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Oral vinorelbine versus etoposide with cisplatin and chemo-radiation as treatment in patients with stage III non-small cell lung cancer: A randomized phase II (RENO study)

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ABSTRACT

Objectives: Concomitant chemo-radiation is the standard treatment for unresectable stage III non-small cell lung cancer (LA-NSCLC). The aim of this study was to assess the safety and efficacy of oral vinorelbine and cisplatin (OVP) compared with etoposide and cisplatin (EP), both in combination with radiotherapy, in this setting.
Material and methods: An open-label, randomized phase II trial was undertaken including 23 hospitals in Spain. Adults with untreated unresectable stage III NSCLC were randomized1:1 to receive: oral vinorelbine (days 1 and 8 with cisplatin on day 1 in 3-week cycles; 2 cycles of induction, 2 cycles in concomitance) or etoposide (days 1–5 and 29–32 with cisplatin on days 1 and 8 in 4-week cycles; 2 cycles in concomitance). Both groups received

Abbreviations: NSCLC, non-small cell lung cancer; EP, etoposide and cisplatin; OVP, oral vinorelbine and cisplatin; OV, oral vinorelbine; T-RT, thoracic radiotherapy; PFS, progression free survival; OS, overall survival; ORR, objective response rate; TTR, time to response; DoR, duration of response; CR, complete response; PR, partial response

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concomitant radiotherapy 2 Gy/day (66 Gy). The primary endpoint was progression free survival (PFS).
Results: One hundred and forty patients were enrolled. Sixty-nine patients received OVP and 71 received EP. Globally adverse events grade 3/4 per cycle were fewer in the vinorelbine arm (19.4%) than in the etoposide arm (62.6%) ($p < 0.001$). One patient (1.5%) in the OVP arm and 12 pts (17.6%) in the EP arm presented esophagitis grade 3/4 ($p = 0.002$). Median PFS was similar in both groups (10.8 [95% CI 7.7–13.8] and 9.6 months [95% CI 4.4–14.8]; $p = 0.457$, respectively). Preliminary median overall survival was 30 months in the OVP arm and 31.9 months in the EP arm ($p = 0.688$).
Conclusions: Our findings show that OVP could be considered a standard combination with similar efficacy and better safety profile for the treatment of LA-NSCLC patients.

1. Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related death worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of new diagnosed cases. Most patients are diagnosed with an unresectable disease and about 22% have a locally advanced disease [2].

Concurrent treatment with chemotherapy and radiotherapy has increased survival at 5 years by 15% in unresectable stage IIIA and IIIB NSCLC patients compared to sequential strategy with both treatments [3–5]. Concomitant radio-chemotherapy has an absolute benefit in overall survival of 5.7% at 3 years and 4.5% at 5 years and decreases

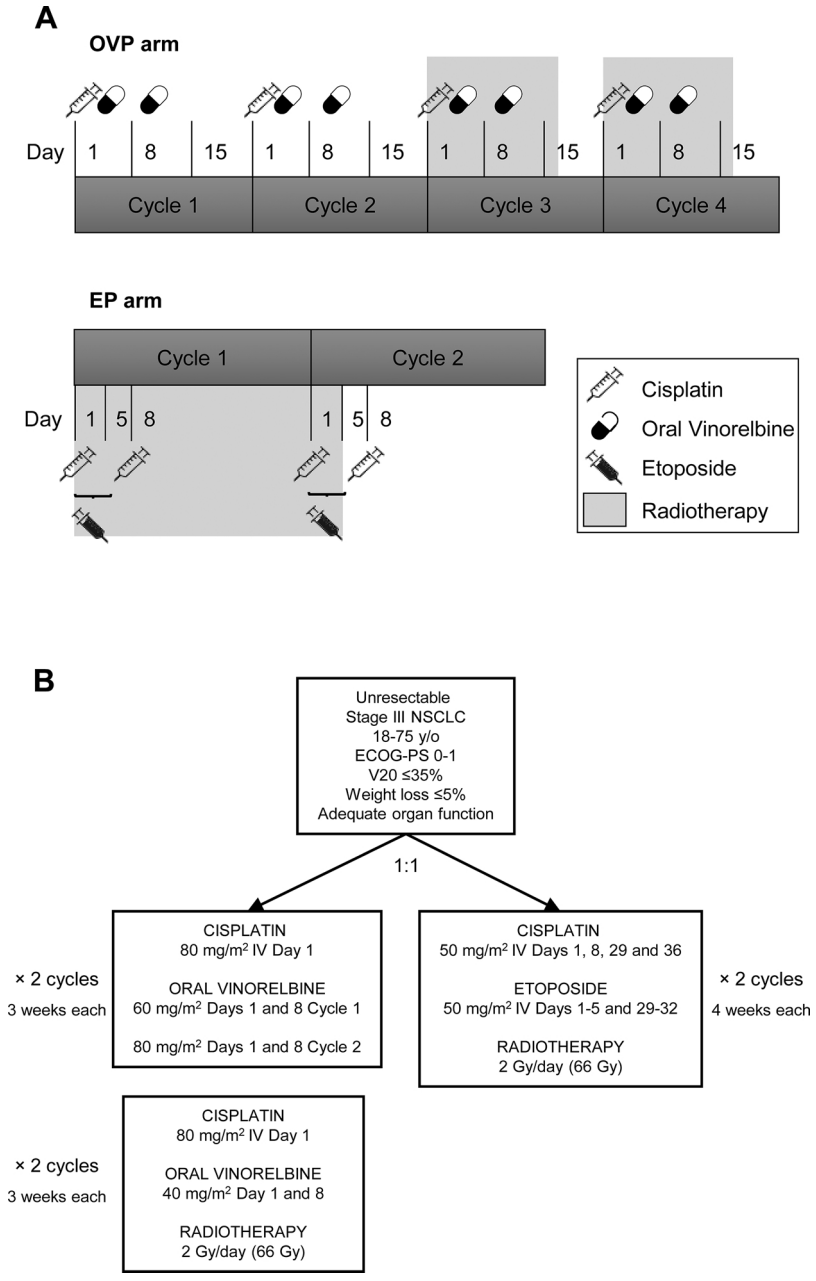

Fig. 1. (**A**) Treatment scheme. (**B**) Study flow chart.**VP**: oral vinorelbine and cisplatin; **EP**: etoposide and cisplatin.

NSCLC locoregional progression [4].However, toxicity is worse in concurrent regimes, especially in the case of esophagitis grade 3 and 4 which increased from 4% up to 18% [4].

Among the available treatments, the combination of etoposide and cisplatin (EP) is one of the most successful, with a median overall survival (OS) of 23.2 months [OS at 3 years of 26.1%, progression-free survival (PFS) around 10 months] [6]. Consolidation docetaxel does not further improve survival in patients with stage III inoperable NSCLC [6,7]. However, EP treatment shows some degree of toxicity (17% grade 3–4 esophagitis and 32% grade3/4 neutropenia) [7].

In this regard, oral cytostatic drugs such as vinorelbine might play an important role. This drug offers several advantages when used concurrently with radiotherapy, such as its oral formulation [8]. Oral vinorelbine (OV) has been shown to be an effective drug in combination with cisplatin in the treatment of locally advanced and metastatic lung cancer with a good safety profile [9–11], with a bioavailability of approximately 40%. In a phase II trial by Krzakowski et al., two cycles of oral vinorelbine in combination with cisplatin, followed by 2 more cycles of oral vinorelbine and cisplatin in combination with radiotherapy have shown a median PFS of 12.5 months and an OS of 23.4 months [12]. The use of oral vinorelbine was associated with low rates of esophagitis grade 3 and 4 (4.3%). In view of these findings, a schedule of active chemotherapy in combination with a radiotherapy treatment planned by the radiotherapist was introduced in Spain [13]. Taking into consideration this common use of the schedule and the promising results, the aim of the present study was to assess the efficacy and tolerance of treatment with induction chemotherapy with oral vinorelbine and cisplatin followed by concomitant radiotherapy (OVP), compared to the conventional intravenous etoposide and cisplatin regimen concomitant with radiotherapy (EP).

2. Methods

2.1. Study design and participants

In this open-label, multicentre, randomized phase II trial (EudraCT Number: 2010-022927-31), eligible participants from 23 hospitals of the Spanish Lung Cancer Group (SLCG) in Spain were enrolled. The full inclusion and exclusion criteria are provided in the supplementary data. Eligibility criteria included histological diagnosis of unresectable stage IIIA or IIIB previously untreated, confirmation of diagnosis by CT or PET scan, measurable evaluable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of > 12 weeks, age older than 18 years, total irradiated lung volume exceeding V20 was $\leq 35\%$, and no history of prior chemotherapy. Key exclusion criteria included: previous chemotherapy for advanced NSCLC, diagnosis of a prior neoplasm in the five years before inclusion, a weight loss $> 5\%$ during the 3 months before inclusion, concomitant or uncontrolled medical disorder, pregnancy or gastrointestinal disorders that may affect absorption of oral vinorelbine (see Tables S1 and S2).

The study was carried out in compliance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. The institutional review board of every participating centre approved the protocol, and all patients provided written informed consent.

2.2. Randomization and masking

Patients were randomly assigned (1:1) to receive OVP or EP via a computer-generated system. Patients were registered via fax after provision of informed consent. Randomization was done centrally by the sponsor (Barcelona, Spain). Investigators and study participants were not masked to the treatment received because patients were treated with drugs with different administration routes and schedules.

2.3. Procedures

Eligible participants in the OVP arm received oral vinorelbine on days 1 and 8 during four 3-week cycles with cisplatin 80 mg/m^2 administered intravenously (IV) on day 1 of each cycle (see Fig. 1). Oral vinorelbine dosage was 60 mg/m^2 on cycle 1, 80 mg/m^2 on cycle 2 and 40 mg/m^2 on cycles 3 and 4. Concomitant radiotherapy consisted on 2 Gy/day administered concomitantly along cycles 3 and 4 (66 Gy). Oral vinorelbine was administered 30–60 min before cisplatin administration, on days 1 and 8 of each cycle after a light meal and antiserotoninergic premedication according to local practice on days 1 and 8 of each cycle. OVP doses could be adjusted according to the results of blood cell count performed on days 8 and 21 of each cycle. Patients who presented from febrile neutropenia could be treated with growth factors according to the centre routine.

Patients in the EP arm received etoposide 50 mg/m^2 IV on days 1–5 of two 4-week cycles and cisplatin 50 mg/m^2 IV on days 1 and 8 of each cycle (Group EP). Concomitant radiotherapy 2 Gy/day (66 Gy) was administered on days 1–33 (Fig. 1).

Both groups of patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) [14] and the International Commission on Radiation Units & Measurements report 50 (ICRU-50) [15].

Treatment was scheduled for four cycles on OVP arm and for two cycles on EP arm unless the patient decided to withdraw, occurrence of intolerable adverse events or disease progression. The duration of treatment was 12 weeks for the OVP arm and 8 weeks for EP arm. The duration of follow-up was 24 months from the end of the study evaluation or until death.

2.4. Endpoints

The primary endpoint was PFS, defined as the time from the date of randomization to the date when disease progression was first observed, or death occurred, including all randomly assigned patients.

Secondary endpoints were: OS, objective response rate (ORR), time to response (TTR), duration of response (DoR) and safety profile.

OS was defined as the time from the date of randomization to the date of death from any cause.

Tumour response was assessed radiographically at baseline. In the OVP arm it was also assessed 6 weeks after treatment initiation. A repeat assessment was performed between 4–8 weeks after completing all treatment according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [16]. After that, tumour evaluations were performed every 6 weeks until progression. The duration of the follow-up was calculated from the end of the study evaluation until death or 24 months after recruitment.

ORR was defined as the percentage of patients who achieved complete response (CR) and partial response (PR) according to RECIST (CR + PR).

TTR was defined as the time from the randomization to the first objective response assessed according to RECIST.

DoR was assessed from the first objective response assessed by RECIST to the date of disease progression or death from any cause.

Safety was assessed by physical examination in the treated population, including all patients who received at least one dose of the assigned treatment. Physical examination included vital signs, body weight and performance status, blood tests including complete blood cell count and serum chemistry. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria version 3.0 [17].

2.5. Statistical analysis

Considering a median PFS of 10 months as unacceptable and 15 months as acceptable in the OVP arm (with a scheduled recruitment period of 24 months and a minimum follow-up of 24 months), median PFS should be longer than 12.58 months, in order to consider the study positive and 61 eligible patients were required to guarantee an α-error of 0.05 (one-tailed test) and a β-error of 0.1. As the EP arm was included with a ratio of randomization 1:1, this arm had to have the same sample size as the OVP arm. The total number of patients was increased by 10% to compensate for the possible inclusion of non-evaluable patients. Thus, a total of 67 patients had to be recruited in each arm. In order to have a power of 90% to detect statistically significant differences, with the use of a two log-rank test and a significance level of 5%, 134 events would be needed. OS and PFS were estimated using the Kaplan-Meier method. OS was censored on the last date that the patient was known to be alive. Response and disease control rates were calculated using binomial proportions and exact 95% confidence intervals (CIs). DoR was censored from partial or complete response to the date of death from any cause or the date of the last follow-up. TTR was censored from the first day of treatment to the date of first response. DoR and TTR were calculated by using Kaplan-Meier curves. The univariate and multivariate analyses compared both treatment arms by using Cox proportional hazards model. A Wald forward selection procedure with selection criterion $p < 0.05$ was performed to identify the significant variables. The best model was constructed, considering the variables entered by this sequential method. Variables included in the model were performance status, histologic grade, disease-free interval, site of metastasis, histology, and treatment arm. Statistical tests were computed using SPSS version 15. Statistical analyses were performed at a significance level of 0.05.

3. Results

Overall 140 patients were enrolled between August 5th, 2011 and December 16th, 2014 in 23 Spanish hospitals of the SLCG (Fig. 2). Ten of these patients were not eligible. Median age for all patients included was 62 years (range 39–76). Most patients were male (n = 121; 86.4%), with ECOG status of 1 (n = 77; 55%) and smokers (n = 74; 52.9%). Patients were randomly assigned to the OVP arm (n = 69) or to the EP arm (n = 71) (Fig. 2). All baseline characteristics were well balanced between both arms (Table 1), except for smoking status, with a majority of former smokers in the OVP arm (n = 36; 52.2%) whereas the EP arm had a majority of smokers (n = 43; 60.6%). One hundred thirty-four patients were evaluable for safety and 126 patients were evaluable for tumour response (n = 63 OVP arm; n = 63 EP arm). Fifty-six patients in the OVP arm and 60 patients in EP arm completed the pre-planned treatment (Fig. 2; Table 2; Table S3).

After a median follow-up of 25 months (interquartile range [IQR] = 0.4–59.6), 78.1% of the patients progressed (n = 50) and 53.1% of the patients (n = 34) died in the OVP arm, compared to 78.8% (n = 52) and 57.6% (n = 38) respectively in the EP arm. Median PFS was 10.8 months ($CI_{95\%}$7.7-13.8) in the OVP arm and 9.6 months in the EP arm ($CI_{95\%}$4.4-14.8). Comparison of median PFS between arms was statistically non-significant (p = 0.457) (Fig. 3A). Preliminary median OS was 30 months ($CI_{95\%}$14.6-45.3) in the OVP arm and 31.9 months in the EP arm ($CI_{95\%}$ 21–36). Preliminary median OS between both arms was not significantly different (p = 0.737) (Fig. 3B). OS rate in the OVP arm was 74.4% ($CI_{95\%}$ 66.4–81.3) at 1 year and 59.4% ($CI_{95\%}$ 47.3–71.4) at 2 years. OS rate in the EP arm was similar (73.3% [$CI_{95\%}$ 66.4–81.3] at 1 year; 59.4% [$CI_{95\%}$ 47.6–71.2]).To assess the impact of treatment regimen adjusted by known prognostic variables, a Cox regression analysis including prognostic factors for survival in the study population was performed. The multivariate analysis identified PS 0 as a significant favourable prognostic factor for OS (HR = 0.603;

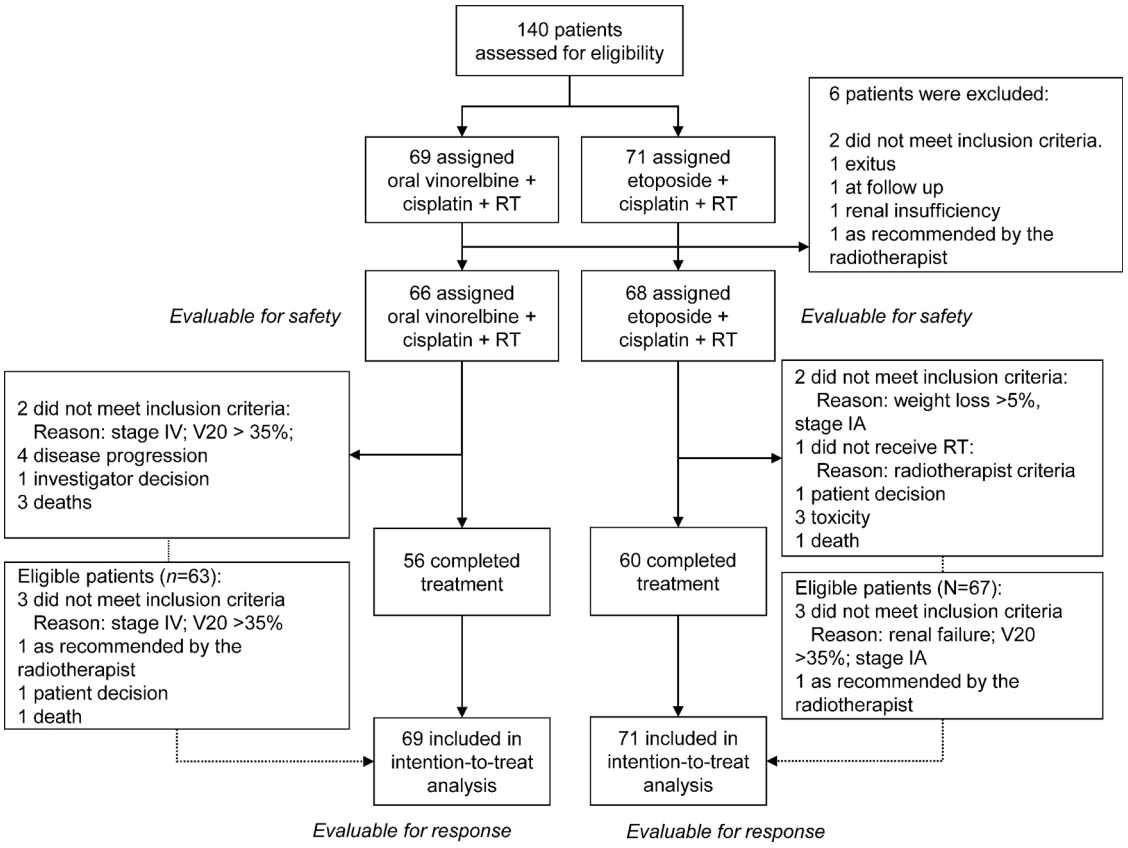

Fig. 2. Trial profile.

Table 1
Baseline patient characteristics.

Treatment arm		Overall Population (n = 140)	OVP (n = 69)	EP (n = 71)
Median age (years)		62 (39-76)	63.6 (39-75)	61 (43-76)
Gender	Male	121 (86.4%)	60 (87%)	61 (85.9%)
	Female	19 (13.6%)	9 (13%)	10 (14.1%)
ECOG-PS	0	63 (45%)	33 (47.8%)	30 (42.3%)
	1	77 (55%)	36 (52.2%)	40 (58.8%)
Smoking status	Smoker	74 (52.9%)	31 (44.9%)	43 (60.6%)
	Former smoker	64 (45.7%)	36 (52.2%)	28 (39.4%)
	Non-smoker	2 (1.4%)	2 (2.9%)	0 (0%)
Median time from diagnosis to randomization (months, range)		1.0	1.1	0.93
		(0.23-5.07)	(0.27-5.07)	(0.23-15.67)
Histology	Squamous	69 (49.3%)	34 (49.3%)	35 (49.3%)
	Adenocarcinoma	63 (45%)	30 (43.5%)	33 (46.5%)
	Large cell	5 (3.6%)	3 (4.3%)	2 (2.8%)
	Non-small cell	2 (1.4%)	2 (2.9%)	0 (0%)
	Carcinoma NOS	1 (0.7%)	0 (0%)	1 (1.4%)
Stage	IA	1 (0.7%)	0 (0%)	1 (1.4%)
	IIIA	62 (44.3%)	32 (46.4%)	30 (42.3%)
	IIIB	74 (52.9%)	35 (50.7%)	39 (54.9%)
	IV	3 (2.1%)	2 (2.9%)	1 (1.4%)

OVP, oral vinorelbine and cisplatin; EP, etoposide and cisplatin.

Table 2
Best tumour response achieved.

Best response (eligible patients)	OVP n = 63	EP n = 63	p-value
Complete Response	1 (1.6%)	1 (1.6%)	0.939
Partial Response	38 (60.3%)	40 (63.5%)	
Stable disease	17 (27.0%)	14 (22.2%)	
Progressive Disease	7 (11.1%)	8 (12.7%)	
Overall Response Rate	39 (61.9%)	41 (63.1%)	0.711
Duration of Response (months, [$CI_{95\%}$])	11.9 [6.8-17]	9.0 [2.6-15.6]	0.556
Time to Response (months, [$CI_{95\%}$])	2.2 [1-4.9]	2.9 [2-4.5]	0.494

OVP, oral vinorelbine and cisplatin; EP, etoposide and cisplatin.

$CI_{95\%}$ 0.37-0.97; p = 0.036). PS 0 (HR = 0582; $CI_{95\%}$ 0.39-0.88) and stage IIIA (HR = 0.643; $CI_{95\%}$ 0.43-0.97) were significant favourable prognostic factors for PFS (Tables S4 and S5). The impact of these factors in OS and PFS was independent of the combination used.

Overall response rate was 61.9% (n = 39) in the OVP arm and 65.1% (n = 41) in the EP arm. Comparison of the overall response rate was non-significantly different (p = 0.711), with 56 patients (88.9%) achieving disease control in the OVP arm vs. 55 patients (87.3%) in the EP arm (p = 0.939) (Table 2). Median DoR was 11.9 months in the OVP arm vs. 9 months in the EP arm (p = 0.556). Median TTR was 2.2 months ($CI_{95\%}$1-4.9) in the OVP arm vs 2.9 months ($CI_{95\%}$2-4.5) in the EP arm (p = 0.494). Three patients (4.5%) in the OVP arm did not receive radiotherapy because of disease progression during the induction period.

Treatment was well tolerated. However, treatment was discontinued in 10 patients (15.2%) in the OVP arm and 8 patients (11.8%) in the EP arm. In the OVP arm, treatment discontinuation due to death was reported in three cases (one death due to disease progression, one to non-treatment-related bronchopulmonary haemorrhage and one to cisplatin-related nephrotoxicity). (Table S3).The safety analysis revealed that grade 3 and 4 adverse events were significantly most frequent in the EP arm (62.6%; n = 82) when compared to the OVP arm (19.7%; n = 48) (p < 0.001). Hematologic grade 3 and 4 adverse effects were significantly more common in the EP arm versus the OVP arm: neutropenia (8.4% *vs*. 2.5%; p = 0.008), thrombocytopenia (4.6% vs. 0%; p = 0.002), and anaemia (3.8%*vs*. 0%; p = 0.005) (Table 3).

Non-hematologic grade 3 and 4 adverse events were also significantly more common in the EP arm when compared to the OVP arm: esophagitis (9.2%*vs*. 0.4%; p < 0.001), pneumonia (3.8%*vs*. 0%; p = 0.005), and sepsis (2.3% *vs*. 0%; p = 0.042) (Table 3).

A complete list of adverse effects can be found in Tables S6 and S7.

4. Discussion

Currently, chemotherapy and concomitant radiotherapy is the standard treatment for patients with unresectable stage III NSCLC clinically selected with good performance status, correct lung function, no weight loss > 5%, and a normal lung volume receiving > 20 Gy (V20) ≤35% [2,5]. However, neither a standard chemotherapy regimen nor a standard dose of radiotherapy has been defined for these patients, so far.

The combination of EP expanded after the results of the phase III study of EP with or without consolidation with docetaxel. The arm without consolidation showed a median PFS and OS of 10 and23.3 months, respectively. However, this schedule associated a high rate of esophagitis grade 3 and 4 that accounted for a 17.2% [7].

Recently, the combination of cisplatin-pemetrexed was compared with EP, where both arms were followed by a consolidation period of monotherapy without cisplatin. The results of the pemetrexed combination did not improve efficacy versus EP, which obtained a median PFS and OS of 9.8 and 25 months, respectively [18].

The combination of OVP as an induction treatment and then a subsequent concomitant treatment with radiotherapy provided very encouraging results in a phase 2 study, although the induction and consolidation schemes did not demonstrate better results than a previous treatment with concomitant therapy only [7,19]. Patients with unresectable stage III NSCLC were treated with two cycles of induction OVP, followed by combined chemoradiation (oral vinorelbine 40 mg/m^2 days 1 and 8 and cisplatin 80 mg/m^2 day 1 every 3 weeks; 66 Gy). Median OS was 23.4 months and median PFS was 12.5 months, with good tolerance and with a very high level of compliance, with the 87% of the patients completing the pre-treatment plan [12].In a recent phase II study, four cycles of OVP with maintained doses of oral vinorelbine were administered, initiating radiotherapy in the second cycle of treatment (oral vinorelbine 60 mg/m^2days 1 and 8 and cisplatin 80 mg/m^2 day 1, 3 weeks; 60 Gy). Median PFS was similar to that achieved in our study (12 months). However, median ORR and OS were higher than in our study (77.3% and 27.9 months, respectively).Nevertheless, this

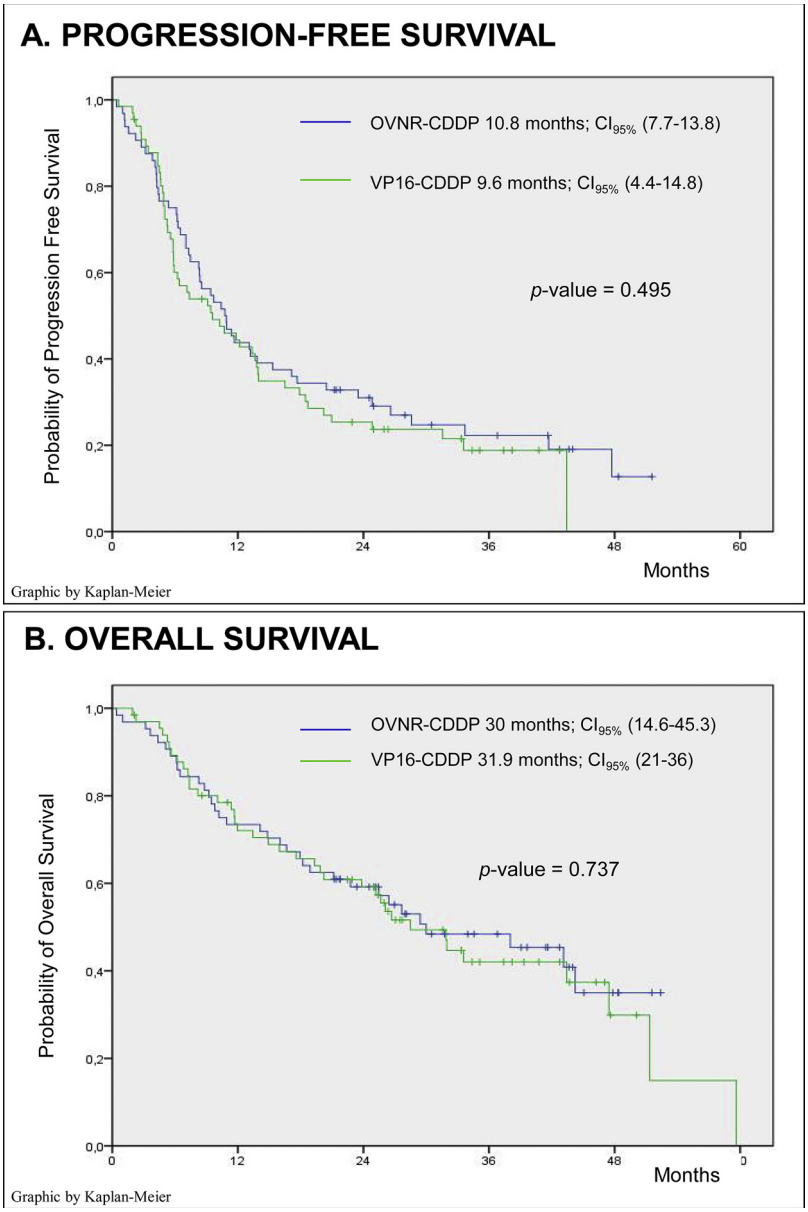

Fig. 3. Log-rank test comparing Kaplan-Meier curves between the oral vinorelbine/cisplatin (**OVP**) and etoposide/cisplatin (**EP**) arms. (A) Progression-free survival. (**B**) Overall survival.**OVNR-CDDP**: oral vinorelbine and cisplatin; **VF16-CDDP**: etoposide and cisplatin; **CI**: confidence interval.

Table 3
Most frequent haematological and non-haematological adverse events per cycle.

G3/4 adverse events per cycles	OVP 244 cycles	EP 131 cycles	*p*-value
Global G3/4 events	48 (19.7%)	82 (62.6%)	< 0.001
Anaemia	–	5 (3.8%)	0.005
Neutropenia	6 (2.5%)	11 (8.4%)	0.008
Febrile Neutropenia	4 (1.6%)	7 (5.3%)	0.055
Thrombocytopenia	–	6 (4.6%)	0.002
Asthenia	6 (2.5%)	1 (0.8%)	0.429
Esophagitis	1 (0.4%)	12 (9.2%)	< 0.001
Infection without neutropenia	2 (0.8%)	5 (3.8%)	0.053
Pneumonia	–	5 (3.8%)	0.005
Sepsis	–	3 (2.3%)	0.042

OVP, oral vinorelbine and cisplatin; EP, etoposide and cisplatin.

benefit is associated to an increase of side-effects, especially in grade 3 and 4 febrile neutropenia (20.9%) and grade 3 and 4 esophagitis (12.5%) [20]. In the present study, chemotherapy consisted of four 3-week cycles of OVP (oral vinorelbine 60 mg/m^2 cycle 1, 80 mg/m^2 cycle 2 and 40 mg/m^2 cycles 3–4; cisplatin 80 mg/m^2 IV day 1) and it was administered with concomitant radiotherapy during cycles 3–4 (66 Gy). Despite the study was negative, a higher median OS (30 months) was found, with similar ORR (61.9%) and PFS (10.8 months) in comparison with other studies [7,12,18,20] To our knowledge, comparison of OVP with other chemotherapy regimens has not been previously conducted. Our findings show that, compared to EP, the OVP arm has similar efficacy results with a better safety profile despite using two more cycles of treatment before initiating concurrent thoracic radiotherapy for NSCLC. Moreover, a recent retrospective study showed that a two 4-week cycles of I.V. 20 mg/m^2 vinorelbine-P treatment had similar efficacy and toxicity than S-1-P treatment in unresectable stage III NSCLC patients [21]. Together these results indicate that OVP treatment is a feasible option, with equal or more benefits than other NSCLC treatments.

The beneficial effects of OVP are further supported by a decrease on the number and type of adverse events, and for the convenience of an oral treatment, which is preferred by 74–80.7% of patients with NSCLC [22,23]. The safety profile of OVP in our study was significantly better compared to EP. These data were especially apparent in relation to grade 3 and 4 esophagitis and hematologic adverse events, but generally grade 3 and 4 adverse events were significantly more frequent in the EP arm when compared to the OVP arm. These findings are consistent with previous results from a phase II trial that showed good tolerance and compliance in patients treated with OV [12]. Our study has some limitations. Since this was a phase II study, treatment schedules were administrated differently and, consequently, tumour assessment was not performed at exactly the same time. Furthermore, the inclusion of enough eligible patients to confirm the hypothesis was not achieved, making the study formally negative. However, our results show that the efficacy of the OVP treatment was, at least, similar to that obtained with EP, and that the OVP regimen might also improve patient quality of life, thanks to its good safety profile and easy administration of the OV schedule. Although these results are encouraging, further work is needed to confirm our findings.

In conclusion, OVP followed by OVP with concurrent thoracic radiotherapy for patients with NSCLC could be considered as a standard regimen similar to the EP schedule in combination with radiotherapy, with similar efficacy results and a better safety profile, warranting further investigation in clinical trials.

Author´s contributions

MP designed the study. All authors enrolled and follow-up patients. All authors helped to draft the manuscript. All authors read and approved the final manuscript

Ethics approval and consent to participate

Yes.

Consent for publication

Yes.

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The study was funded by Pierre Fabre, which did not participate in study design, data collection, data analysis, data interpretation, or writing of the report. The study was sponsored by the Spanish Lung Cancer Group.

Conflict of interest

Dr Provencio received personal fees from Pierre Fabre, Bristol-Myers Squibb, Astra Zeneca, MSD, Roche, Novartis and Takeda. Dr. Massuti and Dr. Álvarez received personal fees from Pierre Fabre. Dr. Ponce received travel and accommodation expenses by Bristol-Myers Squibb and Merck. Dr. Insa received travel and accommodation expenses by Pierre Fabre. The rest of the authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.041.

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