Full-dose Cisplatin and Oral Vinorelbine Concomitant with Radiotherapy in Unresectable Stage III Non-small Cell Lung Cancer: A Multi-center Phase II Study

ÓSCAR JUAN[1], ALFREDO SÁNCHEZ-HERNÁNDEZ[2], SERGIO VÁZQUEZ[3], JOAQUÍN CASAL[4], JOSÉ LUIS FIRVIDA[5], FRANCISCO APARISI[6], JOSÉ MUÑOZ[7], JOSÉ GARCÍA-SÁNCHEZ[8], REGINA GIRONÉS[9], MARTÍN LÁZARO[10] and VICENTE GINER[11]

[1]*Medical Oncology Department, La Fe University Hospital, Valencia, Spain;*
[2]*Medical Oncology Department, Castellón Provincial Hospital Consortium, Castellón, Spain;*
[3]*Medical Oncology Department, Xeral-Calde Hospital Complex, Lugo, Spain;*
[4]*Medical Oncology Department, Meixoeiro Hospital, Vigo, Spain;*
[5]*Medical Oncology Department, University Hospital Complex, Ourense, Spain;*
[6]*Medical Oncology Department, Virgen de los Lirios Hospital, Alcoy, Spain;*
[7]*Medical Oncology Department, Dr. Peset University Hospital, Valencia, Spain;*
[8]*Medical Oncology Department, Arnau de Vilanova Hospital, Valencia, Spain;*
[9]*Medical Oncology Department, Lluis Alcanyis Hospital, Xativa, Spain;*
[10]*Medical Oncology Department, Vigo University Hospital Complex, Vigo, Spain;*
[11]*Medical Oncology Department, Sagunto Hospital, Sagunto, Spain*

Abstract. *Aim: To evaluate the efficacy and toxicities of combination of cisplatin and oral vinorelbine given at full doses concomitantly with radiotherapy for non-small cell lung cancer (NSCLC). Patients and Methods: Untreated patients with locally advanced inoperable stage IIIA/IIIB NSCLC were eligible for study inclusion. Treatment consisted of four cycles of oral vinorelbine at 60 mg/m^2 on days 1 and 8, and cisplatin at 80 mg/m^2 on day 1 every three weeks plus radiotherapy 66 Gy starting on day 1 of cycle 2 in fractions of 2 Gy/day over 6.5 weeks. Results: Forty-eight patients were enrolled. Their characteristics included: median age 61 years; female gender 10%; stage IIIA 46% and IIIB 54%; squamous carcinoma 63%, performance status PS0 42%; PS1 58%. Selected grade 3/4 toxicities were as follows: neutropenia 33%, concomitant febrile neutropenia 14.6%, anemia 12.5%, thrombocytopenia 16.6%, and esophagitis 12.5%. Two treatment-related deaths were reported, both during cycle 1. Radiotherapy was administered to 87.5% of patients; 7.1% of them received less than 60 Gy and 23.8% had delays due to adverse events. The objective response rate was 77.3%, with two complete responses and 32 partial responses. With a median follow-up of 19 months, the median progression-free survival was 12 months, and the 1-year overall survival rate was 72.3%. Median overall survival was 27.8 months, although the 95% confidence interval has not yet been achieved. Conclusion: Full doses of cisplatin and oral vinorelbine can be administered with concomitant radiotherapy, with good efficacy and an acceptable safety profile for patients with stage IIIA/IIIB NSCLC.*

Correspondence to: Óscar Juan Vidal, Department of Medical Oncology, La Fe University Hospital, Bulevar Sur s/n. 46026, Valencia, Spain. Tel: +34 961265877, Fax: +34 961246243, Mob: +34 663976139, e-mail: juan_osc@gva.es

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Lung cancer is one of the most common types of cancer worldwide. More than 85% of cases are of non-small cell lung cancer (NSCLC), a very heterogeneous disease, with histological subtypes and uncertain prognosis, representing a therapeutic challenge. Platinum-based chemotherapy is the standard-of-care for patients with such disease. It is used in combination with several second- and third-generation drugs which have been tested in phase II/III trials with comparable results in terms of tumor response and survival (1-3).

Over recent years, systemic chemotherapy and thoracic radiotherapy of locally advanced non-small cell lung cancer (NSCLC) have been combined, with the aim of fighting the appearance of local and distant relapses, which tend to occur

at similar frequencies. As shown by phase III trials in stage III NSCLC, a concomitant chemoradiotherapy approach has proven superior to sequential treatment (3-6).

Among the different standard regimens (3, 7), the combination of cisplatin and intravenous vinorelbine has been used extensively (8). The relatively new oral formulation for this drug has produced results that are comparable to those of intravenous vinorelbine (9), 60 and 80 mg/m^2 oral vinorelbine being equivalent to 25 and 30 mg/m^2 intravenous vinorelbine, respectively (8, 10).

Oral vinorelbine presents advantages over other intravenous prescriptions, such as ease of administration and increased patient welfare.

Even though several phase II and III studies of locally advanced and metastatic NSCLC have looked at different combinations of induction, concomitant and consolidation therapies with platinum and the oral formulation of vinorelbine (11-17), the optimal dose for the oral administration of vinorelbine in combination with cisplatin and concurrent radiotherapy, is still being investigated.

In the present study, the primary objective was to determine the objective response rate, according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (18), of cisplatin together with oral vinorelbine, administered in induction chemotherapy, followed by concomitant radiotherapy, in inoperable locally advanced NSCLC, while secondary objectives were to determine the safety of this new regimen and to estimate the median duration of response, progression-free survival, overall survival and 1- and 2-year survival rates.

Patients and Methods

Eligibility criteria. This phase II study was a multicenter, national, open-label, non-randomized trial. Patients with histologically- or cytologically-confirmed locally advanced NSCLC at unresectable stage IIIA (only N2) and stage IIIB disease (supraclavicular lymph node involvement and/or malignant pleural effusion excluded) were eligible for this study. Eligible patients also met the following criteria: life expectancy 12 months or more, no prior history of chemotherapy or radiotherapy; performance status of 0 or 1 according to WHO score; age between 18 and 70 years; presence of at least one measurable lesion; absence of any psychological, familial, sociological or geographic conditions that could impede the fulfilment of the study protocol and follow-up schedule. The following laboratory values were required: neutrophil count >2.0×10^9/l, platelet count >100×10^9/l, hemoglobin levels >11 g/dl, total bilirubin ≤1.5×institutional upper normal limit (UNL), creatinine concentration ≤UNL, serum transaminase ≤2.5×UNL and alkaline phosphatase <5×UNL. Pulmonary function requirements included a force expiratory volume in 1 sec (FEV1) >30% or 1 liter, a diffusing capacity of the lung for carbon monoxide (DCLO) >30%, a pCO_2 <45 mmHg and a pO_2 >60 mmHg. Patients were excluded if they were pregnant or breast feeding, had serious concomitant disorders, such as active uncontrolled infection, cardiovascular diseases, or weight loss >10% during three months previous to the start of the study. The protocol of this trial was approved in advance by the Institutional Ethics Committees from each participating hospital. It met the ethical principles stated in the Declaration of Helsinki and was registered under EudraCT number 2009-010436-17. All patients provided written informed consent prior to enrolment. For staging, all patients underwent computed tomographic (CT) scan of the chest.

Study design and treatment modification. Figure 1A depicts the treatment schedule for this study. Induction chemotherapy consisted of one 21-day cycle of intravenous cisplatin at 80 mg/m^2 given on day 1 and oral vinorelbine at 60 mg/m^2 given on days 1 and 8. Systematic anti-emetic treatment with a 5-hydroxytryptamine 3 (5-HT3) antagonist was dispensed prior to oral vinorelbine administration. The cisplatin and oral vinorelbine doses could be adjusted according to the results of weekly hematological testing. They could also be delayed or cancelled, as per protocol, and definitively discontinued if study treatment could not be administered within two weeks.

Patients who suffered from febrile neutropenia or neutropenic infection could be treated with growth factors according to the Institution routine. Best supportive care, based on antibiotics, analgesics, transfusions and corticoids were administered according to the institution protocol.

Concurrent chemoradiotherapy consisted of three cycles of 21 days each, starting from cycle 2, of cisplatin at 80 mg/m^2 on day 1 and oral vinorelbine at 60 mg/m^2 on days 1 and 8; and concurrent radiotherapy at a total dose of 66 Gy, beginning on day 1, administered at 2 Gy/day, five consecutive days per week, over 6.5 weeks.

The target volume for radiotherapy was defined by CT scan. Radiotherapy was interrupted in patients with evidence of disease progression or metastasis (by RECIST), esophagitis requiring parenteral alimentation or neutropenia with fever (until fever disappeared and neutrophils were more than 500/mm^3). If treatment had to be postponed for more than two weeks, it was discontinued definitively.

Evaluation, response and safety. Pre-treatment evaluation comprised a complete medical history and physical examination including performance status, electrocardiogram, laboratory analysis, pulmonary function tests, chest X-rays and CT scan. Normal tissue tolerance criteria were provided as follows: the total lung volume exceeding V20 was ≤30%, maximum esophageal dose was 66 Gy if the area was smaller than 10 cm or 40 Gy if it was greater than 15 cm. Maximum spinal cord dose was 45 Gy and that to the whole heart was not to exceed 55 Gy (for 30% of the cardiac silhouette; if it was more than that, it could receive up to 40 Gy). The maximum dose for both lungs, excluding the gross tumor volume, was 20 Gy.

Tumor assessment was performed at the end of treatment according to RECIST criteria and the response confirmed four weeks later. In case of progression before the twelve weeks, treatment was interrupted and the response was considered as early progression.

Complete (CR) and partial responses (PR), stabilization, and progression were defined using RECIST criteria.

Statistical analysis. The Fleming's method was used to calculate the required number of patients. The working hypothesis was as follows: in a first phase, 25 patients were to be enrolled, assuming a type I risk of 0.05 and a type II risk of 0.10. The phase II study

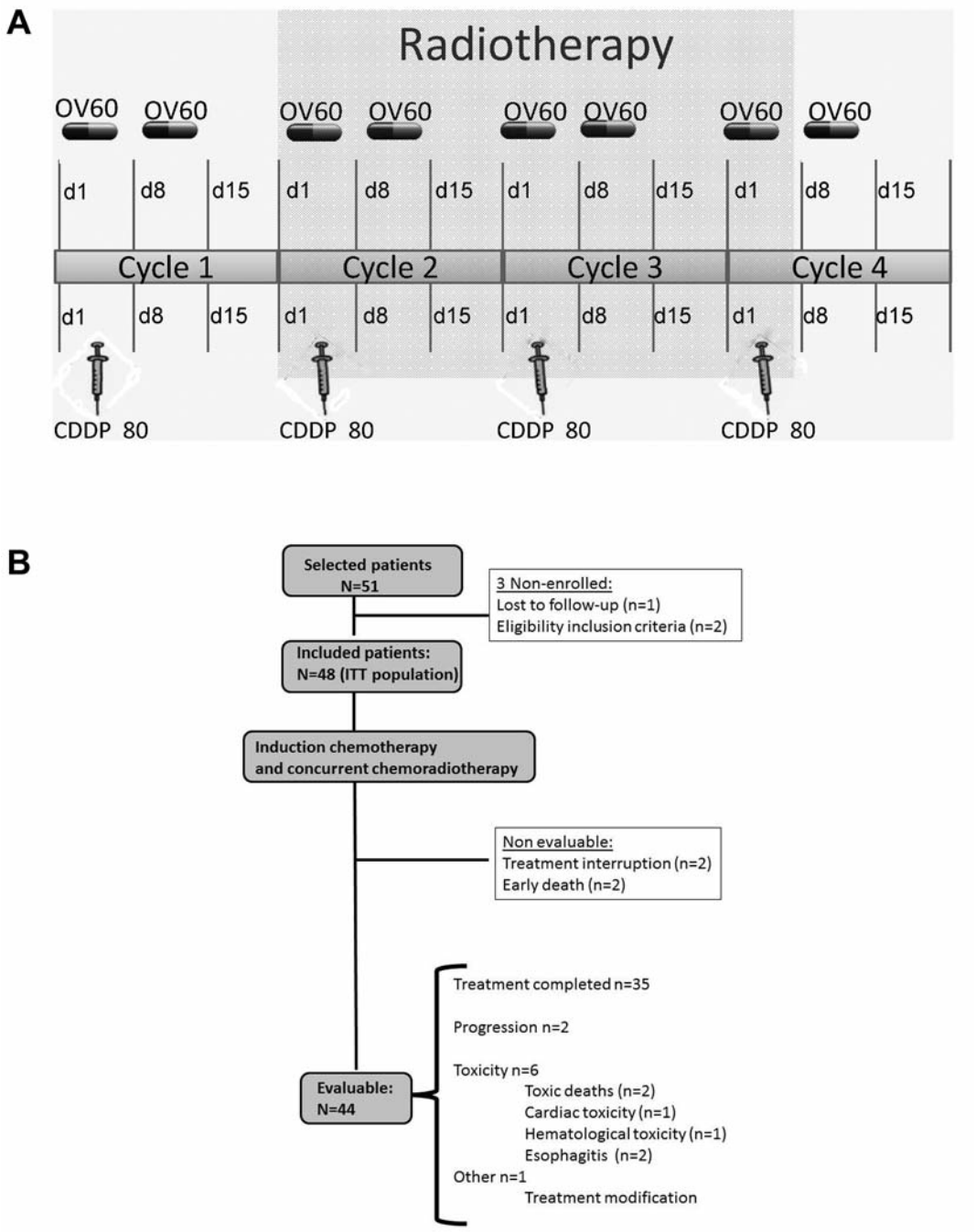

Figure 1. *A: Treatment diagram. OV60 stands for oral vinorelbine 60 mg/m^2, CDDP 80 for Cisplatin 80 mg/m^2 and d, for day. B: Study flow chart.*

was to be continued provided that an objective response rate between 20% and 40% was attained. Thereafter, 20 more patients were to be recruited, for a total of 45 cases. Assuming a loss of cases to follow-up, a total of 51 patients were enrolled. The study was to be considered positive if the objective response rate was at least 30%, calculated on an intent-to-treat basis. Confidence limits of the response rate were estimated at a 95% level (95% Confidence Interval [CI]) by using SAS software version 8.2 (SAS Institute Inc. Cary, North Carolina, USA).

Progression-free survival (PFS) and overall survival (OS) were defined as the time from the date of inclusion to the date of the first evidence of disease progression or death; time-to-progression (TTP) was the time from the date of inclusion to the date of the first evidence of disease progression; 1- and 2-year OS rates were calculated from

Table I. *Patients' characteristics.*

N=48	Number	%
Gender		
Male	43	89.6
Female	5	10.4
Median age, years (range)	61 (34-72)	
Age ≥65 years	20	41.7
ECOG PS		
0	20	41.7
1	28	58.3
Histology		
Squamous	30	63
Adenocarcinoma	14	29
Smoker	25	52.1
Ex-smoker	21	43.8
Stage at diagnosis		
IIIA	22	46
IIIB	26	54
Median time from diagnosis to study entry, days (range)	28.5 (10-288)	

Table II. *Objective response over the evaluable population.*

Response	No. (%)
Complete	2 (4.5%)
Partial	32 (72.7%)
Response rate	77.3% (95% CI=62.2-88.5)
Stable disease	5 (11.4%)
Progression	2 (4.5%)
Non assessable	3 (6.8%)
Median duration of response (months)	10.7 (95% CI=7-14.3)

95% CI: 95% Confidence interval.

Table III. *Survival analysis over the intent-to-treat population.*

Survival	
Progression-free survival (months)	12 (95 % CI=7.3-16.6)
Time-to-progression (months)	13.3 (95% CI=9.7-16.9)
Overall survival (months)	27.9
1-Year overall survival rate	72.3% (95% CI=59.6-85.1)
2-Year overall survival rate	50% (95% CI=34.5-65.5)

95% CI: 95% Confidence interval.

Table IV. *Grade 3 and 4 hematological and non-hematological toxicities.*

	G3		G4	
	Number	%	Number	%
Hematological toxicity (per patient)				
Anemia	6	12.5	0	0
Neutropenia	5	10.4	11	22.9
Febrile neutropenia	1	2.1	9	18.8
Thrombocytopenia	4	8.3	4	8.3
Leukopenia	7	14.6	2	4.2
Non-hematological toxicity (per patient)				
Dyspnea	2	4.2	0	0
Infection	1	2.1	1	2.1
Vomiting	2	4.2	0	0
Diarrhea	-	-	1	2.1
Esophagitis	6	12.5	0	0
Fatigue	1	2.1	0	0
Hypotension	0	0	1	2.1
Pneumonia	1	2.1	0	0

the date of inclusion to death or last follow-up. The median duration of response was calculated for patients with CR or PR, from the first response evaluation to the first evidence of disease progression or death. Kaplan–Meier survival curves were used to describe PFS.

Results

Patients' characteristics. Fifty-one chemonaive patients with histologically confirmed unresectable stage IIIA/IIIB LA NSCLC were initially registered from February 2010 to December 2011. Of these, only 48 were enrolled in the study. Patient characteristics and study flow chart are summarized in Table I and Figure 1B, respectively. Overall, the median age was 61 years (range=34-72 years); 90% of the patients were men; the predominant histology was squamous carcinoma (63%); 54% of the patients had stage IIIB NSCLC; 42% had PS 0, and 58% in PS1, and 52% were smokers, while 43.9% were ex-smokers.

Treatment delivery. The median number of days between initial diagnosis and the start of the study was 28.5. The treatment was completed per protocol by 75% of the patients. A total of 170 cycles were administered during the study, with a median of 3.5 cycles per patient (range=1-5). The median relative dose intensities of cisplatin and oral vinorelbine were 98% and 97%, respectively. Forty-two patients received radiotherapy, 7.1% less than 60 Gy, 23.8% with delays and 2% with interruptions due to hematological toxicities.

Response and survival. A total of 44 patients were evaluable for response, as detailed in Table II. The reasons for non-eligibility for response evaluation are provided in the study flow chart (Figure 1B). The overall response rate during the study among the evaluable population was 77.3% (95% CI=62.8-88.5%), with 2 CRs (4.5%) and 32 PRs (72.7%). Stable disease occurred in five patients (11.4%). The

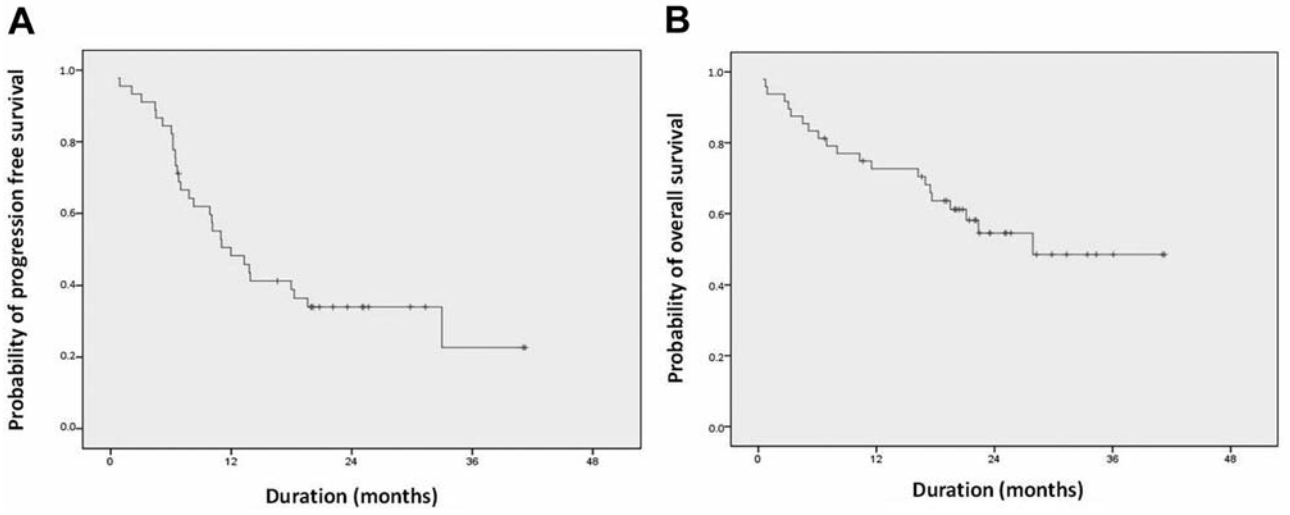

Figure 2. *A: Progression-free survival in the intent-to-treat population. B: Overall survival in the intent-to-treat population.*

estimated median progression-free survival was 12 months (95% CI=7.3-16.6 months) (Figure 2A), while the time to progression was 13.3 months (95% CI=9.7-16.9 months). The median duration of response was 10.7 months (95% CI, 7-14.3 months); 27 patients remained alive after a median follow-up of 19 months (range=0.47-39.4 months) (Tables II and III). Overall survival was 27.9 months, although this value may undergo a slight modification in the future due to the relatively small median follow-up, the number of censored events, and the current impossibility of calculating a 95%CI, as there are still few events subsequent to the median OS (Figure 2B). One and two-year survival rates were 72.3% (95% CI=59.6-85.1%) and 50% (95% CI=34.5-65.5%), respectively.

Safety. Treatment-related toxicity is summarized in Table IV. There were four early deaths, three of them on cycle 1 and the fourth just after completion of chemoradiotherapy. Two of these deaths were unrelated to the treatment (massive hemoptysis and cardiac failure) and the other two, in cycle 1, were chemotherapy-related.

The day 1 dose of oral vinorelbine and cisplatin were delayed in 14.7% of the cycles, 72.1% of them due to hematological toxicity. Cisplatin dose was reduced in 5.3% of cycles, due mainly to hematotoxicity. Day 8 administrations of oral vinorelbine were delayed in 3.5% of cycles, due to administrative issues (67% of delayed administrations) and hematotoxicity (33%). A few administrations had to be cancelled on day 8 (4.7%), mainly due to administrative issues (50% of cancellations), hematotoxicity (37.5%) and non-hematotoxicity (12.5%).

Among the 44 evaluable patients, sixteen suffered grade 3 to 4 neutropenia, six grade 3 anemia, eight grade 3 to 4 thrombocytopenia and 10 febrile neutropenia, although three of the cases were registered during the first cycle, indicating greater bone marrow sensitivity in those patients. Concomitant febrile neutropenia was 14.6%. Regarding non-hematological toxicity, only six patients had symptoms of esophagitis (only grade 3, none of grade 4) which is a reasonable number, considering that this is one of the main adverse effects of concomitant chemoradiotherapy (Table IV).

Discussion

For the past decades, the approach towards a less toxic and more effective treatment of locally advanced unresectable stage III NSCLC has improved enormously. Different cytotoxic drugs, such as cisplatin, carboplatin, taxanes, etoposide, vinorelbine or gemcitabine (19), have been tested, but a standard regimen used in the concomitant setting has not been established.

The selection of the cisplatin-vinorelbine combination and concurrent radiotherapy for our trial was based partly on the results of the study performed by Vokes *et al*. (20) which showed better tolerability with vinorelbine than with gemcitabine or paclitaxel.

From the literature, we understand that the combination of day 1-8 vinorelbine-plus-cisplatin every three weeks was considered less toxic and better tolerated than the regimen of weekly vinorelbine-plus-cisplatin every four weeks (21) for advanced NSCLC, and this fact has been supported over time by clinical practice. Regarding the doses of cisplatin and vinorelbine, different combinations have been tested (22-25).

The phase II trials in locally advanced NSCLC carried out to date with this doublet, using intravenous vinorelbine and concurrent radiotherapy, have achieved an excellent activity/tolerance ratio, with response rates from 56% to 94% (23-29), while the median survival time was between 13 and 42 months and the PFS between 7.3 and 13.3 months.

On the other hand, results from the phase II trials carried out using the oral formulation of vinorelbine with concurrent radiotherapy (14, 30) were very promising in terms of OS and PFS, although more modest results have been accomplished for the response rate, which did not reach over 54%.

On the basis of these premises, we designed our study, aimed at increasing the objective response rate, while preserving tumor-related symptom-free survival as long as possible with the least toxic regimen available. For this purpose, we tailored the schedule of the trial by Krzakowski *et al*. (14), increasing the administered dose of oral vinorelbine to 60 mg/m^2, keeping this constant and planning only one cycle of induction prior to concurrent chemoradiotherapy, instead of the two cycles of induction chemotherapy of the original study.

In our trial, the median dose intensities of oral vinorelbine and cisplatin were 97-98%, and were almost totally accomplished as planned, while radiotherapy of over 60 Gy was administered to 93% of the patients. These data confirm the suitability of this protocol.

As a result, we achieved a significantly better overall response rate of 77% (Table II), with median progression-free survival time of 12 months and a 1-year survival rate of 72.3% (Table III). The results are comparable to those attained with regimens in which vinorelbine was administered intravenously and in a phase I trial with oral vinorelbine (9).

The main toxicity observed was hematological, with grade 3-4 concomitant febrile neutropenia observed in 14.6% of patients. Furthermore, there were two treatment-related deaths in cycle 1 in patients who received full doses of oral vinorelbine and cisplatin, prior to concomitant chemoradiotherapy. Although the mechanism is unknown, some patients have been observed to develop severe hematological toxicity to vinorelbine and require dose reduction, which, in a worst case scenario, could even lead to treatment discontinuation. The administration of an initial cycle of induction chemotherapy could be useful for identifying these patients and providing them with a more suitable strategy during the concomitant step. Non-hematological toxicity was milder, and significant in only six patients (12.5%) with grade 3 radiation esophagitis. The excellent tolerance profile allowed concomitant chemoradiotherapy to be completed in 87.5 % of patients on an intent-to-treat basis.

In some previous studies, the cisplatin–vinorelbine doublet has shown extraordinary efficacy, greater than other doublets in terms of OS and objective response (23, 26). Generally, esophagitis is a major toxicity. However, our new study regimen offers a good efficacy/toxicity profile despite the cytotoxic drugs being administered at full doses with concurrent chemoradiotherapy. This fact is further verified by a recent study by Wang *et al*. (31). Although in that trial, regimens based on either etoposide or paclitaxel were evaluated and compared, the design offers the chance to gain some information about their efficacy and consequent toxicity. While 1- and 2-year survival rates were lower with these alternative regimens than in our current trial and the response rate was similar, the percentage of neutropenia and esophagitis were far above those observed with our vinorelbine regimen. Furthermore, in a review of 12 different phase II and III trials of cisplatin-plus-etoposide, the mean rate for grade 3/4 esophagitis was 21.5%, reaching as high as 53%, while in 10 different trials of carboplatin and paclitaxel, the mean rate for grade 3/4 esophagitis was 23.7%, the highest value being 41.9% (31).

In conclusion, our schedule of cisplatin and full-dose oral vinorelbine combined with concurrent thoracic radiotherapy was highly feasible in patients with advanced NSCLC, with limited toxic effects and a good response rate and OS. It shows an efficacy similar to other standard regimens for intravenous vinorelbine, and higher than other equivalent second- and third-generation drug treatments, with the advantage of a reduced rate of esophagitis compared to other regimens, such as carboplatin–paclitaxel or cisplatin–etoposide.

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