Short report

Phase II study of vinorelbine/ifosfamide/cisplatin for the treatment of advanced non-small-cell lung cancer

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Summary

Purpose: to evaluate the combination of vinorelbine, ifosfamide and cisplatin (VIP) in patients with advanced non-small-cell lung cancer (NSCLC).

Patients and methods: Seventy-six untreated patients with stages IIIb-IV NSCLC; the chemotherapy regimen consisted of vinorelbine (25 mg/sqm on days 1 and 8), ifosfamide (3 g/sqm on day 1 with uroprotective mesna), and cisplatin (80 mg/sqm on day 1). The cycles were administered on an outpatient basis every 3 weeks.

Results: Leukopenia was the most frequent toxicity: grades 3-4 neutropenia was observed in 26% of the cycles and 19 episodes of febrile neutropenia were reported in 289 evaluable courses. Filgrastim 5 μg/kg was administered in 27% of the courses. Sixty-seven of 76 patients were evaluable for response: the overall response rate was 51% (95% confidence interval 35%-77%) with 2 complete responses (3%) and 32 (48%) partial responses. No significant differences in response rate were observed according to histology or stage of disease. The median time to progression was 6 months (range 1 to 29+) and the median overall survival 10 months (range 1-33+).

Conclusion: The combination of vinorelbine, ifosfamide and cisplatin in the dose and schedule employed in this trial shows an interesting response rate with acceptable toxicities. This regimen should be tested in the multimodality therapy of stage IIIA/B NSCLC.

Key words: vinorelbine, ifosfamide, cisplatin, non-small-cell lung cancer

Introduction

The role of chemotherapy in advanced non-small-cell lung cancer (NSCLC) treatment is still controversial; however, recent studies have demonstrated that combination chemotherapy can improve the poor prognosis of these patients [1, 2]. Cisplatin remains the most active single agent but new drugs including ifosfamide, vinorelbine, gemcitabine and taxanes have produced response rates on the order of 15% to 20% in advanced, previously untreated, NSCLC patients [3-7]. A randomized clinical trial recently showed that a cisplatin-based three-drug regimen is superior to two-drug combinations in terms of response rate and survival [2].

On these premises, in 1993 we designed a phase II trial in order to evaluate the activity and toxicity of a new combination regimen consisting of vinorelbine, ifosfamide and cisplatin (VIP) in patients with stages IIIb/IV previously untreated NSCLC. Preliminary results of this study have already been published [8]. We report here the final results of this large phase II study.

Patients and methods

Eligibility criteria were: histologically or cytologically proven NSCLC (stages IIIb-IV), no prior chemotherapy, measurable disease, age <70 years, WHO performance status <2; normal hematological (hemoglobin >11 g/dl, white blood cell count >4.000/μl and platelet count >100.000/μl), renal (serum creatinine <1.5 mg/dl) and liver (bilirubin <2 mg/dl) function, no brain metastases.

Clinical evaluation included: physical examination, chest X-ray, thoracic and brain computed tomography scans, abdominal ultrasound and bone scan or skeletal X-ray.

The regimen included: vinorelbine 25 mg/sqm (as a slow intravenous bolus) on days 1 and 8; ifosfamide 3 g/sqm (infused over 2 hours) and cisplatin 80 mg/sqm (administered with hydration and forced diuresis) on day 1. Mesna (sodium 2-mercaptoethane sulfoxate) was administered for uroprotection at the following doses: 20% of the total ifosfamide dose intravenously, immediately before the drug infusion, and 40% of the total dose orally after 4 and 8 hours on day 1. The cycles were repeated every three weeks. All of the patients received an antiemetic treatment with intravenous ondansetron (8 mg) and dexamethasone (20 mg) before chemotherapy followed by oral ondansetron 8 mg/daily for 3 days.

Blood cell counts were performed weekly, and creatinine and creatine clearance were determined before day 1 of each cycle. In the event of serum creatinine greater than 2 mg/dl, on day 1, the treatment was delayed until normalization and a 25% dose reduc-
tion of cisplatin and ifosfamide was applied in subsequent courses. On day 8 the dose of vinorelbine was modified according to the absolute neutrophil count as follows: grade 2 (WHO) neutropenia, a 25% dose-reduction; grade 3 neutropenia, a 50% dose reduction; in instances of grade 4 neutropenia, vinorelbine was omitted and a prophylaxis with oral ciprofloxacin 500 mg/day and fluconazole 50 mg/day was started. In case of grade 4 neutropenia lasting more than 72 hours, filgrastim 300 µg total dose was administered subcutaneously until WBC >4000/µL.

All of the patients were fully reassessed after 3 courses of chemotherapy and response was defined according to WHO criteria. In case of response patients with metastatic disease were treated for a maximum of 6 courses, while stage IIIB patients received thoracic irradiation starting 4 to 6 weeks after the third course of chemotherapy. A total dose of 60 Gy was given over 6 weeks with 2-Gy daily fractions 5 days per week; the fields consisted of AP-PA personalized ports to cover the primary tumor bed, the mediastinum and the homolateral supraclavicular fossa up to 46 Gy; after 36 Gy was reached, a block was applied to shield the spinal cord on the PA port. A final 14-Gy boost was given to the tumor and enlarged mediastinal nodes with multiportal technique.

Duration of response and survival were calculated according to the beginning of the treatment; patients were withdrawn from the study in the event of disease progression, treatment delay longer than 3 weeks, or treatment refusal.

Results

Pre-treatment characteristics are summarized in Table 1; forty-two patients (55%) had adenocarcinoma, and 51 (67%) had stage IV disease. Sixty-seven patients were evaluable for response after 3 courses of chemotherapy. Nine patients were not evaluable; four were lost to follow-up; one patient was withdrawn from the study because of severe hiccups; two patients died of pulmonary embolism; two patients had to discontinue the treatment, one because of rapid worsening of the performance status and the other because of hallucination.

Two hundred eighty-nine evaluable courses have been administered with a median of four cycles per patient (range 1–6). The median WBC and platelet nadir occurred on day 15 (range 13 to 16) with a median hematological recovery on day 21. Thirty-four of 289 courses (12%) were delayed for one week because of neutropenia. The dose of VNR on day 8 was reduced by 25% in 21 courses (7%), by 50% in 7 courses (2%) and omitted in 25 courses (9%). G-CSF was administered in 77 of 289 courses (26%); 19 episodes of febrile neutropenia were reported, with 3 hospital admissions.

Neurotoxicity was observed in 7 patients: 5 patients reported a grade 2 paraesthesia after six courses; one patient had deafness and one experienced an episode of hallucination after the first course of chemotherapy. No severe gastrointestinal or renal toxic effects were reported (Table 2). The most frequent early toxicity of radiotherapy was esophagitis, grade 2 in 5/25 patients and grade 3 in 2 patients. Late toxicities were: grades 2 and 3 lung fibrosis in 4 and 5 patients, respectively; grade 3 dysphagia was observed in 1 of 25 patients.

The overall response rate was 51% (95% C.I. 35–77%) with 2 CRs (3%) and 32 PRs (48%); 20 patients (30%) had disease stabilization and 13 (19%) progressed during treatment. No significant difference in objective response rates – 55% and 48% for stage IIIB and IV, respectively – was noted with respect to stage of disease. The 3 additional courses of chemotherapy did not improve the response rate in metastatic patients.

The median time to progression of all of the patients entered into the study was 6 months (range 1 to 29+) and the median overall survival was 10 months (range 1 to 33+). For stage IIIB patients the median time to progression was 8 months (range 1 to 21) and median overall survival 14 months (range 1 to 33+).

Discussion

The survival of patients with advanced NSCLC can be improved with combination chemotherapy [1, 2]. The combination of cisplatin and vinorelbine has produced the highest response rate in a very large European randomized trial [9]. The present study was designed to evaluate the feasibility and activity of the cisplatin/vinorelbine combination plus ifosfamide, the latter chosen because of its activity as a single agent and its synergistic antitumor activity with cisplatin in experimental models [3, 10].

The results of this study show that the VIP combination can be safely administered on an outpatient basis with acceptable toxic effects. The dose-limiting acute

Table 1. Pre-treatment patient characteristics.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>25 (32)</td>
</tr>
<tr>
<td>IIIB</td>
<td>25 (32)</td>
</tr>
<tr>
<td>IV</td>
<td>51 (68)</td>
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<table>
<thead>
<tr>
<th>Total</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (81)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance status</th>
<th>Total</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52 (68)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (32)</td>
<td></td>
</tr>
</tbody>
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Table 2. Toxicities WHO (%).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11.5</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>6.6</td>
<td>~</td>
</tr>
<tr>
<td>Emesis</td>
<td>8.7</td>
<td>~</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1.0</td>
<td>~</td>
</tr>
</tbody>
</table>
side effect was myelosuppression, particularly neutropenia, which was usually brief, not cumulative and infrequently associated with infection; only 3 patients required hospital admission. Filgrastim was given in 27% of the courses to maintain the planned drug doses and intervals.

Cisplatin neurotoxicity was not increased by adding vinorelbine, but neurologic side effects were irreversible. The episode of hallucination was probably not attributable to ifosfamide, as this patient experienced the same toxic effect with a different regimen.

Used as first-line therapy the combination of vinorelbine/ifosfamide/ cisplatin produced a 51% (95% C.I. 35%–77%) overall response rate: these results are comparable with those reported for the most active drug combinations [2, 11].

The response rate is particularly interesting in stage IV disease (48%). In stage IIIB disease this regimen produced a 55% objective response rate; three courses of VIP did not compromise the tolerability of subsequent radiotherapy.

The high response rate and the moderate toxicity observed in this study may be partially due to our selection criteria; in fact, the patients treated with VIP chemotherapy represent only about 2/3 of the patients with advanced NSCLC diagnosed in our institution during this period of time.

Because of its activity and acceptable toxicity, we believe the VIP regimen should be considered in the multimodality treatment of stage IIIA/IIIB NSCLC patients with good performance statuses.

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References


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