The ELVIS Trial: A Phase III Study of Single-Agent Vinorelbine as First-Line Treatment in Elderly Patients with Advanced Non-Small Cell Lung Cancer

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ABSTRACT

In a phase III trial, 191 patients aged over 70 with stage III/IV non-small cell lung cancer were randomized to receive best supportive care (BSC) alone or BSC plus vinorelbine on days 1 and 8, q 21 days for up to six cycles. Increasing difficulties in recruitment meant that the investigators, blinded to the results, stopped the trial early. Data from 161 patients have been analyzed. The vinorelbine regimen was well tolerated. Grade 3/4 neutropenia occurred in 10% of patients and grade 2/3 anemia in 16%. The principle nonhematological toxicities were constipation and fatigue. An objective response rate was recorded in 19.7% of the 76 patients treated with vinorelbine. The survival experience of these patients was significantly superior to that among control patients. The median duration of survival was longer (28 versus 21 weeks) and patients receiving vinorelbine were significantly more likely to survive to one year (32% versus 14%). The relative risk of death in the vinorelbine group was 0.65 (95% confidence interval: 0.45-0.93). Quality of life was extensively investigated using European Organization for Research and Treatment of Cancer scales. While aspects of quality-of-life issues that were directly related to drug toxicity (such as nausea and constipation) were lower in the vinorelbine group, patients who received vinorelbine fared better than controls on measures related to lung cancer symptoms and pain and on social, cognitive, and physical functioning. The Oncologist 2001;6(suppl 1):4-7

INTRODUCTION

Around one-third of all patients with non-small cell lung cancer (NSCLC) are over the age of seventy [1]. Elderly patients are likely to tolerate chemotherapy less well than those who are younger because of comorbid conditions and impaired organ function [2, 3]. For this reason, cisplatin-based chemotherapy (with its associated renal and neurological toxicities) is usually avoided in these patients [4].

The semisynthetic vinca alkaloid vinorelbine is relatively well tolerated as well as having proven activity in advanced NSCLC [5-10]. Table 1 presents data from three phase II studies in which the drug was administered to elderly patients, producing rates of objective response which ranged from 16% to 39% and median survival of five to nine months [11-13]. Vinorelbine was therefore chosen for use in this multicenter, randomized trial of best supportive care (BSC) versus supportive care plus chemotherapy in patients with advanced NSCLC (the Elderly Lung Cancer Vinorelbine Italian Study [ELVIS]) [14].

DESIGN AND METHODS

The eligibility criteria for inclusion in the ELVIS were cytohistologically confirmed NSCLC, stage IV or stage IIIB disease (with pleural effusion or metastatic supraclavicular lymph nodes) unsuitable for radiotherapy, age of 70 or greater and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (i.e., ranging from fully active to capable of all self-care but unable to work). All patients gave informed consent.

The primary endpoint of the study was quality of life, measured using the well-validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the lung cancer-specific module QLQ-LC13. Quality-of-life data were analyzed by fitting a linear mixed model for each scale. Three interim survival analyses and a total recruitment of 350 patients were planned. All analyses were by intention-to-treat. Survival curves were plotted and compared using the Mantel-Haenszel test. Relative hazards of death and 95%...
confidence intervals (CI) were calculated by the Cox model. The minimum follow-up period specified was 18 weeks. Patients were randomized centrally by phone call to BSC alone or BSC plus vinorelbine (30 mg/m²) administered i.v. on days 1 and 8 of a 21-day cycle for a maximum of six cycles.

**RESULTS**

The trial began in April 1996. In November 1997, because of a low enrollment rate the recruitment was ended prematurely by the investigators blinded to the results of the study. An interim survival analysis according to the O’Brien-Fleming method was performed. Increasing difficulty in obtaining informed consent for randomization into the control arm had resulted in the accrual rate dwindling from 11 patients per month to five per month.

**Patients**

Of the target number of 350 patients, 191 were randomized. The required minimum 18-week follow-up was available for 161 patients, and 154 were evaluable. The groups randomized to the two treatment arms were well matched on demographic and disease characteristics (Table 2) [14].

**Adverse events**

Vinorelbine was well tolerated in this group of elderly patients. Among the 71 evaluable for toxicity, grade 3/4 leukopenia occurred in 7% and grade 3/4 neutropenia in 10%. World Health Organization grade 2/3 thrombocytopenia was observed in 1% and anemia in 16%.

Of the nonhematological toxicities, 9% of patients experienced grade 2/3 vomiting, 18% grade 2-4 constipation, 21% grade 2/3 fatigue, 11% grade 1 phlebitis, and 4% grade 3 alopecia.

**Efficacy**

Among 71 evaluable patients, a complete response was seen in one case, and partial responses in 14, giving an overall objective response rate of 19.7% (95% CI: 11.5-30.5). Thirty percent of patients had stable disease and disease progressed in 42%.

Patients randomized to vinorelbine plus BSC had a significantly longer median duration of survival and were more likely to be alive at six months and at one year than patients receiving supportive care alone (Table 3). Adjusted by stage and performance status, the relative risk of death in the vinorelbine group was 0.65 (95% CI: 0.45-0.93). The survival curves for control and vinorelbine groups, shown in Figure 1, were significantly different (log-rank test p = 0.03; Cox model p = 0.02)

**Quality of Life**

The EORTC core questionnaire QLQ-C30 contains a number of scales. On two scales relating to nausea plus vomiting and to constipation, patients receiving vinorelbine scored less than control patients. This reflected the drug-related toxicities. No significant difference was detected between treatments on the scales measuring emotional function, sleep disturbance, appetite loss, diarrhea, and the financial impact of illness.

### Table 1. Phase II trials of single-agent vinorelbine in elderly patients with advanced NSCLC [11-13]

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Age (years)</th>
<th>ORR (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veronesi et al. [12]</td>
<td>23</td>
<td>&gt;70</td>
<td>39</td>
<td>NR</td>
</tr>
<tr>
<td>Gridelli et al. [13]</td>
<td>43</td>
<td>&gt;70</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

ORR = overall objective response rate; NR = not responsive

### Table 2. Characteristics of patients randomized to BSC or BSC plus vinorelbine [14]

<table>
<thead>
<tr>
<th></th>
<th>BSC (n = 78)</th>
<th>BSC + Vinorelbine (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>74 years</td>
<td>74 years</td>
</tr>
<tr>
<td>(range)</td>
<td>(70 – 86)</td>
<td>(70 – 85)</td>
</tr>
<tr>
<td>Male</td>
<td>89%</td>
<td>86%</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>28%/72%</td>
<td>27%/73%</td>
</tr>
<tr>
<td>ECOG PS: 0</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>1</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>

### Table 3. Survival in patients randomized to BSC or BSC plus vinorelbine [14]

<table>
<thead>
<tr>
<th></th>
<th>BSC (n = 78)</th>
<th>BSC + Vinorelbine (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>21 weeks</td>
<td>28 weeks</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(16-27)</td>
<td>(23-35)</td>
</tr>
<tr>
<td>Alive at six months</td>
<td>41%</td>
<td>55%</td>
</tr>
<tr>
<td>Alive at one year</td>
<td>14%</td>
<td>32%</td>
</tr>
<tr>
<td>Obs/Expected death rate</td>
<td>1.21</td>
<td>0.84</td>
</tr>
</tbody>
</table>
However, patients receiving vinorelbine in addition to supportive care scored clearly better than controls on seven subscales: global health status/quality of life, role, cognitive, social and physical functioning, fatigue, and pain.

A similar pattern was seen on analysis of data from the lung cancer module LC13. Control patients fared better on measures of peripheral neuropathy and hair loss. The two groups scored the same on measures of mouth soreness and difficulty swallowing. However, vinorelbine patients scored less than controls on extent of dyspnea, cough, hemoptysis, pain in the chest and shoulder, other pain, and need for analgesia.

**DISCUSSION**

The addition of vinorelbine to supportive care significantly prolongs the survival of elderly patients with advanced NSCLC. This benefit is achieved at the cost of some drug-related toxicity, and this is reflected in lower scores on quality-of-life subscales dealing with nausea, constipation, peripheral neuropathy, and hair loss. However, in this randomized trial, patients receiving vinorelbine scored better than controls on overall health status and quality of life, and on the important measures of cognitive, social, and physical function. They also suffered less from the lung cancer symptoms of dyspnea, cough, and hemoptysis; and they experienced less chest and other pain.

Despite the premature ending of recruitment, the ELVIS trial produced results which are clear-cut enough to guide future research. In the population of elderly patients, vinorelbine should form the control arm for future randomized trials of new chemotherapy regimens.

This has been recognized in the design of the MILES (Multicenter Italian Lung Cancer in the Elderly Study) trial in which patients aged over 70 with stage IIIB/IV NSCLC are randomized to vinorelbine, gemcitabine, or vinorelbine plus gemcitabine. The accrual ended November 2000, and 700 patients have been randomized.

**ACKNOWLEDGMENT**

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**REFERENCES**
