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ORIGINAL ARTICLE

A phase II randomized trial of gemcitabine-docetaxel versus gemcitabine-cisplatin in patients with advanced non-small cell lung carcinoma

Joaquín Casal Rubio · S. Vázquez · F. Vázquez · M. Amenedo · J. L. Fírvida · J. R. Mel · G. Huidobro · E. Álvarez · M. Lázaro · G. Alonso · I. Fernández · As representatives of the Galician Group of Lung Cancer (GGCP in the Spanish acronym)

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Abstract
Purpose To test efficacy and tolerability of non-platinum regimens for advanced non-small-cell lung cancer (NSCLC).
Methods Chemonaive patients with measurable stage IIIB/IV NSCLC treated with gemcitabine and cisplatin (GC), or gemcitabine and docetaxel (GD), maximumsix cycles in a phase IIB trial.
Results A total of 108 patients were randomized. Response rates (GC vs. GD, respectively): complete 3.6/2.0%, Partial 30.9/38.0%. Median Overall Survival (OS): 8.9 months in both groups ($P = 0.53$); and median time to progression (TTP): 6.2/5.5 months respectively ($P = 0.61$). Toxicities included (GC vs. GD, respectively): grade 3–4 neutropenia 49.1/41.2%; grade 3 thrombocytopenia 30.9/3.9%; grade 3 anemia 14.5/3.9%. Non-haematological toxicity was similar, except for nausea and vomiting, (16.3/2%); renal toxicity (3.7/0%) and hepatic toxicity (5.6/12.7%).
Conclusions With a higher overall response rate and lower toxicity, GD is a good first treatment option for advanced NSCLC.

Keywords Chemotherapy · Cisplatin · Docetaxel · Gemcitabine · Non-small cell lung cancer · Phase II trial

J. C. Rubio (✉) · G. Huidobro · M. Lázaro
Department of Medical Oncology, Hospital do Meixoeiro, C/Meixoeiro, s/n, 36200 Vigo (Pontevedra), Spain
e-mail: joaquin.casal.rubio@sergas.es

S. Vázquez · J. R. Mel · E. Álvarez
Complejo Hospitalario Xeral-Calde, Lugo, Spain

F. Vázquez
Hospital Arquitecto Marcide, Ferrol, Spain

M. Amenedo
Centro Oncológico de Galicia, A Coruña, Spain

J. L. Fírvida
Complejo Hospitalario, Ourense, Spain

G. Alonso
Hospital Juan Canalejo, A Coruña, Spain

I. Fernández
Hospital Montecelo, Pontevedra, Spain

Introduction

Lung cancer is the most frequent leading cause of cancer-related mortality in the world. Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer cases and shows a 5-year overall survival rate of 15%. Most of patients with NSCLC (80%) show advanced or metastatic disease either at the diagnosis or as the result of a relapse or a progression of previous I–III stages. Chemotherapy is generally indicated for patients with advanced NSCLC, specifically platinum-based chemotherapy which has been traditionally considered the best treatment for the advanced disease as it has shown a higher rate of objective response compared to the non-platinum combinations [1] and a higher 1-year overall survival rate [2, 3], although associated to severe toxicities [4, 5]. Therefore, non-platinum agents such as gemcitabine, docetaxel, paclitaxel, irinotecan and vinorelbine have been developed and have proven their efficacies. Among the new agents, the combination of gemcitabine and docetaxel has emerged as one of the most promising, showing equivalent efficacy with, and less toxicity than platinum-based therapies [6, 7].

Several studies have been conducted to evaluate the therapeutic benefits of gemcitabine and docetaxel [8–10]. The

efficacy of gemcitabine-docetaxel is similar to platinum based regimens, but their combination produces toxicities more tolerable than platinum-based regimens [6] due to their non-overlapping toxicities, mainly in patients with a good performance status.

Gemcitabine is a nucleoside antimetabolite against deoxycytidine internally metabolized to gemcitabine triphosphate, which inhibits DNA synthesis with a good safety profile (basically neutropenia). Several phase II studies with gemcitabine as a single treatment administered on a weekly basis during 3 weeks at a dose between 800 and 1,250 mg/m^2 have shown a response rate around 20% in advanced NSCLC [11], and over 45% when used in combination with cisplatin [12–16].

On the other hand, docetaxel has proven activity and documented survival benefit in the second-line treatment of advanced/refractory NSCLC [17] in addition to pemetrexed [18, 19] and erlotinib [20, 21], and docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition [22, 23].

Based on the published data and on the experience of the Galician Group of Lung Cancer (GGCP in the Spanish acronym), the present study was designed to assess the efficacy and safety of docetaxel and gemcitabine in combination at the standard dose and schema compared to the conventional schema of gemcitabine and cisplatin.

Patients and method

Patient eligibility

Chemonaive patients with histological or cytologically confirmed unresectable TNM stage IIIB or IV NSCLC, who met the following criteria were eligible for the study: advanced or metastatic disease not suitable for surgery or radiotherapy; measurable lesions at least in one dimension (RECIST criteria), not previously radiated; no CNS symptomatic metastases; age between 18 and 75 years; at least 4 weeks from last radiotherapy with acute toxicity resolved; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; a life expectancy of at least 3 months; and adequate organ functions as indicated by absolute neutrophil count $\geq 1.5 \times 109$/l, platelets $\geq 100 \times 109$/l, haemoglobin ≥ 10.0 g/dl, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 times the upper limit of normal, total bilirubin ≤ 1.5 times the upper limit of normal, serum creatinine ≤ 2 mg/dL or creatinine clearance ≥ 60 ml/min; alkaline phosphatase ≤ 5 times the upper limit of normal, with the exception of single bone metastases and without any other hepatic disease).

Patients were excluded from the study if they had any other histological type apart from NSCLC; pregnancy or breastfeeding; active concurrent malignancy; any major surgery within the two previous weeks or any major bone marrow radiotherapy within the four previous weeks; peripheral grade ≥ 2 neuropathy of a non-mechanical ethiology; any serious concurrent illness (e.g. myocardial infarction within 6 months before onset; angina pectoris; uncontrolled arrhythmia, uncontrolled hypertension; uncontrolled diabetes mellitus, hepatopathy, dementia, severe infection, peptic ulcer or gastrointestinal haemorrhage, acute thrombosis or anticoagulant treatment prescribed); history of serious drug allergy to the TWEEN-80® excipient; or any condition that, in the opinion of the investigator, disqualified the patient based on safety issues.

This study was conducted in accordance with the declaration of Helsinki (Hong Kong 1989), the Spanish regulation about clinical trials and the good clinical practice. All patients who entered into the study were previously required for a written informed consent.

Study design and treatment

This was a randomized, open-label, multicenter phase II study of gemcitabine-docetaxel (GD) compared to gemcitabine-cisplatin (GC) in patients with advanced or metastatic stage IIIB/IV NSCLC performed by the Galician Group of Lung Cancer (GGCP in the Spanish acronym).

Patients were randomized by site, ECOG (0–1/2) and tumour stage (IIIB/IV) [24] to either GD (Gemcitabine 1,000 mg/m^2, and Docetaxel 85 mg/m^2) or to GC (Gemcitabine 1,250 mg/m^2 and Cisplatin 75 mg/m^2). Gemcitabine was administered in intravenous infusion for 30 min on days 1 and 8 of every cycle, docetaxel in intravenous infusion during 1 h on day 8, and cisplatin in intravenous infusion during 1 h on day 1; all cycles were repeated every 21 days in a maximum of 6 consecutive cycles per patient.

Patients were discontinued from the study in case of progressive disease, occurrence of any event that required discontinuation according to the investigator's opinion, non-acceptable toxicity, and patient's request to withdraw from the study, and any pregnancy or inadequate birth control.

Statistical considerations

Since the primary endpoint of the study was to compare response rates between the two treatment groups [25], the sample size was estimated to be 54 patients per treatment group to provide a power of 80% to detect a 10% difference in response rates (40 vs. 50%) at the 5% level.

Response rates were presented with a 95% confidence interval calculated with the binomial method and compared with the Fisher's exact test.

Time to disease progression was defined as the time from the date of randomization to the date of the first progression, or to the date of the last follow-up in case of no disease progression. Survival was defined as the time from the date of randomization to the date the patient died or to the date of the last follow-up in case of no death. Progression free survival was defined as the time from the date of randomization to the date of the first progression or to the date the patient died whichever occurred first. Kaplan–Meier estimates were used, and all comparisons were done with the log-rank test.

Adverse events and toxicity incidences were compared using Chi-squared tests.

Results

Patient characteristics

The expected 108 patients were enrolled in 8 centres between January 2002 and December 2004. One patient did not receive any treatment infusion and so was not considered for the safety population which consisted of 107 patients. The intention to treat population consisted of 105 patients: two patients were excluded as they did not receive a complete treatment cycle (one died due to an acute gastrointestinal haemorrhage, and the other was withdrawn for an oesophageal prosthesis surgical placement). Both groups were well balanced for all of the baseline characteristics (Table 1).

Table 1 Patient characteristics and tumour histology

Patients characteristics ($N = 108$)	GC ($N = 56$)	GD ($N = 52$)
Median age (range), years	59.9 (50.1, 69.7)	61.4 (52.4, 70.4)
ECOG performance status		
0–1 (%)	83.3	84.0
2 (%)	16.7	16.0
Disease stage		
IIIB (%)	18.2	14.0
IV (%)	81.8	86.0
Gender		
Men (%)	80.0	90.0
Women (%)	20.0	10.0
Histology		
Adenocarcinoma (%)	40.0	48.0
Epidermoid (%)	36.4	34.0
Large cells (%)	12.7	12.0
Anaplasic (%)	1.8	2.0
Others (%)	9.1	4.0

GC gemcitabine + cisplatin, GD gemcitabine + docetaxel

Treatment administration

A treatment cycle was considered complete if the patient received the whole medication expected for that period. The median number of completed cycles per patient was four for GD and five for GC, with a compliance median of 100.0% in GD and 99.4% in GC. The mean dose per infusion of each drug was close to the planned dose.

Response

The analysis was performed according to the intent-to-treat population. There were no differences between groups (Fisher's exact test; $P = 0.59$), with two complete responders in the GC arm [3.6, 95% confidence interval (CI) 0.4–2.5%] and 17 partial responders (30.9, 95% CI 19.1–44.8%). In the GD arm there was one complete responder (2.0, 95% CI 0.1–10.6%) and 19 partial responders (38.0, 95% CI 24.7–52.8%). Table 2 lists all the response rates.

Survival

No differences were observed in the median time to progressive disease (Log rank test $P = 0.61$): 188 days in GC compared to 166 days in GD (Fig. 1), or in the median progression free survival time either (Log rank test $P = 0.31$): 161 days in GC compared to 126 days in GD.

Overall survival was 267 days with both treatment regimens and 1-year survival was also similar (Fig. 2).

Safety

Drug-related haematological toxicities were observed less frequently in the GD arm (Table 3). Grade 3/4 thrombocytopenia was seen eight times more frequently with GC, and also was anaemia (almost four times more with GC). Although not so evidently, leukopenia and neutropenia were more frequently seen also with GC. With respect to the non-haematological grade 3/4 toxicities, Nausea,

Table 2 Clinical response

Clinical Response ($N = 105$)	GC ($N = 55$)	GD ($N = 50$)
Complete response	2 (3.6%)	1 (2.0%)
Partial response	17 (30.9%)	19 (38.0%)
Stable disease	17 (30.9%)	9 (18.0%)
Progressive disease	16 (29.1%)	14 (28.0%)
Not analysed	1 (1.8%)	0 (0.0%)
Not done*	2 (3.6%)	7 (14.0%)

GC gemcitabine + cisplatin, GD gemcitabine + docetaxel

* Except one (patient/investigator's decision), all the "not-done" responses were from patients who died before the response assessment

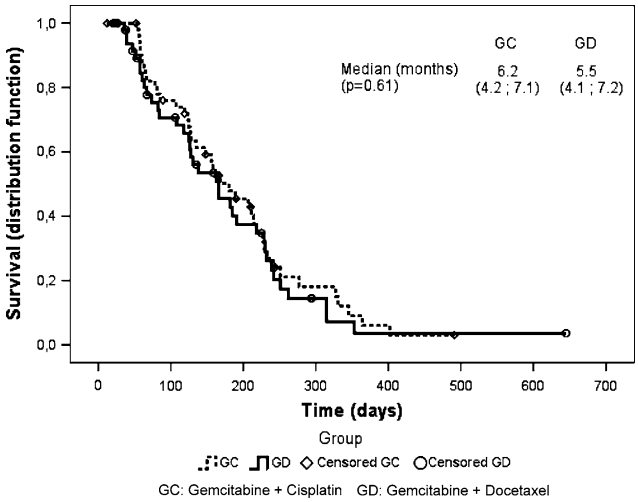

Fig. 1 Time to progressive disease

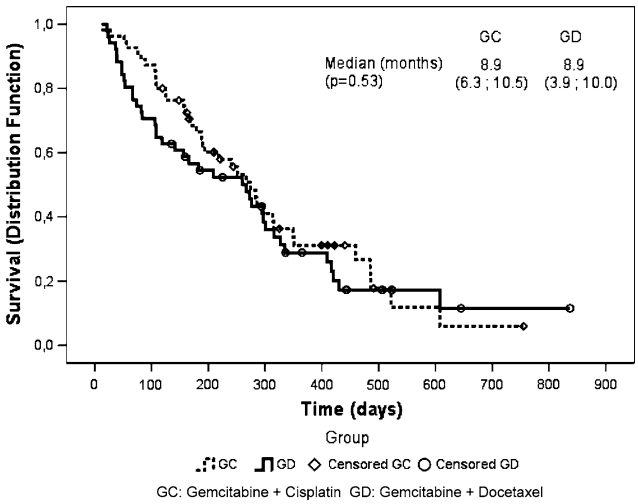

Fig. 2 Overall survival

Vomiting, and Fatigue were more frequently observed with GC (Table 3).

Discussion

Lung cancer remains the most common cause of cancer-related death. Meta-analysis studies have reported a significant survival benefit in NSCLC with platinum-based regimens [2, 26], but these combinations have also reported severe toxicities [27]. The combination of gemcitabine and docetaxel, as one of the most well examined regimen of the new effective non-platinum-based therapies, has shown response rates of 25–50% [6, 8, 17, 28–30] and time-to-progression of 106–132 days.

In our study, the overall response rate (Complete + Partial) was 40.0% for GD, higher than the 34.5% obtained for GC, although not significantly. Time-to-progression was

Table 3 Grade 3/4 toxicities (per patient)

Haematologic toxicities ($N = 107$)	GC ($N = 56$)	GD ($N = 51$)
Platelets	17 (30.9%)	2 (3.9%)
Anaemia	8 (14.5%)	2 (3.9%)
Leukopenia	17 (30.9%)	13 (25.4%)
Neutropenia	27 (49.1%)	21 (41.2%)
Non-haematologic toxicities ($N = 107$)		
Fatigue	6 (11.0%)	4 (7.8%)
Other constitutional symptoms	0 (0.0%)	2 (3.9%)
Anorexia	1 (1.8%)	0 (0.0%)
Dysphagia, oesophagitis, odynophagia	0 (0.0%)	1 (2.0%)
Nausea	2 (3.6%)	0 (0.0%)
Vomiting	7 (12.7%)	1 (2.0%)
Bilirubin elevation	0 (0.0%)	1 (2.0%)
GGT elevation	3 (5.6%)	3 (6.4%)
Alkaline phosphatase elevation	0 (0.0%)	1 (2.1%)
SGPT elevation	0 (0.0%)	2 (4.2%)
Creatinine elevation	2 (3.7%)	0 (0.0%)
Febrile neutropenia	1 (1.8%)	0 (0.0%)
Infection with G3/4 neutropenia	2 (3.6%)	1 (2.0%)
Infection without neutropenia	2 (3.6%)	2 (4.0%)

GC Gemcitabine + Cisplatin, GD Gemcitabine + Docetaxel

166 days, progression free survival time was 126 days, and overall survival was 267 days with no differences with respect to GC. Treatment-related toxicity in GD was clearly lower than that in GC; being the thrombocytopenia and anaemia in GD almost eight and four times lower than in GC, respectively. Leukopenia and neutropenia rates were also lower with GD.

This study confirms the results recently published by our group [28] from a non-comparative phase II study with the same treatment regimen, and shows better results than the 30% overall response published by Matsui [7] and Skarlos [31] (docetaxel 50 mg/m^2), the 37 and 30% overall response published by Georgoulias [6, 32] (docetaxel 100 mg/m^2 and gemcitabine 900 and 1,100 mg/m^2, respectively), the 30% overall response published by Popa [30] (docetaxel 40 mg/m^2), and the 31% overall response published by Pujol [8] (same treatment regimen).

Unlike the results from a metanalysis performed by D'Addario [26], we have obtained that our platinum-based chemotherapy has shown a lower overall response. Nevertheless, similarly as in that metanalysis, we found that the 1-year survival was not significantly prolonged with platinum-based chemotherapy and this last combination was associated to a higher toxicity.

The results support the suggestion from the last ASCO guidelines: first-line chemotherapy of advanced NSCLC should be a two-drug combination regimen, and

non-platinum-based chemotherapy may be used as alternative to platinum-based regimens.

Conclusion

The combination of gemcitabine 1,000 mg/m^2 on days 1 and 8 plus docetaxel 85 mg/m^2 on day 8 could be better tolerated with an equivalent efficacy to the standard cisplatin-based therapy. Nevertheless, the new frontier is represented by the pharmacogenomic approach, whose potential benefits are based on the potential of patient response prediction which could permit selecting the chemotherapeutic combinations with higher efficacy and lower toxicity.

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