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Oral Metronomic Vinorelbine in Advanced Non-small Cell Lung Cancer Patients Unfit for Chemotherapy

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Abstract. *Aim: To explore the feasibility and activity of oral metronomic vinorelbine patients with advanced NSCLC not eligible to standard chemotherapy because of old age (≥70 years), and/or poor Eastern Cooperative Oncology Group performance status (≥2), and/or extensive brain or bone disease, and/or active comorbidities (≥2) requiring for pharmacological treatment. Patients and Methods: In a prospective phase II not randomized study, patients with stage IV NSCLC unfit to chemotherapy were treated with oral metronomic vinorelbine at 30 mg fixed dose three times a week until disease progression. Results: Fifty patients were treated, 19 (38%) in the first-line setting. Five patients (11%) experienced a grade 3 toxicity; no grade 4 toxicity occurred. Overall disease control rate was 32%, 44% and 26% in first and subsequent lines, respectively (p=0.39). Median OS and PFS were 7.3 months (95% confidence interval [CI]=4.7-10.0) and 2.7 months (95%CI=2.0-3.4), respectively. Conclusion: These data support the activity and safety of metronomic vinorelbine in a relevant proportion of patients usually excluded from any specific treatment.*

Lung cancer is the most common cancer in males and the most frequent cause of cancer-related death in both sexes. The incidence of lung cancer is steadily increasing, with 1,824,701 million new cases per year and 1,589,925 million of deaths estimated worldwide in 2012 (1). About 70% of patients present with metastatic or locally advanced disease (2, 3). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all newly-diagnosed lung cancer (4). Patients with advanced lung cancer have an expected median survival of 6 months and a 5-year survival of 2% (5). In this palliative setting, chemotherapy has proven to be a significant improvement of survival, although it is associated with even relevant toxicity (6, 7). A doublet platinum-based chemotherapy in those patients not harbouring an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) molecular alteration or with low or negative PDL1 expression is the preferred chemotherapy regimen (8, 9). Approximately 16% of adenocarcinoma patients with EGFR-mutated and 4% with ALK will benefit more from tyrosine kinase inhibitors (TKIs) (10-13). More recently, immuno-oncology has been changing this scenario leading to an increasing proportion of patients surviving both in the locally advanced or advanced NSCLC (14-18). In the first-line treatment, immune-oncology has replaced chemotherapy in those patients with a high expression of PDL1, representing in clinical trials approximately the 25% of all advanced NSCLC patients (19).

However, a significant proportion of patients are excluded from active treatment of their advanced disease, and underrepresented in clinical trials, due to their older age, poor performance status, comorbidities and high tumor burden.

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Key Words: Non-small cell lung cancer, elderly, unfit, poor performance status, comorbidity, oral metronomic vinorelbine.

Although the median age of patients with newly diagnosed NSCLC in developed countries is approximately 68 years, up to 40% are aged ≥70 years at diagnosis and several studies have demonstrated that age is an important independent prognostic factor affecting survival of patients (20,21). Furthermore, patients with a borderline or poor performance status (*i.e.*, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 or Karnofsky Performance Status (KPS) ≤70) comprise 30-40% of patients with advanced NSCLC (22). Elderly and poor-performance status patients present often with multiple and severe comorbidities that prevent them from effective treatment (23, 24). Patients with multiple brain or bone metastases, occurring in approximately 35-45% of them (25, 26), have a poor prognosis (5), are often excluded from clinical trials and not frequently considered for active treatment in clinical practice. Thus, it can be estimated that approximately one-third to one-half of patients with advanced NSCLC are unfit for conventional chemotherapy, both at first or subsequent lines of treatment.

The aim of this study was to evaluate the feasibility and activity of oral metronomic vinorelbine in this unmet medical need represented by those patients with advanced NSCLC not eligible to standard chemotherapy because of old age (≥70 years), and/or poor ECOG PS (≥2), and/or extensive brain or bone disease, and/or active comorbidities (≥2) requiring pharmacological treatment.

Patients and Methods

Study population. The eligibility criteria for the study included: histological or cytological diagnosis of NSCLC; advanced clinical stage IVA or IVB NSCLC according to the TNM classification version 7.0 (5); ineligibility to standard chemotherapy due to elderly age (≥70 years), and/or poor ECOG PS (≥2), and/or extensive brain or bone disease, and/or active comorbidities (≥2) requiring pharmacological treatment; adequate hematologic, renal and hepatic function; no previous treatment with radiation or chemotherapy. All patients signed a written informed consent to this protocol. Pre-treatment evaluation and baseline clinical staging included: anamnesis; physical examination; computed tomography (CT) scan of brain, chest, abdomen and pelvis; bone scan; laboratory tests for the evaluation of haematological, liver and kidney function; magnetic resonance imaging (MRI) of the brain with gadolinium when clinically indicated.

Chemotherapy. Oral metronomic vinorelbine at the fixed dose of 30 mg three times a week, on Monday, Wednesday and Friday, to be taken after a small meal (such as breakfast), was prescribed to all patients and continued until disease progression (PD) or unacceptable toxicity. Each cycle included four weeks of treatment. As chemotherapy premedication the following drugs were used: a gastroprotective agent during the all therapy period; metoclopramide 10 mg p.o. or ondansetron 8 mg p.o. 30 minutes before the chemotherapy only in case of nausea or vomiting, respectively, to the previous administration of the vinorelbine. A complete blood count was requested on the day 14 of the first cycle. On day 28, patients had clinical evaluation including the evaluation of complete cell blood count (CBC) and laboratory tests for the assessment of hematologic, hepatic and renal function, and possible adverse events (AEs).

Patients were prescribed chemotherapy if the absolute neutrophils count (ANC) was ≥1,500/μL, platelet count was ≥100,000/μL and ≤grade 2 AEs. If the ANC or platelet counts were above these levels, the treatment was held, and a CBC was checked on a weekly basis. In case of febrile neutropenia or grade 3 haematological or non-haematological toxicity, the treatment was held until recovery. In case of more than two weekly delays or recurrence of a grade 3 AE, the chemotherapy was permanently discontinued. Patients who experienced a hematological or non-hematological grade 4 AE were permanently discontinued from chemotherapy. In the case of G3 hematological toxicity, granulocyte-colony stimulating factors (G-CSFs) and hematopoietic growth factors (HGFs) were allowed; when clinically indicated, red blood cell or platelet were transfused.

Assessment of toxicity and disease response. Toxicity was recorded by clinical evaluation according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (27) every 28 days, before each subsequent chemotherapy prescription. The disease response assessment was performed by the use of CT scan every two cycles or 8 weeks of therapy. Patients with progressive disease (PD), or unacceptable toxicity (as previously described), dropped out of the study and were treated with supportive care. At the end of treatment, the follow-up visits were performed every 3 months and included the clinical evaluation, a CT scan of brain, thorax, abdomen and pelvis, further investigations when clinically indicated.

Statistical analysis. The primary objective of the study was the treatment feasibility, including the assessment of toxicity according to the CTCAE v3.0 (27) and of disease control rate (DCR), defined as the sum of complete response (CR), partial response (PR) and stable disease (SD), according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (28). For the SD, the minimal time interval required between basal instrumental evaluation and reassessment was of eight weeks. The secondary endpoints included the duration of treatment, the chemotherapy dose reduction or withdrawal, the progression-free survival (PFS) and overall survival (OS).

Descriptive statistics were used to summarize the patient demographic and treatment characteristics. The disease responses were reported as relative proportions to the total number of patients. Percentages were approximate to the nearest unit. Contingency tables were analyzed using a 2-tailed Fisher exact test (29). The PFS was calculated from the date of the start of protocol treatment until the date of PD, or death from any cause. The OS was calculated from the date of the start of protocol treatment until death or last date of follow-up. Patients who had not died or progressed at the time of the final analysis were censored at the date of the last contact. The PFS and OS were estimated using the Kaplan-Meier method, reported as medians with confidence limits (95% CI) and compared using two-sided log-rank test (30). The confidence limits (95% CI) response rates were estimated according to Simon (31).

The Simon optimal two-stage design was chosen for sample size calculation (32). The expected number of patients for the accrual in this study was calculated to reject a 20% disease control rate in favor of a target disease control rate of 40%. This condition allows a significance level of 0.05 with a statistical power of 80%. The preliminary clinical benefit of oral metronomic vinorelbine would

Table I. *Patient characteristics*.

Characteristic	No.	% (range)
Age[a]		
Median, yr	72	(50-87)
Gender		
Male	38	78
Female	12	22
Histology		
Adenocarcinoma	36	72
Squamous cell	14	28
Stage		
IVA	15	30
IVB	35	70
ECOG PS		
0/1/2/3	0/5/36/9	0/10/72/18
Active comorbidities[b]		
0/1/2/3/4/5	2/6/13/17/10/2	4/12/26/34/20/4
Median	3	(0-5)
Brain metastases	13	26
Bone metastases	19	41
EGFR/ALK status		
EGFR/ALK mutated	5[c]/0	14[d]/0
EGFR/ALK unknown (squamous)	15/37	30/74

ALK, Anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Group Performance Status; EGFR, epidermal growth factor receptor; yr, year. [a]At the start of treatment. [b]Requiring a medical treatment. [c]Two patients had an exon 19 deletion and three patients an exon 21 mutation; all these patients were previously treated with a tyrosine kinase inhibitor. [d]Based on assessable patients.

Table II. *Type of comorbidities and smoking habits*.

Characteristic	No.	%
Comorbidity type[a]		
Cardiovascular	57	46
Metabolic	26	20
Pulmonary	20	16
Gastrointestinal	6	5
Renal	5	4
Psycological	4	3
Prostatic	4	4
Thyroid	3	2
Neurological	2	2
Cutaneous	1	1
Hepatic	1	1
Ocular	1	1
Smoking history[b]		
Heavy smoker	17	34
Ex-heavy smoker	19	38
Ex-light smoker	2	4
Never smoker	12	24

[a]A total of 130 comorbidities was recorded. [b]Smoking history legend: heavy smoker (>30 packs/year); ex-heavy smoker (>30 packs/year); ex-light smoker (0.1-30 packs/year).

be assessed enrolling 13 patients. If there were <4 tumor responses or stable diseases, accrual would need to be terminated. Otherwise, 30 additional patients would need to be entered in the second stage to achieve a target sample size of 43 evaluable patients for disease control. If more than 12 patients experienced disease control among these 43 patients, a further assessment could be suggested.

In order to study the possible influence on the OS and PFS of the main baseline characteristics (gender, disease stage, histology, age, ECOG PS, comorbidities, brain or bone metastases, line of chemotherapy and disease control by chemotherapy), univariate logistic regression model of Cox was used (33), considering differences statistically significant with p-values <0.05. A multivariate analysis of factors that resulted positive at the univariate analysis was planned. All the analyses were performed according to the intention-to-treat (ITT) principle and two-sided tests. Statistical analyses were performed using the statistical software SigmaPlot for Windows version 12.5 (Systat Sotware Inc, Erkrath, Germany).

Results

Characteristics of patients. From May 2006 to July 2017, 50 patients were consecutively enrolled to the study, 38 males, 12 females, with a median age of 72 years (range=50-87), an adenocarcinoma in 36 of them (72%) and a squamous cell carcinoma in 14 (28%). The characteristics of patients are summarized in Table I. Forty-five patients (90%) had ECOG PS of 2 or 3. Thirty-five patients (70%) had a stage IVB disease, with brain and/or bone metastases in 13 (26%) and 19 (41%) patients, respectively. Type of comorbidities and smoking habits are reported in Table II. The median number of active comorbidities was 3 (range=0-5), with 29 patients (58%) having ≥3 of them. Cardiovascular, metabolic and pulmonary were the three most frequent comorbidities observed in 57 (46%), 26 (20%) and 20 (16%) patients, respectively. Fourteen patients (28%) were ex-light or never smoker. Five patients were previously treated with a TKI due to the presence of an EGFR gene mutation (Table I).

Treatment and outcome. The data related to the treatment and disease outcome are shown in Table III. The treatment was administered as the first line in 19 patients (38%) and as second, third or subsequent lines in 31 patients (62%). The median time of chemotherapy duration was 2.6 months (range=0.3-8.4 months). No patient required a chemotherapy dose reduction or withdrawal.

DCR was observed in 16 out of 49 assessable patients (32%), 4 patients had a PR, 12 a SD. DCR was 44% (8 patients) and 26% (8 patients) in those patients who received the treatment as the first line as compared to those treated in second or further lines, respectively (p=0.39). With a median follow-up of 6.6 months, the median PFS was 2.7 months (95% CI=2.0-3.3) and the median OS was 7.3 months (95%

Table III. *Treatment and disease outcome.*

Characteristic	No.	% (range) [95% CI]
Line of treatment		
First line	19	38
Second/Third or subsequent line	14/17	28/34
No. cycles of chemotherapy		
Median	3	(1-8)
Dose reduction/withdrawal	0	0
Response		
PR	4	8
SD	12	24
PD	33	67
NA	1	2
DCR in 1st line/≥2nd line	8/8	44[a,b]/26[b]
Duration of treatment		
Median, months	2.6	(0.3-8.4)
Median follow-up, months	6.6	(0.4-31.7)
Median PFS, months		
All patients	2.7	[2.0-3.3]
1st line/≥2nd line	3.0/2.6[c]	[2.0-3.9]/[1.3-4.0]
Median OS, months		
All patients	7.3	[4.7-10.0]
1st line/≥2nd line	7.9/7.2[d]	[4.1-11.6]/[3.6-10.8]

CI, Confidence interval; DCR, disease control rate (including PR and SD); NA, not assessable; OS, Overall Survival; PD, progressive disease; PFS, Progression-Free Survival; PR, partial response; SD, stable disease. [a]Based on 18 assessable patients. [b]The difference in DCR between 1st line and ≥2nd line was not statistically significant (p=0.39). [c]The difference in PFS between 1st line and ≥2nd line was not statistically significant (p=0.37). [d]The difference in OS between 1st line and ≥2nd line was not statistically significant (p=0.80).

Table IV. *Treatment toxicity.*

Toxicity	G1-G2 No.	G1-G2 %	G3-G4 No.	G3-G4 %	p-Value[a]
All treatment lines (n=50)					
Asthenia	13-8	32-24	1-0	3-0	-
Constipation	7-5	22-14	-	-	-
Nausea	7-2	19-5	-	-	-
Anemia	6-3	8-5	3-0	5-0	-
Neutropenia	0-1	0-0	1-0	3-0	-
First line (n=19)					
Asthenia	6-2	32-10	1-0	5-0	-
Constipation	3-1	16-5	-	-	-
Nausea	4-1	21-5	-	-	-
Anemia	3-3	16-16	1-0	5-0	-
Neutropenia	-	-	1-0	5-0	-
Second/Third or subsequent lines (n=31)					
Asthenia	7-6	23-19	-	-	1.0/0.4
Constipation	4-2	13-6	-	-	1.0
Nausea	3-1	10-3	-	-	0.5
Anemia	3-0	6-0	2-0	6-0	0.1/1.0
Neutropenia	0-1	0-3	-	-	0.6/0.4

[a]It refers to difference in toxicity frequency between 1st line and ≥2nd line treatment.

CI=4.7-10.0) for all patients, without significant differences between first and second or further lines of treatment for both PFS (p=0.37) and OS (p=0.80) (Figure 1).

Toxicity. The toxicity data are reported in Table VI. Overall, five patients (11%) reported a grade 3 toxicity, including 3 anemia, one neutropenia, one asthenia. No grade 4 toxicity occurred. Forty-nine patients (98%) had a grade 1 or 2 toxicity, including asthenia in 21 patients (56%), constipation in 12 (36%), nausea in 9 (24%), anemia in 9 (13%) and neutropenia in one patient. No significant differences in the toxicity pattern and frequency were observed according to the treatment setting; there was only a nonsignificant trend for more frequent G1-G2 nausea and anemia when the treatment was given as the first instead of second or further lines of treatment (26% *vs.* 13%, p=0.5 and 32% *vs.* 6%, p=0.1, respectively).

Prognostic factors. Univariate and multivariate analysis results of possible prognostic factors are reported in Table V. Only the histology (SCC *vs.* adenocarcinoma) resulted as a significant prognostic factor by univariate (p=0.007) and multivariate (p=0.01) analyses on OS, while the ECOG PS (3 *vs.* 1-2) resulted as a significant prognostic factor by univariate (p=0.01) and multivariate (p=0.02) analyses on PFS. A non-significant trend was reported for the stage (IVB *vs.* IVA, p=0.09 and p=0.09) and active comorbidities (≥3 *vs.* <3, p=0.08 and p=0.09) by univariate analysis on OS and PFS, respectively. Disease control (PD *vs.* DCR) resulted as a significant prognostic factor by both univariate and multivariate analyses on PFS (p<0.001 and p<0.001, respectively).

Discussion

The treatment of PS 2 and elderly (≥70 years) NSCLC patients underwent an evolution in the last decade. As these patients are considered not-fit for standard platinum-based chemotherapy, other treatment options were studied to prolong survival and improve quality of life (8,34). Many studies were carried out to explore various approaches including single-agent, non-platinum-based chemotherapy, double agent non-platinum-based chemotherapy and modified platinum-based schedules. The results of these studies were summarized in some meta-analyses (35-37).

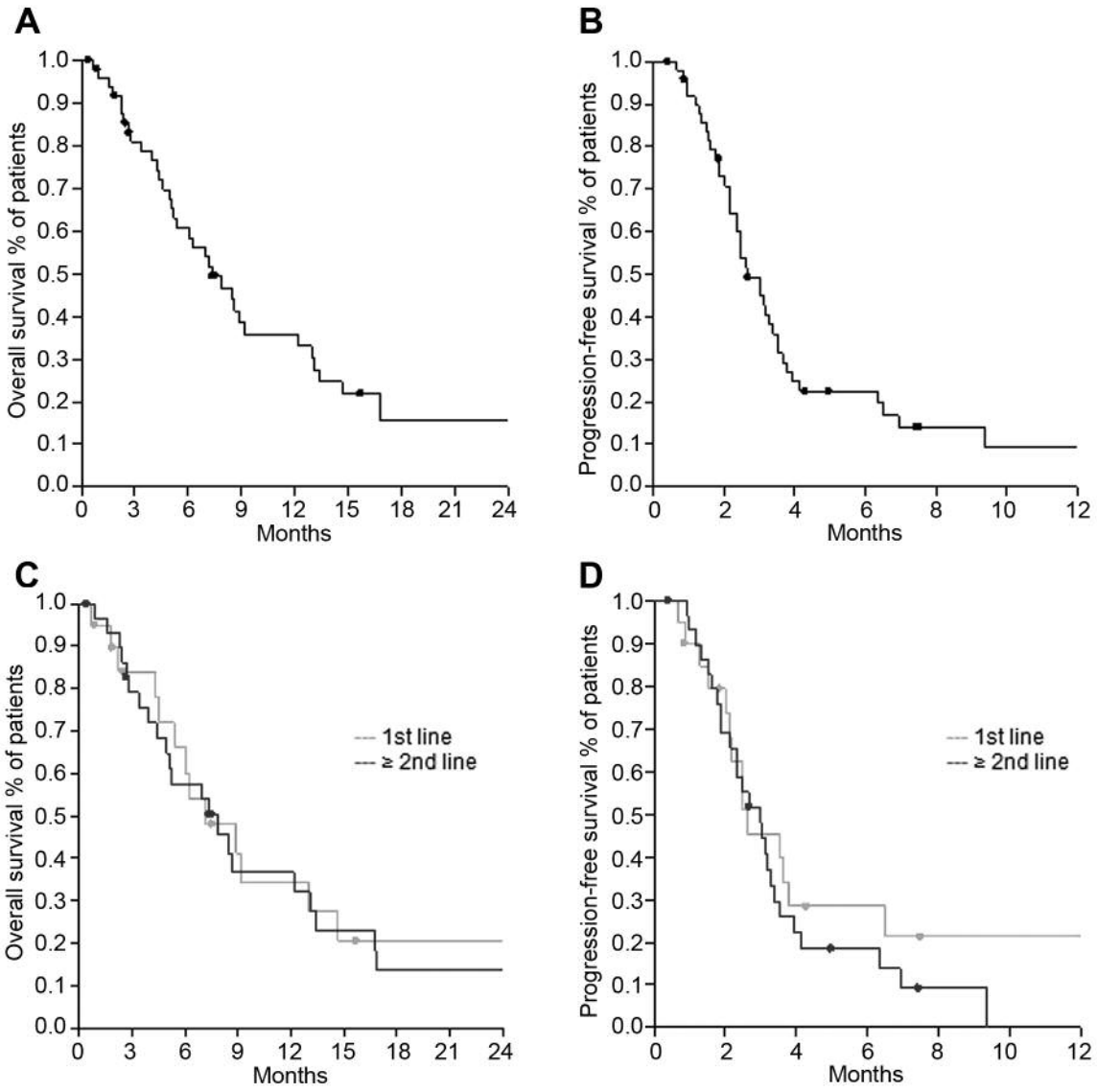

Figure 1. *Overall and progression-free survival of patients. A: Median OS for all patients: 7.3 months (95% CI, 4.7-10.0); B: median PFS for all patients: 2.7 months (95% CI, 2.0-3.3); C: median OS according to 1st line versus ≥2nd line of treatment: 7.9 versus 7.2 months, respectively (p=0.80); D: median PFS according to 1st line versus ≥2nd line of treatment: 3.0 versus 2.6 months, respectively (p=0.37).*

The rationale for the use of a doublet chemotherapy in these categories of patients is based on the practical observation that not all elderly patients have a poor performance status. Moreover, in some PS 2 patients, the general health status is conditioned by high tumor burden so that a tumor response can lead to the improvement of PS. Conversely, some elderly or PS 2 NSCLC patients have comorbidities that limit the use of doublet chemotherapy including platinum-based schedules. For these patients, an alternative option is represented by single-agent chemotherapy with gemcitabine, docetaxel or vinorelbine (38). When different kinds of monotherapies were compared in PS 2 NSCLC patients similar results in terms of survival outcomes were achieved (39). Some other PS 2 or elderly patients cannot even receive single-agent chemotherapy because comorbid conditions can induce a worsening of the PS if treatment-related adverse effects are experienced. The Charlson's score for comorbidities (40) in PS 2 and comprehensive geriatric assessment in elderly patients could be helpful to select those who could be treated with chemotherapy (41-43).

Table V. *Univariate and multivariate analysis for prognostic factors.*

Variables	OS		PFS	
	Univariate *p*-Value	Multivariate *p*-Value	Univariate *p*-Value	Multivariate *p*-Value
Gender				
M *vs.* F	0.61	-	0.43	-
Stage				
IVB *vs.* IVA	0.09	-	0.09	-
Histology				
SCC *vs.* Adeno	0.007	0.01	0.34	-
Age				
≥70 *vs.* <70	0.62	-	0.8	-
ECOG PS				
3 *vs.* 1-2	0.05	0.06	0.01	0.02
Active comorbidities				
≥3 *vs.* <3	0.08	-	0.09	-
Brain metastases				
Yes *vs.* No	0.73	-	0.81	-
Bone metastases				
Yes *vs.* No	0.84	-	0.45	-
Line of therapy				
≥3 *vs.* <3	0.86	-	0.12	-
Disease control				
PD *vs.* DCR	0.21	-	<0.001	<0.001

Adeno, Adenocarcinoma; DCR, disease control rate; ECOG PS, Eastern Cooperative Group Perfomance Status; F, female; M, male; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RT, radiotherapy; SCC, squamous cell carcinoma; *vs.*, *versus*. [a]Multivariate analysis was performed for those factors resulting significantly at univariate analysis.

Since cytotoxic drugs at the maximum tolerated dose (MTD) cannot be administered in PS 2 patients with high comorbidity score and in frail elderly patients, metronomic chemotherapy has been proposed as a valid alternative in various malignancies (44). Metronomic chemotherapy is a term used for the frequent or continuous delivery of cytotoxic agents at low doses (45). Two main mechanisms of action have been proposed to explain the function of metronomic chemotherapy: an antiangiogenic effect and an immunomodulating action (46, 47). This approach aims at prolonging the treatment exposure and consequently patient survival because of its activity and low toxicity rate, as reported in breast cancer (48). Vinorelbine, a drug which targets microtubules, has an antiangiogenic activity through the suppression of endothelial progenitor cells and inhibition of hypoxia-inducible factor (HIF)-1alpha-related pathway, and it can be delivered orally (49, 50). For these reasons, vinorelbine could be considered the best candidate for metronomic chemotherapy, among the cytotoxic agents active in NSCLC (51, 52).

First, a phase I trial evaluated escalating fixed doses of oral vinorelbine delivered daily (20, 30, 40, 50 mg/day) for 21 days in a 28-days cycle. At the MTD of 50 mg/day, the dose-limiting toxicities included neutropenia and fever (53). Subsequently, in four phase II studies, single-agent oral metronomic vinorelbine was used at fixed dose three times weekly. In three out of these four studies the fixed dose was 50 mg and in one was 30 mg. In three studies chemotherapy-naïve elderly patients or with poor PS were included, the remaining one enrolled pretreated NSCLC patients. In studies with untreated patients, disease control rate ranged between 50 and 69%. In pretreated patients, this rate has only reached 20% (54-57).

In the present study, the use of metronomic vinorelbine with the schedule of 30 mg three times per week in a particular setting of patients deemed "unfit" for chemotherapy due to their old age, poor performance status (PS), disease extent and/or comorbidities, led to an overall DCR in pretreated patients in line with the previously reported results and only slightly inferior in the chemotherapy-naïve elderly or poor PS patients. Together with the lack of G4 and the low rate of G3 toxicity, as well as the no need for chemotherapy dose reduction or withdrawal, these data confirmed the activity and safety of metronomic vinorelbine in a relevant proportion of patients usually excluded from any specific treatment.

These findings, together with the results of previous studies, suggest that probably metronomic vinorelbine at the dose of 50 mg three times weekly might be better than 30 mg three times per week, at least in "unfit" chemotherapy-naïve patients. Whereas, the latter option could be addressed to those patients with more than one of the characteristics defining patients "unfit" for chemotherapy, as identified by a panel of experts: age, PS, renal function, heart failure, previous cerebrovascular events, uncontrolled hypertension, neuropathy, hearing loss, symptomatic brain metastases, severe psychiatric disorders and absence of caregiver support (58). Based on the logistic regression analyses of prognostic factors, patients with adenocarcinoma and better PS (of 1-2) could have a more favorable disease outcome in terms of OS and PFS, respectively. These and other biological factors (59-61), along with the stage IVA disease and less than 3 active comorbidities, both showing a trend toward significance as a prognostic role, could be of some help for the choice of the most appropriate schedule of metronomic vinorelbine. A proper evaluation of compliance of these patients for the assumption of oral vinorelbine is a relevant issue that should be included in next clinical studies about metronomic vinorelbine.

Finally, some limitations may have affected the results of the present study. Above all, the lack of a comprehensive geriatric assessment of elderly patients and of a more appropriate evaluation of active comorbidities, for instance, according to the Charlson's score for comorbidities (40).

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