EXPERT OPINION

First-line bevacizumab, cisplatin and vinorelbine plus maintenance bevacizumab in advanced non-squamous non-small cell lung cancer chemo-naïve patients

Luis Leon[†], Sergio Vázquez, José Manuel Gracia, Joaquín Casal, Martín Lazaro, José Luis Firvida, Margarita Amenedo, Lucia Santome & Sonia Macia

[†]*Complexo Hospitalario Universitario de Santiago, Medical Oncology Department, Santiago de Compostela, Spain*

Objective: The aim of this study was to evaluate efficacy and safety of first-line treatment with bevacizumab, cisplatin and vinorelbine and bevacizumab maintenance in non-squamous, non-small cell lung cancer (NSCLC).

Research design and methods: Forty-nine patients with stage IIIB plus pleural effusion or stage IV NSCLC were included in a Phase II clinical trial. Treatment consisted of 3-week cycles of bevacizumab (15 mg/kg on day 1), cisplatin (80 mg/m^2 on day 1) and vinorelbine (25 mg/m^2 on days 1 and 8). After 6 cycles, non-progressing patients received bevacizumab maintenance therapy. The primary end point was progression-free survival (PFS), calculated using the Kaplan–Meier method.

Results: Thirteen (29%) of 45 evaluable patients presented a partial response. PFS and overall survival were 6.0 months (95% confidence interval (CI) 4.5 – 7.5) and 14.7 months (95% CI 8.4 – 21), respectively. Fourteen patients (28%) experienced grade 3 – 4 neutropenia and 7 (14%) experienced febrile neutropenia during the combination treatment. During the maintenance phase, the most frequent grade 3 – 4 adverse event was hypertension. Neither grade 3 – 4 thrombocytopenia nor toxic death was observed.

Conclusions: The studied regimen achieved a similar efficacy to other regimens containing platinum doublets. The data provide further evidence that bevacizumab may be used in combination with multiple standard platinum-based doublets in this setting.

Keywords: bevacizumab, cisplatin, NSCLC, vinorelbine

Expert Opin. Pharmacother. (2012) 13(10):1389-1396

1. Introduction

Incidence of lung cancer was estimated to be around 1 million of new cases world-wide for the year 2008 [1]. Eighty percent of these cases are due to non-small cell lung cancer (NSCLC), which is thereby an important public health problem. Fifteen years ago, cisplatin-based chemotherapy regimens demonstrated a small but clearly established clinical benefit over best supportive care in advanced NSCLC patients. The benefit was evident for two end points: first, overall survival (OS), as it was shown in a large meta-analysis published in 1995, including eight trials (all results favoring cisplatinum-based regimens: a median OS difference of 6 weeks; hazard ratio = 0.73; $p < 0.0001$) [2] and second, quality of life as shown in randomized clinical trials [3,4]. Since then, focus was directed toward platinum

informa healthcare

doublets as the best regimens [5,6]. In addition, a recent meta-analysis confirmed the superior outcomes achieved by chemotherapy in NSCLC, when compared with those achieved by best supportive care [7].

In 2002, a four-arm randomized clinical trial on the treatment of advanced NSCLC patients was published and shed light on that issue. This study showed that four different platinum-based doublets offered an overall response rate (ORR) of around 20%, a median OS of 8 months, a progression-free survival (PFS) of 3.5 months and a 2-year OS of 11% [8]. Furthermore, no advantages of one over each other were observed regarding efficacy or safety profile. Chemotherapy agents tested in this trial, which enrolled more than 1000 patients, were the most frequently used and, considered by many, the most effective at that time (cisplatin, carboplatin, paclitaxel and docetaxel), only missing vinorelbine, whose platinum doublets did not demonstrate different outcomes in other randomized clinical trials [9,10]. On the other hand, non-platinum doublets demonstrated a slightly lower efficacy than that shown by platinum doublets [11].

These results showed that platinum doublets had reached a therapeutic plateau [12]. New concepts, rather than new regimens, were clearly needed in the early years of the 21st century. As a matter of fact, not only one but four new concepts have been approached in the last few years in advanced NSCLC: efficacy and safety of new targeted agents [13], the importance of treating different histological subtypes with different regimens [14], the use of pharmacogenomic markers as a useful clinical tool [15] and the efficacy and feasibility of performing a maintenance therapy strategy [16].

Many of new targeted agents have been investigated in combination with chemotherapy in NSCLC patients in the first-line setting [17]. However, among them, the most advanced in clinical development are agents targeting both EGFR and angiogenic signaling pathways [18]. Two EGFR-tyrosine kinase inhibitors (EGFR-TKI), gefitinib and erlotinib, and also the humanized monoclonal antibody anti-VEGF, bevacizumab, are the first three targeted agents which have been approved for its use in advanced NSCLC. Results of clinical trials on EGFR-TKI [19,20] led to the recognition that treatment-associated efficacy depends on histology (better results on adenocarcinoma) and that EGFR mutations are strongly predictive of efficacy of EGFR-TKI, with a higher efficacy in tumors carrying an EGFR mutation [19,21,22].

Tumor growth critically depends on the formation of new blood vessels, which ensure blood supply to tumor tissues. Angiogenesis plays a central role in NSCLC carcinogenesis through one of its key mediators, the VEGF. In patients with established lung tumors, there is an association between high circulating levels or intratumoral overexpression of VEGF and poor prognosis [23-27]. VEGF may also facilitate pleural dissemination of lung cancers [28]. In preclinical models of NSCLC, VEGF blockade has been shown to inhibit angiogenesis [29], decrease tumor growth [30], stimulate apoptosis of cancer cells [30] and enhance antineoplastic chemotherapy effects [31]. Taken together, these data support the evaluation of anti-VEGF therapies in patients with NSCLC.

A number of antiangiogenic agents have been investigated to date in NSCLC, most of which being small molecule, VEGF-pathway TKIs such as sorafenib, sunitinib, vandetanib or motesanib [32]. Bevacizumab is a monoclonal antibody that binds VEGF and prevents the activation of the VEGF-receptor and its associated signaling pathway and has previously shown efficacy in other tumors such as colorectal and breast cancer. Bevacizumab is the only anti-VEGF monocolonal antibody approved for the first-line treatment of patients with non-squamous NSCLC on the basis of the results of two large randomized Phase III clinical trials: the Eastern Cooperative Group Phase III trial, E4599, comparing bevacizumab 15 mg/kg plus carboplatin and paclitaxel versus carboplatin and paclitaxel [33] and the placebo-controlled Phase III trial, AVAiL, in which the addition of bevacizumab 7.5 or 15 mg/kg to cisplatin and gemcitabine was investigated [34]. Both trials used bevacizumab maintenance strategy and showed that bevacizumab improved efficacy outcomes when compared with chemotherapy alone.

Although mainly cisplatin–gemcitabine but also carboplatin–paclitaxel are commonly used in Europe for front-line treatment in patients with NSCLC, cisplatin–vinorelbine is, among others, a standard chemotherapy regimen that has been proven similar outcomes for the treatment of NSCLC patients [9].

The authors initiated a Phase II clinical trial to evaluate the efficacy and safety of a regimen consisting of cisplatin and vinorelbine standard dose plus bevacizumab 15 mg/kg followed by maintenance bevacizumab, in advanced, non-squamous NSCLC patients, whose results are reported herein.

2. Patients and methods

2.1 Study design and patients selection

This study was conducted as a multicenter single-arm, open-label Phase II study. The study was approved by the institutional review boards of each participating center and was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines and local laws and regulations. Patients were required to give written informed consent before enrolment.

In order to be included in the trial, Caucasian patients ≥ 18 and ≤ 75 years old were required to have histological or cytological confirmed, stage IIIB with malignant pleural effusion or stage IV, non-squamous NSCLC (TNM-UICC 2002 6th edition). Other inclusion criteria were: no previous systemic antineoplastic treatment; measurable disease, as defined by RECIST 1.0, outside of previously irradiated fields; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 and adequate hematologic, hepatic and renal functions (including proteinuria ≤ 1.0 mg/dl, serum creatinine ≤ 1.6 mg/dl and creatinine clearance > 45 ml/min).

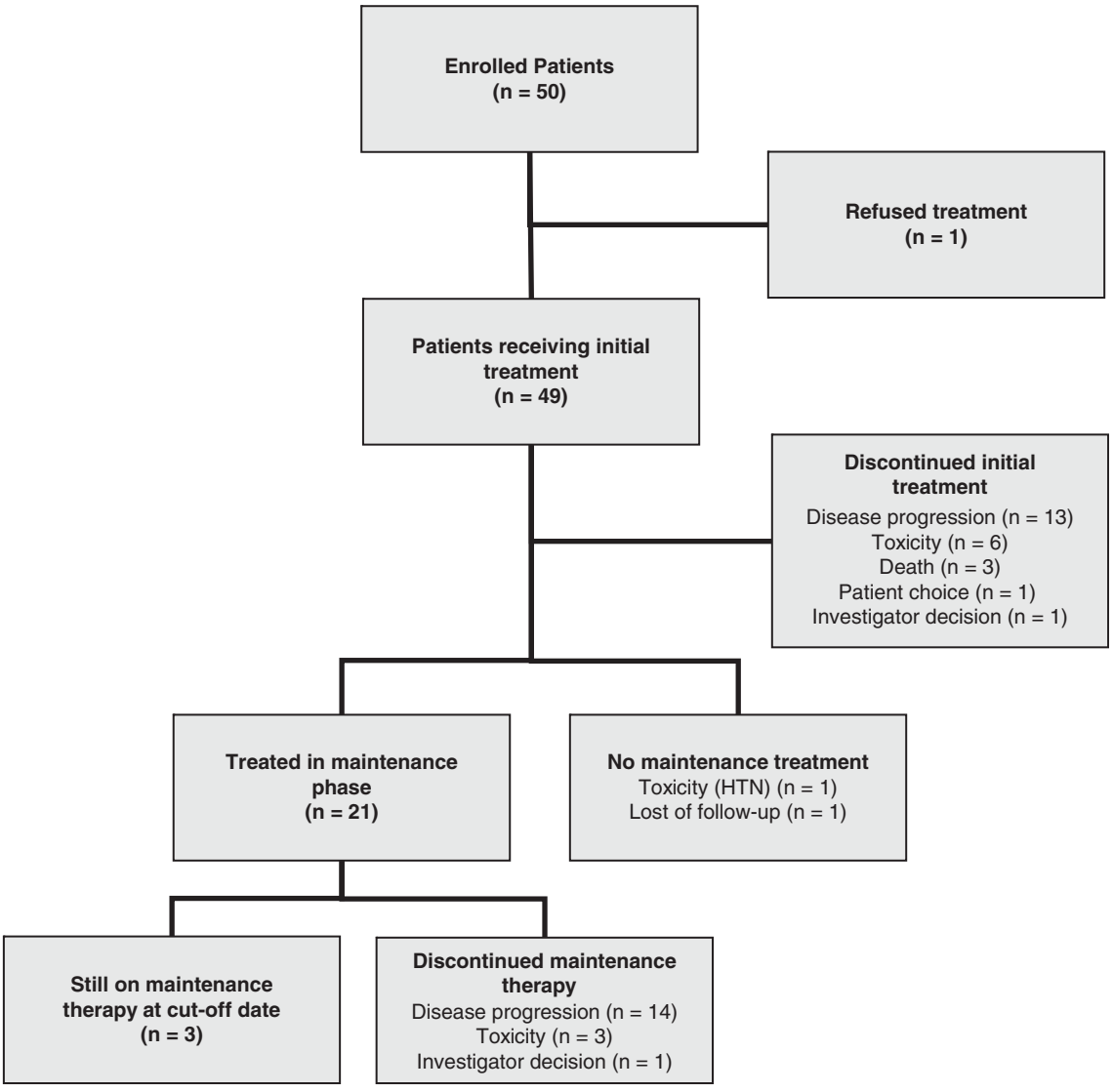

Figure 1. Patient disposition.

Exclusion criteria were: histological evidence of predominantly squamous cell cancer; primary tumor in close proximity to a major vessel or with cavitation; history of gross hemoptysis; central nervous system metastases; pregnancy or lactation; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin (> 325 mg/day), non-steroidal anti-inflammatory agents or any other anti-aggregant agents; clinically significant cardiovascular disease; uncontrolled hypertension; radiation therapy within 21 days or major surgery within 28 days before enrolment. An interval higher than 6 months was required for patients who previously received cisplatin as neo- or adjuvant treatment.

2.2 Treatment

One cycle of treatment consisted of bevacizumab 15 mg/kg i.v. on day 1, cisplatin 80 mg/m^2 i.v. on day 1 and vinorelbine 25 mg/m^2 i.v. on days 1 and 8. On day 1, patients received i.v. standard high-dose cisplatin hydration and antiemetic prophylaxis, including 5-HT3 antagonists and corticosteroids. Cycles were repeated every 21 days for up to six cycles, unless evidence of disease progression or unacceptable toxicity. After having received six chemotherapy cycles, patients who achieved complete response (CR), partial response (PR) or stable disease (SD) received maintenance therapy, consisting of bevacizumab 15 mg/kg every 3 weeks until evidence of disease progression or unacceptable toxicity.

Dose of both cisplatin and vinorelbine were reduced 25% in patients experiencing nadir platelet counts lower than 50,000/µl. If absolute neutrophil count was below 1000/µl or platelet count was below 50,000/µl on day 1, chemotherapy was discontinued until recovery. After these dose reductions, return to the initial dose was not allowed.

Table 1. Baseline characteristics of enrolled patients.

Characteristic	N = 49
Median age, years (range)	59 (36 – 75)
Gender, *n* (%)	
Female	13 (26)
Male	36 (73)
ECOG PS, *n* (%)	
0	16 (33)
1	33 (68)
Stage, *n* (%)	
IIIB with pleural effusion	11 (22)
IV	38 (78)
Histological type, *n* (%)	
Adenocarcinoma	40 (82)
Large cell	9 (18)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Efficacy outcomes.

Outcome	N = 45
Objective response rate	
Complete response, *n* (%)	0 (0)
PR, *n* (%)	13 (29)
SD, *n* (%)	20 (44)
Progressive disease, *n* (%)	12 (27)
Median PFS, *months* (95% CI)	6.0 (4.5 – 7.5)
Median OS, *months* (95% CI)	14.7 (8.4 – 21.0)
Median duration of response, *months* (95% CI)	4.6 (2.9 – 6.4)

CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

2.3 Adverse events and tumor assessments

Tumor status was assessed at baseline and then every three cycles. If patients withdrew from the study for reasons other than progressive disease, follow-up tumor assessments were performed every 9 weeks until disease progression. Tumor response was assessed by the site investigators, according to RECIST. Assessment of quality of life was not performed.

Complete blood counts and serum liver and renal function tests were obtained on day 1 before each cycle of treatment; on day 8, a complete blood count was obtained before administration of vinorelbine. A quantitative measurement of proteinuria was obtained on day 1 before administration of bevacizumab. Adverse events (AEs) were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTC-AE) version 3.0.

2.4 Statistical methods

The primary end point of the study was PFS, defined as time from registration to documented disease progression or death from any cause. Secondary end points were OS defined as time from registration to death from any cause, ORR defined as the sum of the PR rate plus CR rates according with the Response Evaluation Criteria in Solid Tumors (RECIST), duration of response defined as time from the best response to progression or death, 1-year OS and safety profile. The authors estimated the historical median PFS as approximately 4.5 months in patients treated with cisplatin and vinorelbine [35]. An increase in median PFS to 6.3 months with the addition of bevacizumab would be considered significant. Assuming a one-sided type I of 10% and exponential PFS, a study with 50 patients would have at least 81% power to detect the aforementioned treatment effect. No interim analyses were planned. All patients who received at least one dose of the study treatment were analyzed for efficacy and toxicity end points. Continuous variables are presented using median (range). Categorical variables are summarized in frequency tables. Time-to-event end points were computed using the Kaplan–Meier method. Statistical analyses were done with SAS (version 9.1).

3. Results

3.1 Patient characteristics, patient disposition and population analysis

A total of 50 patients diagnosed with advanced non-squamous NSCLC were enrolled in the study between September 2007 and May 2009, in nine centers in Spain. One patient received no study therapy as a result of consent withdrawal. Among 49 patients managed as per protocol, 21 (43%) continued bevacizumab as a single-agent maintenance. Thus, 49 patients were evaluable for these three outcomes: efficacy of the combination regimen (cisplatin–vinorelbine–bevacizumab), efficacy of the whole strategy (cisplatin–vinorelbine–bevacizumab plus bevacizumab maintenance) and safety of combination therapy. A total of 21 patients were evaluable for safety and efficacy of bevacizumab maintenance. **Figure 1** shows a flowchart of the disposition of the patients during the whole process of the study. This figure expands information on the number of patients available for inclusion in the analyses of efficacy and toxicity, as well as the number of patients who continued further bevacizumab maintenance after chemotherapy.

Thirty-six patients (73%) were male, 33 (68%) had ECOG-PS1, 4 patients (8.2%) were previously surgically managed and 2 patients (4.1%) received previous radiotherapy. Baseline demographic characteristics of the patients are listed in **Table 1**.

3.2 Treatment

In the combination treatment, 23 patients (46.9%) completed six cycles of therapy; a total of 220 cycles of chemotherapy and 219 bevacizumab infusions were administered to 49 patients. In the maintenance treatment, 96 bevacizumab infusions were administered to 21 patients during a median of 12 weeks, range (1 – 27). Three and five patients required cisplatin and vinorelbine reductions, respectively. Vinorelbine

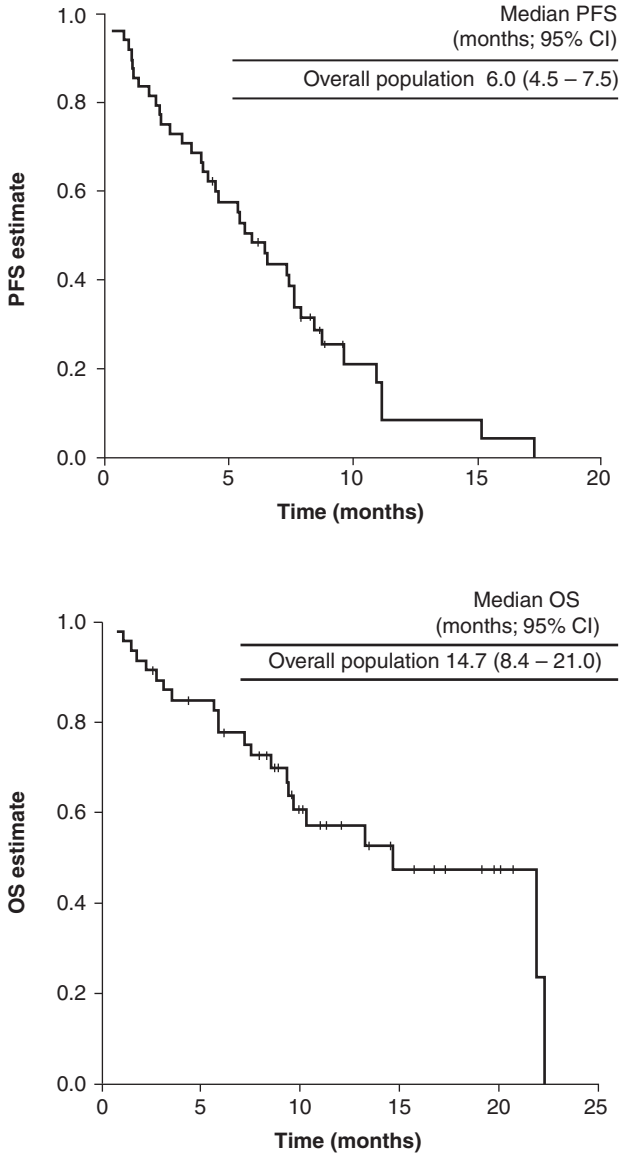

Figure 2. Kaplan–Meier estimates of progression-free survival and overall survival.

was omitted in 16% of the planned infusions. Reasons for stopping treatment were disease progression (27 patients), toxicity (10 patients), death (3 patients), physician decision (2 patients), patient choice (1 patient) and lost to follow-up (1 patient).

3.3 Efficacy

Forty-five patients were evaluable for tumor response (**Table 2**). No complete responses were observed whereas 13 patients (29%) achieved a PR, leading to an ORR of 29% (95% confidence interval (CI) 16 – 42%). Twenty patients (44%) achieved SD as their best response. With a median follow-up of 8.8 months (range 1 – 22 months), median PFS and OS were 6.0 months (95% CI 4.5 – 7.5) and 14.7 months (95% CI 8.4 – 21), respectively. Lung and lymph nodes were the main sites for the progression of the illness. The 1-year OS rate was 57% (95% CI 41 – 73). Median duration of response was 4.6 months (95% CI 2.9 – 6.4). As of the last cut-off date of analysis (December 2009), 3 patients were still on maintenance bevacizumab and 28 patients (57%) were still alive. **Figure 2** shows Kaplan–Meier estimated curves for PFS and OS.

3.4 Safety

Grade 3 – 4 hematological and non-hematological AEs are shown in **Table 3**. During combination treatment (n = 49), 14 patients (28%) experienced grade 3 – 4 neutropenia and 7 (14%) experienced febrile neutropenia. Thromcytopenia grade 1 – 2 was observed in 13 (26%) patients. The most frequent non-hematological grade 3 – 4 AEs were vomiting, fatigue and hypertension. During the maintenance phase (n = 21), the most frequent AE were grade 3 hypertension in two patients (10%), one patient (5%) experienced grade 3 hemoptysis and another one had a pneumothorax. Aside from the aforementioned case of hemoptysis, no other hemorrhagic events were observed. Neither case of grade 3 – 4 thrombocytopenia nor of toxic death was observed.

4. Discussion

The present study shows that a strategy based on a cisplatin–vinorelbine–bevacizumab induction regimen followed by bevacizumab maintenance results in the same outcomes achieved with other similar regimens of chemotherapy plus bevacizumab, possibly with an advantage in toxicity profile. To our knowledge, a regimen consisting of cisplatin–vinorelbine–bevacizumab has not previously been investigated in NSCLC patients. The only one trial investigating this combination was recently closed due to poor accrual [36]. Results from a Phase II trial show that the combination bevacizumab plus vinorelbine is active in breast cancer [37].

Two aspects on the safety results should be highlighted: first, only 1 out of 49 patients had grade 3 – 4 hemoptysis and second, no patients experienced major hemorrhagic events nor hemorrhagic events-related deaths have been observed. The authors used bevacizumab 15 mg/kg, as others previously did, in view of the results of the Phase III E4599 trial [33] where patients in the 15 mg/kg arm achieved a higher ORR, a longer median PFS and a longer median OS when compared with the chemotherapy alone arm. In addition, the Phase III placebo-controlled AVAiL trial demonstrated that the addition of bevacizumab to cisplatin–gemcitabine resulted in a significant benefit in both ORR and PFS over the placebo arm [34] although it failed in demonstrating an OS advantage [38]. Regarding dose selection, the authors designed the study before the results of the AVAiL trial, which suggest that bevacizumab 7.5 mg/kg could be an alternative for 15 mg/kg, were fully reported.

Table 3. NCI-CTC version 3.0 AEs (per patient).

Toxicity	Grade 1 – 2	Grade 3	Grade 4	Grade 3 – 4
Initial treatment (n = 49) n (%)				
Anemia	37 (75)	1 (2)	-	1(2)
Neutropenia	18 (37)	11 (22)	3 (6)	14 (28)
Febrile neutropenia	-	2 (4)	5 (10)	7 (14)
Thrombocytopenia	13 (26)	-	-	-
Hypertension	5 (10)	4 (8)	-	4 (8)
Proteinuria	9 (18)	-	-	-
Headache	10 (20)	1 (2)	-	1 (2)
Vomiting	20 (41)	4 (8)	1 (2)	5 (10)
Fatigue	34 (69)	3 (6)	-	3 (6)
Hemoptysis	3 (6)	-	-	-
Epistaxis	10 (20)	-	-	v
Maintenance treatment (n = 21) n (%)				
Anemia	10 (48)	-	-	-
Neutropenia	6 (29)	-	-	-
Febrile neutropenia	-	-	-	-
Thrombocytopenia	1 (5)	-	-	-
Hypertension	5 (24)	2 (10)	-	2 (10)
Proteinuria	4 (20)	-	-	-
Diarrhea	-	1 (5)	-	1 (5)
Hemoptysis	-	1 (5)	-	1 (5)
Epistaxis	3 (14)	-	-	-
Pneumothorax	-	1 (5)	-	1 (5)
Optic neuropathy	-	1 (5)	-	1 (5)

AE: Adverse event: CTC: Common Toxicity Criteria.

The low occurrence of thrombocytopenia may explain our better results on life-threatening hemorrhagic AEs. This study used cisplatin–vinorelbine, a regimen well known for causing thrombocytopenia less frequently than other chemotherapy doublets [9,39,40]. Of note, although not statistically significant, a difference of 4 versus 10% grade 3 – 4 thrombocytopenia was reported in a head-to-head comparison versus carboplatin–paclitaxel [8]. The incidence of severe hemorrhagic events in the AVAiL trial, whose gemcitabine–cisplatin–placebo arm resulted in a 23% grade 3 – 4 thrombocytopenia [34], was similar to that reported in the E4599 trial. On the contrary, no cases of grade 3 – 4 thrombocytopenia occurred in the 49 patients in the present Phase II trial. This result was not surprising as none of the 125 patients enrolled in the cisplatin–vinorelbine arm of another previously reported randomized trial experienced grade 3 – 4 thrombocytopenia [40]. Thus, the platinum-doublet chemotherapy partner of bevacizumab seems to be important on safety profile and the results of the present study support that cisplatin–vinorelbine may favorably be compared with other platinum doublets. However, this study is a non-randomized trial, and did not directly compare chemotherapy regimens, which precludes drawing definitive conclusions on this issue. Another limitation of this study is associated with the possibility of having some type of selection bias, specially by having selected the patients with better prognosis (non-progressive) for continuation with maintenance bevacizumab.

The present study showed a large interval of more than 7 months between median PFS and median OS. This result is in agreement with previous studies using a chemotherapy plus bevacizumab continuation maintenance in advanced non-squamous NSCLC [33,34] and supports the concept that second-line treatments have preserved their efficacy in spite of having used an intensive strategy of platinum doublet plus a biologic and continuation maintenance in first-line treatment. High efficacy results of second lines after a bevacizumab-based regimen have also been reported in the AVAiL trial, in which 62% of the patients received second-line treatments. As a matter of fact, the authors of the AVAiL study stated that a cross-over effect, due to efficacy of second-line treatments, probably obscured a possible benefit in OS [38].

A strategy which includes maintenance therapy may be considered as an option in NSCLC as a result of previous clinical trials. Two types of maintenance therapy may be utilized: the so-called continuation maintenance, when an agent used in the front-line treatment is continued until disease progression, and the so-called switch maintenance, when a different new agent is started as maintenance. The authors used a continuation maintenance strategy with single-agent bevacizumab. An advantage of continuation maintenance therapy over the switch strategy is to preserve the availability of more drugs for the second- and further-line setting, an approach which may improve OS results.

Bevacizumab antitumor effect is reached more by normalizing an irregular and tortuous tumoral vasculature and, as a consequence of this, improving the delivery of chemotherapy agents, rather than causing hypoxia in tumor tissues [41]. However, efficacy of single agent bevacizumab maintenance therapy has been clearly demonstrated in randomized clinical trials in NSCLC and our results on PFS, OS and 1-year OS are in agreement with these previous results. Actually, adding pemetrexed to bevacizumab in a double-agent continuation maintenance strategy resulted in an OS of 14.1 months in a Phase II study [42], which suggest that this strategy fails in adding any benefit to continuation maintenance with bevacizumab as a single agent.

Another debatable issue on the present trial is the choice of PFS instead of the classic ORR as a main end point in a Phase II clinical trial. However, this approach has been considered an option when the study objectives are focused on efficacy of biologics because they may achieve longer median PFS or OS without a significant tumour shrinkage [43].

Future research on the utilization of bevacizumab in NSCLC will be focused on the search of a biomarker which could help to predict efficacy of this agent. Several molecular (adhesion molecules, angiogenic factors) pathologic (microvessel density) and imaging (dynamic contrast enhanced MRI) markers have been investigated [44]. However, the definitive predictive value of these biomarkers remains controversial and thereby this issue needs further studies.

5. Conclusions

This is the first reported study to use cisplatin, vinorelbine and bevacizumab combination. This study demonstrated that the regimen is effective as a first-line treatment for advanced, non-squamous NSCLC, with a better safety profile than other regimens containing other different platinum doublets in combination with bevacizumab. The data provide further evidence that bevacizumab may be used in combination with multiple standard platinum-based doublets in this setting.

Acknowledgements

The authors would like to thank M Mas (Trial Form Support) for assistance in manuscript preparation and editorial assistance.

Declaration of interest

This work was supported in part by a grant from Roche. All authors declare no conflict of interest.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. GLOBOCAN 2008. International Agency for Research on Cancer. Available from: http://globocan.iarc.fr/factsheet.asp [Last accessed 2 May 2012]
2. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899-909
3. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999;17:3188-94
4. Pallares C, Maroto P, Andres L, et al. Relationship between quality of life and clinical outcome in advanced non-small cell lung cancer: prospective randomized trial of best supportive care versus best supportive care plus chemotherapy [ESMO Meeting Proceedings, abstr 426]. Ann Oncol 1996;7:89
5. Kosmidis P. Chemotherapy in NSCLC: historical review. Lung Cancer 2002;38(Suppl 3):S19-22
6. Bunn PA Jr. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? J Clin Oncol 2002;20:23-33
7. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26:4617-25
• **This study showed that chemotherapy improves outcomes in NSCLC when compared with best supportive care.**
8. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8
• **This trial showed that four platinum-based regimens resulted in similar outcomes in NSCLC.**
9. Kelly K, Crowley J, Bunn PA Jr, et al. 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;19:3210-18
10. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002;20:4285-91
11. Rajeswaran A, Trojan A, Burnand B, et al. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer 2008;59:1-11
12. Carney DN. Lung cancer–time to move on from chemotherapy. N Engl J Med 2002;346:126-8
13. Hirsh V. Systemic therapies in metastatic non-small-cell lung cancer with emphasis on targeted therapies: the rational approach. Curr Oncol 2010;17:13-23
14. Neal JW. Histology matters: individualizing treatment in non-small cell lung cancer. Oncologist 2010;15:3-5
15. Socinski MA. The emerging role of biomarkers in advanced non-small-cell lung cancer. Clin Lung Cancer 2010;11:149-59
16. Coate LE, Shepherd FA. Maintenance therapy in advanced non-small cell lung cancer. J Thorac Oncol 2010;5:723-34
17. Herbst RS, Lynch TJ, Sandler AB. Beyond doublet chemotherapy for advanced non–small-cell lung cancer: combination of targeted agents with first-line chemotherapy. Clin Lung Cancer 2009;10:20-7
18. Horn L, Sandler A. Epidermal growth factor receptor inhibitors and antiangiogenic agents for the treatment of non-small cell lung cancer. Clin Cancer Res 2009;15:5040-8
19. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57
20. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32
21. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8
22. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67
23. Yuan A, Yu CJ, Kuo SH, et al. Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non-small-cell lung cancer. J Clin Oncol 2001;19:432-41
24. Shimanuki Y, Takahashi K, Cui R, et al. Role of serum vascular endothelial growth factor in the prediction of angiogenesis and prognosis for non-small cell lung cancer. Lung 2005;183:29-42

25. Kaya A, Ciledag A, Gulbay BE, et al. The prognostic significance of vascular endothelial growth factor levels in sera of non-small cell lung cancer patients. Respir Med 2004;98:632-6

26. Han H, Silverman JF, Santucci TS, et al. Vascular endothelial growth factor expression in stage I non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis. Ann Surg Oncol 2001;8:72-9

27. Fontanini G, Faviana P, Lucchi M, et al. A high vascular count and overexpression of vascular endothelial growth factor are associated with unfavourable prognosis in operated small cell lung carcinoma. Br J Cancer 2002;86:558-63

28. Ishii H, Yazawa T, Sato H, et al. Enhancement of pleural dissemination and lymph node metastasis of intrathoracic lung cancer cells by vascular endothelial growth factors (VEGFs). Lung Cancer 2004;45:325-37

29. Savai R, Langheinrich AC, Schermuly RT, et al. Evaluation of angiogenesis using micro-computed tomography in a xenograft mouse model of lung cancer. Neoplasia 2009;11:48-56

30. Takayama K, Ueno H, Nakanishi Y, et al. Suppression of tumor angiogenesis and growth by gene transfer of a soluble form of vascular endothelial growth factor receptor into a remote organ. Cancer Res 2000;60(8):2169-77

31. Kabbinavar FF, Wong JT, Ayala RE, et al. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice [abstract 2906]. Proc Am Assoc Cancer Res 1995;36:488

32. Horn L, Sandler AB. Angiogenesis in the treatment of non–small cell lung cancer. Proc Am Thorac Soc 2009;6:206-17

33. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50

•• **This trial showed that bevacizumab improves OS when added to chemotherapy in NSCLC.**

34. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009;27:1227-34

35. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol 1998;16:2459-65

36. Available from: http://clinicaltrials.gov/ct2/show/NCT00620971 [Last accessed 25 August 2010]

37. Burstein HJ, Chen HY, Parker LM, et al. VEGF as a marker for outcome among advanced breast cancer patients receiving anti-VEGF therapy with bevacizumab and vinorelbine chemotherapy. Clin Cancer Res 2008;14:7871-7

38. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21:1804-9

•• **This trial showed that bevacizumab improves PFS when added to chemotherapy in NSCLC.**

39. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-23

40. Souquet PJ, Tan EH, Rodrigues PJ, et al. GLOB-1: a prospective randomised clinical phase III trial comparing vinorelbine-cisplatin with vinorelbine-ifosfamide-cisplatin in metastatic non-small-cell lung cancer patients. Ann Oncol 2002;13:1853-61

41. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58-62

42. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-9

43. Hunsberger S, Zhao Y, Simon R. Comparison of Phase II Study Strategies. Clin Cancer Res 2009;15:5950-5

44. Das M, Wakelee H. Targeting VEGF in lung cancer. Expert Opin Ther Targets 2012;16:395-406

Affiliation

Luis Leon[†1] MD, Sergio Vázquez[2], José Manuel Gracia[3], Joaquín Casal[4], Martín Lazaro[5], José Luis Firvida[6], Margarita Amenedo[7], Lucia Santome[8] & Sonia Macia[9]

[†]Author for correspondence

[1]Complexo Hospitalario Universitario de Santiago,
Medical Oncology Department,
Travesía da Choupana, s/n,
15706 Santiago de Compostela, Spain;
E-mail: luis.leon.mateos@sergas.es

[2]Complexo Hospitalario Xeral-Calde,
Medical Oncology, Lugo, Spain

[3]Hospital de Cabueñes,
Medical Oncology, Gijon, Spain

[4]Complexo Hospitalario Universitario de Vigo – Hospital Do Meixoeiro,
Medical Oncology, Vigo, Spain

[5]Complexo Hospitalario Universitario de Vigo – Hospital Xeral-Cies,
Medical Oncology, Vigo, Spain

[6]Complexo Hospitalario de Ourense,
Medical Oncology, Ourense, Spain

[7]Centro Oncologico de Galicia,
Medical Oncology, A Coruña, Spain

[8]Hospital POVISA,
Medical Oncology,
Vigo, Spain

[9]Hospital General de Elda,
Medical Oncology, Elda, Spain