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PHASE II STUDIES

Pulmonary toxicity in patients treated with gemcitabine plus vinorelbine or docetaxel for advanced non-small cell lung cancer: outcome data on a randomized phase II study

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Summary Studies with the gemcitabine/vinorelbine (GV) or the gemcitabine/docetaxel (GD) combinations have shown similar efficacy and less toxicity compared to platinum-based chemotherapies, in patients with advanced non-small-cell lung cancer (NSCLC). The present trial was designed to test the efficacy and safety of both, GV and GD, combinations. Chemotherapy-naïve patients (n=39)≤75 years of age, KPS≥60% and adequate hematological, renal and hepatic function were randomly assigned to receive G 1,000 mg/m^2 +either V 25 mg/m^2 or D 35 mg/m^2 (all of which were administered i.v.) on days 1 and 8 every 21 days. Baseline characteristics were comparable in GV (n=20) and GD (n=19) groups. Results indicated objective response of 7 (35%) vs 6 (31%) patients and median time-to-treatment failure of 120 versus 90 days in the GV and GD arms, respectively. The most common non-hematological toxicities were (GV vs GD): grade 2–4 pulmonary toxicity in 1 (5%) vs 7 (37%); grade 2–3 diarrhea 0 versus 4 (21%) and edema 1 (5%) vs 3 (16%); grade 3–4 hematological toxicities occurred in 3 (15%) vs 1 (5%) patients. Our results indicate that the combination of gemcitabine/docetaxel does not have a favorable safety profile with this schedule of administration, particularly in terms of pulmonary toxicity.

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Introduction

New cytotoxic agents developed for the treatment of non-small cell lung cancer (NSCLC), possess different mechanisms-of-action and encouraging toxicity profiles, while demonstrating significant activity. Of these, gemcitabine, vinorelbine and docetaxel are notable. Each has shown significant anti-tumor activity as single agents, with objective response (OR) rates of 15 to 20%. In randomized studies comparing single agent *vs* best supportive care (BSC), all of them have demonstrated an ability to improve the patient's quality-of-life (QoL) [1–8]. These same agents have been combined with cisplatin giving rise to third generation combinations which were compared with combinations of cisplatin with other drugs considered as second generation such as vindesin or etoposide. In all these comparative studies better results were confirmed in the majority of the parameters of efficacy analyzed and, as such, the third generation cisplatin combinations have become the standard treatment for this tumor pathology [9–12]. Of these third generation regimens no combination has been shown to be markedly better that the others with respect to increasing the median survival. There have been differences, however, with respect to the clinical features of the patients included, and the toxicity profiles. All of these combinations are able to induce 30–40% OR, a median time to progression (TTP) of 4–5 months, a median overall survival (OS) of 8–10 months and a survival at 1 year of 30–40% in selected groups of patients with adequate performance status (WHO levels 0–1) [13–16].

The advantages offered by cisplatin-based doublets are often offset by serious nephrotoxicity, ototoxicity, peripheral toxicity, and emesis, all of which adversely affect the QoL-adjusted survival. Hence, much research has been directed towards developing combinations of the third generation agents that exclude platinum in order to achieve therapeutic efficacy but with a reduction in associated toxicities, especially in the treatment of patients with advanced NSCLC. For example, phase I/II clinical trials with gemcitabine + vinorelbine have achieved OR in about 35% of patients, with a median TTP and OS of 4.5 and 9 months, respectively and with a low toxicity profile [17–19]. Similarly, phase I/II studies [20–23] have shown gemcitabine + docetaxel to be a well-tolerated combination with similar efficacy. The results of these trials provided the basis for subsequent studies comparing third generation cisplatinum combinations with gemcitabine and either vinorelbine [24–27] or docetaxel [28–30]. All these randomized trials demonstrated no disadvantages, in terms of primary end points and OS, in the groups of patients treated with non-platinum chemotherapy regimens. All of the above data, together with a recent meta-analysis of the published studies comparing platinum-based versus non-platinum based chemotherapy [31], suggest that the combination of third generation drugs without platinum could offer similar therapeutic benefits with lower toxicity compared to those regimens considered as "standard" and which included platinum. This concurs with the latest recommendations of the Expert Panel of the American Society of Clinical Oncology Treatment [32]. Nevertheless, for other authors the current standard of care for first line treatment of the of NSCLC patients with good performance status remains a platinum-based doublet [33, 34] making 3rd generation non-platinum combinations appropriate only for patients who are unlikely to tolerate the toxicity of cisplatin. Despite the promising results, toxicity continues being a major concern, and further testing and comparing of ostensibly well-tolerated two-drug combinations without platinum is an area requiring investigation.

The scientific data discussed above provided the rationale for our prospective randomized phase II trial to evaluate the activity and tolerability of gemcitabine/vinorelbine and gemcitabine/docetaxel combinations in advanced NSCLC patients.

Patients and methods

Patient eligibility

Eligible patients had histologic or cytologic diagnosis of NSCLC with stage IIIB or stage IV disease (pleural or pericardial malignant effusion, according to the International Staging System for lung cancer). Other eligibility criteria included: measurable or evaluable disease; age between 18 and 75 years; Karnofsky performance status (KPS) ≥60; adequate hematological function (neutrophil count$>1.5\times10^9$/L, platelet count$>100\times10^9$/L, and hemoglobin>10 g/L); adequate hepatic function and renal function (bilirubin<1.5 mg/dL, transaminases <3 times upper limit of normality (ULN) and creatinine<1.5×ULN). Patients were excluded for uncontrolled comorbidities, prior chemotherapy, second malignancies, symptomatic brain metastases and peripheral neuropathy (WHO grade>1). The study was conducted according to the principles of the Declaration of Helsinki. Signed informed consent was obtained from all patients prior to entry into the study.

Study design and sample size

This was a randomized, double arm, phase II study. The primary end point was objective response (OR). We anticipated an OR of 35% in both treatment groups within the ranges described for standard chemotherapy in advanced NSCLC. Assuming 35% OR for an active chemotherapy regimen for advanced NSCLC, a minimum of 50 patients in each treatment group would be necessary to confirm efficacy with a statistical power of 80% and a two-sided type 1 error of 5% [35].

Treatment schedule

Patients were randomized to receive either: gemcitabine 1,000 mg/m^2 and vinorelbine 25 mg/m^2, (GV group), or gemcitabine 1,000 mg/m^2 and docetaxel 35 mg/m^2 (GD group). All drugs were administered in the outpatient clinic on days 1 and 8, every 21 days. Vinorelbine was administered over 10 min, followed by gemcitabine given over 30 min. Docetaxel was given over 30 min immediately before gemcitabine, and prophylactic i.v. ranitidine (50 mg), diphenhydramine (25 mg) and dexamethasone (8 mg) were prescribed just prior its administration.

Anti-emetic therapy was not prescribed routinely in this study. However, in the event of emesis, the patient received intravenous metoclopramide 20 mg as prophylaxis in subsequent treatment cycles. Additional intravenous ondansetron (8 mg) was administered for emesis that had not been brought under control with the above medications.

A minimum of four treatment cycles were planned for all patients, unless disease progression occurred. Additional cycles were administered in patients who continued to respond to treatment and in whom toxicity was tolerable. Treatment was stopped when stable disease was the best response following a new cycle of treatment, or until intolerable toxicity occurred.

Dose modification

Chemotherapy doses on day 8 were adjusted depending on neutrophil and platelet counts on that day. If, on day 8, neutrophil and platelet counts were 1 to 1.5×10^9/L and $\geq100\times10^9$/L, respectively, the doses of all three drugs were reduced by 25%. If neutrophil and platelet counts were 1 to 1.5×10^9/L and 75 to 100×10^9/L, respectively, doses were reduced by 50%. Day-8 doses were omitted if neutrophil count was $<1.0\times10^9$/L, platelet count $<75\times10^9$/L, or if there were any non-hematological toxicities >2 grade (except for alopecia). Thereafter, all subsequent cycles and all drug doses were reduced by 25%. This reduction applied as well if grade 4 neutropenia or thrombocytopenia, or febrile neutropenia had occurred in the previous cycle. An administration of a cycle on day 1 was delayed if a neutrophil count showed $<1.5\times10^9$/L, platelet count $<100\times10^9$/L, or if there were any grade≥2 non-hematological toxicities. Dose adjustments for neurotoxicity were based on the signs and symptoms occurring on the day of treatment. If neurotoxicity grade≥2 occurred, the docetaxel and/or vinorelbine dose was delayed for one week. If any toxicity grade≥2 persisted for>2 weeks, the patient was transferred out of the study.

Baseline and treatment assessments

Baseline evaluations included medical history, physical examination, complete blood cell count, blood chemistries for hepatic and renal function, electrocardiogram, and radiological staging (chest X-ray plus computed tomography scan of the thorax, mediastinum, and abdomen). Except for symptomatic patients, a computed tomography scan of central nervous system was not routinely performed. Physical examination and blood analyses were repeated before the beginning of each new cycle. All patients underwent a thorough reevaluation, including a repeat of all previously abnormal radiology studies every 6 weeks, or if clinical progression of the disease was suspected. Eligible patients were evaluable for toxicity if they had received at least half of a cycle of the treatment. The patients were evaluable for efficacy if they had received at least one full cycle of treatment. Toxicity and efficacy were assessed using standard WHO criteria [36] and the response evaluation criteria in solid tumors [37], respectively. Response rates were calculated on an intent-to-treat basis and, toxicity evaluations were based on the worst episodes recorded regardless of the number of times they had occurred. Time-to-treatment-failure (TTF) was measured from the time of administration of the first dose until progression, death, or cessation of treatment for any other reason. All patients who had not had disease progression, or had not died by the time of the last scheduled outpatient visit, were censored for the present statistical analysis. Kaplan–Meier curves were constructed for all survival data [38].

Results

Patient characteristics

Between September 1999 and May 2003, a total of 39 patients were enrolled in this prospective randomized study. Groups GV (n=20) and GD (n=19) were well balanced with respect to performance status, stage of disease and number of disease sites. The main characteristics of the patients are summarized in Table 1.

Only one dose of the scheduled protocol was administered in 2 patients in the GV group (due to the administration in a 2-week schedule) and to 3 patients in the GD group (because of early death due to disease progression in the brain, prior chemotherapy, and loss to follow-up). Hence, these patients were considered evaluable for toxicity but not for response analysis. Nevertheless, these patients were included in the denominator in the response evaluation on an intent-to-treat basis.

Dose administration

The GV group received a total of 78 cycles (range 1–8) while the GD group received 48 cycles (range 1–6); the median number of cycles administered per patient in each group being 4 and 2, respectively. Due to progressive disease, 70 and 17% of patients in the GV and GD group, respectively, were withdrawn from the current treatment protocol. Withdrawal due to toxicity was 5% of GV patients and 63% of GD patients while 25 and 20%, respectively, withdrew because maximal response had occurred. Delays and/or dose reductions of planned treatment were needed in 45 and 63% of patients in the GV and GD groups, respectively.

Efficacy

Within a median follow-up of 9.5 months, all patients had stopped the treatment due to toxicity, disease progression or maximal response. Median time-to-treatment-failure (TTF) was 120 days (95% CI: 30–395) for GV and 90 days (95% CI: 15–160) for GD group. Response rates calculated on an intent-to-treat basis indicated an overall response rate of 35% (95% CI: 56–14%) in the GV group; 2 complete responses (CR) and 5 partial responses (PR) among the 20 enrolled patients. Response rate was 31% (range: 52–10%) in the GD group; 6 PR in the 19 enrolled patients. The proportions of patients with either stable disease (SD) or disease progression (DP) were similar in the two treatment groups; 35 and

Table 1 Patients' characteristics on entry into the trial

Characteristic		GV group		GD group	
		N	Percent (%)	*N*	Percent (%)
Total number of patients included		20		19	
Age median, years (range)		63 (42–74)		69 (48–76)	
Gender (male/female)		17/3	85/15	16/3	84/16
Karnofsky PS score; median (range)		70 (60–80)		70 (60–90)	
90–80		5	25	4	21
70		9	45	11	58
60		6	30	4	21
Histology	Adenocarcinoma	11	55	9	47
	Squamous cell	8	40	7	37
	Large cell	1	5	3	16
Stage IIIB/IV		3/17	15/85	3/16	16/84
Disease sites	Lung	12	60	10	53
	Bone	5	25	4	21
	Liver	2	10	2	10
	Soft tissue	2	10	3	16
	Adrenal gland	2	10	3	16
N° of disease sites	1	11	55	9	47
	2–3	9	45	10	53
Median *N*° of sites (range)		1 (1–3)		1 (1–3)	

20%, respectively, in the GV treatment group, and 42 and 10%, respectively, in the GD treatment group (Table 2).

Toxicity

As with published data in other trials using taxanes with the weekly administration scheme, the most frequently observed toxicities in the GD group were the non-hematological toxicities (Table 3). However, the most notable toxicity observed in our study was pulmonary toxicity grade 3–4 observed in seven patients (37%) treated with the GD combination and in one patient (5%) treated with the GV combination. The pulmonary toxicity involved bilateral interstitial pulmonary infiltrates with progressive moderate-to-intense fatigue, resting hypoxia in the absence of fever in six patients, and one patient had bilateral pleural effusion. This clinical condition failed to improve with antibiotics. Bronchoscopy was performed in three of these patients, and a transbronchial biopsy showed diffuse alveolar damage with atypical squamous cells and reactive columnar cells suggestive of drug-associated tissue damage. This toxicity appeared at a median of 6 weeks (range 3–18) following the commencement of the treatment. Of note, as well, were the episodes of diarrhea grade 2/3 in four patients (21%) of the GD group *vs* none of the GV group. The pulmonary damage and the diarrhea were considered as reversible phenomena since resolution was achieved by suspending the treatment and, in the case of the pulmonary toxicity, by the prescription of additional corticoids. Other non-hematological toxicities were less frequent in both treatment arms, and were less than

Table 2 Summary of response and time-to-treatment failure

Treatment outcomes		GV Group		GD Group	
		N	Percentage (%)	*N*	Percentage (%)
Total number of patients					
Response	CR	2	10	0	
	PR	5	25	6	31
	OR (95%CI)	7	35 (56–14)	6	31 (52–10)
	SD	7	35	8	42
	DP	4	20	2	10
	NE	2	10	3	16
Time to treatment failure	Median (95%CI)	120 (30–395)		90 (15–160)	

CR Complete response, *PR* partial response, *SD* stable disease, *DP* disease progression, *NE* not evaluable

Table 3 Hematological and non-hematological toxicities in the two treatment arms

Toxicity		GV Group				GD Group			
		Grade 1/2		Grade 3/4		Grade 1/2		Grade 3/4	
		N	Percentage (%)	*N*	Percentage (%)	*N*	Percentage (%)	*N*	Percentage (%)
Hematological	Anemia	8	40			5	26		
	Neutropenia	3	15	3	15	2	10	1	5
	Thrombocytopenia	1	5					1	5
Non-Hematological	Pulmonary	1	5			1	5	6	31
	Diarrhea					2	10	3	16
	Edema	1	5			1	5	2	10
	Nausea/Vomiting	3	15			1	5		
	Nail					2	10		
	Ocular					1	5		
	Alopecia	2	10			2	10		
	Fever	1	5					1	5
	Infection							1	5
Discontinuance due to toxicity		1		5		12		63	

grade 2 except for edema grade 2–3 recorded in three patients (15%) of the GD group *vs* 1 patient (5%) of the GV group. Hematological toxicity was rarely seen in this study, although neutropenia grade 3–4 was registered in three (15%) patients treated in the GV group and one (5%) patient treated in the GD group. In addition, grade 1–2 anemia was seen in eight (40%) and five (26%) patients treated in the GV and GD group, respectively (Table 3).

Discussion

In patients with advanced NSCLC, platinum-based combinations with paclitaxel, docetaxel, gemcitabine or vinorelbine have become standard treatment options. Nevertheless, other published studies comparing third generation doublets suggest that combinations without cisplatin could offer similar therapeutic benefits with lower toxicity, compared to those regimens considered as "standard" that include cisplatin. In this sense, gemcitabine combined with vinorelbine (GV) or with docetaxel (GD) are considered as the more active, less toxic, and more promising of the non-platinum combinations. We present the results of our randomized phase II trial designed to evaluate the activity and tolerability of both non-platinum combinations. The analysis of safety data prompted the early discontinuation of the trial.

Although we are conscious that our study is underpowered in terms of sample size of patients included in this analysis, both treatment groups exhibited a range of activity as has been described previously i.e. OR of around 30% particularly with the GV regimen which, additionally, showed a median TTF of 120 days.

With respect to the toxicity, attention needs to be drawn to the pattern and distribution of the toxicities observed in the present trial. Of note was that overall toxicities were reduced compared to other schedules that included cisplatin [24–30]. Conversely, and this has been the most important finding of this trial, the non-hematological toxicity, although not causing any toxic deaths, occurred with a higher incidence in the docetaxel treatment combination. This is seen clearly in the percentage of patients with diarrhea and pulmonary toxicity (in 21 and 37% of patients, respectively) treated with the GD combination. In three cases there was histological confirmation of lung tissue damage caused by the drug. However, in all of the seven patients, the radiological findings and the clinical symptoms were completely reversible when the medication was suspended, and corticoid therapy was implemented. Of concern is that this pulmonary adverse effect had not been described previously as a dose-limiting toxicity in phase I trials with weekly docetaxel [39] although it had been noted with other administration schedules of this drug [40, 41] as well as with gemcitabine [42, 43]. As such, there could be some relationship with an increase of this phenomenon in the GD treatment group. As well, the toxicity could have been related to the pre-medication used in the present study, or with the order of administration of both drugs or, even, with the schedule of administration. In our study, dexamethasone (8 mg) was administered just before each infusion of docetaxel which, in the experience of other authors, this dose appears to be appropriate and sufficient as a pre-medication for a weekly schedule of docetaxel administration [44]. Conversely, no differences in clinical toxicities have been described previously with docetaxel administered before gemcitabine, i.e. the reverse sequence of

administration [45]. The GD combination has been evaluated in a number of tumor types while using different schedules of administration. Administration of docetaxel only on day 8 every 21 days was used in most of phase I/II and comparative trials; the pulmonary toxicity described ranging between 0 to 8% [21, 22, 29, 30, 44, 46]. More recently, the schedule of administration of both drugs on days 1 and 15 (every 2 weeks) has been tested with no pulmonary toxicity being recorded [47, 48]. Conversely, the administration of docetaxel on day 1 (± day 8) every 21 days seems to be related to a higher incidence of pulmonary toxicity when combined with gemcitabine [49, 50]. Dunsford et al. [49] published four cases with pulmonary toxicity from seven patients with metastatic transitional cell carcinoma treated with the GD regimen in which docetaxel was administered on day 1. Popa et al [50] using a similar schedule of administration as in our study (i.e. days 1 and 8) noted that 6 of 32 (19%) chemotherapy-naïve patients treated for NSCLC experienced grade 3 pneumonitis. It is unclear whether the higher pulmonary toxicity registered was a chance phenomenon related to patients' comorbidities (characteristics) or whether there is a real enhanced risk with this particular combination. The randomized design of the present study, however, gives credence to the pulmonary toxicity being related to the gemcitabine + docetaxel combination and not to the prior co-morbidity characteristics of the patients included in the GD treatment arm. For example, our previous experience with the GV combination treatment for chemotherapy-naïve patients with advanced NSCLC, there was no pulmonary toxicity related to the treatment [19, 27]. In a randomized phase II trial using taxanes as second-line treatment for patients previously treated with platinum-based chemotherapy, we reported a higher incidence of pulmonary toxicity in the group of patients treated with docetaxel [51]. The only factor in common in the patients in that study who had developed pulmonary toxicity was that they had all been treated previously with gemcitabine and, as such, the toxicities could be related in some way to a recall phenomenon, or an additive pulmonary toxicity of the two drugs, even when administered sequentially. A similar experience has been described by other investigators [52].

To the best of our knowledge there have been no reports published comparing GV to GD in patients with advanced NSCLC. The design and characteristics of the present study and the data obtained do not allow categorical conclusions to be drawn with respect to efficacy. However, in agreement with other trials, the poorer-tolerated regimen seems to be the combination of gemcitabine + docetaxel. On the basis of these findings it may be prudent to avoid the schedule of administration and the doses of the GD combination used in the present study and, as well, to exclude patients with significant preexisting pulmonary pathology. In other situations with this combination, and using different schedules and dose administration, the patients need to be carefully monitored. If there are any complaints of dyspnea or radiological images showing pulmonary infiltrates, the treatment should be discontinued. Also, other causes of pulmonary infiltrates need to be excluded by bronchoscopy and transbronchial biopsy.

In summary, the search for, and development of, platinum-free combinations continues. The results of our prospective randomized trial suggests that the gemcitabine + docetaxel regimen, especially if administered on days 1 and 8 every 21 days, is associated with an elevated level of pulmonary toxicity. There need to be more studies designed to investigate the best schedule of administration of this combination (for example, every 2 weeks) and whether there are any real differences among 3rd generation platinum-free combinations.

References

1. Gatzemeier U, Shepherd FA, Le Chevalier T, Weynants P, Cottier B, Groen HJ, Rosso R, Mattson K, Cortes-Funes H, Tonato M, Burkes RL, Gottfried M, Voi M (1996) Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre extended phase II study. Eur J Cancer 32A:243–248
2. Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA (1994) Efficacy and safety profile of gemcitabine in non-small cell lung cancer: a phase II study. J Clin Oncol 12: 1535–1540
3. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH (1994) Single-agent activity of weekly gemcitabine in advanced non-small cell lung cancer: a phase II study. J Clin Oncol 12:1821–1826
4. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC (1991) A phase II study of Navelbine (vinorelbine) in the treatment of non-small cell lung cancer. Am J Clin Oncol 14:115–119
5. The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 91:66–72
6. Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, Milroy R, Maughan TS, Falk SJ, Bond MG, Burt PA, Connolly CK, McIllmurray MB, Carmichael J (2000) Gemcitabine plus best supportive care (BSC) versus BSC in inoperable non-small cell lung cancer—a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer 83(4): 447–453
7. Cerny T, Kaplan S, Pavlidis N, Cerny T, Kaplan S, Pavlidis N, Schoffski P, Epelbaum R, van Meerbeek J, Wanders J, Franklin HR, Kaye S (1994) Docetaxel (Taxotere) is active in non-small-cell lung cancer: a phase II trial of the EORTC Early Clinical Trial Group (ECTG). Br J Cancer 70:384–387
8. Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, Parisi A, Pham Tran N, Olivares R, Berille J (2000) A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naïve patients with metastatic or non-resectable localized non-small-cell lung cancer. Lung Cancer 27:145–157

9. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. J Clin Oncol 12:360–367
10. Cardenal F, Lopez-Cabrerizo MP, Anton A, Alberola V, Massuti B, Carrato A, Barneto I, Lomas M, Garcia M, Lianes P, Montalar J, Vadell C, Gonzalez-Larriba JL, Nguyen B, Artal A, Rosell R (1999) Randomized phase III study of gemcitabine–cisplatin versus etoposide–cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 17:12–18
11. Crino L, Scagliotti GV, Ricci S, De Marinis F, Rinaldi M, Gridelli C, Ceribelli A, Bianco R, Marangolo M, Di Costanzo F, Sassi M, Barni S, Ravaioli A, Adamo V, Portalone L, Cruciani G, Masotti A, Ferrara G, Gozzelino F, Tonato M (1999) Gemcitabine and cisplatin versus mitomycin, ifosfamide and cisplatin in advanced non-small-cell lung cancer: a randomized phase III study of the Italian Lung Cancer Project. J Clin Oncol 17:3522–3530
12. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Yokota S, Yoneda S, Matsui K, Kudo S, Shibuya M, Isobe T, Segawa Y, Nishiwaki Y, Ohashi Y, Niitani H, Japanese Taxotere Lung Cancer Study Group (2004) Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 22(2):254–261
13. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, Eastern Cooperative Oncology Group (2002) Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 346:92–98
14. Smit EF, van Meerbeeck JP, Lianes P, Debruyne C, Legrand C, Schramel F, Smit H, Gaafar R, Biesma B, Manegold C, Neymark N, Giaccone G, European Organization for Research and Treatment of Cancer Lung Cancer Group (2003) Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer. A phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group-EORTC 08975. J Clin Oncol 21:3909–3917
15. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L, Tonato M, Italian Lung Cancer Project (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small cell lung cancer. J Clin Oncol 20:4285–4291
16. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of Docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study Group. J Clin Oncol 21:3016–3024
17. Gridelli C, Frontini L, Perrone F, Gallo C, Gulisano M, Cigolari S, Castiglione F, Robbiati SF, Gasparini G, Ianniello GP, Farris A, Locatelli MC, Felletti R, Piazza E (2000) Gemcitabine plus vinorelbine in advanced non-small cell lung cancer: a phase II study of three different doses. GEMVIN Investigators. Br J Cancer 3(6):707–714
18. Lorusso V, Carpagnano F, Frasci G, Panza N, Di Rienzo G, Cisternino ML, Napoli G, Orlando S, Cinieri S, Brunetti C, Palazzo S, De Lena M (2000) Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small-cell lung cancer. J Clin Oncol 18(2):405–411
19. Esteban E, Fra J, Corral N, Valle M, Carrasco J, Sala M, Puerta J, Estrada E, Palacio I, Vieitez JM, Buesa JM, Lacave AJ (2002) Phase I/II study of gemcitabine plus vinorelbine in non-small cell lung cancer. Invest New Drugs 20:73–82
20. Bhargava P, Marshall JL, Fried K, Williams M, Lefebvre P, Dahut W, Hanfelt J, Gehan E, Figuera M, Hawkins MJ, Rizvi NA (2001) Phase I and pharmacokinetic study of two sequences of gemcitabine and docetaxel administered weekly to patients with advanced cancer. Cancer Chemother Pharmacol 48(2):95–103
21. Georgoulias V, Kouroussis C, Androulakis N, Kakolyris S, Dimopoulos MA, Papadakis E, Bouros D, Apostolopoulou F, Papadimitriou C, Agelidou A, Hatzakis K, Kalbakis K, Kotsakis A, Vardakis N, Vlachonicolis J (1999) Front-line treatment of advanced non-small cell lung cancer with docetaxel and gemcitabine: a multicenter phase II trial. J Clin Oncol 17:914–920
22. Rebattu P, Quantin X, Ardiet C, Morere JF, Azarian MR, Schuller-Lebeau MP, Pujol JL (2001) Dose-finding, pharmacokinetic and phase II study of docetaxel in combination with gemcitabine in patients with inoperable non-small cell lung cancer. Lung Cancer 33:277–287
23. Popa IE, Stewart K, Smith FP, Rizvi NA (2002) A phase II trial of gemcitabine and docetaxel in patients with chemotherapy-naïve, advanced non-small cell lung carcinoma. Cancer 95(8):1714–1719
24. Alberola V, Camps C, Provencio M, Isla D, Rosell R, Vadell C, Bover I, Ruiz-Casado A, Azagra P, Jimenez U, Gonzalez-Larriba JL, Diz P, Cardenal F, Artal A, Carrato A, Morales S, Sanchez JJ, de las Penas R, Felip E, Lopez-Vivanco G, Spanish Lung Cancer Group (2003) Cisplatin/gemcitabine versus a cisplatin-based triplet versus non-platinum sequential doublets in advanced non-small-cell lung cancer: a Spanish Lung Cancer Group Phase III Randomized Trial. J Clin Oncol 21:3207–3213
25. Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, Manzione L, Barbera S, Frontini L, Veltri E, Findlay B, Cigolari S, Myers R, Ianniello GP, Gebbia V, Gasparini G, Fava S, Hirsh V, Bezjak A, Seymour L, Perrone F (2003) Gemcitabine plus Vinorelbine compared with Cisplatin plus vinorelbine or Cisplatin plus Gemcitabine chemotherapy for advanced non-small cell lung cancer: a phase III trial of the Italian GEMVIN investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:3025–3034
26. Laack E, Dickgreber N, Muller T, Knuth A, Benk J, Lorenz C, Gieseler F, Durk H, Engel-Riedel W, Dalhoff K, Kortsik C, Graeven U, Burk M, Dierlamm T, Welte T, Burkholder I, Edler L, Hossfeld DK, German and Swiss Lung Cancer Study Group (2004) Randomized phase III study of gemcitabine and vinorelbine versus gemcitabine, vinorelbine, and cisplatin in the treatment of advanced non-small-cell lung cancer: from the German and Swiss Lung Cancer Study Group. J Clin Oncol 22:2348–2356
27. Esteban E, Fra J, Fernández Y, Corral N, Vieitez JM, Palacio I, de Sande JL, Fernández JL, Muñiz I, Villanueva N, Estrada E, Mareque B, Uña E, Buesa JM, Lacave AJ (2006) Gemcitabine and Vinorelbine (GV) versus Cisplatin, Gemcitabine and Vinorelbine (CGV) as First-line Treatment in Advanced Non Small Cell Lung Cancer: results of a Prospective Randomized phase II Study. Invest New Drugs 24:241–248
28. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis I, Greek Oncology Cooperative Group (GOCG) for Lung Cancer (2001) Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer. Lancet 357:1478–1484
29. Georgoulias V, Ardavanis A, Tsiafaki X, Agelidou A, Mixalopoulou P, Anagnostopoulou O, Ziotopoulos P, Chatzidaki D (2005) Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 23 (13):2937–2945
30. Pujol JL, Breton JL, Gervais R, Rebattu P, Depierre A, Morere JF, Milleron B, Kessler R, Janicot H, Spaeth D, Quantin X, Clary C

(2005) Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncology 16(4):602–610
31. D'Addario G, Pintillie M, Cerny T, Feld R, Leighl N, Shepherd FA (2003) Platinum-based versus non-platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC): a meta-analysis of the published literature (Abstract). Lung Cancer 41(2): S68–S69 (O-233)
32. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR, American Society of Clinical Oncology Treatment of Unresectable Non-Small-Cell Lung Cancer Guidelines (2004) Update 2003. J Clin Oncol 22:330–353
33. Le Chevalier T, Scagliotti G, Natale R, Danson S, Rosell R, Stahel R, Thomas P, Rudd RM, Vansteenkiste J, Thatcher N, Manegold C, Pujol JL, van Zandwijk N, Gridelli C, van Meerbeeck JP, Crino L, Brown A, Fitzgerald P, Aristides M, Schiller JH (2005) Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. Lung Cancer Jan 47 (1):69–80
34. Pujol JL, Barlesi F, Daures JP (2006) Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer Mar 51(3):335–345
35. Schaid DJ, Wieand S, Therneau TM (1990) Optimal two-stage screening designs for survival comparisons. Biometrika 77:507–513
36. World Health Organization Handbook for reporting results of cancer treatment. WHO offset publication #48 Geneva 1979
37. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92: 205–216
38. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observation. J Am Stat Assoc 53:457–481
39. Hainsworth D, Burris HA, Erland JB, Thomas M, Greco FA (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16: 2164–2168
40. Merad M, Le Cesne A, Baldeyrou P, Mesurolle B, Le Chevalier T (1997) Docetaxel and interstitial pulmonary injury. Ann Oncol 8:191–194
41. Read WL, Mortimer JE, Picus J (2002) Severe interstitial pneumonitis associated with docetaxel administration. Cancer 94:847–853
42. van der Els N, Millar V (1998) Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. Chest 114:1779–1781
43. Gupta N, Ahmed I, Steinberg H, Patel D, Nissel-Horowitz S, Mehrotra B (2002) Gemcitabine-induced pulmonary toxicity case report and review of the literature. Am J Clin Oncol 25:96–100
44. Stemmler J, Mair W, Stauch M, Papke J, Deutsch G, Abenhardt W, Dorn B, Jackisch C, Brudler O, Stamp J, Malekmohammadi M, Heinemann V (2002) Weekly docetaxel with or without corticosteroid premedication as first or second-line treatment in patients with metastatic breast cancer (Abstract). Proc Am Soc Clin Oncol 21:58a
45. Rizvi NA, Spiridonidis CH, Davis TH, Bhargava P, Marshall JL, Dahut W, Figuera M, Hawkins MJ (1999) Docetaxel and gemcitabine combinations in non-small cell lung cancer. Semin Oncol 26(suppl 16):27–31
46. Georgoulias V, Kourousis C, Androulakis N, Kakolyris S, Dimopoulos MA, Bouros D, Papadimitriou C, Hatzakis K, Heras P, Kalbakis K, Kotsakis T, Vardakis N, Meramveliotakis N, Hatzidaki D (1997) Docetaxel (Taxotere) and gemcitabine in the treatment of non-small cell lung cancer: preliminary results. Semin Oncol Aug 24(4 Suppl 14):S14-22–S14-25
47. Galetta D, Gebbia V, Giotta F, Durini E, Romito S, Borsellino N, Cazzato C, Pezzella G, Colucci G (2002) Gemcitabine and docetaxel every 2 weeks in advanced non-small cell lung cancer: a phase II study of the Gruppo Oncologico Italia Meridionale. Lung Cancer Oct 38(1):79–84
48. Pelegrí A, Calvo L, Antón A, Mayordomo JI, Vazquez S, Martín-Richard M, Carrasco E, Virizuela J (2005) Docetaxel/gemcitabine combination administered every two weeks in first line in metastatic breast cancer: final results of a phase II trial. Clin Breast Cancer 6:433–438
49. Dunsford ML, Mead GM, Bateman AC, Cook T, Tung K (1999) Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. Ann Oncol Aug;10(8):943–947
50. Popa IE, Stewart K, Smith FP, Rizni NA (2002) A phase II trial of gemcitabine and docetaxel in patients with chemotherapy-naïve, advanced non-small cell lung carcinoma. Cancer 95:1714–1719
51. Esteban E, González de Sande L, Fernández Y, Corral N, Muñiz I, Fra J, Blay P, Sánchez R, Sala M, Palacio I, Fernández JL, Vieitez JM, Estrada E, Lacave AJ (2003) Prospective randomized phase II study of docetaxel versus paclitaxel administered weekly in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. Ann Oncology 14:1640–1647
52. Hosoe S, Komuta K, Shibata K, Harada H, Iwamoto Y, Ohsaki Y, Furuse K, Fukushima M, Origasa H, Kawahara M (2002) Gemcitabine and Vinorebine followed by Docetaxel in patients with advanced non-small cell lung cancer: final results of multi-institutional phase II trial of sequential non-platinum triplet combination chemotherapy (JMTO LCOO-02) (Abstract). Proc Am Soc Clin Oncol 21:315a