RESEARCH COMMUNICATION

# Vinorelbine in Combination with Carboplatin followed by Single-agent Consolidation Therapy for Unresectable Localized or Metastatic Non-small-cell Lung Carcinomas

**Suleyman Alici[1], Ugur Coskun[2], Necati Alkis[3], Alper Sevinc[4], Faysal Dane[5], Mahmut Gumus[6], Metin Ozkan[7], Ali Osman Kaya[2], Gokhan Celenkoglu[3], Suleyman Buyukberber[6], Mustafa Altunbas[2], Mustafa Benekli[8]; for the Anatolian Society of Medical Oncology**

## Abstract

**Background: Adding more than four cycles of the combination regimen increase toxicities. The availability of an intravenous (i.v.) and oral form of vinorelbine appeared as a particularly convenient way to provide a consolidation treatment to patients who have achieved an objective response or stable disease. Patients and methods: This study was retrospectively designed to investigate the efficacy in terms of response and safety of i.v. vinorelbine 25 mg/m$^2$ on day 1 and oral vinorelbine 60 mg/m$^2$ on day 8 given with carboplatin area under the curve (AUC) 5 once every 3 weeks (q3w) for four cycles followed by consolidation therapy with single-agent vinorelbine in non-progressive patients with advanced non-small-cell lung cancer (NSCLC). Results: Seventy-two patients enrolled into the study from October 2006 to July 2009 received the combination regimen. Thirty-seven patients (51.3%) also received the subsequent consolidation treatment. Partial tumor responses were obtained in 25 patients (34.7%) of 72 evaluable patients. Stable disease was observed in 26 (36.1%) of patients. The median progression free-survival was 4 months (95% CI 3.1-4.8). The median overall survival time was 10 months (95% CI 8.2-11.7) and the 1 year survival was 38.1%. The main toxicities recorded were hematological. Grade 3-4 neutropenia were observed in 17 patients (23.6%). Only two patients experienced grade three febrile neutropenia in the induction period, and there was no occurrence of febril neutropenia in the consolidation period. Nausea and vomiting were the major non-hematological toxicities reported. Toxicities occurred primarily during the initial combination phase of the chemotherapy. Conclusions: Despite the low dose of vinorelbine (25mg/m$^2$ i.v. on day 1 and only 60 mg/m$^2$ oral on day 8, every 3 weeks) achieved during the study, the response rate of 34.7%, the disease control of 70.8% and the 10 months median overall survival with tolerable toxicity profile, confirmed that this combination, offers an active and safe regimen for patients with advanced NSCLC**

**Key Words:** Non-small-cell-lung cancer - vinorelbine - carboplatin - consolidation - Turkey

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## Introduction

Approximately two thirds of all patients with newly diagnosed non-small - cell lung cancer (NSCLC) have advanced disease (stage IIIB or IV) that is only amenable to palliative chemotherapy. In this setting chemotherapy has a proven efficacy and platinum-based doublet regimens are the mainstay of front-line therapy (Non-small Cell Lung Cancer Collaborative Group, 1995; Pfisher et al., 2004).

Vinorelbine has demonstrated single-agent activity in NSCLCs during the early 1990s and has been recognized later as being also efficacious in combination with a platinum salt, cisplatin or carboplatin in several randomized trials leading to the recognition of a vinoralbine doublet as a reference regimen for the treatment of advanced NSCLC (De Vita et al., 1997). The vinorelbine and carboplatin combination has proved to be active in first line treatment of advanced NSCLC. The response rates across studies have ranged from 13% to 40% with a median survival from 4.5 to 14.6 months (Crawford and O'Rourke, 1994; Jacoulet et al., 1995; Masotti et al., 1995; Garst et al., 1996; Pronzato et al., 1999; Tan et al., 2005).

*[1]Oncology Department, Private Goztepe Medical Park Hospital, Kanser Hospital Goztepe, Istanbul, [2]Oncology Department, Medical School of Gazi University, Ankara, [3]Oncology Department, Ankara Oncology Hospital, Ankara, [4]Oncology Department, Medical School of Gaziantep University, Gaziantep, [5]Oncology of Department, Medical School of Marmara University, Istanbul, [6]Oncology Department, Kartal Treaning-Research Hospital, Istanbul, [7]Oncology Department, Medical School of Erciyes University, Kayseri, [8]Oncology Department, Dıskapi Training-Research Hospital, Ankara, Turkey *For Correspondence: suleymanalici@yahoo.com*

Several questions remains unanswered in the treatment of advanced NSCLC: Even if the oncologic community accepts that there is no advantage in giving more than four cycles of platin-based chemotherapy on the basis of a number of phase III trials in stage IV disease, clinicians would likely give further therapy in patients who are still responding. The issue of further therapy in patients with stable disease to induce further responses with delayed progressive disease is interesting and the concept of using lower toxicity (non-platin) maintenance therapy merits consideration in advanced stage. Another question is about the quality of life of these patients, an answer already implemented by many oncologist is the use of carboplatin doublet and for some of them, its combination with a potent oral chemotherapy which may become an additional improvement for the patient's convenience.

Therefore this study was designed to explore the role of combination of iv treatment on day 1 and oral on day 8 vinorelbine with carboplatin in a 3-week schedule and the merits of consolidation therapy with iv on day 1 and oral on days till 8 vinorelbine as a complement to the combination regimen given to patients suffering from inoperable or metastatic NSCLC.

## Patients and Methods

*Eligibility criteria*

Eligible patients were required to have histologic or cytologic diagnosis of advanced NSCLC (stage III B disease with pleural effusion and/or positive supraclavicular nodes, or stage IV disease) not amenable to curative treatment. All patients had to be chemotherapy naïve. Other selection criteria included (1) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; (2) age between 18 and 70 years; (3) adequate liver, renal, and bone marrow function; (4) life expectancy of ≥ 3 months; (5) measurable disease according to the requirements of World Health Organization (WHO) criteria (10 ); (6) adequate bone marrow reserve (white blood cell (WBC) > 3.5 x 109 /L, and hemoglobin >10 gm/dl), and childbearing potential either terminated or attenuated by the use of an approved contraceptive method. Prior radiotherapy (up to 60 Gy) was permitted if the irradiated area was not the only source of measurable disease.

Exclusion criteria were: active infection, presence of symptomatic central nervous system metastases, inadequate liver function (bilirubin >1.5 times upper normal limit and alanine transaminase (ALT) or aspartate transaminase (AST) >3.0 or up to 5.0 UNL in the presence of hepatic metastases), inadequate renal function (creatinin>1.25 times UNL), serious concomitant systemic disorder incompatible with the study, and second primary malignancy.

Pretreatment screening consisted of physical examination, complete blood count, biochemistry tests, ECG, chest X-ray, CT scan of the chest including adrenal glands, brain CT scan or MRI, liver CT scan, bone scintigraphy.

*Treatment schedule*

This study was retrospectively designed to investigate the efficacy in terms of response and safety of i.v. vinorelbine 25 mg/m$^2$ on day 1 and oral vinorelbine 60 mg/m$^2$ on day 8 given with carboplatin AUC 5 once every 3 weeks (q3w) for four cycles followed by consolidation therapy with single-agent vinorelbine in non-progressive patients.

Survival information was collected every 3 months until death. Patients were to receive at least two cycles of iv on day 1 and oral on day 8 vinorelbine and carboplatin combination. Those with an objective response, i.e. complete response (CR) plus partial response (PR), or stable disease (SD) were to receive two additional cycles of oral vinorelbine and carboplatin combination, and they were continued (unless progression) with oral vinorelbine as a single agent for consolidation until progressive disease (PD), unacceptable toxicity or patient's refusal to continue. Treatment schedule consisted of the combination therapy of i.v. vinorelbine 25 mg/m$^2$ on day 1 and oral vinorelbine 60 mg/m$^2$ on day 8 with carboplatin AUC 5 on day 1 every 3 weeks for four cycles. The consolidation therapy consisted of the administration of iv vinorelbine 25 mg/m$^2$ on day 1 and oral vinorelbine 60 mg/m$^2$ on day 8 every 3 weeks for four cycles.

Routine prophylactic antiemetics were administred to cover day 1 of chemotherapy. Oral 5 HT3 antagonist was recommended to cover the day 8 of oral vinorelbine. Treatment was to be modified in the case of haematological and /or non haematological toxicity. Haematological toxicity including neutropenia or thrombocytopenia at grade ≥2 on day 1 would resuld in treatment delay and reassessment 1 week later. On day 8, the same level of toxicity would result in the omission of the planned oral vinorelbine dose. In case of episode of grade 4 or 2 consecutive episodes of grade 3 neutropenia, the oral vinorelbine dosage would be given at 50 mg/m$^2$ during all study treatment. Neurological toxicity at grade 2 would be resulted of oral vinorelbine omission and the treatment discontinuation would be discussed on a case by case basis, and at grade 3 or 4, the treatment would be discontinued. Hepatic toxicity at grade 2 on day 1 would result in delay and reassessment after 1 week, and at grade 3 or 4 treatment would be discontinued. Renal toxicity was assessed by creatinine clearance with dose modification of cisplatin as follows: ≥55 ml/min, no modification; 45-54ml/min, 50% dose reduction; <45ml/min, delay of both vinorelbine and carboplatin and reassessment 1 week later. There were no dose modification for nausea/vomiting.

*Study dosing*

The aims of the study were activity and toxicity of of i.v. vinorelbine 25 mg/m$^2$ on day 1 and oral vinorelbine 60 mg/m$^2$ on day 8 given with carboplatin AUC 5 once every 3 weeks (q3w) for four cycles followed by consolidation therapy with single-agent vinorelbine in non-progressive patients.

Response to therapy was assessed after the every two cycles and then every other cycle; only patients with objective response continued treatment. Standard SWOG criteria were used for the assessment of efficacy criteria,

including progression free survival (PFS) and tumor response (Geen et al., 1992).

PFS for the whole trial was defined as the time interval between the dates of first treatment administration and first observation of PD, while for the maintenance period it was defined as the time interval between the dates of randomization and first observation of PD. Survival was defined as the time from the date of the first treatment administration to the date of death due to any cause. Toxicity was evaluated at any administration according to WHO criteria (1979). All patients who received at least one chemotherapy cycle were evaluated for safety.

*Statistical analyses*

Sample size was determined using a two stage design, as described by Fleming (1982). With 72 evaluable patient, a null hypothesis for the true response rate of 15% and an alternative hypothesis of 35%, the type I error was less than 5% and the type II error ß was less than 10%. Categorical date were presented in with frequencies and percentages. Continuous data were summarized using median, minimum and maximum values. Confidence intervals were calculated at the 95% level. Time dependent parameters were analyzed using the Kaplan-Meier method and 95% confidence interval for the median was reported (Kaplan and Meier, 1958). Considering safety analysis, worst NCI-CTC version 2.0 grade was reported by patient and by cycle on all treated patients.

## Results

*Patient characteristics*

A total of 72 patients were enrolled in the study in eight centres from October 2006 to July 2009. The median age of the patient population was 60 years (range, 41-82 years). The ECOG PS was 0 in 2 patients, 1 in 47 patients, and 2 in 23 patients. The sex radio was 63.(M) to 9 (F). Metastatic disease accounted for 54 of the cases (75%), inoperable locoregional disease for only 18 cases (25%). Histologic types were as follow: squamous, 30 paients; adenocarcinoma, 41 patients; anaplastic, 1 patients; Patients demographics and other characteristics at basaline are summarized in Table 1.

The median time interval from diagnosis to study entery was 10 days (range, 0-160). All patients were evaluable for response and toxicity. Among the 72 enrolled on to the study, 37 (51%) also received the consolidation therapy thereafter. The median duration of treatment was 14 weeks (range, 4-32). The median follow-up was 10 months (95%CI 8.2-11.7).

*Clinical efficacy*

A total of 347 cycles were delivered, including 95 three-week cycles of combination and 252 three-week cycles of consolidation. The median number of cycles was 3 (range,1-4) in combination and 7 (range, 5-8) in consolidation. The median relative dose intensity was 90.4% and 94.5% for vinorelbine and carboplatine, respectively. During consolidation phase, the median relative dose intensity was 85.3% for vinorelbine. Treatment delays occurred in 18.9% (18/95) of cycles during the initial chemotherapy period, and in 9.1% (23/252) of cycles during the consolidation therapy. Myelotoxicity led to 10% of dose delays in the initial period, and only 5.3% of cycles were delayed more than 7 days. In the consolidation period, hematologic toxicity accounted for 4.9% of cycles delays, and only 5.2% of cycles were delayed more than 7 days.

Among the 72 patients included, 25 (34.7%) achieved a partial response. Stable disease was recorded in 26 patients (36.1%), progressive disease in 21 (29.2%). (Table 2). The median duration of response was 4.1 months (95%CI 3.2-5.1) and the median progression-free survival amounted to 4 months(95%CI 3.1-4.8). The median overall survival was 10 months (95%CI 8.2-11.7) and 1-year survival was 38.1%.

Overall, toxicity was mild (Table 3), with neutropenia representing the most frequent treatment-related

**Table 1. Characteristics of the Patients/Episodes**

| Characteristic | Catergory | n=72 | % |
|---|---|---|---|
| Sex | Male | 63 | 87.5 |
| | Female | 9 | 12.5 |
| Median age (range) (year) | | 60 | (41-82) |
| Median time from diagnosis to study entry, days (range) | | 10 | (0-160) |
| Performance status (ECOG) | 0-1 | 49 | 68.0 |
| | 2 | 23 | 32.0 |
| Prior therapy | Surgery | 4 | 5.5 |
| | Radiotherapy | 2 | 2.7 |
| Extent of disease at study entry | Locoregional | 18 | 25.0 |
| | Metastatic | 54 | 75.0 |
| Histology | Epidermoid | 30 | 41.6 |
| | Adenocarcinoma | 41 | 56.9 |
| | Large cell carc | 1 | 1.3 |
| Sites of metastasis | Liver | 18 | 25.0 |
| | Lung | 35 | 48.6 |
| | Bone | 12 | 16.6 |

**Table 2. Efficacy Results**

| Characteristic | n=72 | % (95%CI) |
|---|---|---|
| Partial response | 25 | 34.7 |
| Stable disease | 26 | 36.1 |
| Disease control | 51 | 70.8 |
| Progressive disease | 21 | 29.2 |
| Median progression-free survival, months | 4 | (3.1-4.8) |
| Median survival, months | 10 | (8.2-11.7) |
| One-year survival, % | 38.1 | |

**Table 3. Worst Hematological/Non-hematological NCI-CTC Grade (3-4) during Combination and Consolidation Therapy**

| | Induction (n=72) | Consolidation (n=37) |
|---|---|---|
| Anemia | 0 | 0 |
| Neutropenia | 17 (23.6) | 0 |
| Febrile neutropenia | 2 (2.7) | 0 |
| Trombocytopenia | 0 | 0 |
| Nausea-vomiting | 3 (4.1) | 0 |
| Constipation | 0 | 0 |
| Stomatitis | 0 | 0 |

complication. Only two patients experienced grade three febrile neutropenia in the induction period, and there was no occurrence of febril neutropenia in the consolidation period. Grade 3/4 nause and vomiting were the most common non-hematologic toxicities, but the incidence of each was less than 6%. They occurred primarily during the initial combination phase of the chemotherapy.

## Discussion

TThis retrospective study in patients with advanced NSCLC showed that consolidation therapy with single-agent vinorelbine following four cycles of induction vinorelbine plus carboplatin led to improved PFS with a manageable toxicity profile. A number of studies have shown the efficacy of vinorelbine plus carboplatin combination in advanced NSCLC (Crino et al., 1997; Anton et al., 1998; Cardenal et al., 1999). These findings have recently been confirmed in a meta-analysis (LeChevalier et al., 2005). However, the optimal duration of chemotherapy remains uncertains. This issue is of particular importance given the palliative nature of treatment, and need to balance potential therapeutic gains against the toxicity due to chemotherapy.

Our hypothesis was that the use of more tolerable consolidation therapy is likely to slow down progression of disease and improve symptom control in the patients with objective clinical benefit after four cycles of initial therapy. Vinorelbine was selected for consolidation therapy based on its favorable toxicity profile and single –agent activity (Aapro et al., 1998; Spira and Ettinger, 2004). The present trial is in line with the previous finding from Reck et al (2009) and O'Brien et al (2004) on the combination of carboplatin with an alternating regimen of i.v. and oral formulations of vinorelbine. Survival data, as well as the safety profile of this combination including oral vinorelbine, are typical of carboplatin-based doublets. The consolidation phase allowed to improve safety and response.

Used as a single agent, oral vinorelbine demonstrated a comparable activity as i.v. form in advanced NSCLC (Jassem et al., 2001). Results on the combination with cisplatin was reported by Jassem et al (2003) by using oral vinoralbine on weekly schedule. The efficacy recorded was similar with that obtained of i.v. vinoralbine. Our study demonstrated that vinorelbine given i.v. on day 1 and orally on day 8 of 3-week cycle combined with carboplatin at an optimal dose, was as efficacious as a weekly regimen with only i.v. or orally vinorelbine. Interestingly, the dose intensity was optimal for both drugs (90.4% for vinorelbine and 94.5% carboplatin).

A response obtained in evaluable patients was associated with a 10 months median survival and a 38.1% survival at one year. In terms of tumor response on the intent to treat (ITT) population, which was the primary efficacy endpoints, 25 patients (34.7%) achieved PR, and 26 patients (36.1%) had SD. Objective response rate 34.7% and the disease control rate (70.8%) was in line with what currently reported in advanced NSCLC. The median duration of response was 4.1 months (95%CI 3.2-5.1). Combination chemotherapy followed by consolidation with single agent oral vinorelbine weekly (De Lena et al., 2005) has been also tested in a previous trials with oral vinorelbine and carboplatin (Reck et al., 2009) or cisplatin (De Lena et al., 2005).

This retrospective study, reported a similar median survival of 10 months (95%CI 8.2-11.7), in line with the results published with other platinum based doublets. From recent publications we know that cisplatin may have a small benefit in terms of median survival over carboplatin (Ardizzoni et al., 2007). This marginal benefit is contra balanced by difference in terms of tolerance, cisplatin having mostly renal toxicity and neurotoxicity with carboplatin having essentially hematological toxicities which are not of so much concern for oncologists since easily manageable. Other major findings with this regimen included the tolerance profile and convenience of the iv on day 1 (25mg/m$^2$) and oral on day 8 (60mg/m$^2$) vinorelbine. Indeed, the dose of vinorelbine was good tolerated. Balancing risks of unwanted toxicity against potential patient benefits remains one of the major practical problems in the palliative management of advanced cancer. Several chemotherapy regimens are available for the treatment of advanced NSCLC. However, since palliation is the only attainable objective, priority is generally given to regimens with the best therapeutic index. Consolidation therapy after 4 cycles of a highly efficacious combination regimen may be the best option available to the prescribing physician.

In the current study, hematological and non-hematological toxicity reported during the combination therapy was low to that commonly observed with carboplatin therapy, with grades 3-4 neutropenia in 23.6% of patients, febrile neutropenia in 2.7% of patients, anemia in 0% of patients, thrombocytopenia in 0% of patients, and grades 3-4 non-hematological toxicity in 4.1% of patients. This relative low incidence of toxicity may be linked in part the vinorelbine use as on day 8 (only 60 mg/m$^2$).

Vinorelbine as a consolidation therapy was delivered to 37 patients after induction chemotherapy. There were no severe or very rare cases of toxicity. This consolidation therapy with single agent vinorelbine as only 60 mg/m$^2$ may be a good opportunity for patients to reduce the platinum-doublet toxicity and to continue on chemotherapy after 4 cycles in non-progressing patients. Park et al. comparing 4-6 cycles of platinum based chemotherapies, reported that 6 cycles were significantly better than 4 for the time to progression with no significant difference in overall survival (Park et al., 2007). The impact of this approach is still investigational and it is questionable whether prolongation of treatment may improve survival.

In conclusion, despite the low dose of vinorelbine (25mg/m$^2$ i.v. on day 1 and only 60 mg/m$^2$ oral on day 8, every 3 weeks) achieved during the study, the response rate of 34.7%, the disease control of 70.8% and the 10 months median overall survival with tolerable toxicity profile, confirmed that this combination offers an active and safe regimen for patients with advanced NSCLC.

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