Cisplatin plus continuous infusion vinorelbine for the treatment of advanced non-small cell lung cancer: a phase I-II study

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**Background.** In this Phase I/II trial, the maximum-tolerated dose (MTD) and activity of cisplatin plus vinorelbine (VRL) administered in continuous infusion as first-line treatment of advanced non small cell lung cancer (NSCLC) was determined in 12 consecutive chemotherapy-naive patients with advanced NSCLC.

**Patients and methods.** The dose of cisplatin was 100 mg/m² in all patients, and vinorelbine was administered as an initial intravenous (iv) bolus of 8 mg/m² on day 1 followed by a 4-day continuous iv infusion at 4 different 24 h dose levels (DLs) to be repeated every 21 days. All 12 patients (47 cycles) were evaluable for response and toxicity.

**Results.** The MTD was 8 mg/m² bolus followed by a continuous iv infusion of 8 mg/m² per day over 4 days. The dose limiting toxicities (DLT) were febrile neutropenia in 4 patients and grade 5 mucositis in 1 patient. There was less neuro-toxicity and compared to the weekly bolus scheme. There was no significant cumulative toxicity after 5 cycles. Partial responses were observed in 6 patients; an overall response rate of 50% (95% CI: 50-65%). Median time to progression was 5.5 months (95% CI: 1.5-11 months) and median survival was 11 months (95% CI: 5-20 months).

**Conclusions.** The results demonstrate that, in this setting of first-line treatment of NSCLC, cisplatin plus vinorelbine at 8 mg/m² bolus followed by a continuous infusion of 8 mg/m² per day over 4 days is the recommended schedule. Further trials would be useful to establish activity of this combination.

**Key words:** continuous infusion vinorelbine, maximum tolerated dose, non small cell lung cancer.

**INTRODUCTION**

Non-small cell lung cancer (NSCLC) represents 70-80% of patients with lung cancer. The majority of these patients have advanced disease (stages III/IV) at the time of initial diagnoses. Several meta-analyses using data from multiple randomized trials identified a statistically significant improvement for Cisplatin (CDDP)-based chemotherapy in median survival compared to those who received best supportive care alone. Also, the 1-year survival rate was increased from 15% to 25%, with an improvement in patient quality of life. However, the toxicities observed with most chemotherapy regimens limit their administration to 4-6 cycles. Thus, although chemotherapy produce a survival advantage in advanced NSCLC, the search for better strategies using newer, more active, and better tolerated chemotherapy regimens clearly warrants continued investigation.

Vinorelbine (VRL) is a new semi synthetic vincor alkaloid that, as with its analogs, has a mechanism of action that inhibits the polymerization of microtubules in the mitosis stage of cell replication. In preclinical studies, vinorelbine appears to be more active than vinblastine and vincristine in murine tumors as well as in human tumor xenografts. Also, its more favorable therapeutic index has been confirmed in clinical practice. Pharmacokinetic studies indicate avid tissue uptake (especially in lung tissue), and other preclinical data suggest less neuro-toxicity because it has a lesser effect on axonal microtubules compared with other vinca alkaloids.

The activity of vinorelbine as single agent in treatment-naive inoperable NSCLC has been assessed in several published phase II/III studies with overall re-
sponse of 14% in phase III trials. There has been a significant benefit in survival when comparing monotherapy VIL with best-supportive-care in metastatic first-line NSCLC. In many studies of combination therapy, the contribution of cisplatin appears to be very important despite the fact that its level of activity as a single agent is no greater than that of other active drugs. So studies combining vinorelbine and cisplatin have been an obvious development. There have been several published large randomized studies comparing cisplatin plus vinorelbine with other schedules. The sample comprised a total of 1500 patients, with an overall response rate of 29% (range 24-43%) and the median survival time of 8.9 months (range 8-10.1 months).

A continuous IV infusion of vinorelbine was explored in patients with previously treated advanced breast cancer in two phase I/II trials. The dose limiting toxicity was neutropenia and mucositis. Based on our previous phase I-II trial with continuous infusion vinorelbine as single agent for the treatment of previously untreated advanced non-small cell lung cancer patients, we designed this new phase I/II trial of cisplatin plus continuous infusion vinorelbine to determine the maximum tolerated dose (MTD) and to evaluate and to quantify the toxic effect and efficacy of the combination while establishing the frequency, duration, and intensity of administration.

PATIENTS AND METHODS

Patient eligibility

Patients recruited into this study were required to have histologically confirmed non-small cell lung cancer (NSCLC). All patients were to have measurable disease target lesions on physical examination (photographs), or computed tomography (CT). Other eligibility criteria were age > 18 years, World Health Organization (WHO) performance status (PS) ≤ 2 with a life expectancy > 5 months, adequate bone marrow reserve (absolute granulocyte count, > 1.500 µl; platelet count, > 100.000 µl; hemoglobin level > 10 g/dl), as well as adequate renal and hepatic function (serum creatinine, AST, ALT and bilirubin levels < 1.25 times the upper limit of normal). Exclusion criteria were the presence of other concomitant or metachronous cancers, brain or leptomeningeal metastases, radiation to the only measurable disease or within 4 weeks of starting chemotherapy, a previous chemotherapy regimen, simultaneous infection disease or polyneuropathy, severe cardiac arrhythmia or heart failure, pregnancy or breast feeding.

Pre-treatment evaluation

Baseline assessments included medical history, physical examination, complete blood cell count and chemistry profiles to evaluate liver and renal function. Disease extent was quantified by CT scan of thorax and upper abdomen, and photographs of any metastatic skin lesions. All measurable disease was evaluated at least for 4 weeks before inclusion in the study. Bone scintigraphy or a brain CT scan was performed if clinically necessary and bone radiography was limited to suspected areas indicated by radio-nuclide scan. Laboratory tests were performed before each chemotherapy cycle.

Drug administration protocol

Cisplatin was administered to a fixed dose of 100 mg/m² before vinorelbine. All patients received an antiemetic prophylaxis consisting of 5-hydroxytryptamine-3-receptor antagonist plus 20 mg of dexamethasone. Vinorelbine ditartrate was presented as vials (1 or 5 ml) ready for patient administration and containing 10 mg/ml of vinorelbine base. A bolus dose of 8 mg/m² was administered as a rapid iv injection over 5 minutes on day 1 followed immediately, by a 96 hour continuous iv infusion delivered via a portable pump. Vinorelbine was administered to all patients via a central venous catheter. The study sought a compromise protocol between the theoretical rationale and the logistics of its implementation in a schedule that could be compatible with outpatient or home-based patient care as well as amenable to integration within other protocols.

Dose levels and study design

The 96-hours continuous iv infusion of vinorelbine was thought to be progressively escalated at successive dose levels (DL) as follows: DL1 = 8 mg/m²/d; DL2 = 9 mg/m²/d; DL3 = 10 mg/m²/d; DL4 = 11 mg/m²/d. The total doses per cycle will be 40, 44, 48 and 52 mg/m², respectively. Treatment was to be repeated every 21 days provided the patient's absolute granulocyte and platelet count were > 1.500 µl and 100.000 µl, respectively, or nonhematological toxicity was grade < 2, excluding alopecia. Chemotherapy administration was continued until a maximum of 6 cycles, disease progression or until, in the opinion of the attending physician, toxicity levels exceeded the benefits of further chemotherapy administration to the patients with stable disease.

A minimum cohort of 3 patients was to be entered at each DL. If 1 case of dose-limiting toxicity (DLT) was encountered among these 3 patients, 3 additional patients were to be entered for treatment at the same DL. Dose escalation continued if no DLT was found in these first 3 patients included at each level; or if DLT was observed in only 1 or 2 of 6 patients. DLT was defined as grade 3/4 non-hematological toxicity, excluding nausea/vomiting and alopecia, febrile neu-