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## Short Communication

# Vinorelbine Treatment of Advanced Non-small Cell Lung Cancer with Special Emphasis on Elderly Patients

A. Veronesi,[1] D. Crivellari,[2] M.D. Magri,[2] G. Cartei,[3] M. Mansutti,[3] S. Foladore[4] and S. Monfardini[2]

[1]Division of Preventive Oncology; [2]Division of Medical Oncology; Centro di Riferimento Oncologico, 33081 Aviano (Pordenone); [3]Division of Medical Oncology, General Hospital, Udine; and [4]Service of Oncology, General Hospital, Gorizia, Italy within the framework of the North-Eastern Italian Oncology Group (G.O.C.C.N.E.)

**The aim of this study was to investigate the activity and the toxicity of vinorelbine (VNB) in a population of patients with locally advanced inoperable or metastatic non-small cell lung cancer (NSCLC) including elderly patients unfit for cisplatin-based chemotherapy. VNB was administered at a dose of 25–30 mg/m², intravenously, weekly until progression. Of the 83 patients who entered the study (median age 63 years, number of patients aged ≥70 years = 23, median performance status = 80, stage IV in 58 patients, previous chemotherapy in 15 patients), 76 were evaluable. One complete remission and 22 partial remissions were noted (30.2% reponse rate). Toxicity was mild. Median survival was 9 months. No effect of age upon outcome was detected. Thus, single agent VNB is a reasonable option for advanced NSCLC, particularly in elderly patients.** 

**Key words: vinorelbine, non-small cell lung cancer, elderly patients**
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## INTRODUCTION

VINORELBINE (VNB) is a recently developed semisynthetic analogue of vinblastine [1]. It has been found to have activity against non-small cell lung cancer (NSCLC) both in non-randomised [2] and in randomised [3] studies. The toxicity profile of VNB is encouraging, the main toxic effect being transient leucopenia. In April 1992, a phase II study aiming to evaluate the activity and the toxicity of VNB in an unselected population of patients with advanced NSCLC was activated at our Institutions. Special emphasis was given to the management of elderly patients unfit for cisplatin-based chemotherapy.

## PATIENTS AND METHODS

From April 1992 to September 1994 all eligible patients presenting at our Institutions were considered for the study. Conditions of eligibility included histologically proven NSCLC, locally advanced inoperable or metastatic disease, measurable lesions, Karnofsky performance status greater than 40, white blood cell counts >4000/mm³, platelet counts >120000/mm³ and oral informed consent. No age limits were set.

Staging procedures included complete blood counts, serum chemistry, chest X-rays, liver ultrasound and bone scan. A chest CT scan was obtained when deemed necessary for the definition of stage and/or evaluation of response; a brain CT scan was performed in the presence of symptoms suspicious for brain metastases.

Treatment consisted of VNB 25 mg/m² intravenously, weekly, until progression (PD) or until development of toxicity preventing further treatment, whichever occurred first. The dosage was increased to 30 mg if no toxicity occurred in the first three weekly administrations. Half the dose was administered in the event of grade I leucothrombocytopenia. In the event of leucothrombocytopenia more severe than grade I, VNB administration was stopped until recovery (i.e. grade 0 toxicity). Granulocyte-colony stimulating factor (G-CSF) was administered only in the event of grade IV leucopenia. G-CSF was not administered prophylactically.

VNB was diluted in 250 ml of normal saline and infused over 30–45 min. The vein was flushed with normal saline 3–4 times during the infusion. Additional normal saline was infused after VNB. Patients were premedicated with alizapride or metoclopramide.

Correspondence to A. Veronesi.
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Complete blood counts were obtained before each administration of VNB. The pertinent examinations for the evaluation of response were made every six doses of VNB.

Standard WHO criteria for response and toxicity [4] were used in this study. Response was categorised as complete response (CR), partial response (PR), stable disease (SD; no progression determined by two observations not less than 4 weeks apart) and PD.

Univariate analysis was carried out to estimate the survival curve relative to different prognostic factors by means of the Kaplan–Meier product limit method [5]. Comparison between curves was accomplished by the logrank test [6]. Multivariate analysis was based on the Cox proportional hazard regression model [7].

## RESULTS

83 eligible patients entered the study. The characteristics of the study population and of the patients aged ≥70 years are separately listed in Table 1. Elderly patients had locoregional disease more frequently and none had been pretreated with chemotherapy.

Six hundred and ninety-two VNB cycles were administered to the 83 patients (median, 7 cycles/patient, range 2–34). The dose was escalated to 30 mg/m²/week in 59 patients. The median dose intensity was 18.9 mg/m²/week (range 8.7–33.3 mg/m²/week). 7 patients were not evaluable for response because of early death in 2 cases, intercurrent diseases in 1, refusal of treatment in 2 and loss to follow-up in 2.

In the 76 evaluable patients, 1 CR, 22 PR, 24 SD and 29 PD were noted, a response rate of 30.2%. Although the response rate was higher in patients with stage III disease (41.7%), in those aged 70 years or more (39.1%), in those previously untreated with chemotherapy (33.3%), and in those with a PS >80 (34%), none of these differences reached statistical significance. Histology and previous chemotherapy did not influence the response rate. The median duration of response was 6.2 months. It should be noted that 6/10 responding patients with locally advanced disease received radiotherapy and one underwent surgery after chemotherapy. The median duration of response in stage IV patients was 4.5 months.

*Table* 1. *Patient characteristics*

| | All patients | Patients ≥70 |
|---|---|---|
| No. of patients | 83 | 23 |
| Median age in years (range) | 63 (38–80) | 72 (70–80) |
| Male/female ratio | 71/12 | 22/1 |
| Median performance status (range) | 80 (50–100) | 80 (50–100) |
| Histology | | |
| Squamous cell | 37 | 12 |
| Adenocarcinoma | 34 | 8 |
| Large cell | 12 | 3 |
| Stage | | |
| IIIb | 25 | 12* |
| IV | 58 | 11* |
| Metastatic sites | | |
| Lymph nodes | 12 | 9 |
| Bone | 13 | 2 |
| Liver | 5 | — |
| Adrenals | 9 | — |
| Brain | 9 | 2 |
| Lung | 13 | 4 |
| Choroid | 1 | — |
| Pleura | 5 | — |
| Skin | 2 | — |
| Previous chemotherapy | | |
| Yes | 15 | — |
| No | 68 | 23 |

*$\chi^2_1 = 7.35$; $P = 0.007$.

All patients except one were evaluable for toxicity, which is reported in Table 2. Overall, toxicity was not a major problem in this study, and no toxic deaths occurred. Out of the 692 VNB cycles administered, 115 were delayed and 56 were administered at half the dose due to bone marrow toxicity. G-CSF was administered to the 2 patients with grade IV leucopenia. Treatment was discontinued in those 2 patients and in 4 additional patients with long lasting (>4 weeks) leucopenia. No influence of age upon toxicity was noted.

Median survival was 9 months. Patients with age less than 70 years, PS equal to or greater than 80, adenocarcinoma histology, stage III disease and no previous chemotherapy enjoyed longer median survival times; however, none of these differences were statistically significant at univariate analysis.

After adjustment for PS, age, stage, histology and previous chemotherapy, patients responding to VNB (CR + PR; 23 cases) had a statistically significant ($\chi^2_1 = 20.10$, $P \leq 0.001$) longer survival than those with SD or PD (53 cases).

## DISCUSSION

Considerable interest has been raised in recent years by the finding of a high level of activity of VNB in breast cancer and, to a lesser extent, in non-small cell lung cancer [2, 3, 8, 9–12].

In our series, VNB was confirmed to possess a degree of activity comparable to that observed with single agents active in NSCLC (vindesine, mitomycin C, vinblastine). With a 30.2% response rate and a median survival time of 9 months, the activity of VNB was superimposable on or better than that observed in a previous randomised study [13] comparing two combination chemotherapy regimens (cyclophosphamide, doxorubicin, methotrexate and procarbazine (20.8% response rate and 5 months median survival) versus cisplatin and etoposide (38.2% response rate and 7 months median survival)). This is of interest taking into account the worse prognosis of the VNB population of patients (18% of patients were pretreated with chemotherapy, 11% had brain metastases, 28% were aged 70 years or more). No influence of age upon response rate, toxicity and survival was apparent in this study.

*Table* 2. *Toxicity* (82 *patients evaluable-worst toxicity*)

| | WHO grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Bone marrow | 11 (4) | 18 (7) | 19 (5) | 2 |
| Nausea/vomiting | 5 (1) | 3 | — | — |
| Phlebitis | 6 (1) | 1 | — | — |
| Neurosensory | 1 | 7 (1) | — | — |
| Constipation | 16 (2) | 6 (2) | — | — |
| Liver | 1 | — | — | — |
| Myalgia | 4 | — | — | — |
| Stomatitis | 1 (1) | 1 (1) | 2 | — |
| Alopecia | 5 (2) | — | 1 | — |

Figures for the 23 patients aged 70 years or more are reported in parentheses.

An interesting finding was the longer survival, after adjustment for several prognostic factors, of responders as compared to non-responders. Although this finding should be taken with caution, in view of the intrinsic bias of this type of analysis, we think it adds to the impression of a favourable influence of VNB on the course of the disease.

In conclusion, single agent VNB is a reasonable option for locally advanced, inoperable or metastatic NSCLC, particularly in elderly patients. In view of the reported superiority of combinations including VNB over VNB alone [3, 10], the use of single agent VNB in relatively young, fit patients should be based upon cost–benefit considerations directly involving the patient.


1. Comis RL, Friedland DM. New chemotherapy agents in the treatment of advanced non-small cell lung cancer: an update including data from the Seventh World Conference on Lung Cancer. *Lung Cancer* 1995, **12**(Suppl.), 63–99.
2. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC. A phase II study of Navelbine (vinorelbine) in the treatment of non-small-cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115–119.
3. Le Chevalier T, Brisgand D, Douillard J-Y, *et al.* Randomized study of Vinorelbine and Cisplatin versus Vindesine and Cisplatin versus Vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994, **12**, 360–367.
4. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
6. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
7. Cox RD. Regression models of life tables. *J R Stat Soc* 1972, **34**, 187–220.
8. Lonardi F, Pavanato G, Jirillo A, Ferrari V, Bonciarelli G, Balli M. Vinorelbine as single-agent chemotherapy in advanced non small cell lung cancer patients. *Proc Am Soc Clin Oncol* 1994, **13**, 338.
9. Carrato A, Rosell R, Artal A, *et al.* Preliminary results of a phase II trial of biweekly Vinorelbine as a single agent in non-small cell lung cancer. Spanish Lung Cancer Group. *Proc Am Soc Clin Oncol* 1994, **13**, 338.
10. Depierre A, Lebeau B, Chastang C, *et al.* Results of a phase III randomized study of Vinorelbine versus Vinorelbine–Cisplatin in non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 340.
11. O'Rourke M, Crawford J, Schiller J, *et al.* Survival advantage for patients with Stage IV NSLC treated with single agent Navelbine in a randomized controlled trial. *Proc Am Soc Clin Oncol* 1993, **12**, 343.
12. Kusunoki Y, Furuse K, Yamori S, *et al.* Randomized phase II study of Vinorelbine vs Vindesine in previously untreated non-small cell lung cancer: final results. *Proc Am Soc Clin Oncol* 1995, **14**, 353.
13. Veronesi A, Magri MD, Tirelli U, *et al.* Chemotherapy of advanced non-small cell lung cancer with Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine versus Cisplatin and Etoposide. A randomized study. *Am J Clin Oncol* 1988, **11**, 566–571.