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Vinorelbine in Non-Small Cell Lung Cancer: Real-World Data From a Single-Institution Experience

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The use of vinorelbine as a single agent or in combination regimens in non-small cell lung cancer (NSCLC) is associated with satisfactory clinical activity. However, the role of vinorelbine-based chemotherapy in chemonaive locally advanced unresectable or metastatic NSCLC patients, according to real-world treatment patterns, has still not been widely explored. Eighty-one patients treated at a single institution were retrospectively analyzed. Thirty-seven received standard first-line single-agent vinorelbine, and 44 received vinorelbine plus platinum drugs, based on physician's choice; 61.7% were older than 70 years, and 60.5% were affected by 2 comorbidities. Sixty-three patients were evaluable for objective response: 22% achieved partial response and 41% stable disease. Median progression-free survival (PFS) was 5.4 months. A benefit in PFS was observed in patients treated with combinations vs. single-agent vinorelbine (6.7 vs. 3.5 months, $p = 0.043$). Median overall survival (OS) was 10.4 months without a statistically significant difference between treatments (12.4 vs. 7.5 months). In 55 stage IV patients, OS was positively correlated with combination regimens, M1a stage, or 2 metastatic lesions. Grade 3–4 toxicity occurred in 33% of patients, and dose reduction in 11%. A statistically significant higher incidence of toxicity was observed in patients receiving combinations, in women, in patients younger than 75 years, or patients with metastases. In this real-word analysis, we confirmed the efficacy and tolerability of vinorelbine as a single agent or combined with platinums in patients usually underrepresented in controlled clinical trials. Single-agent vinorelbine may represent a suitable option in elderly or unfit NSCLC patients and warrants investigation as a potential drug candidate for immunochemotherapy combination regimens.

Key words: Vinorelbine; Non-small cell lung cancer (NSCLC); Elderly; Unfit

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in Italy and worldwide[1]. The 5-year survival rate in metastatic non-small cell lung cancer (NSCLC) is <5%[1]. The increasing availability of anticancer agents (i.e., targeted agents, immunotherapy) offers today a wide choice of lung cancer treatment options. However, before the approval of first-line immunochemotherapy combinations (still not approved in Italy), platinum doublet chemotherapy has represented the first-line treatment of choice in patients with advanced NSCLC without sensitizing epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK)/ROS rearrangements, and with programmed death ligand 1 (PD-L1) tumor proportion score less than 50%.

Platinum-based combinations include cisplatin or carboplatin in association with a third-generation drug (i.e., vinorelbine, taxanes, gemcitabine, pemetrexed)[2–4]. Overall, these combinations provide a significant benefit in terms of overall survival (OS) compared with second-generation regimens[2]. However, such treatments may

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show relevant adverse effects. Thus, in elderly or unfit patients for doublet chemotherapy, a single-agent chemotherapy may represent a suitable option.

Vinorelbine is a semisynthetic derivative of the Vinca rosea alkaloid vinblastine. It has a cytotoxic effect due to its interaction with tubulin, leading to the impairment of the microtubule function. In fact, it binds to the -subunit of the tubulin dimer at the Vinca binding site, resulting in a block of -tubulin polymerization with -tubulin. The cells exposed to the drug are particularly affected during metaphase because of the alteration of the mitotic spindle organization, with a final effect of inhibition of cell proliferation and blockage of mitosis[5,6].

The use of single-agent vinorelbine or vinorelbine-based combination regimens in NSCLC is associated with satisfactory clinical activity, comparable to other third-generation regimens[2,7]. The selection of the most suitable chemotherapeutic treatment choice represents a challenge for oncologists. When administered alone, vinorelbine has a favorable tolerability profile even in frail or elderly patients[8], with a response rate (RR) of about 20%[9]. Vinorelbine is also available in an oral formulation, which offers a benefit in the management of care. Based on patient characteristics and preferences, clinicians can choose oral or intravenous administration[10].

Although in recent years the use of these vinorelbine-based regimens in advanced disease has been resized due to a lower consensus score in clinical guidelines, there is evidence of a substantial comparable activity of different third-generation regimens[3,8]. Cisplatin plus vinorelbine still retains a prominent role in adjuvant therapy of patients with completely resected NSCLC (stage IB–IIIA), with an absolute 5-year survival advantage ranging from 8.6% to 15% versus observation[11,12].

However, since clinical practice guidelines are based on results of controlled clinical trials including selected patients, real-world studies may help in the comprehension of the impact of these treatments on patient outcome in routine clinical practice. To date, with the exception of very few studies[13,14], there is still very limited information on real-life data concerning the use of first-line vinorelbine-based chemotherapy in NSCLC.

Thus, the aim of this study was to evaluate according to real-world treatment patterns the efficacy and tolerability of single-agent vinorelbine or vinorelbine combined with cisplatin or carboplatin in a cohort of chemonaive locally advanced unresectable or metastatic NSCLC patients.

PATIENTS AND METHODS

Patients and Treatment

This retrospective observational monoinstitutional real-world analysis was conducted at the Unit of Translational Oncology of the Careggi University Hospital between November 2008 and May 2015.

The study procedures were in accordance with the ethical standards of the institution and with the Helsinki Declaration. Signed informed consent for treatment was obtained from all patients. Because of the descriptive, exploratory nature of the study, sample size was not based on any statistical test.

The study population consisted of previously untreated 18-year-old patients with histological or cytological examination documenting a NSCLC. According to the American Joint Committee on Cancer (AJCC)[15], stages admitted to the analysis were IIIA or IIIB not suitable for surgery or chemoradiotherapy, and IV. Patients were also eligible if they had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. In addition, patients had adequate bone marrow, renal, and hepatic functions.

Baseline evaluation included medical history (including comorbidities and concomitant drugs), blood examination (complete blood count and metabolic panel), and computed tomography (CT) scan. After the beginning of chemotherapy, patients underwent clinical examination, including blood tests, at least twice a month. Radiological assessments were usually performed every 10–14 weeks or when clinically required.

Eighty-one patients (53 males and 28 females) with NSCLC were included in the analysis. Thirty-seven received vinorelbine alone, and 44 received vinorelbine plus cisplatin ($n = 22$) or carboplatin ($n = 22$) as first-line chemotherapy. All patients undergoing single-agent chemotherapy received vinorelbine as oral formulation, whereas only 25% of patients who underwent combination chemotherapy received oral vinorelbine. The choice of treatment was mainly based on clinical criteria, including age, PS, and comorbidities. The median age was 72 years (range: 37–86 years); 13.6% of patients had a baseline PS 1. Forty-two patients (51.9%) had an adenocarcinoma, 33 (40.7%) a squamous cell carcinoma, and 6 (7.4%) other histologies (adenosquamous carcinoma, large cell carcinoma, and undifferentiated NSCLC). Fifty-five patients (67.9%) had stage IV, 16 (20%) stage IIIB, and 10 (12%) stage IIIA disease. Overall, all patients with adenocarcinoma treated after approval in 2010 of first-line gefitinib in Italy ($n = 28$) underwent EGFR mutation analysis. Among them, 26 were EGFR wild type and 2 EGFR mutated. Both of them interrupted cytotoxic chemotherapy to start gefitinib (one patient after one cycle) and erlotinib (one patient after two cycles) as soon as analysis results were available. EGFR mutation analysis was also performed in 5 out of 14 adenocarcinoma patients treated prior to 2010, and only one cancer was found to be mutated. Such finding brought in this patient the second-line treatment of a tyrosine kinase inhibitor following disease progression.

In most patients (78%), KRAS was not determined. ALK translocation analysis was performed in only three

patients following vinorelbine-based chemotherapy since first-line treatment with crizotinib was not approved in Italy until May 2018. Thus, the ALK translocation analysis was performed in such patients only for second-line therapy purpose since crizotinib was available in Italy for second-line treatment from March 2015. No ALK rearrangement was detected in these cases. These and other characteristics of patients are listed in Table 1.

Treatment Regimens

Patients included in the analysis were treated according to standard regimens. Chemotherapy combinations were represented by vinorelbine 25 mg/m^2 intravenously (IV) day 1, 8 q21 or 60 mg/m^2 per os (PO) day 1, 8 q21 plus carboplatin (AUC 4/5 mg/ml/min, day 1 q21), or vinorelbine (as above) plus cisplatin (75 mg/m^2, day 1 q21).

Single-agent vinorelbine was administered as follows: 60 mg/m^2 PO day 1, 8 q21 or day 1, 15 q28. Single-agent maintenance with oral vinorelbine was also performed.

Assessment of Efficacy

Objective response (OR) was recorded according to RECIST (v. 1) criteria in patients who underwent at least one instrumental reevaluation. Progression-free survival (PFS) and OS were calculated from the beginning of chemotherapy to the occurrence of the first progression or death/lost to follow-up, respectively.

Evaluation of Toxicity

All toxicities were scored according to World Health Organization criteria [Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0]. The evaluation of toxicity was planned for patients who received at least one cycle of chemotherapy.

Statistical Analysis

PFS and OS were analyzed using the Kaplan–Meier method (log-rank test). The impact of clinical/pathological characteristics of metastatic patients on PFS and OS was assessed by univariate and multivariate COX proportional hazard model [hazard ratio (HR), 95% confidence interval (CI)]. The exact Fisher's test and the chi-square test were used to assess correlations between OR and treatment type and toxicity and patients' characteristics. All comparisons were performed by considering no more than two categories per variable. Statistical analysis was performed using the SPSS software (version 23.0). Statistical significance was defined as a value of $p < 0.05$.

RESULTS

Factors Driving the Treatment Choice

Significant statistical associations were reported between physician's administered treatment regimens

Table 1. Demographic and Baseline Characteristics of 81 Non-Small Cell Lung Cancer (NSCLC) Patients

Characteristic	Number (%)
Sex	
Male	53 (65.4)
Female	28 (34.6)
Age (years)	
Median	72
Range	37–86
<70	31 (38.3)
70–75	24 (29.6)
76–80	16 (19.8)
>80	10 (12.3)
Performance status (ECOG)	
0	70 (86.4)
1	10 (10.3)
2	1 (1.2)
Comorbidities	
0	7 (8.6)
1	25 (30.9)
2	36 (44.4)
3	13 (16.0)
Concomitant drugs	
Yes	73 (90.1)
No	8 (9.9)
Smoking status	
No	9 (11.1)
Yes	72 (88.9)
Ex smokers	54 (75.0)
Smokers	18 (25.0)
Stage (AJCC)	
IIIA	10 (12.3)
IIIB	16 (19.8)
IV	55 (67.9)
M1a	27 (49.1)
M1b	28 (50.9)
Number of metastases	
1–2	26 (47.3)
3	29 (52.7)
Histotype	
Adenocarcinoma	42 (51.9)
Squamous cell carcinoma	33 (40.7)
Squamous adenocarcinoma	1 (1.2)
Large cell carcinoma	1 (1.2)
Non-small cell carcinoma NOS	4 (4.9)
EGFR status	
Wild type	35 (43.2)
Mut	4 (4.9)
Not available	42 (51.9)
KRAS status	
Wild type	13 (16.0)
Mut	5 (6.2)
Not available	63 (77.8)
ALK status	
Wild type	3 (3.7)
Rearranged	–
Not available	78 (96.3)

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

(single agent vs. combination regimens) and age or comorbidities. Single-agent vinorelbine was administered mainly to patients older than 75 years and with 2 comorbidities ($p < 0.001$ and $p = 0.013$, respectively). Other factors such as sex, PS, concomitant drugs, smoking history, histology, and stage did not significantly correlate with the administered treatments.

Study Drug Exposure

Eighty-eight percent of patients received more than one cycle of chemotherapy. Overall, the median number of cycles was 4 (range: 1–6). Twenty-eight patients (34.6%) discontinued treatment by the fourth cycle of treatment due to early disease progression (57%), toxicity (21%), worsening of clinical conditions (14%), and other causes (7%) (Table 2).

Seventy-two patients (88.9%) received chemotherapy without dose reductions (Table 2). In the remaining nine patients (11.1%), dose reductions from 25% to 35% of one or both drugs were performed due to the occurrence of toxicity. Overall, 315 cycles of treatment were administered, 289 (91.7%) as full dose and 26 (8.3%) as reduced dose.

Efficacy

Sixty-three of 81 patients treated with vinorelbine-containing regimens underwent a CT scan reassessment. In the remaining 18 patients, OR was not evaluated because of early worsening of clinical conditions or unacceptable toxicity or other causes that led to an early drug discontinuation.

According to RECIST criteria, 14 patients (22.2%) achieved a partial response (PR) and 26 (41.3%) a stable disease (SD), with a disease control rate (DCR) of 63.5%. Twenty-three patients had a progressive disease (PD), and no patient had a complete response (CR) (Table 3).

Median PFS of the entire case series was 5.4 months (95% CI: 2.8–8.0). A PFS benefit of the combination regimens compared with single-agent chemotherapy was observed: median PFS were 6.7 and 3.5 months, respectively (HR: 0.55; 95% CI: 0.31–0.98; $p = 0.043$). Multivariate analysis confirmed a significantly longer PFS in patients who received combination therapy (HR: 0.25; 95%: CI, 0.11–0.59; $p = 0.001$) (Table 4, Fig. 1A).

Median OS of the entire case series was 10.4 months (95% CI: 5.6–15.0). Median OS of patients treated with vinorelbine plus a platinum complex was 12.4 months, and that of patients treated with single-agent vinorelbine was 7.5 months. However, no statistically significant difference was found ($p = 0.432$) (Table 4, Fig. 1B).

Univariate and multivariate analyses of the entire case series did not show significant correlations between patients' characteristics and treatment outcome.

Table 2. Treatment Characteristics

Variable	All Regimens [*n* (%)]	Combination Chemotherapy [*n* (%)]	Single-Agent Chemotherapy [*n* (%)]
Treatment	81 (100.0)		
Vinorelbine + cisplatin	–	22 (27.2)	–
Vinorelbine + carboplatin	–	22 (27.2)	–
Vinorelbine	–	–	37 (45.7)
Vinorelbine maintenance treatment			
Yes	16 (19.8)	13 (29.5)	3 (8.1)
No	65 (80.2)	31 (70.5)	34 (91.9)
No. of cycles			
Mean ± SD	4 ± 1.66	4.1 ± 1.64	3.6 ± 1.69
Median	4	4	4
Range	1–6	1–6	1–6
1–2	19 (23.5)	9 (20.4)	10 (27.0)
3–4	35 (43.2)	19 (43.2)	16 (43.2)
5–6	27 (33.3)	16 (36.4)	11 (29.7)
Vinorelbine formulation			
Oral	48 (59.3)	11 (25.0)	37
Intravenous	33 (40.7)	33 (75.0)	0
Dose reduction			
Yes	9 (11.1)	8 (18.2)	1 (2.7)
No	72 (88.9)	36 (81.8)	36 (97.3)
Treatment interruption			
Yes	28 (34.6)	13 (29.5)	15 (40.5)
No	53 (65.4)	31 (70.5)	22 (59.5)

Table 3. Evaluation of Response in Patients Evaluable for Objective Response (OR)

	All Regimens		Combination Chemotherapy		Single-Agent Chemotherapy		
	OR (*n*)	(*n* = 63)	OR (*n*)	(*n* = 38)	OR (*n*)	(*n* = 25)	*p*
ORR		22.2%		27.3%		5.4%	0.033
DCR		63.5%		65.9%		29.7%	0.015
Complete response	–	–	–	–	–	–	
Partial response	14	22.2%	12	31.6%	2	8.0%	
Stable disease	26	41.3%	17	44.7%	9	36.0%	
Disease progression	23	36.5%	9	23.7%	14	56.0%	
Not evaluable	18		6		12		

ORR, overall response rate; DCR, disease control rate.

When the analysis was limited to 55 stage IV patients, response to treatment was significantly associated with the administered regimen, with a higher OR rate (ORR) in patients receiving combination chemotherapy compared with single-agent chemotherapy ($p = 0.041$). Similar results were found for PFS and OS either by univariate or multivariate analysis (Table 5, Fig. 1C and D): prolonged PFS and OS were observed in patients treated with combination chemotherapy ($p < 0.001$ in both cases).

PFS and OS were both associated with sites of metastases: patients with only pulmonary metastases and/or pleural effusion (M1a AJCC), compared with patients with distant metastases (M1b AJCC), showed an advantage in both PFS (7.9 vs. 3.5 months; $p = 0.043$) and OS (17.9 vs. 7.5 months; $p = 0.009$) (Table 5, Fig. 1E and F).

Also, OS significantly related to the number of metastatic lesions: patients with 2 metastatic lesions showed a prolonged OS compared with patients with >2 lesions (15.6 vs. 5.6 months; $p = 0.050$) (Table 5, Fig. 1G and H).

Toxicity

Adverse events (AEs) are detailed in Table 6. Grade 3 or 4 toxicity was observed in 27 patients (33%), with prevalence of neutropenia (22%) and hepatotoxicity (7%). Overall, six patients (7.4%) discontinued treatment because of grade 3 or 4 AE. Sixty-six percent of patients experienced only grade 1 or 2 AEs, maintaining a good quality of life during treatment. The most common grade 1–2 AEs were anemia (85.2%), asthenia (33.3%), leukopenia (32.1%), nausea (32.1%), elevated alanine aminotransferase or aspartate aminotransferase (27.2%), constipation (18.5%), and diarrhea (17.3%).

As expected, patients who received vinorelbine combination regimens showed a significantly higher incidence of treatment-related toxicity than patients treated with vinorelbine alone (grade 3 or 4 in 43.2% vs. 21.6; $p < 0.001$) (Table 7). In particular, a higher incidence of neutropenia (grade 2 in 50% vs. 10.8%; $p = 0.001$), leukopenia (grade 2 in 25.0% vs. 8.1%; $p = 0.051$), anemia (grade 2 in 27.3% vs. 0%; $p < 0.001$), and dyspepsia (grade 2 in 22.7% vs. 2.7%, $p = 0.010$) was observed (data not shown).

A dose reduction in one or both drugs was required in 11% of patients treated with the combination chemotherapy, due to the occurrence of severe AEs. In the single-agent vinorelbine group, a dose reduction was required in only two patients (5.4%). A higher number of patients treated with doublets discontinued treatment compared with those treated with the vinorelbine single agent ($p = 0.035$).

Also, a higher incidence of AEs in women compared with men was found (grade 3 in 42.9% vs. 28.3%; $p = 0.030$) (Table 7), especially in relation to gastrointestinal toxicity (grade 2 in 50% vs. 18.9%; $p = 0.003$), including nausea (grade 2 in 28.6% vs. 7.6%; $p = 0.014$) and diarrhea (grade 2 in 10.7% vs. 0.0%; $p = 0.038$) (data not shown).

Table 4. Efficacy Evaluation in the Intent-to-Treat Population

	All Regimens (*n* = 81)	Combination Chemotherapy (*n* = 44)	Single-Agent Chemotherapy (*n* = 37)	HR (CI 95%)*
Median PFS (months)	5.4	6.7	3.5	0.55 (0.31–0.98), $p = 0.043$
CI 95% PFS	2.8–8.0	4.0–9.5	2.8–4.3	
Median OS (months)	10.4	12.4	7.5	0.80 (0.45–1.41), $p = 0.432$
CI 95% OS	5.6–15.1	7.5–17.2	3.6–11.3	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.
*Cox proportional hazard model.

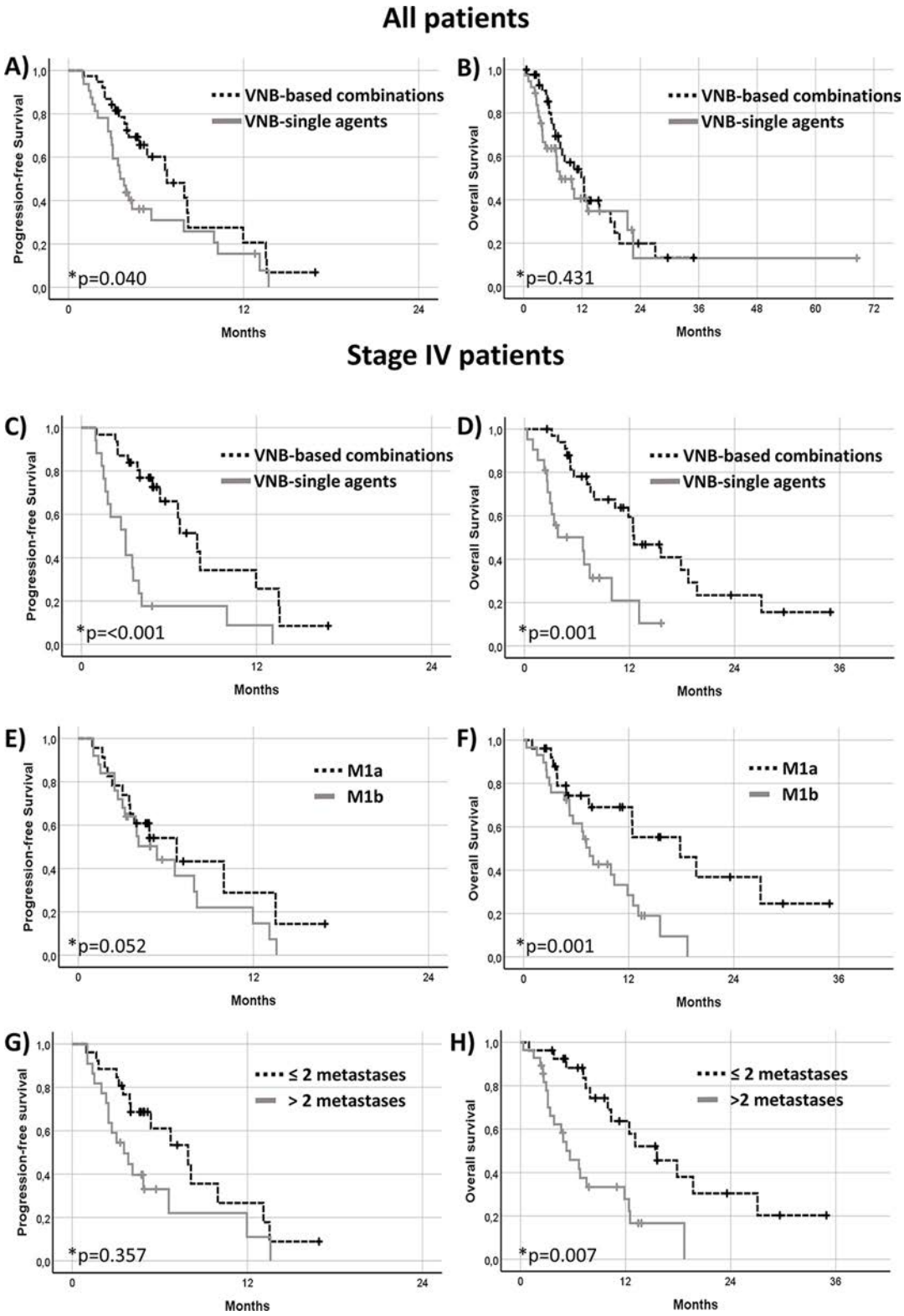

Figure 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) of all patient population according to treatment regimens. Kaplan–Meier estimates of progression-free survival (C) and overall survival (D) of stage IV patients (dotted line: vinorelbine-based combinations; solid line: single-agent vinorelbine). Kaplan–Meier estimates of progression-free survival and overall survival of stage IV patients according to sites of metastases (dotted line: M1a; solid line: M1b) (E, F) or number of metastases (dotted line: 2; solid line: >2) (G, H). *Log-rank test.

Table 5. Correlations Between PFS, OS, and Characteristics of 55 Stage IV Patients

	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	*p*	HR (CI 95%)	*p*
PFS				
Metastasis (AJCC)				
M1b (*n* = 28)	1		1	
M1a (*n* = 27)	0.45 (0.25–0.97)	0.050	0.47 (0.23–0.97)	0.043
Number of metastatic lesions				
3 (*n* = 29)	1		1	
1–2 (*n* = 26)	0.72 (0.35–1.46)	0.362	0.81 (0.33–1.19)	0.644
Treatment type				
Single-agent chemotherapy (*n* = 21)	1		1	
Combination chemotherapy (*n* = 34)	0.27 (0.13–0.56)	<0.001	0.26 (0.10–0.44)	<0.001
OS				
Metastasis (AJCC)				
M1b (*n* = 28)	1		1	
M1a (*n* = 27)	0.30 (0.15–0.63)	0.001	0.36 (0.16–0.78)	0.009
Number of metastatic lesions				
3 (*n* = 29)	1		1	
1–2 (*n* = 26)	0.36 (0.17–0.78)	0.009	0.45 (0.20–0.96)	0.050
Treatment type				
Single-agent chemotherapy (*n* = 21)	1		1	
Combination chemotherapy (*n* = 34)	0.30 (0.15–0.62)	0.001	0.28 (0.13–0.61)	0.001

Table 6. Toxicity Observed During First-Line Therapy in Relation to Chemotherapeutic Regimens and in Overall Population

	Combination Chemotherapy			Single-Agent Chemotherapy			All Regimens		
Observed Toxicity	Grade 0–1	Grade 2	Grade 3–4	Grade 0–1	Grade 2	Grade 3–4	Grade 0–1	Grade 2	Grade 3–4
Hematological toxicity	43.2%	22.7%	34.1%	89.2%	2.7%	8.1%	64.2%	13.6%	22.2%
Leukopenia	75.5%	11.4%	13.6%	91.9%	8.1%	-	82.7%	9.9%	7.4%
Neutropenia	50.0%	15.9%	34.1%	89.2%	2.7%	8.1%	67.9%	9.9%	22.2%
Febrile neutropenia	93.2%	–	6.8%	100.0%	–	–	96.3%	–	3.7%
Anemia	72.7%	27.3%	–	100.0%	–	–	85.2%	14.8%	–
Thrombocytopenia	97.7%	–	2.3%	97.3%	–	2.7%	97.5%	–	2.5%
Gastrointestinal toxicity	61.4%	38.6%	–	81.1%	13.5%	5.4%	70.4%	27.2%	2.5%
Diarrhea	93.2%	6.8%	–	100.0%	–	–	96.3%	3.7%	–
Constipation	100.0%	–	–	94.6%	2.7%	2.7%	97.5%	1.2%	1.2%
Nausea	79.5%	20.5%	–	91.9%	5.4%	2.7%	85.2%	13.6%	1.2%
Vomiting	97.7%	2.3%	–	100.0%	–	–	98.8%	1.2%	–
Mucositis	95.5%	4.5%	–	94.6%	5.4%	–	95.1%	4.9%	–
Dyspepsia	77.3%	22.7%	–	97.3%	2.7%	–	86.4%	13.6%	–
Neurological toxicity	95.5%	4.5%	–	97.3%	2.7%	–	96.3%	3.7%	–
Liver toxicity	86.4%	4.5%	9.1%	91.9%	2.7%	5.4%	88.9%	3.7%	7.4%
Renal toxicity	97.7%	–	2.3%	100.0%	–	–	98.8%	–	1.2%
Asthenia	93.2%	6.8%	–	97.3%	2.7%	–	95.1%	4.9%	–
Fever	97.7%	2.3%	–	100.0%	–	–	98.8%	1.2%	–
Maximum toxicity (all types)	13.6%	43.2%	43.2%	56.8%	21.6%	21.6%	33.3%	33.3%	33.3%

Table 7. Correlations Between Patient Characteristics and Maximum Grade Toxicity Observed During First-Line Therapy

Characteristics	Total *n*	Grade 0–1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3–4 [*n* (%)]	χ^2 Test
Patients (*N*= 81)		27 (33.3)	27 (33.3)	27 (33.3)	
Sex					0.030
Male	53	23 (43.4)	15 (28.3)	15 (28.3)	
Female	28	4 (14.3)	12 (42.9)	12 (42.9)	
Age (years)					0.016
<75	50	11 (22.0)	21 (42.0)	18 (36.0)	
75	31	16 (51.6)	6 (19.4)	9 (29.0)	
PS (ECOG)					0.900
0	70	24 (34.3)	23 (32.9)	23 (32.9)	
1	11	3 (27.3)	4 (36.4)	4 (36.4)	
Comorbidities (number)					0.275
0–1	32	9 (28.1)	9 (28.1)	14 (43.8)	
>1	49	18 (36.7)	18 (36.7)	13 (26.5)	
Concomitant therapies					0.870
Yes	73	24 (32.9)	25 (34.2)	24 (32.9)	
No	8	3 (37.5)	2 (25.0)	3 (37.5)	
Smoking					0.687
Yes	72	23 (31.9)	25 (34.7)	24 (33.3)	
No	9	4 (44.4)	2 (22.2)	3 (33.3)	
Histotype					0.382
Nonsquamous	47	13 (27.7)	16 (34.0)	18 (38.3)	
Squamous	34	14 (41.2)	11 (32.4)	9 (26.5)	
Therapeutic setting					0.050
Local advanced	26	12 (46.2)	10 (38.5)	4 (15.4)	
Metastatic	55	15 (27.3)	17 (30.9)	23 (41.8)	
Treatment type					<0.001
Combination chemotherapy	44	6 (13.6)	19 (43.2)	19 (43.2)	
Single-agent chemotherapy	37	21 (56.8)	8 (21.6)	8 (21.6)	
Vinorelbine formulation					0.003
Oral	48	23 (47.9)	11 (22.9)	14 (29.2)	
Intravenous	33	4 (12.1)	16 (48.5)	13 (39.4)	
Palliative radiotherapy/symptomatic					0.917
Yes	14	4 (28.6)	5 (35.7)	5 (35.7)	
No	67	23 (33.3)	22 (32.8)	22 (32.8)	

As far as age was concerned, patients younger than 75 years experienced more toxicity (grade 3 in 36% vs. 29%; $p = 0.016$) (Table 7), mainly in relation to anemia (grade 2, 8% vs. 4%; $p = 0.025$), leukopenia (grade 2, 22.6% vs. 14%; $p = 0.050$), and nausea (grade 2, 20% vs. 6.4%; $p = 0.050$) (data not shown).

Finally, patients with metastatic disease experienced higher toxicity compared with patients with locally advanced disease (grade 3, 42% vs. 15%; $p = 0.050$) (Table 7) mainly in relation to hematological toxicity ($p = 0.012$) (data not shown).

Maintenance Therapy

Sixteen of 81 vinorelbine-treated patients (20%) with documented SD ($n = 7$) or PR ($n = 9$) after four to six courses of monochemotherapy (19%) or combination chemotherapy (81%) underwent maintenance therapy with vinorelbine. This treatment option was not offered to clinically unfit patients with unfavorable features, such as ECOG PS 1 or major comorbidities. Eleven patients received oral vinorelbine (60 mg/m^2 day 1, 8 every 21) and 5 IV vinorelbine (25 mg/m^2 day 1, 8 every 21). Overall, a total of 77 courses were administered (median number of courses: 4.8, range: 2–10). According to the RECIST criteria, two patients (13%) achieved a PR and nine (56%) an SD. Median PFS was 9.9 months (95% CI: 5.4–14.5), and OS was 12.4 months (95% CI: 12.3–12.5) (data not shown).

The outcome parameters (PFS and OS) of this group of patients were compared with those of 18 patients who received at least four courses of induction chemotherapy but were not candidate for maintenance therapy. No statistically significant differences were observed in PFS or OS of such subgroups (respectively, $p = 0.593$ and $p = 0.241$) (data not shown).

The vinorelbine maintenance treatment was generally well tolerated and safe, with low rates of severe AEs.

Only two patients (12.5%) experienced grade 3 or 4 toxicity (data not shown).

DISCUSSION

Regimens including vinorelbine constitute a valid therapeutic option in advanced NSCLC. The efficacy of combinations including a platinum complex and vinorelbine is comparable to that of regimens that include other third-generation drugs[3,7,8,16,17]. Also, vinorelbine-based regimens display a relatively favorable tolerability profile[7,16,17].

In patients with unfavorable clinical characteristics (e.g., elderly, poor PS, comorbidities), a treatment with single agent vinorelbine may also be considered[8,9,18–20].

Interestingly, the oral formulation of vinorelbine has also shown to be active and well tolerated according to a metronomic administration in frail patients[21,22]. We conducted a retrospective observational analysis to evaluate the efficacy and tolerability of first-line therapy with vinorelbine-based regimens in a cohort of NSCLC patients consecutively treated at the Translational Oncology Unit of the Careggi University Hospital according to real-world treatment patterns between 2008 and 2015. In this context, we demonstrated the efficacy and tolerability of the administered regimens also in patients usually underrepresented in controlled clinical trials. A relevant percentage of patients were, in fact, older than 70 years (61.7%) and were affected by 2 comorbidities (60.5%).

Our findings, despite the limited number of patients analyzed, are comparable with those of larger controlled clinical trials that evaluated vinorelbine-based regimens in patients with unresectable stage III or metastatic disease[7,9,23–27].

Median OS and PFS we observed in patients treated with vinorelbine-based doublets were even slightly higher than those observed in main randomized phase III clinical trials. Median OS values ranged, in fact, from 8.1 to 10.1 months for vinorelbine–cisplatin[7,16,17]. Median OS of 7.3 months was reported for vinorelbine–carboplatin combinations[28]. In the same trials, PFS ranged from 4.0 to 5.7 months. This finding appears notable and highlights the importance of real-life studies in the context of clinical investigations.

Median OS and PFS observed in our cohort of patients treated with single-agent vinorelbine were both within the ranges reported in randomized controlled trials in which vinorelbine was administered according to standard schedules (median OS from 6.5 to 10.2 months, median PFS from 3.1 to 6.0, respectively)[29,30].

Our results are also in substantial agreement with those available from a large European prospective real-world study performed in advanced/metastatic NSCLC patients and including different cohorts treated with first-line third-generation drug combinations. In particular, OS and PFS in a cohort of 300 patients treated with platinum–vinorelbine doublets were, respectively, 10.7 and 5.6 months[13]. Such cohort included 15% of patients with PS 2–3 but only 28% of patients older than 70 years. A second retrospective real-word study, based on a SEER–Medicare database analysis including more than 5,000 NSCLC patients, did not report efficacy data on vinorelbine-based treatment, probably due to the small number of patients treated with this drug ($n = 25$)[14].

The significant benefit we observed either in PFS and OS of stage IV patients with M1a disease compared with those with distant metastases (M1b) confirms the prognostic advantage derived from the presence of only pulmonary metastases. The finding that tumor burden correlated with treatment outcome was also in agreement with the results of others[31] and may be related to a different cytokinetic status (lower growth fraction, longer doubling time) and consequent lower responsiveness to drug therapy.

Vinorelbine-based chemotherapy was generally well tolerated with an overall 33.3% grade 3–4 toxicity in the entire population and with dose reduction occurring in 11% of cases. The higher incidence of grade 3–4 hematological and gastrointestinal toxicities observed in patients treated with combination chemotherapy compared with single-agent vinorelbine was expected, although the frequency we observed was lower compared with data of other studies[7,16,30,32,33].

The observation of a higher incidence of AEs in women, patients younger than 75 years, and patients with metastatic disease may be respectively explained by sex-related differences in pharmacokinetics and pharmacodynamics of drugs[34], as well as by a reduced responsiveness of women to antiemetic drugs[35] and a higher use of the combination chemotherapy in younger patients as well as in metastatic patients.

The lack of difference we observed between efficacy parameters of the small subcohort of patients who received maintenance therapy and the comparator subgroup of patients who did not received it is in agreement with results of studies investigating vinorelbine according to this therapeutic strategy[24–26]. The incidence of AEs was instead substantially lower compared with that reported in clinical trials[24–26].

In the years in which these patients were treated, platinum-based doublets represented the most active and appropriate first-line choice for most of patients with NSCLC in Italy. EGFR inhibitors (i.e., gefitinib and erlotinib) as first-line treatment of NSCLC carrying EGFR activating mutations have been available in Italy only from 2010 and 2013, respectively. First-line treatment with an ALK inhibitor (crizotinib) has been possible in Italy in 2018 only, after the conclusion of this study. Fortunately, in more recent years, new agents have radically changed

the state-of-the-art NSCLC treatment. The breakthrough of immunotherapy into the NSCLC treatment scenario has enriched the spectrum of the therapeutic armamentarium, offering increasing options to satisfy different clinical necessities. In particular, immune checkpoint inhibitors targeting the programmed death 1 (PD-1)/PD-L1 axis have shown notable clinical activity in nononcogenic addicted NSCLC with high RR and durable responses[36–40].

It is known that cancer activates escape mechanisms (e.g., adaptive and innate evasion) against the host immune response. NSCLC establishes an immunosuppressive microenvironment with the fundamental role of regulatory T cells (Tregs), upregulating molecules with immunosuppressive activity such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4), T-cell immunoglobulin mucin 3 (TIM-3), and PD-1[41].

Accumulating evidence shows that cytotoxic chemotherapy can modulate the immune microenvironment by increasing the immunogenicity of cancer cells, enhancing the cytotoxicity of T cells and NK cells, and fostering the accumulation of interferon- (IFN-) and tumor necrosis factor- (TNF-)[42]. In addition, cytotoxic agents may decrease immunosuppressive immune cells, such as Tregs, with a consequent reduction in inhibitory cytokines such as TGF- [42]. Cytotoxic agents that show such immunomodulatory properties are mainly represented by platinum compounds, taxanes, and vinca alkaloids, including vinorelbine[42,43].

On this basis, vinorelbine could exert a synergistic activity with immunotherapy. Available data show that the adjuvant treatment of NSCLC patients with cisplatin plus vinorelbine was associated with intense alterations on the circulating immune cells status, mainly represented by increased cytotoxic T-lymphocyte (CTL)/Treg ratio and consequent reduction in Treg activity in most of the patients[44].

Although the mutagenic properties of vinorelbine are still controversial, there is evidence on its ability in inducing oxidative DNA damage[45]. Thus, another mechanism by which vinorelbine may contribute to the antitumor immune response and consequent promotion of immunogenic cell death concerns the induction of mutation-dependent neoantigens[46]. This feature, which is common to DNA-damaging agents[47], could be thus exploited using vinorelbine to improve the therapeutic efficacy of immune checkpoint inhibitors. Additional information about the combination of vinorelbine with immune checkpoint inhibitors will be available from the ongoing phase II study (NCT03801304) that is evaluating the efficacy and safety of metronomic vinorelbine in combination with atezolizumab as second-line treatment.

CONCLUSION

Overall, despite the limited number of patients, this retrospective analysis confirms the efficacy and safety profile of vinorelbine-based regimens, even in elderly or unfit NSCLC patients, and underscores the utility of real-world evidences. The selection of the optimal sequence of treatments plays a crucial role in the therapeutic pathway of patients with NSCLC. Single-agent vinorelbine, in particular as oral formulation, may represent a suitable option in elderly or unfit NSCLC patients and warrants investigation as a potential drug candidate for immunochemotherapy combination regimens.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30.
2. Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: A meta-analysis. J Thorac Oncol. 2007;2(9):845–53.
3. Grossi F, Aita M, Defferrari C, Defferrari C, Rosetti F, Brianti A, Fasola G, Vinante O, Pronzato P, Pappagallo G. Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: A meta-analytical approach. Oncologist 2009;14(5):497–510.
4. Scagliotti GV, Parikh P, von Pawel J. Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543–51.
5. Johnson IS, Armstrong JG, Gorman M, Burnett JP Jr. The vinca alkaloids: A new class of oncolytic agents. Cancer Res. 1963;23:1390–427.
6. Himes RH. Interactions of the catharanthus (Vinca) alkaloids with tubulin and microtubules. Pharmacol Ther. 1991;51(2):257–67.
7. Scagliotti GV, De Marinis F, Rinaldi M, Crinò L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L, Tonato M; Italian Lung Cancer Project. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002;20(21):4285–91.
8. Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, Reck M, Smit EF, Syrigos K, Stahel R, Felip E, Peters S; Panel Members; ESMO. 2nd ESMO Consensus Conference on Lung Cancer: Non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol. 2014;25(8):1475–84.
9. Gridelli C. The ELVIS Trial: A phase iii study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Oncologist 2001;6(Suppl 1):4–7.
10. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol. 1997;15(1):110–5.
11. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzáles-Larriba JL, Grodzki T, Pereira JR, Le Groumellec A, Lorusso V, Clary C, Torres AJ, Dahabreh

J, Souquet PJ, Astudillo J, Fournel P, Artal-Cortes A, Jassem J, Koubkova L, His P, Riggi M, Hurteloup P. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. Lancet Oncol. 2006;7(9):719–27. Erratum in: Lancet Oncol. 2006;7(10):797.

12. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352(25):2589–97.
13. Moro-Sibilot D, Smit E, de Castro Carpeño J, Lesniewski-Kmak K, Aerts J, Villatoro R, Kraaij K, Nacerddine K, Dyachkova Y, Smith KT, Taipale K, Girvan AC, Visseren-Grul C, Schnabel PA. Outcomes and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study. Lung Cancer 2015;88(2):215–22.
14. Bittoni MA, Arunachalam A, Li H, Camacho R, He J, Zhong Y, Lubiniecki GM, Carbone DP. Real-world treatment patterns, overall survival, and occurrence and costs of adverse events associated with first-line therapies for Medicare patients 65 years and older with advanced non-small-cell lung cancer: A retrospective study. Clin Lung Cancer 2018;19(5):e629–45.
15. American Joint Committee on Cancer (AJCC) TNM classification 6th edition Philadelphia: Lippincott Raven Publisher. 2002.
16. Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol. 2001;19(13):3210–8.
17. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21(16):3016–24.
18. NCCN Clinical Practice Guideline in Oncology (NCCN Guidelines) – Older Adult Oncology [online]. Version 1.2020 - February 7, 2020.
19. Bakirhan K, Sharma J, Perez-Soler R, Cheng H. Medical treatment in elderly patients with non-small cell lung cancer. Curr Treat Options Oncol. 2016;17(3):13.
20. Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavolé A, Dauba J, Debieuvre D, Souquet PJ, Bigay-Game L, Dansin E, Poudenx M, Molinier O, Vaylet F, Moro-Sibilot D, Herman D, Bennouna J, Tredaniel J, Ducoloné A, Lebitasy MP, Baudrin L, Laporte S, Milleron B; Intergroupe Francophone de Cancérologie Thoracique. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378(9796):1079–88.
21. Pujol JL, Coffy A, Camerini A, Kotsakis A, Mencoboni M, Gusella M, Pasini F, Pezzuto A, Banna GL, Bilir C, Samantas E, Barlesi F, Roch B, Guillou A, Daurès JP. An individual patient-data meta-analysis of metronomic oral vinorelbine in metastatic non-small cell lung cancer. PLoS One 2019;14(8):e0220988.
22. Platania M, Pasini F, Porcu L, Boeri M, Verderame F, Modena Y, Del Conte A, Nichetti F, Garassino MC, Martinetti A, Sottotetti E, Cavanna L, Vattemi E, Pozzessere D, Bertolini A, Irtelli L, Verri C, Sozzi G, Proto C, Pastorino U, Torri V, Fraccon AP, Spinnato F, Signorelli D, Lo Russo G, Tuzi A, Gallucci R, Cinieri S, Mencoboni M, Antonelli P, Giacomelli L, de Braud F. Oral maintenance metronomic vinorelbine versus best supportive care in advanced non-small-cell lung cancer after platinum-based chemotherapy: The MA.NI.LA. multicenter, randomized, controlled, phase II trial. Lung Cancer 2019;132:17–23.
23. Martoni AA, Melotti B, Sperandi F, Giaquinta S, Piana E, Pavesi L, Da Prada G, Lelli G. Hybrid (intravenous and oral) administration of vinorelbine plus cisplatinum followed by oral vinorelbine as first-line therapy of advanced non-small cell lung cancer: A phase II study. Lung Cancer 2008;60(3):387–92.
24. Reck M, Macha HN, Del Barco S, Cornes P, Vaissière N, Morand M, Riggi M, Abratt R. Phase II study of oral vinorelbine in combination with carboplatin followed by consolidation therapy with oral vinorelbine as single-agent in unresectable localized or metastatic non-small cell lung carcinoma. Lung Cancer 2009;64(3):319–25.
25. Farhat FS, Ghosn MG, Kattan JG. Oral vinorelbine plus cisplatin followed by maintenance oral vinorelbine as first-line treatment for advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2015;76(2):235–42.
26. Westeel V, Quoix E, Moro-Sibilot D, Mercier M, Breton JL, Debieuvre D, Richard P, Haller MA, Milleron B, Herman D, Level MC, Lebas FX, Puyraveau M, Depierre A; French Thoracic Oncology Collaborative Group (GCOT). Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. J Natl Cancer Inst. 2005;97(7):499–506.
27. Bennouna J, Havel L, Krzakowski M, Kollmeier J, Gervais R, Dansin E, Serke M, Favaretto A, Szczesna A, Cobo M, Ciuffreda L, Jassem J, Nicolini M, Ramlau R, Amoroso D, Melotti B, Almodovar T, Riggi M, Caux NR, Vaissière N, Tan EH. Oral vinorelbine plus cisplatin as first-line chemotherapy in nonsquamous non-small-cell lung cancer: Final results of an International randomized phase II study (NAVotrial 01). Clin Lung Cancer 2014;15(4):258–65.
28. Helbekkmo N, Sundstrøm SH, Aasebø U, Brunsvig PF, von Plessen C, Hjelde HH, Garpestad OK, Bailey A, Bremnes RM; Norwegian Lung Cancer Study Group. Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. Br J Cancer 2007;97(3):283–9.
29. Hirsh V, Desjardins P, Needles BM, Rigas JR, Jahanzeb M, Nguyen L, Zembryki D, Leopold LH. Oral versus intravenous administration of vinorelbine as a single agent for the first-line treatment of metastatic nonsmall cell lung carcinoma (NSCLC): A randomized phase II trial. Am J Clin Oncol. 2007;30(3):245–51.
30. Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K, Shinkai T, Sawa T, Goto I, Semba H, Seto T, Ando M, Satoh T, Yoshimura N, Negoro S, Fukuoka M. Phase III study of docetaxel compared with vinorelbine in

elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol. 2006;24(22):3657–63.
31. Oh Y, Taylor S, Bekele BN, Debnam JM, Allen PK, Suki D, Sawaya R, Komaki R, Stewart DJ, Karp DD. Number of metastatic sites is a strong predictor of survival in patients with nonsmall cell lung cancer with or without brain metastases. Cancer 2009;115(13):2930–8.
32. Depierre A, Chastang C, Quoix E, Lebeau B, Blanchon F, Paillot N, Lemarie E, Milleron B, Moro D, Clavier J. Vinorelbine versus vinorelbine plus cisplatin in advanced non-small cell lung cancer: A randomised trial. Ann Oncol. 1994;5(1):37–42.
33. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multi- center trial including 612 patients. J Clin Oncol. 1994;12(2):360–7.
34. Soldin O, Mattison D. Sex Differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143–57.
35. Schmetzer O, Flörcken A. Sex differences in the drug therapy for oncologic diseases. Handb Exp Pharmacol. 2012;214:411–42.
36. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35.
37. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
38. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): A phase 3, open-label, multicentre randomized controlled trial. Lancet 2017;389(10077):255–65.
39. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92.
40. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, Ready NE, Gerber DE, Chow LQ, Juergens RA, Shepherd FA, Laurie SA, Geese WJ, Agrawal S, Young TC, Li X, Antonia SJ. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31–41.
41. Whiteside TL. The role of regulatory T cells in cancer immunology. Immunotargets Ther. 2015;4:159–71.
42. Zheng H, Zeltsman M, Zauderer MG, Eguchi T, Vaghjiani RG, Adusumilli PS. Chemotherapy-induced immunomodulation in non-small-cell lung cancer: A rationale for combination chemoimmunotherapy. Immunotherapy 2017;9(11):913–27.
43. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015;28(6):690–714.
44. Roselli M, Cereda V, di Bari MG, Formica V, Spila A, Jochems C, Farsaci B, Donahue R, Gulley JL, Schlom J, Guadagni F. Effects of conventional therapeutic interventions on the number and function of regulatory T cells. Oncoimmunology 2013;2(10):e27025
45. Mhaidat NM, Alzoubi KH, Khabour OF, Alawneh KZ, Raffee LA, Alsatari ES, Hussein EI, Bani-Hani KE. Assessment of genotoxicity of vincristine, vinblastine and vinorelbine in human cultured lymphocytes: A comparative study. Balkan J Med Genet. 2016;19(1):13–20.
46. Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: More haste, less speed. Br J Cancer 2018;118(3):312–24.
47. Franzese O, Torino F, Fuggetta MP, Aquino A, Roselli M, Bonmassar E, Giuliani A, D'Atri S. Tumor immunotherapy: drug-induced neoantigens (xenogenization) and immune checkpoint inhibitors. Oncotarget 2017;8(25):41641–69.