at least 12 weeks; adequate bone marrow reserves defined as an absolute neutrophil count (ANC) ≥2,000/mm³; platelet count (PLTS) ≥100,000/mm³ and hemoglobin level ≥10.0 mg/dL; adequate renal and hepatic function [serum creatinine ≤1.5 mg/dL, serum bilirubin, AST and ALT ≤1.5 times the upper normal limit (UNL), alkaline phosphates ≤2 times UNL, except in case of bone metastases]. Exclusion criteria were: previous treatment with regimens other than cisplatin or carboplatin and vinorelbine; more than one previous chemotherapy line; the presence of prior malignancies (except for basal cell carcinoma of the skin or carcinoma in situ of the cervix); a pre-existing WHO Grade ≥2 sensory neuropathy; a history of recent (6 months) myocardial infarction, congestive heart failure or a history of atrial or ventricular arrhythmia requiring medical treatment. Prior radiotherapy was allowed as long as the irradiated area was not the only source of measurable disease and the therapy was completed at least 3 weeks before enrolment in the study. Brain or leptomeningeal involvement was not considered to be an exclusion criterion if the patient presented with another metastatic target lesion. The study was approved by our Institutional Review Board. Written informed consent was obtained from all patients.

Assessment of response and toxicity. Baseline evaluation included medical history, physical examination, ECOG-PS assessment,
Table II. Toxicity (WHO criteria).

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>3(9%)</td>
<td>16(47%)</td>
<td>14(41%)</td>
<td>3(9%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>9(27%)</td>
<td>2(6%)</td>
<td>7(21%)</td>
<td>3(9%)</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>19(56%)</td>
<td>10(29%)</td>
<td>2(6%)</td>
<td>3(9%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>24(70%)</td>
<td>14(41%)</td>
<td>9(27%)</td>
<td>4(12%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26(76%)</td>
<td>3(9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>28(82%)</td>
<td>4(12%)</td>
<td>2(6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>10(29%)</td>
<td>9(27%)</td>
<td>6(17%)</td>
<td>7(21%)</td>
<td>3(9%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>23(67%)</td>
<td>8(24%)</td>
<td>3(9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18(52%)</td>
<td>4(12%)</td>
<td>4(12%)</td>
<td>5(15%)</td>
<td>3(9%)</td>
</tr>
</tbody>
</table>

NOTE. The most severe instance of toxicity was taken into account for each patient.

Dose modifications were performed as follows: on day 1 of each new cycle the drugs were administered at full doses if the ANC was ≥1,500/mm³ and the PLTS ≥100,000/mm³; otherwise, the cycle was delayed until recovery or a maximum of 3 weeks. Patients went off study if the delay exceeded 4 weeks. On days 8 and 15, paclitaxel and gemcitabine administration was omitted if the ANC was <1,000/mm³ and/or the PLTS <75,000/mm³, while the dose of both drugs was reduced to 75% for a PLTS count between 75,000 and 100,000/mm³ and/or for an ANC count between 1,000 and 1,500/mm³. Whenever febrile neutropenia, grade 4 neutropenia lasting more than 5 days or grade 4 thrombocytopenia occurred, the doses of the two drugs were reduced to 75% in the subsequent cycles. No dose adjustment was performed in case of grade 1 neurotoxicity. In case of grade 2 neurotoxicity, paclitaxel was administered at 50% of the planned dose. In case of grade 3 neurotoxicity or worse, patients were withdrawn from the study. Supportive care included blood transfusion and the administration of analgesic, antiemetic and growth factors as appropriate. Prophylactic use of G-CSF to maintain dose intensity was not permitted.

Relative dose-intensity was defined as the actual weekly doses of each drug at the end of treatment divided by the planned weekly dose.

Statistical analysis. The primary end-point of the study was the assessment of the response rate (intent to treat analysis). According to the optimal two-stage phase II study design of Simon (24), the sample size was assessed in order to refuse response rates ≤5% (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 20% response rate. The upper limit for first-stage drug rejection was no responses out of the first 10 consecutive patients; the upper limit of second-stage rejection was 3 responses out of 29 consecutively enrolled patients. Response duration and survival were assessed using Kaplan-Meier survival curves. A 2-sided significance of the 5% level was applied to all tests. All statistical analyses were performed using the Statistica for Windows software program.

Results

Patients. From June 1999 to June 2002, a total of 34 patients entered the study. All patients were enrolled at the Medical Oncology Unit of Ospedale San Giovanni Battista-Molinette in Turin, Italy. Patient characteristics are listed in
Table I. Most patients were men and had a favorable PS. The predominant histological type was adenocarcinoma; more than 80% of patients had stage IV disease including 18% of cases with brain involvement. First-line chemotherapy consisted of a platinum-based doublet: cisplatin-vinorelbine in 13 patients (38%); carboplatin-vinorelbine in 21 (62%). Six patients (18%) had achieved a partial response to first-line chemotherapy, 8 (23%) had documented stable disease and 20 (59%) had experienced progressive disease. Ten patients (29%) had received radiotherapy to thoracic lesions before enrolment in the study. Twenty patients (58%) had refractory disease defined as progression at or within 3 months of the end of first-line therapy.

*Treatment administered and toxicity.* A total of 124 chemotherapy courses were given, with a median of 3 cycles per patient (range 1-6). The median dose intensity was 69 mg/m²/week for paclitaxel (86% of planned dose) and 588 mg/m²/week for gemcitabine (88% of planned dose). All 34 patients received at least one chemotherapy cycle and were therefore included in the toxicity analysis. The worst toxicities per patient are shown in Table II. The most frequent toxicity was hematological: grade 3 anemia and thrombocytopenia occurred in 3 patients (8%) and grade 3 and 4 neutropenia in 7 (20%) and 3 (9%) patients, respectively. No febrile neutropenia was noted. Severe non-hematological toxicity was uncommon: grade 3 asthenia in 5 patients (15%), grade 3-4 alopecia in 8 (24%) and grade 1-2 sensory neuropathy in 11 (33%). Three patients experienced grade 2 sensorial neuropathy. In all cases, this adverse event occurred at the end of the treatment program and so did not require dose adjustments. One patient without a history of cardiopathy died from documented myocardial infarction 4 days after the first administration of paclitaxel and gemcitabine.

Fourteen cycles (11%) in 13 patients (38%) were delayed for a maximum of 3 weeks because of toxicity, non-neutropenic infections or because of other reasons unrelated to treatment. Dose reductions of both gemcitabine and paclitaxel were required on day 8 in 3 cycles (2%). Gemcitabine and paclitaxel administration on day 8 and paclitaxel administration on day 15 were omitted mainly because of hematological toxicity in 10 cycles (8%) in 5 patients and in 21 cycles (16%) in 12 patients, respectively.

*Activity.* Thirty-three patients were assessable for response; one was not evaluable due to early death. The treatment activity in all enrolled patients according to intention-to-treat analysis is reported in Table III. Four patients (12%) attained a PR (95% confidence interval: 1-23), 17 (50%) had stable disease, while 12 (36%) progressed. The response durations were 12, 12, 13 and 20 weeks, respectively. The median time to progression and the median survival were 12 weeks (range 3-50 weeks) and 28 weeks (range 3-91 weeks), respectively; the 1-year survival rate was 23%. Responder patients stratified by disease response to previous chemotherapy regimen showed 3 (21%) responses documented in 14 patients with a clinical benefit (disease response or stabilization) to first-line treatment, while only 1 out of 20 patients (5%) refractory to platinum and vinorelbine obtained a disease response to second-line treatment.

**Discussion**

The association of cisplatin or carboplatin and vinorelbine is a widely employed first-line chemotherapy in advanced NSCLC (19). Yet virtually all patients ultimately develop disease progression and many of those who maintain a good performance status are offered the option of second-line treatment. Weekly paclitaxel plus weekly gemcitabine has been found to be extremely active in a phase II trial involving chemo-naive NSCLC patients (22). These results look promising for a good activity of this combination regimen as a second-line approach.

In our study of advanced NSCLC patients uniformly pretreated with platinum and vinorelbine, weekly paclitaxel plus gemcitabine was found to be moderately active. The response rate (12%) substantially replicated that of other similar doublets or new generation single agents (25). The main reason for the limited activity of this combination regimen was the low non-cross resistance to the previously administered platinum and vinorelbine regimens. Three major responses after gemcitabine and paclitaxel were, in fact, achieved among the 14 patients showing disease response or stabilization to previous cisplatin (or carboplatin) and vinorelbine, whereas only one disease response was obtained in the 20 patients who progressed after first-line treatment. The median survival of 6.5 months and the 1-year survival rate of 23% fall within the range of those reported in similar studies conducted on patient populations consisting mainly of patients with stage IV disease.

The combination of gemcitabine and paclitaxel as a second-line approach in NSCLC patients had been previously tested in two phase II studies. The treatment activity varied consistently according to patient selection. In one study (20), in which 73% of patients had stage IIIIB disease, the response rate was 38%, whereas in the second (26), which included mostly patients with stage IV disease, the response rate was 18%. In both trials paclitaxel was administered once every 21 days at doses ranging between 175 and 210 mg/m² and gemcitabine (900 and 1000 mg/m²) was administered on days 1 and 8 every 21 days, as in our study. In both trials, the patients had previously been treated with a variety of cisplatin-containing regimens. Androulakis et al. also included a number of patients (14%) pretreated with a non-platinum-containing regimen.
Similarly to our results, the response to second-line paclitaxel and gemcitabine in both the study by Androulakis et al. and that by Iaffaioli et al. was mainly confined to the patient subset that had obtained a disease response to previous first-line chemotherapy.

In a phase I study conducted at Indiana University (27) on pretreated patients with different tumor histologies, a weekly schedule of gemcitabine 1000 mg/m² on days 1, 8 and 15 and paclitaxel 110 mg/m² on days 1, 8 and 15 every 4 weeks was proposed for phase II trials. This schedule, however, was found to be too toxic in a phase II trial that enrolled untreated NSCLC patients only (28). In our study, weekly paclitaxel (80 mg on days 1, 8 and 15 every 21 days) administered in association with gemcitabine (conventional schedule of 1000 mg on days 1 and 8 every 21 days) was well-tolerated by our pretreated patients. The major toxicity was hematological: grade 3-4 neutropenia was observed in 29% of patients. Other treatment-related toxicities were clinically unremarkable. Neurotoxicity is notoriously more frequent when paclitaxel is administered on a weekly schedule than on a 3-week regimen (29). In our patients this side-effect was mild to moderate and never dose-limiting. The absence of severe neurotoxicity in our study could be, at least partly, attributable to the previous administration of carboplatin instead of cisplatin in most patients. A patient without a history of cardiopathy died of myocardial infarction 4 days after the first administration of paclitaxel and gemcitabine. Since both paclitaxel and gemcitabine are not cytotoxic drugs leading to severe cardiotoxicity, it is difficult to attribute this serious adverse event to the treatment administered, even though this possibility could not be excluded.

In conclusion, our study indicates that a weekly paclitaxel plus gemcitabine regimen is safe and moderately active as a second-line approach in advanced NSCLC patients previously treated with platinum and vinorelbine. As reported in two other trials that tested this combination with paclitaxel administered every 3 weeks (20,26), platinum failure is predictive for a lower chance to obtain a disease response to this association. Our results suggest that the administration of paclitaxel at a dose-dense schedule in association with gemcitabine fails to overcome the limited non-cross resistance with platinum and vinorelbine.

References


