Long Term Analysis of Survival in the European Randomized Trial Comparing Vinorelbine/Cisplatin to Vindesine/Cisplatin and Vinorelbine Alone in Advanced Non-Small Cell Lung Cancer

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**ABSTRACT**

In the period 1989-1991, 612 patients with inoperable stage IIIA/B and IV non-small cell lung cancer (NSCLC) were randomized in a phase III trial comparing three chemotherapy regimens. Survival data at five and six years of follow-up confirm the overall benefit of treatment with a combination of vinorelbine and cisplatin compared to vindesine plus cisplatin or vinorelbine alone. Of the 612 patients randomized at the start of the study, 17 have survived beyond five years. Of these patients, eight had entered the trial with metastatic disease. Multivariate analysis to detect prognostic factors suggested a possible interaction between the effect of having cisplatin in the chemotherapy received and baseline performance status.

Subgroup analysis subsequently confirmed that the survival benefit of the vinorelbine plus chemotherapy regimen is evident only in patients with initial World Health Organization performance status (PS) of 0-1. Among these patients, the one-year survival rate is 38% for the vinorelbine/cisplatin arm, 29% for vindesine/cisplatin and 34% for vinorelbine alone. The corresponding figures for median survival are 43, 33 and 36 weeks. Among inoperable NSCLC patients with a PS of 2, who appear from this trial not to have benefited from the presence of cisplatin in their chemotherapy, use of single agent vinorelbine is an appropriate treatment option.

**INTRODUCTION**

Vinorelbine, one of the most active vinca alkaloids [1], has undergone extensive clinical trials in the treatment of non-small cell lung cancer (NSCLC). Promising activity was observed with vinorelbine in phase II trials, and the phase III studies have confirmed vinorelbine is active in the treatment of NSCLC [2-8].

In a phase III trial conducted between June 1989 and May 1991 in 45 European centers, a total of 612 patients with NSCLC were randomized to one of three treatments. The three arms of the study were: vinorelbine alone at a dose of 30 mg/m² weekly; vinorelbine 30 mg/m² plus cisplatin 120 mg/m² on days 1 and 29 and then q 6 weeks; and a control treatment consisting of vindesine 3 mg/m² weekly and cisplatin (120 mg/m²) was superior to a lower dose regimen (CAP) and BSC in a study performed by the National Cancer Institute (NCI)-Canada, and was considered a reference treatment arm at the time of the design of our study [12].

The results of the trial were reported in 1994 [8]. The present paper summarizes the characteristics of the patients involved in the trial. It also presents survival data at five years of follow-up. In addition, factors predictive of survival are considered, together with evidence of an interaction between the chemotherapy regimen administered and baseline performance status (PS) [13].

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RESULTS

Patient Characteristics

The demographic and disease characteristics of patients in the three treatment arms were well balanced and are shown in Table 1. The great majority of patients enrolled were male. There was a predominance of patients with metastatic disease. Approximately 80% of patients across the three treatment groups had a World Health Organization (WHO) PS of 0 or 1. However, the study included an appreciable minority with poorer PS, and the implications of treatment for this group are considered below. Reflecting the fact that this was a European study, the most frequent histology was squamous cell carcinoma.

Response and Survival

The response rate was 14% among patients assigned to vinorelbine alone, 30% among patients assigned to vinorelbine plus cisplatin, and 19% in patients receiving vindesine plus cisplatin. The response rate in the arm combining vinorelbine with cisplatin was significantly superior to the control arm of vindesine plus cisplatin ($p = 0.02$) and to vinorelbine alone ($p < 0.01$).

Table 1. Characteristics of patients assigned to treatments in the European study [8, 13]

<table>
<thead>
<tr>
<th>$n$ of patients</th>
<th>Vinorelbine + Cisplatin ($n = 206$)</th>
<th>Vindesine + Cisplatin ($n = 200$)</th>
<th>Vinorelbine ($n = 206$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>182</td>
<td>179</td>
<td>188</td>
</tr>
<tr>
<td>Median age</td>
<td>59 years</td>
<td>59 years</td>
<td>60 years</td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>23</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>IIIB</td>
<td>58</td>
<td>49</td>
<td>65</td>
</tr>
<tr>
<td>IV</td>
<td>102</td>
<td>109</td>
<td>97</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mestastic after local treatment</td>
<td>19</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>WHO PS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57</td>
<td>38</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>107</td>
<td>125</td>
<td>107</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Histology:</td>
<td>Squamous cell</td>
<td>115</td>
<td>100</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>65</td>
<td>79</td>
<td>57</td>
</tr>
<tr>
<td>Large cell</td>
<td>26</td>
<td>21</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2. Patients surviving longer than five years: response and second-line treatment [8, 13]

<table>
<thead>
<tr>
<th>$n$ of patients</th>
<th>Vinorelbine + Cisplatin ($n = 8$)</th>
<th>Vindesine + Cisplatin ($n = 5$)</th>
<th>Vinorelbine ($n = 4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Response:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>NC</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Second-line treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Surgery alone</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>- RT alone</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- Surgery + RT</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- RT + CT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- RT + CT + surgery</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>- No treatment</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

PR = partial response; NC = no change; RT = radiotherapy; CT = chemotherapy
At one year, the proportion of patients alive was 34% for vinorelbine plus cisplatin, 27% for vindesine plus cisplatin, and 30% with vinorelbine alone. The 40-week median survival among patients randomized to vinorelbine plus cisplatin was significantly longer than the 32-week median survival observed in patients receiving vindesine plus cisplatin, and the 31-week median survival with vinorelbine alone. The superiority of the combination of vinorelbine and cisplatin over the other two arms was confirmed after six years of follow-up ($p < 0.02$ for both comparisons). The survival curves are shown in Figure 1.

Factors Associated with Long-Term Survival

A total of 17 patients lived longer than five years from the start of the trial. Of these patients, eight received vinorelbine/cisplatin, five vindesine/cisplatin, and four vinorelbine alone as first-line chemotherapy. Among these 17 survivors, the initial disease stage was locally advanced (IIIA or B) in nine. However, there were also eight patients with metastatic disease who were cured. Among this latter group, five were treated initially with vinorelbine/cisplatin. Of the 17 survivors at five years, 11 had experienced a partial response to chemotherapy and no change had been observed in six (Table 2).

Second-line treatments were used in all but 2 of the 17 long-term survivors. Three were treated by surgery, three had radiotherapy, five surgery plus radiotherapy, three radiotherapy plus chemotherapy, and one radiotherapy plus chemotherapy plus surgery (Table 2).

Overall Prognostic Factors

To detect possible differences in the effect of treatment on different subgroups of patients, baseline characteristics were entered into a Cox analysis. Possible interactions between treatment and selected factors were tested for by adding interaction terms into the model. The final model included seven factors which were predictive of survival in this study.

On univariate analysis, the most significant factor predictive of outcome was neutrophil count. Patients with a count of $>10^4$ neutrophils had a risk ratio of 2.2. The confidence intervals (CI) of this risk ratio and those associated with other prognostic factors are shown in Table 3.

There were no significant interactions between platinum-containing regimens and the prognostic factors. However, the interaction between randomization to vinorelbine plus cisplatin and baseline PS of 2 was of borderline significance ($p = 0.056$).

This suggested that the effect of treatment with vinorelbine/cisplatin was different in patients with different PS. This is supported by the subgroup analysis shown in Table 4 which shows that the benefit of treatment with vinorelbine plus cisplatin is evident in patients of PS 0-1 but not in patients of poorer PS.

**DISCUSSION**

The combination of vinorelbine with cisplatin should be considered one of the gold standards in the therapy of patients with advanced NSCLC. The results of this study demonstrate that in patients with a good performance status (WHO PS 0-1), treatment with vinorelbine plus cisplatin is superior to the vindesine plus cisplatin or vinorelbine alone options in terms of overall survival and the proportion of patients alive at one year. In patients with a poorer PS, however, there is no benefit in receiving vinorelbine plus cisplatin rather than vinorelbine alone. Given the lack of benefit derived from the presence of cisplatin in the regimen administered, chemotherapy using active single agents such as vinorelbine should be considered appropriate in poor PS patients with inoperable NSCLC. In this respect, the group of patients with PS 2 are similar to the elderly patients treated in the Elderly Lung Cancer Vinorelbine Italian Study Group trial [14].

**Table 3.** Factors predictive of prognosis [8, 13]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Ratio</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils $&gt;10^4$</td>
<td>2.2</td>
<td>(1.6-3.1)</td>
</tr>
<tr>
<td>WHO PS 2</td>
<td>1.7</td>
<td>(1.3-2.2)</td>
</tr>
<tr>
<td>GGT $&gt;60$ IU</td>
<td>1.5</td>
<td>(1.2-1.8)</td>
</tr>
<tr>
<td>Body mass index &lt; 24</td>
<td>1.4</td>
<td>(1.2-1.8)</td>
</tr>
<tr>
<td>Vinorelbine alone($p=0.003$)</td>
<td>1.4</td>
<td>(1.1-1.8)</td>
</tr>
<tr>
<td>Vindesine/cisplatin ($p=0.02$)</td>
<td>1.3</td>
<td>(1.1-1.7)</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>1.3</td>
<td>(1.3-1.5)</td>
</tr>
</tbody>
</table>

* Body mass index: weight/height (kg/m$^2$)

GGT = gamma-glutamyltransferase

Figure 1. Survival at five years by treatment group [8, 13].
Table 4. Median and one-year survival according to treatment in patients with different PS [8, 13]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival</th>
<th>One-year survival</th>
<th>Median survival</th>
<th>One-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine + cisplatin</td>
<td>43 wks</td>
<td>38%</td>
<td>18 wks</td>
<td>17%</td>
</tr>
<tr>
<td>Vindesine + cisplatin</td>
<td>33 wks</td>
<td>29%</td>
<td>18 wks</td>
<td>13%</td>
</tr>
<tr>
<td>Vinorelbine alone</td>
<td>36 wks</td>
<td>34%</td>
<td>17 wks</td>
<td>15%</td>
</tr>
</tbody>
</table>


