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Hybrid (intravenous and oral) administration of vinorelbine plus cisplatinum followed by oral vinorelbine as first-line therapy of advanced non-small cell lung cancer: A phase II study

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Summary
Background: The combination of alternate i.v./oral (hybrid) administration of vinorelbine (VNR) plus cisplatin (CDDP), followed by oral VNR, could result in a more suitable first-line regimen for patients (pts) with advanced non-small cell lung cancer (aNSCLC) in the outpatient setting.
Methods: The induction treatment consisted of CDDP 80 mg/m^2 i.v. and VNR 25 mg/m^2 i.v. day 1 and VNR 60 mg/m^2 oral day 8, every 3 weeks for 4 courses. A dose escalation of VNR to 80 mg/m^2 oral from day 8 of the second course and to 30 mg/m^2 i.v. from day 1 of the third course was planned in the absence of G3–4 toxicity. Pts with disease control after 4 courses underwent consolidation treatment with oral VNR 80 mg/m^2 days 1 and 8 every 3 weeks up to intolerance or progression.
Results: Fifty-three pts entered the study: 80% males; median age 63 years (range 43–71); median ECOG PS 0 (range 0–1); histotype: adenocarcinoma 59%, epidermoid 31%, undifferentiated 10%; disease stage: IIIB 22%, IV 70%, recurrent disease 8%. The objective response was as follows: 1 (2%) CR, 20 (38%) PR, 16 (30%) SD, 11 (21%) PD and 5 (9%) pts were not assessable. Median TTP and OS were 6 and 10 months, respectively. G3–4 neutropenia was observed in 23 and 24% of pts in the induction and in the consolidation phases, respectively, with febrile neutropenia in 6 pts (11%) and 2 (8%), respectively. G3–4 non-haematological toxicity was rare, being represented by nausea–vomiting and neurotoxicity in 3 pts (6%) in the induction phase.
Conclusions: This combination regimen including hybrid administration of VNR plus CDDP is feasible, tolerable and effective as a first-line treatment in pts with aNSCLC.

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1. Introduction

At present 4–6 cycles of a two-drug regimen containing platinum-derivatives are considered the standard treatment for advanced NSCLC (aNSCLC) in patients with a good performance status [1]. However, the activity of these regimens is very limited, being represented by a few months' prolonging of median overall survival and temporary control of disease related symptoms in a quarter of the treated patients. Owing to these results, the minimization of toxicity and simplification of the treatments should be pursued in order to foster an acceptable quality of life for patients.

Vinorelbine (VNR) is a vinca derivative that had demonstrated an activity in aNSCLC by the end of the 1980s. At the weekly i.v. dose of 30 mg/m^2 an objective remission rate was reported in about 15% of cases [2,3]. Today, regimens based on the combination of i.v. VNR and cisplatin (CDDP) are one of the most used doublets in the first-line treatment of patients with aNSCLC [4–6]. The dose-limiting toxicity of VNR as a single agent and in combination with CDDP at doses $\leq$80 mg/m^2 is myelosuppression. Another side-effect that may prevent the continuation of the treatment is represented by the vesicant effect at local level if drug extravasation occurs.

An oral formulation of VNR has been available for a number of years. It is rapidly absorbed and the doses of 60 and 80 mg/m^2 achieved equivalent blood exposure of 25 and 30 mg/m^2 i.v., respectively, with a bioavailability of around 33–40% [7,8]. In a comparative phase II trial, oral and i.v. formulations of VNR proved they could induce a similar antitumor activity in aNSCLC patients with similar safety profiles [9]. The combination of oral VNR with CDDP (80 mg/m^2) followed by consolidation therapy with oral VNR monotherapy demonstrated activity comparable to the CDDP plus i.v. VNR combination, and suggested a possible contribution of consolidation therapy towards prolonging disease control [10]. The present phase II study was designed to explore the feasibility and activity of a combination regimen including CDDP plus VNR administered i.v. on day 1 and p.o. on day 8 as induction treatment and followed by a consolidation therapy with oral VNR as first-line therapy of aNSCLC. The possible advantages of such a hybrid regimen over the classical fully i.v. regimen is the avoidance of the central venous line implant in patients with good peripheral accesses, along with the simplification of the treatment on day 8 obtained by the oral administration of VNR, which could be administered in some patients at home under hospital surveillance or which could reduce the time of stay in the hospital.

2. Patients and methods

2.1. Patients

The eligibility criteria for inclusion in the study were as follows: histologically or cytologically confirmed NSCLC; non-resectable and ineligible for radiotherapy stage IIIB, stage IV or recurrent disease after a prior surgical treatment; age >18 and $\leq$70; ECOG performance status 0–1; life expectancy >12 weeks; at least one bi-dimensionally measurable lesions of at least 20 mm $\times$ 10 mm on CT scan; no previous chemotherapy or radiotherapy; adequate marrow, liver, and kidney functions: in particular neutrophils $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin > 11 g/dl, total bilirubin $\leq 1.5 \times$ ULN, AST and ALT < 2.5 $\times$ ULN, creatinine $\leq$ ULN (or clearance creatinine $\leq$ 60 ml/min); informed patient consent. The exclusion criteria included central nervous system metastases, grade 1 symptomatic neuropathy according NCI criteria; severe obstructive chronic bronchopneumodisease; active or recent cardiovascular disease of clinical relevance (e.g. cardiac infarction or cerebrovascular event in the last 3 months, arterial hypertension or arrhythmia not controlled); infections requiring antibiotics; metabolic disorders not fully controlled by therapy, malabsorption syndrome; dementia or other alterations of mental status, history of a second primary malignancy (except *in situ* carcinoma of the cervix or adequately treated basal-cell carcinoma of the skin).

All the patients were staged according to standard protocol (computed tomography (CT) scan of the chest, ultrasound or CT scan of upper abdomen, bronchoscopy, and bone scan, ECG, complete blood count and biochemistry). Complete blood cell count was performed weekly; biochemical tests and ECG were carried out at entry and before each subsequent course.

2.2. Treatment

The treatment consisted of an induction phase with four cycles at 21-day intervals of VNR plus CDDP combination followed by a consolidation phase with single agent oral VNR in the absence of progressive disease. Drug doses and scheduling during the induction phase were as follows: on cycle 1 VNR i.v. at 25 mg/m^2 plus CDDP 80 mg/m^2 on day 1, VNR p.o. at 60 mg/m^2 on day 8; on cycle 2 VNR i.v. at 25 mg/m^2 plus CDDP 80 mg/m^2 on day 1, VNR p.o. at 80 mg/m^2 on day 8; on cycle 3 and 4 VNR i.v. at 30 mg/m^2 plus CDDP 80 mg/m^2 on day 1, VNR p.o. at 80 mg/m^2 on day 8. Anti-emetics and hydration treatment on day 1 was applied in accordance with the standard protocol. Oral VNR monotherapy during the consolidation phase was administered at 80 mg/m^2 on days 1 and 8 and recycled at 21-day intervals. Oral VNR was taken in the morning after a light meal and with anti-emetic prophylaxis with a 5-HT3 antagonist. The consolidation treatment was continued until disease progression, unacceptable toxicity or patient request.

2.2.1. Dose modifications

If the neutrophil count was 1000–1500 $\times 10^6$/l or the platelet count was 50,000–100,000 $\times 10^6$/l on the day 1 of the cycles 2–4, the treatment was postponed up to a maximum of 2 weeks; if the neutrophil count reached $\geq$1500 $\times 10^6$/l the subsequent VNR and CDDP i.v. dose was administered as planned. If the neutrophil count was <1000 $\times 10^6$/l or the platelet count was <50,000 $\times 10^6$/l on the day 1 of the cycles 2–4, the treatment was postponed up to a maximum of 2 weeks; if the neutrophil count reached $\geq$1500 $\times 10^6$/l the subsequent VNR i.v. dose was administered at 25 mg/m^2 and not increased to 30 mg/m^2. If the recovery was not reached within 2 weeks, the treatment was definitively stopped. If the neutrophil count was 1000–1500 $\times 10^6$/l or the platelet count was 50,000–100,000 $\times 10^6$/l on the day 8 of the cycles 1–4,