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Single-agent vinorelbine as third-line chemotherapy for refractory non-small cell lung cancer

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ABSTRACT

The role of third-line chemotherapy for metastatic non-small cell lung cancer (NSCLC) is still unclear. The aim of this phase II study was to investigate the efficacy and safety of vinorelbine in patients with metastatic NSCLC pretreated with platin- and taxane-based chemotherapy. A total of 16 patients with metastatic NSCLC were enrolled. Patients received vinorelbine at a dose of 30 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, on an outpatient basis. A total of 39 treatment cycles were administered. All patients were assessable for response, toxicity, and survival. No objective responses were documented. Stabile disease was achieved in two (12.5%) patients. The median progression-free survival was 44 days (95% CI 32-57 days) and the estimated median overall survival was 103 days (95% CI 78-129 days). Neutropenia was the main toxicity. This single institution study demonstrated that vinorelbine given at this schedule and dose in patients with refractory NSCLC had limited activity. [Turk J Cancer 2006;36(3):133-137].

KEY WORDS:

Vinorelbine, third-line chemotherapy, refractory non-small cell lung cancer, salvage regimen

INTRODUCTION

Metastatic non-small cell lung cancer (NSCLC) remains an important clinical challenge for the oncologist. Platin-based chemotherapy is the standard first-line treatment for patients with metastatic NSCLC. It provides symptom palliation and extends survival compared with best supportive care alone (1-3). Despite the survival benefit associated with first-line chemotherapy, the majority of patients will experience relapse or disease progression. Docetaxel was the first of the new agents to show activity in second-line therapy of these patients and became the standard of care in this setting (4-5). Since then, several chemotherapeutic agents have been evaluated in the second-line setting and the efficacy of second-line chemotherapy has been shown.

However, patients which progressed on second-line chemotherapy have very limited therapeutic options. Patients who have an acceptable performance status may be candidate for additional treatment. The role of third-line cytotoxic chemotherapy for these patients is still unclear. Because treatment is palliative in this setting, the selection of a regimen that provided anti-tumor activity while offering good tolerability is desirable.

Vinorelbine, a semi-synthetic vinca alkaloid, is a highly active drug for NSCLC. It has a generally mild toxicity

profile that is conducive to long-term treatment. Therefore, we designed the present study, to determine efficacy and toxicity profile of weekly 30 mg/m^2 vinorelbine, when used as third-line chemotherapy in patients with metastatic NSCLC previously treated with platin- and taxane-based chemotherapy.

PATIENTS AND METHODS

Patients with histologically or cytologically confirmed diagnoses of metastatic NSCLC who failed both platin- and taxane-based chemotherapy regimens were eligible for enrollment. The patients had to have bidimensionally measurable disease. Patients were required to be ≥18 and ≤70 years of age, to be ambulatory and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, have adequate bone marrow, renal and liver functions (absolute neutrophil count (ANC) >1500/mm^3, platelet ≥100000/mm^3, serum creatinin and biluribin <1.5 times the upper limits of normal (ULN) and aspartate aminotransferase and alanine aminotransferase <3 times the ULN) and to provide written informed consent. Patients with bone metastases as the only measurable site of disease and patients with brain metastases or uncontrolled concurrent medical disease were excluded from the study.

Vinorelbine was administered at 30 mg/m^2 diluted in 100 ml 0.9% normal saline over 15-min by intravenous infusion on days 1, 8, and 15. Cycles were repeated every 28 days until disease progression or unacceptable toxicity. Granulocyte-colony stimulating factor was administered subcutaneously at the dose of 5 μg/kg daily, in the case of ANC <500 /mm^3 persisting for >5 days or complicated by fever, and continuing until the reversal of neutropenia. All the patients received an antiemetic prophylaxis (granisetron or tropisetron) prior to the application of chemotherapy. Chemotherapy-induced toxicity was graded according to the World Health Organization (WHO) toxicity criteria (6). In the case of Hb <9gr/dl, ANC <1000/mm^3, and/or platelet count <100000/mm^3, treatment was postponed by one week. In the patients who delayed treatment for >2 weeks, treatment was discontinued. In the presence of grade 4 neutropenia or thrombocytopenia, the doses of vinorelbine were reduced by 20% in the next cycles. Clinical evaluation of response was planned every two cycles, and response registered according to the WHO criteria (6).

The primary endpoint of the current trial was to evaluate the tumor response rate of vinorelbine. Secondary endpoints included toxicity, time to progression (TTP) and overall survival. TTP and overall survival were calculated from the day of start of the vinorelbine therapy until the day of documented progression or death or last observation using Kaplan-Meier method.

RESULTS

A total of sixteen patients with metastatic NSCLC were treated with weekly vinorelbine. All patients were assessable for response and toxicity. Demographic and clinical characteristics of patients were given in table 1. The median age of patients was 58 years (range 46-66). Fifteen patients had liver metastasis, 3 had adrenal gland, 2 had bone, and 2 had other lung. Five patients had metastasis to more than one site. Performance status was 1 (n=11) or 2 (n=5).

A total of 39 treatment cycles were administered. The median number of cycles per patient was 3 (1-7). Neutropenic fever, requiring hospitalization, was observed in two (12.5%) patients. Granulocyte colony-stimulating factor was administered to four (25%) patients. A 20% dose reduction was required for four (25%) patients. We observed grade 3-4 neutropenia in 6 (37%) patients, grade 3 anemia in 2 (12.5%) patients, and grade 1 thrombocytopenia in 1 (6.25%) patient. There were no grade 3 or 4 non-hematologic adverse events. Among them, the most frequent were asthenia (4 patients), nausea (2 patients), and neuropathy (2 patients). There was no any vascular complication associated with vinorelbine treatment. Hematological and non-hematological toxicities are shown in table 2.

No complete or partial response was observed. Stable disease was achieved only in 2 (12.5 %) patients. These patients were still alive at the time of data analysis (120+ and 210+ days). Median TTP was 44 days (95% CI 32-57) and median survival was 103 days (95% CI 78-129).

Table 1
Patients' characteristics

	n
Characteristics	
Number of patients	16
Median age (range; years)	58 (46-66)
Sex	
Male	13 (81%)
Female	3 (19%)
ECOG Performance status	
1	11 (69%)
2	5 (31%)
Number of metastatic sites	
1	11 (69%)
2	5 (31%)
Metastatic sites involved	
Liver	15 (93%)
Adrenal	3 (19%)
Bone	2 (12.5%)
Other lung	2 (12.5%)
Histology	
Adenocarcinoma	9 (57%)
Squamous cell carcinoma	7 (43%)

Table 2
Summary of hematologic and non-hematologic toxicity (n=16)

	Grade 1-2 No. Patients (%)	Grade 3-4 No. Patients (%)
Hematologic		
Neutropenia	6 (37)	6 (37)
Anemia	3 (18.75)	2 (12.5)
Thrombocytopenia	1 (6.25)	0 (0)
Non-hematologic		
Asthenia	4 (25)	0 (0)
Nausea	2 (12.5)	0 (0)
Neuropathy	2 (12.5)	0 (0)

DISCUSSION

After failure of second-line chemotherapy in patients with metastatic NSCLC, treatment options are very limited. Te role of salvage chemotherapy for these patients is still unclear. The goals of salvage chemotherapy should be to reduce tumor burden, to improve or maintain performance status and to increase TTP and possibly prolong overall survival. Drug efficacy has to be balanced against toxicity and gain in the time of progression-free survival and overall survival.

In a study reported by Ozdogan et al. (7), 16 cisplatin-pretreated NSCLC patients who received third-line chemotherapy were evaluated retrospectively. In this study, seven patients were treated with weekly gemcitabine, four with taxanes, three with weekly vinorelbine, one with cisplatin+gemcitabine, and one with docetaxel+vinorelbine. The authors reported a partial response in one (6.2%) patient who was treated with weekly gemcitabine and stabile disease in four (24.8%) patients. The median time to progression and the median overall survival was 46 days and 132 days, respectively.

Single-agent vinorelbine also has been used in the second-line treatment in patients with advanced NSCLC, and variable and conflicting results have been reported. In Santoro et al.'s study (8), VNB produced objective responses in 20% of previously treated NSCLC patients whereas in two other studies no responses were reported (9,10).

In our small study, the results of weekly vinorelbine as salvage treatment for metastatic NSCLC are unsatisfactory. No responses were observed and median TTP (44 days) and median survival (103 days) were relatively short. Disease stabilization was achieved in only two patients. This poor outcome may be linked to our drug choice for salvage therapy. Vinorelbine has similar mechanisms of action (microtubule inhibition) and drug resistance (p-glycoprotein over-expression) with taxanes, which have been used in second-line chemotherapy for our patients. Since it has a different mechanism action, gemcitabine is probably more suitable monotherapy choice among the third-line generation chemotherapeutics. Chen et al (11) reported a median survival time of 4.5 months in the 17 patients receiving gemcitabine as third-line therapy. They obtained a partial response in two patients. In our series, 12 patients have received gemcitabine in combination with taxanes for their second-line chemotherapy.

A promising new approach in third-line therapy for NSCLC is that inhibition of the tyrosine kinase signaling pathways associated with growth receptors (12). The results of our study were also worst than that reported for daily oral selective epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. In a phase II trial of gefitinib in patients with advanced NSCLC who had previously treated with a platinum-based therapy and docetaxel, the response rate for the 102 evaluable patients receiving 250 mg/day gefitinib was 11.8% and median survival was 6.1 months (13). In the trial was conducted by the National Cancer Institute of Canada Clinical Trials Group, erlotinib was compared with placebo for the treatment of patients with locally advanced or metastatic NSCLC. Approximately half of the patients were assigned to third-line treatment and the other half to second-line. In this study, an improvement in survival was obtained in the erlotinib arm; patients on placebo had a median survival of 4.7 months whereas those on erlotinib had a median survival of 6.7 months. The response rate to erlotinib was 8.9% (14). Unfortunately, these EGFR-TKIs are not available yet in our country.

Although the response rate, TTP and median survival were disappointing, vinorelbine was well tolerated by the patients. The main toxicity was myelosuppression. The most common non-hematologic toxicities were asthenia, nausea and neuropathy.

In conclusion, the administration of weekly vinorelbine as a single agent has a favorable toxicity profile, but appears has no relevant clinical activity in third-line chemotherapy for patients with NSCLC. This regimen is not recommended for third-line chemotherapy for patients pretreated with platin- and taxanes-based combination chemotherapies. Further evaluation of other salvage regimens seems to be warranted.

References

1. Rapp E, Pater JL, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer - report of a Canadian multi-center randomized trial. J Clin Oncol 1998;6:633-41.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899-909.
3. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non-small cell lung cancer: A meta-analysis. Lancet 1993;342:19-21.
4. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
5. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small-Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-62.
6. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47:207-14.
7. Ozdogan M, Samur M, Bozcuk H, et al. Is the third-line chemotherapy feasible for non-small cell lung cancer? A retrospective study. Turk J Cancer 2004;34:19-23.
8. Santoro A, Maiorino L, Santoro M. Second-line with vinorelbine in the weekly monochemotherapy for the treatment of advanced non-small cell lung cancer. Lung Cancer 1994;11(Suppl 1):130.
9. Rinaldi M, Della GM, Vanturo I, et al. Vinorelbine as a single agent in the treatment of advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 1994;13:p360.
10. Pronzato P, Landucci M, Vaira F, et al. Failure of vinorelbine to produce responses in pretreated non-small cell lung cancer patients. Anticancer Res 1994;14:1413-6.
11. Chen YM, Tsai CM, Perng RP. Clinical experience with single-agent gemcitabine chemotherapy in patients with non-small-cell lung cancer in whom previous chemotherapy has failed. J Chin Med Assoc 2005; 68:163-6.
12. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. J Clin Oncol. 2005;23:3235-42.
13. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 2003;290:2149-58.
14. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.