Carboplatin and Vinorelbine in Advanced Non-Small Cell Lung Cancer: A Phase I/II Study

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ABSTRACT
Standard options for advanced non-small cell lung cancer have focused on cisplatin-based regimens, including the combination of cisplatin with vinorelbine shown in randomized trials to be at least as effective as comparator regimens. Given its lower incidence of nonhematological toxicity, carboplatin may be an attractive alternative agent in combination with vinorelbine. To determine the tolerability of this regimen, a phase I/II study was conducted in 21 patients with stage III/IV disease. A fixed dose of carboplatin (area under the concentration time curve = 2.5) was administered on days 1 and 8 q 21 days, together with vinorelbine also on days 1 and 8 at doses increasing from 20 mg/m² to 25 mg/m². This regimen was very well tolerated: only one case of grade 4 hematological toxicity and one case of grade 3 nonhematological toxicity occurred. Objective responses were seen. Given its tolerability and activity, the combination of carboplatin with vinorelbine at the doses and schedule studied should be further evaluated. The Oncologist 2001;6(suppl 1):12-15

INTRODUCTION
Vinorelbine has proven activity in non-small cell lung cancer (NSCLC) and is well tolerated. Following the results of four randomized phase III trials (Table 1), the combination of cisplatin with vinorelbine has become a standard treatment for advanced NSCLC. These trials are consistent in showing that cisplatin plus vinorelbine is equal or superior to other single-agent or combination regimens in terms of response rate, and median and one-year survival [1-4]. In the four studies, the response rate to cisplatin plus vinorelbine ranged from 26% to 43%, median survival ranged from 33 to 40 weeks, and one-year survival rates ranged from 33% to 36% [1-4].

However, although clearly active, the combination of vinorelbine with cisplatin is associated with significant toxicity, principally related to cisplatin. In the study of Le Chevalier et al., 79% of patients receiving cisplatin plus vinorelbine experienced grade 3/4 neutropenia, 58% nausea and vomiting and 32% alopecia [1]. In the single-agent vinorelbine arm of this study, the corresponding incidences of these toxicities were 53%, 12%, and 14%, demonstrating that cisplatin is a major contributor to the toxicity of the combination.

The substitution of carboplatin for cisplatin therefore makes sense on the grounds of toxicity. This drug is associated with less nephrotoxicity, ototoxicity, and neurotoxicity than cisplatin [5]. It is likely to be more acceptable to patients given the lower incidence of nausea and vomiting. Further, carboplatin can be given over a shorter period of infusion and does not require hydration. However, a potential disadvantage of carboplatin is the greater myelosuppression experienced, and this has proved its dose-limiting toxicity.

The combination of carboplatin and vinorelbine has shown activity in NSCLC. For example, Garst et al., in a study of 42 patients administered carboplatin to an area under the concentration time curve (AUC) of 7 plus vinorelbine at 30 mg/m² with G-CSF support, reported a one-year survival rate of 41% (Table 2) [6]. Pronzato et al. found a median survival of 10 months in 32 patients treated with 350 mg/m² carboplatin and 25 mg/m² vinorelbine [9]. Using the same doses, the median survival was 9.5 months in 77 patients treated by Santomagio et al. [12]. The response rates in these three studies ranged from 16% to 31%.
The phase I/II study presented here, conducted in the Evanston Northwestern Healthcare System with the collaboration of Northwestern University, was designed with these considerations in mind [14]. In addition, we anticipated that use of divided day 1 and 8 dosing might improve tolerance of carboplatin (by reducing the severity of neutropenia in particular) and that administering both drugs on two of every three weeks might enable a greater dose intensity to be delivered without the need for growth factor support.

**DESIGN**

**Aim**

The purpose of the study was to investigate the activity and tolerability of the combination of carboplatin with vinorelbine in advanced NSCLC. The trial aimed to define the dose-limiting toxicity (DLT) of the combination and the maximum tolerated dose (MTD) of vinorelbine when given with a fixed carboplatin dose. Response rate, time to progression and survival data were also gathered.

**Eligibility**

The eligibility criteria for the study were documented advanced stage IIIB or IV NSCLC, an Eastern Cooperative Oncology Group performance status of 0-2, and adequate hematological, renal and liver function. One prior chemotherapy regimen was permitted. Signed, informed consent was given.

**Treatment**

Throughout the trial, the dose of carboplatin administered was designed to achieve an AUC of 2.5. The accompanying dose of vinorelbine began at 20 mg/m² for the first cohort of patients and was escalated to a final dose of 25 mg/m². Both drugs were administered on days 1 and 8. Treatment was repeated q 21 days.

**Defining Toxicities**

DLTs were defined during cycles 1 and 2 as myelosuppression leading to neutropenic fever or platelet transfusion, nonhematological toxicity (except nausea/vomiting) of grade 3 or greater, and the presence of grade 2 or greater toxicity on the day scheduled for next treatment.

The MTD was defined as the dose at which less than one-third of patients experienced DLT. If DLT was seen in more than one-third of patients at a given dose level, the previous dose level was to be considered the MTD. Given the toxicity observed in previous trials, it was not intended that the dose of vinorelbine should be escalated beyond 25 mg/m².

**RESULTS**

**Patients**

From August 1999 to March 2000, 21 patients were recruited into the study. Eleven were male and ten female. They had a median age of 67 years (range 43-79). Eight had stage IIIB disease and 13 were stage IV. Performance status was 0 in 11 patients, 1 in 9 patients and 2 in 1 patient. Only one patient had received prior chemotherapy. Eleven patients had one site of metastatic disease, seven had two sites of involvement, and three patients had metastases in three sites.

**Adverse Events**

No grade 3 or 4 toxicities were observed when carboplatin was combined with 20 mg/m² vinorelbine.

The only significant hematological toxicity observed was in one patient who received 25 mg/m² vinorelbine and experienced grade 4 neutropenia with fever. There were no cases of grade 3/4 thrombocytopenia and no grade 4 anemia (two patients had grade 2 anemia).

No patient experienced any grade 4 nonhematological toxicity. There was one case of grade 3 nausea and vomiting (in the patient who developed neutropenic fever) and one case of grade 2 alopecia (no grade 3).

**Table 1. Cisplatin plus vinorelbine: the results of four phase III trials [1-4]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n of Patients</th>
<th>Response Rate (%)</th>
<th>Median (wks)</th>
<th>Survival Time One-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Chevalier [1]</td>
<td>CDDP + VRB</td>
<td>574</td>
<td>30</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>CDDP + Vind</td>
<td></td>
<td>19</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>VRB</td>
<td></td>
<td>14</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>CDDP</td>
<td></td>
<td>12</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Pacl + Carb</td>
<td></td>
<td>27</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Depierre [4]</td>
<td>CDDP + VRB</td>
<td>231</td>
<td>43</td>
<td>33</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>VRB</td>
<td></td>
<td>16</td>
<td>32</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported; CDDP = cisplatin; VRB = vinorelbine; Vind = vindesine; Pacl = paclitaxel; Carb = carboplatin
DISCUSSION

The combination of carboplatin (AUC=2.5) with vinorelbine (20-25 mg/m\(^2\)) administered on days 1 and 8 q 21 days is an extremely well-tolerated regimen and shows promising activity. The divided carboplatin dose appeared to be important in the low incidence of toxicity observed. This regimen is worthy of further investigation in large phase II or phase III trials. Elderly patients in particular may benefit from its minimal toxicity.

The combination studied would also be appropriate for use in trials which seek to combine chemotherapy with new biologic agents such as angiogenesis inhibitors, antitumor antibodies and new small molecules.

<table>
<thead>
<tr>
<th>Study</th>
<th>n of Patients</th>
<th>Treatment</th>
<th>Response Rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garst [6]</td>
<td>42</td>
<td>Carbo: 7, VRB: 30 + G-CSF</td>
<td>16%</td>
<td>37% (one-yr)</td>
</tr>
<tr>
<td>Crawford [7]</td>
<td>22</td>
<td>Carbo: 7, VRB: 0.375 + G-CSF</td>
<td>15%</td>
<td>NR</td>
</tr>
<tr>
<td>Masotti [8]</td>
<td>55</td>
<td>Carbo: 300, VRB: 25</td>
<td>40%</td>
<td>NR</td>
</tr>
<tr>
<td>Santomaggio [12]</td>
<td>77</td>
<td>Carbo: 350, VRB: 25</td>
<td>31%</td>
<td>9.5 mo</td>
</tr>
</tbody>
</table>

NR = not reported; VRB = vinorelbine (mg/m\(^2\)); Carbo = carboplatin (AUC or mg/m\(^2\))

REFERENCES

