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Efficacy of metronomic vinorelbine in elderly patients with advanced non-small-cell lung cancer and poor performance status

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ABSTRACT

Background Metronomic chemotherapy—administration of low-dose chemotherapy—allows for a prolonged treatment duration and minimizes toxicity for unfit patients diagnosed with advanced non-small-cell lung cancer (NSCLC).

Methods Oral metronomic vinorelbine at 30 mg thrice weekly was given to 35 chemotherapy-naïve patients who were elderly and vulnerable to toxicity and who had been diagnosed with advanced NSCLC.

Results Median age in this male-predominant cohort (29:6) was 76 years (range: 65–86 years). Histology was squamous cell carcinoma in 21 patients and adenocarcinoma in 14. There were no complete responses and 9 partial responses, for an overall response rate of 26%. Stable disease was seen in 15 patients (43%), and 11 patients (31%) had progressive disease. The 1-year survival rate was 34%, and the 2-year survival rate was 8%. The survival analysis showed a median progression-free survival duration of 4 months (range: 2–15 months) and an overall survival duration of 7 months (range: 3–24 months).

Conclusions Metronomic vinorelbine had an acceptable efficacy and safety profile in elderly patients with multiple comorbidities who had been diagnosed with advanced NSCLC. Metronomic vinorelbine could be a treatment option for elderly patients with poor performance status who are unfit for platinum-based chemotherapy and intravenous single-agent chemotherapy, and who are not candidates for combination modalities.

Key Words Metronomic vinorelbine, non-small-cell lung cancer, poor performance status

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in developing countries[1]. It is the most common cancer in men and the 5th most common cancer in women in Turkey, with 81% of cases being diagnosed as stage III or IV[2].

Treatment for NSCLC depends on the tumour cell type, disease stage, molecular results, performance status (PS), comorbid illness, and overall social life of the patient. Most patients in developed countries are more than 65 years of age at the time of their NSCLC diagnosis[3]. Medical oncologists might hesitate to start cytotoxic chemotherapy, especially when the patient has a poor PS with comorbid illness, is prejudiced against treatment choices, resides in a rural area, receives insufficient health care (especially in less-developed countries), and presents contraindications to multimodal treatments. In all of those cases, metronomic chemotherapy could be an appropriate option, as determined on a case-to-case basis. Metronomic chemotherapy, which is the consistent administration of low-dose chemotherapy, allows for a prolonged treatment duration and might minimize toxicity[4].

In the present study, we investigated the efficacy of oral metronomic vinorelbine in elderly patients with poor PS who were diagnosed with advanced NSCLC.

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METHODS

Eligibility Criteria

Starting after December 2013, patients 65 years of age and older who were diagnosed with NSCLC (adenocarcinoma or squamous cell carcinoma) in stage III or IV (according to the 7th edition of the American Joint Committee on Cancer staging manual), with measurable disease (based on the Response Evaluation Criteria in Solid Tumors, version 1.1) were eligible for the study. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) PS of 2; life expectancy of more than 3 months; ineligibility for chemoradiation or surgery for stage III disease; *EGFR* and *ALK* wild-type status, or status unknown because of an insufficient pathology sample; unsuitability for systemic intravenous chemotherapy (based on physician decision) because of at least 1 serious comorbidity (such as hypertension, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, valvular heart disease, diabetes mellitus, or uncontrolled arrhythmia with 1 medication or with hospitalization and treatment using an intravenous antiarrhythmic drug); need for caregiver support; and refusal of intravenous chemotherapy. The exclusion criteria were an ECOG PS of 0 or 1, inadequate hepatic or renal function, insufficient bone marrow reserve, a history of chemotherapy, and concomitant malignancies.

All patients provided informed consent before receiving treatment. Our retrospective study was approved by the local ethics committee, and the procedures applied accorded with the Helsinki Declaration. Staging was performed using imaging by computed tomography or positron-emission tomography. The baseline evaluation included physical examination, PS determination, laboratory and radiologic evaluation, and a medical history. All data were analyzed retrospectively. Toxicity was evaluated according to the U.S. National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Study Design and Treatment

Oral vinorelbine was started at a dose of 30 mg (1 capsule) thrice weekly (every Monday, Wednesday, and Friday) until disease progression or grade 4 toxicity. The vinorelbine capsules were to be taken after a meal, without chewing, and primary antiemetic prophylaxis with a serotonin receptor antagonist was recommended.

The dose was to be reduced to 20 mg thrice weekly upon the occurrence of a first grade 3 or 4 toxicity or upon persistent grade 2 toxicity with reduced quality of life. If the grade 3 or 4 toxicity continued, treatment was to be stopped; if the toxicity abated to grade 2, the dose was to be reduced to 20 mg twice weekly (every Monday and Friday), and then permanently stopped if necessary.

The patients received palliative treatment as needed. "One-step dose reduction" meant dose reduction after the 1st month of treatment. Patients who received assistance for more than half their activities of daily living during the daytime were considered to have caregiver support.

All patients were evaluated during the first 7–10 days after starting vinorelbine and then monthly thereafter. Each follow-up visit included a complete blood count and liver and kidney function tests based on blood samples. If a patient had a specific complaint, the appropriate test—such as echocardiography, hormone test, or radiologic exam—was ordered. All patients were followed by computed tomography to determine tumour response every 3 months in year 1 and every 4–6 months thereafter.

Statistical Analyses

All statistical analyses were performed using the IBM SPSS Statistics software application (version 22.0: IBM, Armonk, NY, USA). Continuous data are summarized as medians, with minimum and maximum values; categorical data are expressed as frequencies and percentages. Confidence intervals were calculated at the 95% level. Time-dependent values were analyzed by the Kaplan–Meier method. Unpaired t tests were used for data with a normal distribution, and the Mann–Whitney U-test was used for data with a non-normal distribution. Correlations were determined using the Spearman rho. Overall survival was analyzed by the Kaplan–Meier method and Cox regression analysis. All p values are two-tailed.

Primary efficacy was defined as either a complete (CR) or a partial response (PR); the overall response rate was defined as the disease control rate [CR plus PR plus stable disease (SD)]. Survival curves for progression-free survival (PFS) and overall survival (OS) were constructed by the Kaplan–Meier method, and log rank tests were used to evaluate the differences between groups. Cox proportional hazards models (univariate and multivariate) were used to evaluate variables that are potentially prognostic for PFS, including sex, age, PS, histologic subtype, T stage, N stage, clinical stage, and treatment method. Safety and toxicity analyses were performed for patients who received at least 1 dose of the study treatment. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient Characteristics

The study included 35 patients with a median age of 76 years (range: 65–86 years) and a male predominance of 29:6. Table I shows the baseline characteristics of the study population. Histology was squamous cell carcinoma in 21 patients and adenocarcinoma in the remaining 14. None of the adenocarcinoma patients had a known *EGFR* or *ALK* status, and all patients had an ECOG PS of 2 with a median of 2 comorbid illnesses (range: 1–5 comorbid illnesses). The most common of the comorbid illnesses were chronic obstructive pulmonary disease [which was diagnosed in 26 patients (74%), 5 of whom used oxygen therapy] and hypertension [which was present in 20 patients (57%), most of whom used combination therapy]. Heart failure was diagnosed in 10 patients (29%), 3 of whom had an ejection fraction of less than 35%; and diabetes mellitus was present in 7 patients (20%), all of whom were receiving insulin therapy. In addition, 5 patients (14%) had undergone coronary artery bypass graft, all of whom had an ejection fraction less than 50%, with 3 patients having an ejection fraction less than 35%. A cerebrovascular event with sequelae had occurred in 5 patients (14%) who therefore required caregiver support, and 4 patients (11%) had cardiac arrhythmia. In this cohort, 15 patients (43%) required caregiver support from

family members; 1 patient lived in a nursing home. Brain metastases had occurred in 2 patients, who were treated with whole-brain radiation before the study chemotherapy.

TABLE I Baseline characteristics of the study population

Characteristic	Value
Patients (*n*)	35
Age (years)	
Median	76
Range	65–86
Sex (*n*)	
Men	29
Women	6
ECOG PS (*n*)	
0–1	0
2	35
Stage (*n*)	
IIIA/B	14
IV	21
Histology [*n* (%)]	
Squamous cell carcinoma	21 (60)
Adenocarcinoma	14 (40)
Smoking status (*n*)	
Never-smoker	2
Past smoker	29
Current smoker	4
Metastatic site [*n* (%)]	
Bone	12 (57)
Liver	6 (28)
Adrenal gland	4 (19)
Brain	2 (9)
Mean laboratory values	
AST (IU/μL)	18.9±10
ALT (IU/μL)	16±13
Creatinine (mg/dL)	0.9±0.6
Platelet count (×1000/mL)	299±145
Hemoglobin (g/dL)	12.1±1.9
White blood cells (/mL)	9300±3800
Body mass index	
Median	21
Range	17–26
Body surface area (m^2)	
Median	1.5
Range	1.25–1.8
Comorbidities [*n* (%)]	
1	4 (11)
2	15 (43)
3	10 (29)
>3	6 (17)

ECOG PS = Eastern Cooperative Oncology Group performance status; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Treatment

Median follow-up in the group was 7 months (range: 3–24 months). All patients received at least 1 cycle of vinorelbine (360 mg during 1 month), and the median dose during the study period was 1440 mg (range: 360 mg–5400 mg). In this cohort, 87% of patients received vinorelbine without a dose reduction; in 13%, dose reduction was used. Only 1 patient did not receive subsequent cycles of vinorelbine, having refused the treatment.

Two patients of advanced age with heart failure started on 30 mg vinorelbine thrice weekly; however, after the 1st vinorelbine tablet was given, the dose was reduced to 20 mg thrice weekly. In those 2 patients, ejection fraction remained stable at 30%. Clinically, however, the patients had mild edema and physical activity restrictions; thus, their heart failure medications had to be adjusted. A one-step dose reduction to 20 mg thrice weekly occurred in 5 patients (because of fatigue in 3 patients and neutropenia in the other 2). In 2 patients, a two-step dose reduction to 20 mg twice weekly was required because of grade 2 diarrhea and thrombocytopenia. After the dose reductions, the patients did not complain of any further significant toxicity. High treatment compliance was observed in the study population.

Efficacy

At the time of the final analyses, 22 of the 35 patients had died. All patients were evaluable for both efficacy and safety. The group experienced 9 PRs and no CRs, for an overall response rate of 26%, with 15 patients having SD (43%), and 11 patients (31%) having progressive disease. The 1- and 2-year survival rates were 34% and 8% respectively. The survival analysis showed a median PFS of 4 months (range: 2–15 months) and a median OS of 7 months (range: 3–24 months; Table II, Figure 1). Only 2 patients were able to receive weekly paclitaxel as second-line chemotherapy. The PFS and OS analyses showed no significant differences by histologic subtype (squamous cell carcinoma and adenocarcinoma).

Toxicity and Quality of Life

No deaths related to treatment toxicity occurred, and only 1 patient had grade 3 fatigue and diarrhea that required hospitalization. Grades 3 and 4 toxicities were rare, especially in patients with severe heart failure (ejection fraction less than 35%) and in immobile patients with cerebrovascular events. No incidences of febrile neutropenia, transfusion-requiring anemia, or thrombocytopenia occurred.

Regardless of severity, the main toxicities observed were neutropenia (22% of patients), anemia (14%), and fatigue (17%). Among the gastrointestinal toxicities observed were nausea (14%), diarrhea (8%), constipation (8%), and vomiting (4%); however, most events were assessed as grade 1 or 2. Just 1 patient was admitted to hospital for a gastrointestinal toxicity.

DISCUSSION

In the present study, we showed that a metronomic 30 mg dose of vinorelbine given thrice weekly until disease progression is a safe and effective treatment regimen for elderly

TABLE II Clinical efficacy and toxicity data for the study patients

Characteristic	Value	
Treatment response [*n* (%)]		
Complete response	0	
Partial response	9 (26)	
Stable disease	15 (43)	
Progressive disease	11 (33)	
Survival [*n* (%)]		
1-Year	12 (34)	
2-Year	3 (9)	
PFS duration (months)		
Median	4	
Range	2–15	
OS duration (months)		
Median	7	
Range	3–24	
Dose reduction rate (%)	13	
Toxicity (%)	All	Gr. 3–4
Neutropenia	22	2
Anemia	14	2
Leucopenia	10	0
Fatigue	17	2
Nausea	14	0
Diarrhea	8	2

PFS = progression-free survival; OS = overall survival; Gr = grade.

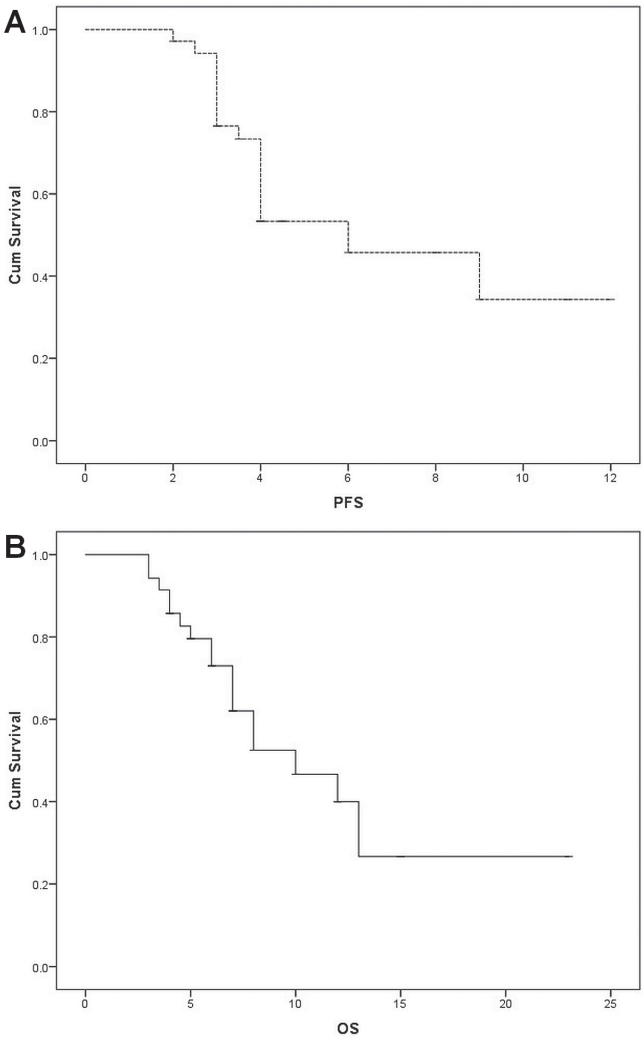

FIGURE 1 Kaplan–Meier plots of (A) progression free survival (PFS) and (B) overall survival (OS) in the patient cohort. Cum = cumulative.

patients with advanced NSCLC who are not candidates for systemic intravenous chemotherapy or multimodal approaches. The median PFS was 4 months (range: 2–15 months), and the median OS was 7 months (range: 3–24 months). The 1- and 2-year survival rates were 34% and 8% respectively.

Single-agent chemotherapy should be the first-line treatment for selected populations, especially elderly and frail patients. Platinum derives could also be options; however, comorbidities and organ function can be a barrier to the latter choice. Thus, metronomic therapies have recently attracted interest. Vinorelbine was developed as an intravenous drug, although it is currently available in an oral formulation. It has a relatively safe profile and can be used both as monotherapy and as part of combination regimens.

Increasingly, the research involving vinorelbine has focused on elderly and unfit patients diagnosed with NSCLC[5]. Earlier studies used vinorelbine mostly in combination chemotherapy. In a phase II trial in locally advanced NSCLC, 54 patients were treated with chemoradiation that included oral vinorelbine plus cisplatin; the investigators found a 54% response rate with a PFS of 12.5 months and an OS of 23.4 months[6]. A similar regimen in another phase II trial showed a 65% response rate[7]. Lastly, vinorelbine as a single agent with radiation therapy was well tolerated, and the response rate was approximately 60%[8]. In combination trials in NSCLC, an acceptable safety and efficacy profile was observed with vinorelbine plus platinum-based chemotherapy, as well as with oral or intravenous formulations of vinorelbine alone, compared with platinum plus taxanes[9–12].

In our clinical practice, many of the patients diagnosed with NSCLC are of older age or have poor PS, potentially needing caregiver support or having multiple comorbidities. In addition, they can have social problems, which, together with their poor PS, make the selection of the optimal treatment choice challenging. Those patients should therefore be evaluated in terms of the risk–benefit ratio of treatment. Many prefer oral rather than intravenous treatment[5,13,14]. Chemotherapy with a single agent is an acceptable option for a significant percentage of patients with stage III or IV NSCLC[15]. The ELVIS trial—which was stopped early because of a low enrolment rate—showed a survival advantage for intravenous vinorelbine (30 mg/m^2 on days 1 and 8 every 3 weeks) compared with best supportive care in elderly patients with stage IIIB or IV NSCLC and a poor PS. The treatment also contributed to better quality of life. Median survival was 28 weeks, and the survival rates were 41% and 14% at 6 and 12 months respectively[16]. Only 24% of patients

in that study, compared with all the patients in the present work, had an ECOG PS of 2. Thus, we can speculate that metronomic vinorelbine has an efficacy comparable with that for intravenous vinorelbine. Other data also support that hypothesis. In a phase II trial, Jassem *et al.*[17] compared oral with intravenous vinorelbine in 115 patients diagnosed with stage IIIB or IV NSCLC. The efficacies of the two dosage forms were similar; the objective response rates were, respectively, 12% and 11%; and the OS durations were 9.3 and 7.9 months.

A phase I trial investigated the oral vinorelbine dose in patients with advanced NSCLC. Oral doses of vinorelbine up to 30 mg daily do not have dose-limiting toxicity, and 50 mg daily is the maximum tolerated dose[18]. In a phase II study, 46 heavily pretreated NSCLC patients received 50 mg oral metronomic vinorelbine thrice weekly. Median OS was 9.4 months, and the 1-year survival rate was 30.1%. Grade 3 or 4 neutropenia was observed in 23.9% of cases, and febrile neutropenia in 10.9% of patients. Grade 3 fatigue was the most common severe nonhematologic toxicity (10·9%)[19]. Given those findings, we hesitated to give a dose of 50 mg thrice weekly to our elderly patients with a poor PS.

In an Asian phase II trial, chemotherapy-naïve patients 70 years of age and older with advanced NSCLC were randomized to receive either oral erlotinib 150 mg daily or oral vinorelbine 60 mg/m^2 on days 1 and 8 every 3 weeks. Erlotinib was found to be superior to vinorelbine in terms of objective response rate and PFS, but the difference in OS was not statically significant (median survival duration: 11.6 months vs. 9.3 months respectively)[20].

Thus far, three studies in groups similar to our study population have been published. Two of those studies used (non-metronomic) oral vinorelbine, and one applied metronomic oral vinorelbine[14,21,22]. Kosmidis *et al.*[22] compared two single agents, paclitaxel (intravenous) and vinorelbine (oral), in NSCLC patients with an ECOG PS of 2. The drug doses were 60 mg/m^2 vinorelbine given orally on days 1, 8, and 15 every 4 weeks and 90 mg/m^2 paclitaxel given intravenously for 1 hour on days 1, 8, and 15 every 4 weeks. No significant difference in the objective response rate (CR + PR) was found between the two groups (20% and 31% respectively), and the survival analyses also showed no significant differences. The PFS was 2.1 months for patients in the vinorelbine group and 2.6 months for those in the paclitaxel group ($p = 0.49$). The OS durations were 3.1 months and 5.1 months respectively ($p = 0.95$)[22]. The OS duration in that trial was lower than in the present work (3.1 months vs. 7 months), although both studies included only patients with an ECOG PS of 2.

There could be reasons for some of the differential findings in the two studies. The trial by Kosmidis *et al.* had more patients with stage IV disease (86% vs. 60%), and the study population included patients who had previously received radiation therapy (28%), which might have resulted in higher toxicity. Further, the patients in the Kosmidis *et al.* study experienced more grades 3 and 4 toxicity, especially hematologic toxicity. That toxicity profile was not significantly different from the profile in the paclitaxel group; overall, however, toxicities were more common in their cohort than in ours. Metronomic oral vinorelbine might result in fewer toxicities than oral vinorelbine: we gave nearly 60 mg/m^2 vinorelbine as a metronomic regimen (30 mg on days 1, 3, and 5 weekly); the previous studies gave oral vinorelbine at 60 mg/m^2 once weekly.

Camerini *et al.* published two reports on this topic, showing survival results similar to those observed in the present work. The first trial[21] investigated the efficacy of single-agent oral vinorelbine (60 mg/m^2 on days 1–8 every 3 weeks) in 43 elderly patients with poor PS diagnosed with advanced NSCLC. The overall clinical response to oral vinorelbine (CR + PR + SD) was about 50%. The median PFS was 4.0 months (range: 2–22 months), and the median OS was 8.0 months (range: 3–35 months). In that study, 46% of patients had previously received chemotherapy; thus, grades 1 and 2 and nonhematologic toxicities were especially common (range: 10%–48%). The more recent study[14] investigated the role of oral metronomic vinorelbine as a single agent in the first-line treatment of elderly patients with advanced NSCLC. That study included 43 chemotherapy-naïve elderly patients (70 or more years of age), with a PS of 0–2 in stages IIIB–IV NSCLC. The objective response rate was 18.6%, with 7 PRs and 1 CR. Of the 43 patients, 17 had SD lasting more than 12 weeks, and the clinical response rate was 58%. The median PFS in the study was 5 months (range: 2–21 months), and the median OS was 9 months (range: 3–29 months). In addition, the 1- and 2-year survival rates were 37.2% and 9.3% respectively[14].

Our study population included only patients with an ECOG PS of 2 and multiple comorbidities; however, we found survival and efficacy rates comparable to those in the Camerini *et al.* trials[14,21]. The lower toxicity and improved safety profile were also similar. Metronomic vinorelbine might therefore be a better choice than non-metronomic protocols of oral vinorelbine, a possibility supported by the findings of Camerini and colleagues. The nonhematologic toxicity profile of metronomic vinorelbine was better than that in the first trial by Camerini *et al.*[21].

In addition to directly killing tumour cells, metronomic chemotherapy is now known to have other antitumour effects, such as reduction of T-regulatory cells and prevention of immune escape. Continuous administration of the drug in low doses also lessens tumour angiogenesis and inhibits circulating endothelial progenitor cells[23]. Thus, metronomic chemotherapy could be good choice in certain cancer types and in selected patients, as well as in some combination or maintenance therapies.

A major limitation of our research is its retrospective design, although the analyses included real data on the metronomic schedule of elderly patients with poor PS. We chose a dose of 30 mg thrice weekly because, compared with previous studies, our study population included patients with a poorer PS and multiple comorbidities, most of whom refused intravenous chemotherapy.

CONCLUSIONS

The present study showed that metronomic vinorelbine had an acceptable efficacy and safety profile in elderly patients with multiple comorbidities who had been diagnosed with advanced NSCLC. Consistent with earlier studies, our results indicate that metronomic vinorelbine could represent a treatment option for elderly patients with poor PS who are

not candidates for systemic intravenous chemotherapy or combination modalities.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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