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ORIGINAL ARTICLE

Gemcitabine plus docetaxel as first-line chemotherapy in patients with advanced non-small cell lung cancer: a lung cancer Galician group phase II study

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Abstract
Background Numerous phase II and III clinical trials have demonstrated a higher activity of combined gemcitabine plus docetaxel schedules against non-small cell lung cancer (NSCLC) than that of both agents in monotherapy.

Methods This phase II study evaluated a 3-week based schedule of docetaxel 85 mg/m^2 (1-h i.v. infusion, d8) combined with gemcitabine 1,000 mg/m^2 (30-min i.v. infusion; d1,8) as first-line chemotherapy for patients with advanced NSCLC.
Results Forty-one patients with non-resectable, stage IIIB/IV, and bidimensionally measurable disease were enrolled. A total of 182 chemotherapy cycles (median 6, range 1–6) was administered to 40 patients during the study; one patient did not receive chemotherapy due to a protocol deviation. Two patients were not evaluable for treatment efficacy. The overall response rate found was 44% (95% CI, 29–59%): three patients (7%) had a complete response and 15 patients (37%) had a partial response (median duration of response = 4.0 months). With a median follow-up of 8.7 months, the median time to disease progression was 4.4 months and the median overall survival was 7.3 months. The combined gemcitabine plus docetaxel chemotherapy was well tolerated except for pulmonary toxicity. The main grade 3–4 hematological toxicity was neutropenia (28% of patients, 9% of cycles). Two cases of febrile neutropenia were reported. The main grade 3–4 non-hematological toxicity was pulmonary toxicity (23% of patients, 6% of cycles).
Conclusion Gemcitabine 1,000 mg/m^2 on days 1 and 8 in combination with docetaxel 85 mg/m^2 on day 8 given in 3-week cycles is an active and well-tolerated first-line chemotherapeutic regimen for advanced NSCLC.

Keywords Gemcitabine · Docetaxel · NSCLC, first-line · Phase II

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Introduction

Gemcitabine, a pyrimidine analogue, and docetaxel, a semi-synthetic taxane analogue, are active single agents in advanced non-small cell lung cancer (NSCLC). Objective responses ranging from 25–33 to 20–22% have been reported in chemotherapy naïve NSCLC patients after treatment with docetaxel [1, 2] or gemcitabine [3, 4], respectively.

Docetaxel and gemcitabine have non-overlapping toxicities and their combination has been evaluated in NSCLC using different treatment schedules. In most previous phase II and phase III studies [5–12], gemcitabine and docetaxel were administered together at 80–100% of their single-agent doses using an every-3-week cycle recommended from phase I results [13, 14]. The every-3-week schedules used administered a docetaxel dose of 75–100 mg/m^2 on day 1 [5, 6, 15, 16] or on day 8 [7–10, 12]; gemcitabine was administered in two doses (900–1,000 mg/m^2) on day 1 and day 8 except in one study, which administered gemcitabine on day 1 and day 10 [16]. Response rates of 26–50.0 and 29.0–38.0%, and median overall survival times of 7–13 months and 9.5 months were found in these phase II [6, 7, 10, 15] and phase III trials [5, 8, 9] respectively.

Another evaluated regimen was a low docetaxel dose (35–50 mg/m^2) administered twice (on days 1 and 8) concomitantly with the usual two doses of gemcitabine 1,000 mg/m^2 in an every-3-week cycle [17–20]. The response rate and median overall survival found were 10–45% and 7.9–12.5 months, respectively. Finally, a phase-II study evaluated an every-2-week schedule, which administered both docetaxel 50 mg/m^2 and gemcitabine 2,000 mg/m^2 on day 1 [6]. The response rate was 38.3% and the median overall survival was 10.5 months.

The overall results reported in these phase-II and III clinical trials have demonstrated an activity of combined gemcitabine plus docetaxel against NSCLC higher than that of both agents in monotherapy [5–10, 12, 15, 17–20]. Another relevant finding was that all the studied gemcitabine plus docetaxel schedules were well tolerated except for pulmonary toxicity. Therefore, this combination might represent an alternative to cisplatin-based NSCLC chemotherapy. Most of these studies supported the further evaluation and extended use of this combined chemotherapy; only one phase-II study did not [19].

A previous phase-I/II study recommended docetaxel 85 mg/m^2 given on day 8 and combined with gemcitabine 1,000 mg/m^2 delivered on days 1 and 8 of a 3-week cycle for the treatment of patients with inoperable NSCLC [10]. However, no more studies have explored this recommended dose and schedule. In the present phase-II clinical trial, we evaluated this schedule as first-line chemotherapy for patients with advanced NSCLC.

Methods

Selection of patients: inclusion and exclusion criteria

The patients included were 18–75 years old and had histologically-confirmed, non-resectable, stage-IIIB (with pleural effusion) or stage-IV NSCLC, bidimensionally measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, and a life expectancy >12 weeks. The laboratory requirements before inclusion in the study were the following: leukocyte count $\geq 4.0 \times 10^9$/l, absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, Hb $\geq$ 10 g/dl, serum creatinine $\leq 1 \times$ upper normal limit (UNL), bilirubin $\leq 1 \times$ UNL, transaminases (AST and ALT) $\leq 2.5 \times$ UNL, and alkaline phosphatase $\leq 5 \times$ UNL. Nevertheless, the patients were excluded from the study if AST and/or ALT $\geq 1.5 \times$ UNL were concomitant with alkaline phosphatase $\geq 2.5 \times$ UNL.

The patients were excluded from the study if they had received prior chemotherapy, if they had prior motor or sensory neurotoxicity $\geq$ grade 2, if other severe diseases were concurrent (congestive heart failure, unstable angina pectoris, myocardial infarction during the previous year, uncontrolled hypertension or high risk of uncontrolled arrhythmia, uncontrolled active infection, peptic ulcer, unstable diabetes), if leptomeningeal or cerebral metastases were present, or if prior or concurrent neoplasias different from NSCLC were present except for resolved carcinoma of cervix uteri, cutaneous basal carcinoma or other tumors resolved before inclusion. Patients were also excluded if they had a contraindication for corticosteroid therapy or were lactating, pregnant, or women of reproductive age not using adequate contraceptive measures. Other antitumoral concomitant treatments were not allowed (except for radiotherapy in stage IV tumors, if evaluable lesions were located outside the irradiated area) and, if needed, corticosteroid therapy had to be started >6 months before inclusion and at low doses ($\leq$methylprednisolone 20 mg or equivalent). Previous radiotherapy was allowed except if the radiated area was to be used for measurement or if $\geq$20% of the bone marrow was irradiated in the previous 4 weeks. The trial protocol was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines, and all patients provided their written informed consent prior to inclusion.

Treatment plan

The treatment consisted of gemcitabine 1,000 mg/m^2 (30-min i.v. infusion) on day 1 and 8 plus docetaxel 85 mg/m^2 (1-h i.v. infusion) on day 8. The treatment was repeated every 3 weeks for a total of six cycles unless disease progression, unacceptable toxicity or consent withdrawal occurred.

All patients were given prophylactic dexamethasone 8 mg p.o. six times: three before (in the previous evening, when waking up and 1 h before infusion) and three after docetaxel infusion (in the evening, the next morning and at the following night). Equivalent drugs (methylprednisolone 40 mg p.o. or prednisone/prednisolone 50 mg p.o.) were also allowed. Prophylactic antiemetic treatment with 5-HT$_3$ receptor antagonists was recommended. No treatment for diarrhea was initially indicated; however, prophylactic loperamide was administered to patients with grade 2–3 diarrhea in previous cycles. Patients with mild to moderate fluid retention were allowed to continue chemotherapy while treated with furosemide 20 mg/day p.o. No treatment with hematopoietic-stimulating factors was included in the trial protocol.

Dose modifications

Full doses were administered if ANC was $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l on the day of treatment. Nevertheless, dose modifications were planned for severe toxicity. Gemcitabine and docetaxel doses were reduced to 800 and 75 mg/m^2, respectively, when grade 4 neutropenia or febrile neutropenia was present for more than 7 days, or in case of grade 4 thrombocytopenia. Febrile neutropenia was defined as grade 4 neutropenia concomitant with grade ≥ 2 fever requiring antibiotherapy and/or hospitalization.

In the event of grade 2 neurotoxicity or baseline grade 1 neurotoxicity, the docetaxel dose was reduced to 75 mg/m^2. Grade > 2 neurotoxicity excluded patients from the study. In those cases showing diarrhea, stomatitis and/or grade ≥ 3 esophagitis, the docetaxel dose was reduced to 75% of the initial dose. If no recovery was detected, the patients were taken off the study. Other grade 3 toxicities (except for alopecia and anemia) led to treatment delay for a maximum of 2 weeks until grade ≤ 1 toxicity was achieved.

Doses reduced for toxicity could only be re-escalated in the event of changes in hepatic function that finally recovered. If AST or ALT levels were over normal values (with or without concomitant increase of alkaline phosphatase), the docetaxel dose was reduced to 20% of the initial dose until recovery for a maximum of 2 weeks. If bilirubin levels were higher than normal values, treatment was postponed for a maximum of 2 weeks until recovery of normality. A treatment delay longer than 2 weeks excluded the patient from the study in all toxicity cases.

Evaluation of efficacy and toxicity

Baseline evaluation included medical history, physical examination, complete differential blood count, serum biochemistry, chest X-ray, and standard thoracoabdominal CT scans. Adverse events were documented, and physical examination and blood biochemistry were performed after each treatment cycle. Other tests were carried out as determined by the clinical manifestations. Hematological analyzes were conducted on days 1, 8 and 15 of each treatment cycle. When hematological toxicity appeared, blood counts were repeated every 2 days until recovery.

Response to treatment was evaluated after three and six chemotherapy cycles and classified according to WHO criteria and confirmed 4 weeks later [21]. Moreover, all patients were evaluated during each treatment cycle and upon completion of the treatment schedule for toxicity. The patients were monitored for clinical and laboratory toxicity and were asked to report any occurrence of adverse experiences to the investigator. All toxicities were documented and graded according to the National Cancer Institute common toxicity criteria [22]. After the end of the study period, the patients were evaluated in follow-up visits once every 2 months.

Symptomatic improvement during this study was assessed before each of the cycles using the EORTC QLQ-LC13, the 13-item lung cancer-specific questionnaire module of the core quality of life questionnaire EORTC QLQ-C30 [23] validated for Spanish language and culture [24]. EORTC QLQ-LC13 was designed for patients receiving treatment with chemotherapy and/or radiotherapy. This module contains 13 questions/items assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), chemotherapy/radiotherapy-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia) and pain medication. The items were evaluated in a scale from 1 (absent) to 4 (very much present).

Data analysis and endpoints

According to Simon's method [25], we defined $p_1 - p_0 = 20$, where p_1 was the optimum drug activity (response rate = 30%) and p_0 was the minimum desirable activity (response rate = 10%). Thus, a minimum and maximum sample size of 18–35 patients was

calculated assuming a two-sided protection level against type I errors of 0.05 and a statistical power of 90%. After enrollment of the first 18 patients, the study had to be stopped if response was found in less than two patients.

The primary endpoint for this study was the overall response rate (ORR), while secondary endpoints were time to disease progression, survival, and analysis of toxicity. Objective response rates were calculated with 95% confidence intervals (CI). Time to disease progression was defined as the period of time from the start of the treatment to the first progression or death. Survival was calculated from the date of first treatment administration to the date of death by any causes. Actuarial survival curves were constructed using the method of Kaplan and Meier [26]. Toxicity analyzes were performed on patients who received at least one i.v. infusion.

Results

Patient characteristics

The main baseline characteristics of the 41 patients enrolled in the study are shown in Table 1. Histological diagnosis showed adenocarcinoma (44%) and squamous cell carcinoma (41%) in most patients. The median baseline ECOG PS was one and most patients showed stage IV disease (78%). Thirty-two patients (78%) showed metastatic sites while nine patients (22%) showed locally advanced tumors. The median number of target lesions was four and the median number of metastatic sites was two. Metastases were mainly located in lung (97%), lymph nodes (63%), and bone (31%). According to the protocol, no previous chemotherapy treatments were reported, and one patient erroneously receiving paclitaxel, was withdrawn from the trial.

Table 1 Patient characteristics at baseline ($n = 41$)

Characteristics	*n*	%
Age (years)		
Median	59	
Range	44–71	
WHO performance status		
0	9	22
1	25	61
2	7	17
Disease stage		
IIIB	9	22
IV	32	78
Number of metastatic sites	36	86
No of sites involved		
2	5	16
3	9	28
≥4	18	56
Disease sites[a]		
Bone	10	31
Liver	5	16
Lung	31	97
Lymph nodes	20	63
Others	15	47

[a] Some patients showed more than one metastatic site

Chemotherapy

One patient did not receive chemotherapy due to a protocol deviation (the patient received paclitaxel). A total of 182 chemotherapy cycles (median 6, range 1–6) was administered in 40 patients during the study. The gemcitabine dose was reduced in four infusions (0.5%) due to hematological toxicity and related adverse events. The docetaxel dose was reduced in eight infusions (4.4%) due to non-hematological toxicity ($n = 4$), hematological toxicity ($n = 3$) and causes unrelated to study medication ($n = 1$). The gemcitabine infusions on day 1 were delayed in 29 cycles (16%) and on day 8 in 11 cycles (6%) mostly due to hematological toxicity. The docetaxel infusions were delayed in 10 cycles (5%) due to both hematological and non-hematological toxicities. The relative median dose intensity (RDI) was 0.98 for both gemcitabine and docetaxel.

Antitumoral response, time to progression and survival

On an intention-to-treat basis, all patients were included in the efficacy analysis (Table 2). Two patients were not evaluable for efficacy due to protocol deviations and to having received only one cycle of treatment. Three patients (7%) showed a complete response and 15 patients (37%) showed a partial response, with an ORR of 44% (95% CI, 29–59%). The median duration of response was 4.0 months (95% CI, 2.4–6.4) Stable disease was reported in 7 patients (17%), and 14 patients (34%) progressed during the period of active treatment studied. Thus, the rate of tumor control was 61% (95% CI, 46–76%).

With a median follow-up of 8.7 months (range 0.7–24.7 months), the median time to disease progression

Table 2 Overall response rate (ORR) to treatment ($n = 41$)

	n	%
Complete response	3	7
Partial response	15	37
Stable disease	7	17
Progressive disease	14	34
Not evaluable	2	5
ORR, % (CI 95%)	44 (29–59%)	

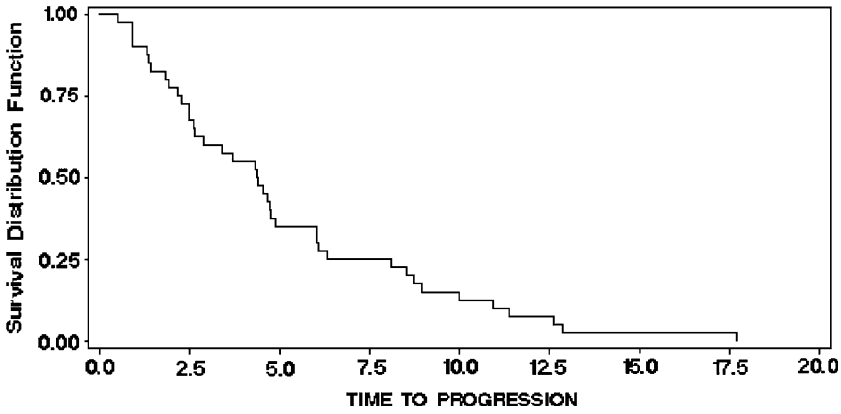

Fig. 1 Time to progression ($n = 41$, median follow-up = 8.7 months)

was 4.4 months (95% CI, 2.7–4.9) (Fig. 1) and the median overall survival was 7.3 months (95% CI, 5.9–13.2) (Fig. 2). The 1-year survival rate was 37.5% (95% CI, 22.7–54.2).

Changes in the EORTC QLQ-LC13 questionnaire scores revealed a further benefit of the treatment, with symptomatic improvement in most items during the study. Marked benefits were noted on symptoms like cough, hemoptysis, dyspnea at rest or pain (Table 3). No attempt was made to correlate changes in individual symptom improvement and response rates.

Table 3 Changes in individual symptom scores according to the EORTC QLQ-LC13 lung cancer-specific questionnaire module of the core quality of life questionnaire EORTC QLQ-C30 (lower values indicate a reduced symptom load)

Item	Initial	Final	Mean change
Cough	10.5	16.7	6.2
Hemoptysis	76.3	93.7	17.4
Dyspnea at rest	65.8	77.8	12.0
Dyspnea walking	47.4	33.3	−14.1
Dyspnea climbing stairs	48.6	33.3	−15.3
Pain in mouth/tongue	92.1	88.2	−3.9
Trouble swallowing	94.6	88.2	−10.3
Peripheral neuropathy	76.3	72.2	−4.1
Alopecia	97.4	11.1	−86.3
Pain in chest	47.4	70.6	23.2
Pain in shoulder	71.1	94.1	23.0
Pain elsewhere	53.1	77.8	24.7
Pain medication	47.1	75.0	27.9
Pain medication help	11.1	22.2	11.1

Data shown are percentage of patients

Toxicity

All patients who received chemotherapy ($n = 40$) were evaluated for safety. The combined gemcitabine plus docetaxel chemotherapy studied here was well tolerated except for pulmonary toxicity. Hematological and non-hematological toxicities per cycle and per patient are shown in Table 4. The main grade 3–4 hematological toxicity was neutropenia (28% of patients, 9% of cycles). Two cases of febrile neutropenia were reported, but both patients were able to continue receiving treatment. The main grade 3–4 non-hematological toxicities were pulmonary toxicity (23% of patients, 6% of cycles), asthenia (19% of patients, 4% of cycles), and pain (12% of patients, 3% of cycles). Other toxicities (e.g., cardiovascular, diarrhea, infection, skin toxicity, etc.) were found in less than 10% of the patients.

Discussion

Lung cancer is the most common cause of cancer-related death and most diagnosed patients present with

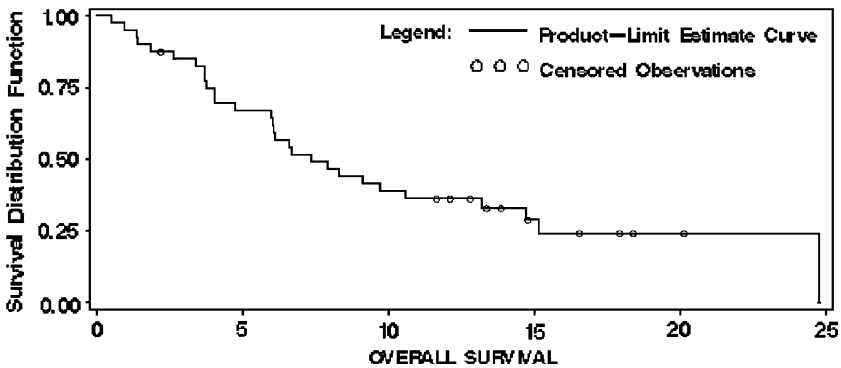

Fig. 2 Overall survival ($n = 41$, median follow-up = 8.7 months)

Table 4 Grade 3–4 treatment-related toxicity

Toxicity	Patient (n = 40)	Cycle (n = 182)
Haematological		
Anaemia	1 (3%)	1 (0.5%)
Febrile neutropenia	2 (5%)	2 (1%)
Leukopenia	1 (2%)	1 (0.5%)
Neutropenia	11 (28%)	17 (9%)
Thrombocytopenia	2 (5%)	2 (1%)
Non-haematological		
Asthenia	8 (19%)	8 (4%)
Cardiovascular	3 (7%)	3 (2%)
Cough	3 (7%)	4 (2%)
Diarrhea	2 (5%)	2 (1%)
Digestive toxicity	3 (7%)	3 (2%)
Hemoptysis	2 (5%)	2 (1%)
Infection	2 (5%)	3 (2%)
Pulmonary toxicity	9 (23%)	11 (6%)
Nausea/vomiting	1 (3%)	2 (1%)
Neuropathy/neuromotor	1 (3%)	1 (0.5%)
Pain	5 (13%)	5 (3%)
Skin toxicity	1 (3%)	1 (0.5%)

Data shown are n (%). One enrolled patient did not receive chemotherapy

locally advanced or metastatic disease [27]. The overall prognosis of these patients is poor, with a median survival <1 year in patients with stage IIIB/IV disease, and the goals of therapy are palliation of symptoms, improvement in quality of life, and prolongation of survival [28]. However, the integration of novel, non-platinum, chemotherapeutic agents into clinical practice has resulted in modest benefits in terms of survival.

The combination of gemcitabine (1,000 mg/m^2, days 1 and 8) and docetaxel (85 mg/m^2, day 8) studied in this phase-II trial as first-line chemotherapy of patients with advanced NSCLC showed a high antitumoral activity and was well-tolerated. The rate of antitumoral response found was 44% and three patients (7%) showed a complete response. The response rate found here fell into the range previously reported in phase-II trials that administered a unique dose of docetaxel 75–100 mg/m^2 [6, 7, 10, 15, 16] and tended to be higher than responses obtained with low-dose docetaxel (40 mg) combined with gemcitabine in previous trials. As in previous trials, the high response rate found here did not correspond to a longer overall survival (7.3 months) compared to the range found in previous phase-II (7.8–12.5 months) [6, 7, 10, 12, 15, 17–20] and phase-II trials (9.5 months) [5, 8, 9]. This discrepancy can arise from the inclusion of different types of tumors, as adenocarcinomas have higher response rates and our population included 44% of patients with such tumors, or differences in baseline characteristics, like WHO PS, metastatic sites, etc. This has not been analyzed in detail, but the same holds true for most trials in NSCLC. However, gemcitabine plus docetaxel shows a manageable toxicity that prevents platinum-related chronic and cumulative side effects such as peripheral neuropathy, nephrotoxicity, or ototoxicity [8, 28]. An improved tolerance would result in palliative benefits for NSCLC patients. In agreement with previous studies, which reported a favorable neurotoxic incidence for gemcitabine/docetaxel compared to cisplatin/docetaxel [10], the present study showed a low incidence of severe neurotoxicity (3%) with the gemcitabine/docetaxel combination (Table 5).

Myelosuppression is the main dose-limiting toxicity reported in phase-I trials on gemcitabine plus docetaxel chemotherapy [29, 30]. Growth colony-stimulating factor (G-CSF) support is often used with high docetaxel doses [8], whereas G-CSF is not routinely used at lower doses [18] or with a biweekly schedule [6]. In the schedule studied in a previous phase-I/II study [10] and used here, the administration of docetaxel simultaneously with the second administration of gemcitabine allows a 13-day hematological rest period following the concomitant drug delivery which avoids the use of prophylactic hematopoietic growth factors. In agreement with previous findings [10], the schedule and doses used here without G-CSF support resulted in a mild to moderate, manageable myelosuppression and allowed the delivery of the combined chemotherapy with a minimal rate of treatment administration delay.

Grade 3–4 pulmonary toxicity was found in 23% of patients, but no life-threatening events were reported and no patients withdrew from the study due to this toxicity. These results agree with previously published studies, which reported gemcitabine and docetaxel-related pneumonitis [10, 31]. Gemcitabine is structurally closely related to cytarabine, a compound that has been associated with non-cardiogenic pulmonary edema [32]. Mild and self-limited dyspnea has been found in 5–8% of patients treated with gemcitabine but fatal pulmonary toxicity has been only observed in a minority of treated patients [33]. Moreover, docetaxel has been associated with cumulative dose-dependent fluid retention that might produce lung edema, but the risk of fluid retention is significantly reduced by steroid premedication [34]. Therefore, pulmonary symptoms need to be carefully evaluated during treatment with this combined chemotherapy in order to enable the early discontinuation of chemotherapy and the prompt implementation of steroid therapy. Dyspnea was assessed during this study by the EORTC QLQ-LC13 lung cancer-specific questionnaire module and, at the end of the study period, most patients (77%) reported absence of dyspnea at rest, while about 15% of patients reported a slight increase in dyspnea at exercise.

Table 5 Clinical trials on docetaxel plus gemcitabine as first-line chemotherapy of patients with advanced non-small cell lung cancer

Reference	*n*	Schedule (weeks)	Dose (mg/m^2)		RR (%)	Survival (months)	Toxicity grade 3–4 (% of patients)		
			GEM	DOC			Neutropenia/febrile neutropenia	Neurotoxicity	Diarrhea
Phase II (DOC d1)									
Binder et al.[a] [15]	19	3	900	75	44.0	NA	26/0	0	0
Hejna et al. [16]	34	3	1,000	80	50.0	13	18/0	NS	NS
Galetta et al. [6]	47	2	2,000	50	38.3	10.5	17/0	2	2
Phase II (DOC d8)									
Georgoulias et al. [7]	51	3	900	100	37.5	13	8/8	0	6
Rebattu et al. [10]	33	3	1,000	85	33.3	11.2	50/11[c]	3	0
Present study	41	3	1,000	85	44.0	7.3	28/5	3	5
Phase II (DOC d1,8)									
Hirsh et al. [17]	43	3	1,000	36	10	7.8	2/2	NA	7
Soto Collins et al. [20]	26	3	1,000	35	45	12.5	1/0	0	2
Popa et al. [18]	32	3	1,000	40	30	7.9	19/0	0	3
Skarlos et al. [19]	20	3	1,000	50	30	9.6	20/0	NS	NS
Phase III (DOC d1)									
Binder et al.[a] [5]	26	3	900	75	38.0[b]	NA	35/NA	NA	NA
Phase III (DOC d8)									
Georgoulias et al. [8]	222	3	1,100	100	33.3	9.5	22/11	3	3
Kakolyris et al.[a] [9]	134	3	1,000	100	29.0	NA	17/7	2	3

RR response rate, *GEM* gemcitabine (d1,8 except in Hejna et al. [16] where d1,10), *DOC* docetaxel, *NS* non-stated, *NA* non-available

[a] Preliminary results

[b] Average of patients treated with GEM/DOC and sequential cisplatin/GEM/DOC

[c] Including phase I data

In conclusion, gemcitabine 1,000 mg/m^2 on days 1 and 8 in combination with docetaxel 85 mg/m^2 on day 8 given in every-3-weeks cycles is an active and well-tolerated, except for pulmonary toxicity, first-line chemotherapeutic regimen for advanced NSCLC. The present results agree with the good clinical benefit/risk relationship found for this combination in previous studies, which supports the extension of its clinical use as first-line treatment of patients with advanced NSCLC.

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