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CLINICAL TRIAL REPORT

Docetaxel/gemcitabine or cisplatin/gemcitabine followed by docetaxel in the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC): results of a multicentre randomized phase II trial

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Abstract
Background Most patients (pts) with metastatic non-small cell lung cancer (NSCLC) receive either single agents or chemotherapy doublets. Recent studies have demonstrated that triple-agent therapies may improve the response rate, but are associated with significant toxicity, and frequently do not prolong survival. A sequential triple-agent schedule may combine acceptable tolerability and good efficacy. We therefore conducted a multicentre, prospectively randomized study that evaluates a sequential three-drug schedule and a platinum-free doublet regimen.
Patients and methods The pts with union international contre le cancer (UICC) stage IV NSCLC were randomized to one of two schedules: in arm Doc-Gem, they received gemcitabine (900 mg/m^2, 30 min infusion) on days 1 and 8, and docetaxel (75 mg/m^2, 1 h infusion) on day 1, repeated every 3 weeks up to six cycles. In arm Cis-Gem→Doc, gemcitabine (900 mg/m^2, days 1 and 8) and cisplatin (70 mg/m^2, 1 h infusion, day 1) were given for three cycles, followed by three cycles of docetaxel (100 mg/m^2, day 1, repeated every 3 weeks).
Results One hundred and thirteen pts were randomized to arms Doc-Gem (55 pts) and Cis-Gem→Doc (58 pts). With Doc-Gem, 20.4% of pts responded to the treatment whereas 31.0% responded in arm Cis-Gem→Doc (overall response, intent-to-treat, difference not significant). The median time to progression was 3.6 months in arm Doc-Gem [95% confidence interval (CI) 1.4, 5.9] and 5.2 months in arm Cis-Gem→Doc (95% CI 3.1, 7.3). The median survival was 8.7 months with treatment Doc-Gem (95% CI 5.7, 11.6) and 9.4 months with treatment Cis-Gem→Doc (95% CI 7.8, 11.0). The 1-year survival rates were 34 and 35%, respectively. Mild to moderate leukopenia was frequently seen with both schedules. Other common adverse events (AE) were nausea/vomiting, thrombocytopenia, anaemia, diarrhoea, and infections. No significant differences in AEs were observed between the schedules except for nausea/vomiting, which occurred more frequently with Cis-Gem→Doc.
Conclusion The sequential therapy comprising cisplatin, gemcitabine, and docetaxel demonstrated promising tumour control whereas the platinum-free combination (docetaxel/gemcitabine) was very well tolerated. However, the schedules resulted in comparable survival to recent large trials in pts with advanced NSCLC. The present results do not justify further phase III investigation.

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Keywords Non-small-cell lung cancer · Chemotherapy · Randomized phase II study · Sequential therapy design

Introduction

According to a recent survey, 381,500 cases of lung cancer were diagnosed in Europe and 341,800 deaths were recorded from lung cancer in the year 2004 [2]. Non-small cell lung cancer (NSCLC) accounts for about 80% of lung cancer cases and approximately one-third of NSCLC patients (pts) initially present with metastatic disease [16, 26]. Furthermore, many pts initially treated with curatively intended surgery or radiotherapy experience recurrence or progression later.

In pts with metastatic NSCLC, combination chemotherapy has led to a modest improvement in overall survival and increased quality of life [18]. For non-elderly pts in good performance status, platinum-based double combinations represent the standard treatment [24]. However, the effectiveness of chemotherapy appears to have reached a plateau, the range of objective response rates observed has been 17–32%, and median survival between 7.4 and 11.3 months [11, 22, 23].

Recently, a meta-analysis of randomized trials comparing either one substance with a doublet or a doublet with a triplet in advanced NSCLC was published [4]. By extracting 65 trials with 13,601 pts, the authors demonstrated a significant increase in tumour response, 1-year survival, and median survival in favour of the doublet regimen when compared with monotherapy. However, although an increase was observed in the tumour response rate in favour of the triplet regimen, advantages in 1-year survival and median survival were not evident, possibly because concurrent triplet regimens have a significant degree of toxicity. Sequential triple agent schedules may combine the high efficacy seen in trials with concurrent triplet schedules with the favourable tolerability of doublet regimens. The individual agents can be fully dosed with fewer dose reductions necessary while additive toxicities can be avoided. On the other hand, platinum compounds account for a great part of the felt toxicity. Numerous recent trials demonstrated that omitting platinum agents is not associated with a worse survival but allows better tolerable therapy. We therefore conducted a multicentre, prospectively randomized phase II study that evaluates a sequential three-drug schedule and a platinum-free doublet regimen. The aim of both regimens was acceptable tolerability while maintaining high efficacy.

Patients and methods

Eligibility criteria

One hundred and thirteen pts were enrolled at three centres in Germany. Chemo-naïve pts aged $\geq$ 18 years with histologically confirmed, metastatic [stage IV Union internationale contre le cancer (UICC)] were eligible. The pts had to have two-dimensionally measurable disease (as assessed by computed tomography) that was not amenable to curative surgery or radiation therapy. Entry criteria also included an eastern cooperative oncology group (ECOG) performance score of ≤ 2 and adequate organ function (absolute neutrophil count $\geq 2 \times 10^9$/l, thrombocytes $\geq 100 \times 10^9$/l, creatinine $\leq$ 1.5-fold the upper limit of normal, and bilirubin $\leq$ 1.25-fold the upper limit of normal). All pts enrolled provided written informed consent. The study has been reviewed by an ethics committee and has therefore been performed in accordance with the ethical standards of the Declaration of Helsinki.

Treatment

The pts were randomized to one of the following schedules (Fig. 1): gemcitabine (900 mg/m^2, 30 min infusion) on days 1 and 8, and docetaxel (75 mg/m^2, 1 h infusion) on day 1, repeated every 3 weeks up to six cycles (arm Doc-Gem). A CT scan of the thorax was mandatory after cycle three; subjects with progressive tumour disease terminated the study treatment.

In the sequential Cis-Gem→Doc arm, pts received three cycles of gemcitabine (900 mg/m^2, days 1 and 8) and cisplatin (70 mg/m^2, 1 h infusion, day 1). If complete or partial response (PR) or stable disease (SD)

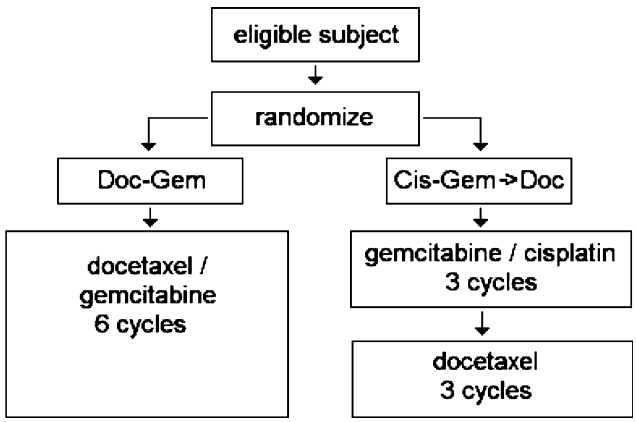

Fig. 1 Synopsis of study protocol: patients were randomly assigned to one of the two therapies

were detected in the CT scan, pts were given three cycles docetaxel (100 mg/m^2, day 1, repeated every 3 weeks, 1 h infusion).

Palliative radiotherapy, haematopoietic growth factors, and erythropoietin/darbepoetin were permitted during the trial and given at the discretion of the local investigator. If tumour progression or unacceptable toxicity occurred during treatment, pts discontinued from the study. Further therapies started at the time of relapse or progression were at the discretion of the local investigator.

Treatment evaluation and statistical methods

The primary endpoint of this randomized phase II trial was to assess the proportion of pts alive at 1 year from randomization. Secondary endpoints included response to treatment, time to tumour progression, and treatment toxicity. Response to treatment and toxicity were assessed according to World health organization (WHO) criteria.

Patients who received at least one dose of therapy were evaluable for toxicity. The population evaluable for response comprised of pts who completed one full cycle of treatment or more.

The group sequential design of the study comprised five steps with 11 pts per step for each arm (total planned accrual 55 per arm), $p_1 = 0.40$, $p_2 = 0.65$, power 0.80, $\alpha = 0.05$.

Kaplan–Meier curves were used to plot overall survival and time to progression. Survival time was defined as interval between randomization and death or last known follow-up. Time to progression was calculated from the day of randomization until tumour progression (based on radiological methods or clinical presentation), death, or last follow-up. Differences in these parameters were tested using the log rank test. The pts' baseline characteristics and adverse events (AE) were compared using the chi-square test.

Results

Patient characteristics

One hundred and thirteen pts were enrolled (55 for the Doc-Gem and 58 for the Cis-Gem→Doc schedule). Five pts did not begin chemotherapy because of early death ($n = 3$) or being lost to follow-up ($n = 2$). One patient randomized to Doc-Gem was later excluded from analysis owing to violation of inclusion criteria. Patient characteristics at baseline were well balanced between the groups (Table 1).

Table 1 Patient characteristics at baseline

Characteristic	Doc-Gem ($n = 54$)	Cis-Gem→Doc ($n = 58$)
Patients beginning treatment, *n*	53	54
Median age, years (range)	64.0 (42–75)	64.5 (36–74)
Gender, *n* (%)		
Female	15 (28)	17 (29)
Male	39 (72)	41 (71)
Tumour histology (%)		
Squamous cell carcinoma	18 (33)	15 (26)
Adenocarcinoma	25 (46)	30 (52)
Large cell carcinoma	4 (7)	7 (12)
Other	7 (13)	6 (10)
ECOG performance status (%)		
0	14 (26)	10 (17)
1	28 (52)	36 (62)
2	11 (20)	10 (17)
Data missing	1 (2)	2 (3)
Organs metastatic		
1	30 (56)	32 (55)
2	19 (35)	17 (29)
3	5 (9)	7 (11)
>3	0	2 (3)

ECOG Eastern cooperative oncology group

Treatment delivery

The median number of treatment cycles administered was three in the Doc-Gem protocol and four cycles for pts receiving Cis-Gem→Doc. Fourteen pts (26% of intent-to-treat population) in the Doc-Gem arm and 21 pts (36%) in the Cis-Gem→Doc arm received the planned six cycles. In arm Cis-Gem→Doc, 32 pts (55%) received three cycles or more and switched to the docetaxel treatment as scheduled.

Response

There was no significant difference in response between the arms (see Table 2). In the Doc-Gem arm, 11 pts had a PR corresponding with an overall response rate (ORR) of 20.4% (intent-to-treat). In the sequential Cis-Gem→Doc schedule, two pts had a complete response (CR) and 16 had a PR (intent-to-treat, ORR of 31.0%). In the Cis-Gem→Doc regimen, the disease control rate (CR + PR + SD) was 66% compared to 48% with Doc-Gem. The difference approached statistical significance ($p = 0.06$, chi-square test). Eleven (20%)/seven pts (12%) in the Doc-Gem/Cis-Gem→Doc treatment were not evaluable for response, most frequently due to early

Table 2 Response rate (intent-to-treat calculation)

Best response	Number of patients (%)		*p* value
	Doc-Gem ($n = 54$)	Cis-Gem→Doc ($n = 58$)	
Complete response (CR)	0	2 (3)	–
Partial response (PR)	11 (20)	16 (28)	–
Overall response rate (ORR)	11 (20)	18 (31)	0.20
Stable disease (SD)	15 (28)	20 (34)	–
Disease control (CR + PR + SD)	26 (48)	38 (66)	0.06
Progressive disease	17 (31)	13 (22)	–
Not evaluable	11 (20)	7 (12)	–

discontinuation of the study medication before the first scheduled staging.

Survival and progression

At median follow-up of 16.8 months, the median survival was 8.7 months with schedule Doc-Gem [95% confidence interval (CI) 5.7, 11.6] and 9.4 months with treatment Cis-Gem→Doc (95% CI 7.8, 11.0). We observed 1-year survival rates of 34 and 35% (Doc-Gem/Cis-Gem→Doc, respectively, see Fig. 2).

The median time to progression was 3.6 months with Doc-Gem arm (95% CI 1.4, 5.9) and 5.2 months with Cis-Gem→Doc (95% CI 3.1, 7.3, see Fig. 3).

Toxicity

Six pts died during chemotherapy for reasons that could not be clearly attributed to tumour progression. Conditions included pulmonary arterial embolism and myocardial infarction in the Doc-Gem arm and pulmonary arterial embolism, apoplectic stroke, port-a-catheter sepsis, and non-neutropenic pneumonia in the Cis-Gem→Doc arm. Chemotherapy had to be stopped prematurely in additional 8/6 of the pts due to patient intolerability (Doc-Gem/Cis-Gem→Doc, respectively).

There were no significant differences except for nausea/vomiting (see Table 3). In addition, three pts suffered from moderate to severe dyspnoea under

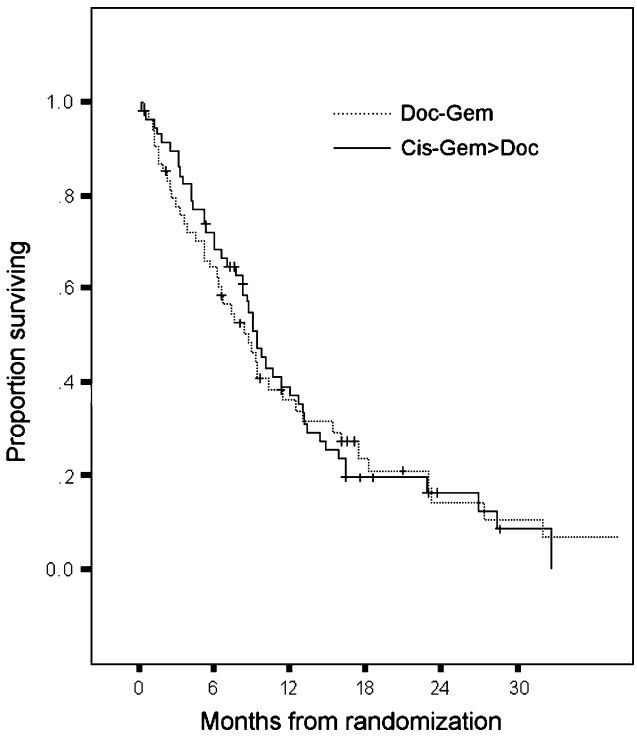

Fig. 2 Overall survival: median 8.7 months (Doc-Gem), 9.4 months (Cis-Gem→Doc)

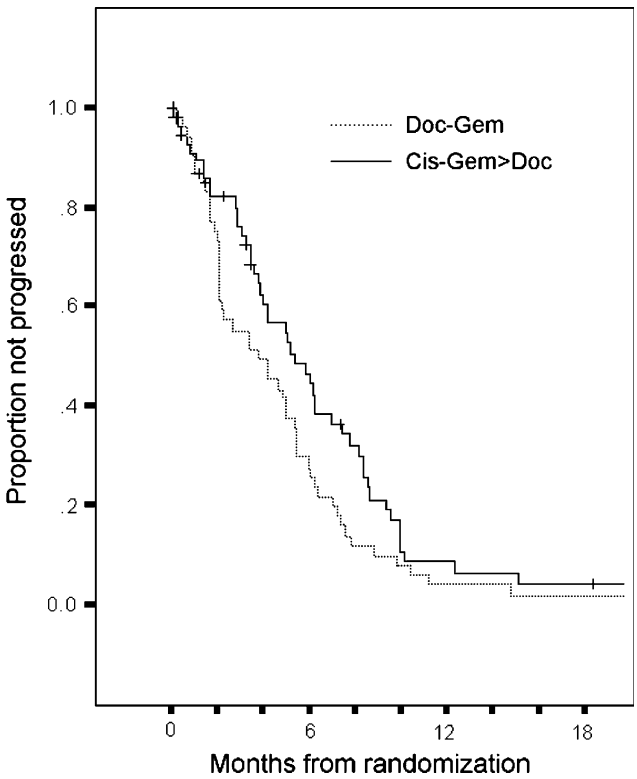

Fig. 3 Time to tumour progression: median 3.6 months (Doc-Gem), 5.2 months (Cis-Gem→Doc)

Table 3 Toxicities (regardless of relationship to study treatment, WHO criteria)

Adverse event	Doc-Gem ($n = 53$)			Cis-Gem→Doc ($n = 54$)			p value
	Grade II n (%)	Grade III n (%)	Grade IV n (%)	Grade II n (%)	Grade III n (%)	Grade IV n (%)	
Leukopenia/neutropenia	12 (23)	11 (21)	4 (8)	16 (30)	9 (17)	4 (7)	NS
Febrile neutropenia	0	1 (2)	0	0	1 (2)	0	NA
Anaemia	3 (6)	3 (6)	0	7 (13)	5 (9)	0	NS
Thrombocytopenia	4 (8)	7 (13)	0	7 (13)	9 (17)	0	NS
Nausea/vomiting	3 (6)	3 (6)	0	14 (26)	8 (15)	0	0.002
Diarrhoea	5 (9)	2 (4)	1 (2)	2 (4)	1 (2)	0	NS
Bleeding	0	1 (2)	2 (4)	0	0	1 (2)	NA
Transaminases	0	2 (4)	0	0	1 (2)	0	NA
Renal	1 (2)	0	0	1 (2)	0	0	NA
Dyspnoea	5 (9)	1 (2)	2 (4)	3 (6)	1 (2)	0	NS
Non-neutropenic infections	8 (15)	2 (4)	1 (2)	7 (13)	4 (7)	0	NS
Thrombembolism	0	1 (2)	0	1 (2)	1 (2)	3 (6)	NA
Neuropathy	1 (2)	1 (2)	0	3 (6)	1 (2)	0	NA

NS Not significant, *NA* Not applicable, low case number, *WHO* World health organization

Doc-Gem not associated with tumour progression, pleural effusion, obstructive lung disease, or pulmonary arterial embolism.

Discussion

We conducted a randomized phase II study testing a sequential triplet combination and a platinum-free doublet combination in the first-line treatment of advanced NSCLC. In the present study, both schedules were active and well tolerated. We observed response rates and median survival durations that comply with other chemotherapy trials in advanced NSCLC [11, 22, 23]. PS 2 pts have been primarily included as this study tests a platinum-free treatment.

In the meta-analysis recently published by Delbaldo et al. [4], the authors demonstrated that triple-agent schedules, when compared to chemotherapy doublets, can be associated with superior tumour response. However, these combinations were not associated with increased survival. This may be due to higher toxicity, e.g. infections during neutropenia. We started with a platinum-based doublet regimen comprising cisplatin and gemcitabine. This combination is well established and demonstrated its efficacy in several large chemotherapy trials [22, 23]. After the administration of three cycles, we switched to docetaxel. Docetaxel is known for its efficacy even in platinum-refractory pts [10]. A similar design with docetaxel sequentially following a platinum-based doublet was tested by Edelman et al. [8] and Hosoe et al. [15] earlier.

Sequential chemotherapy regimens comprising three drugs were tested by several other investigators. The phase III study reported by Gebbia et al. [12] tested two standard doublet combinations versus two sequential regimens each comprising four drugs (cisplatin, vinorelbine, ifosfamide, gemcitabine). The investigators reported poor time to progression at interim analysis in the sequential arm that initially used ifosfamide and prematurely closed *both* sequential arms, although the other sequential regimen was not inferior. Alberola et al. [1] compared a standard doublet combination (gemcitabine and cisplatin) with a concurrent triplet (gemcitabine and vinorelbine and cisplatin) and a sequential regimen with three cycles of gemcitabine/vinorelbine followed by three cycles of vinorelbine/ifosfamide. This large trial with 557 evaluable pts demonstrated equal median survival in all three arms although the objective response rate was significantly weaker in the sequential arm. The two randomized studies could not demonstrate advantages for the sequential therapies, although in the study conducted by Gebbia et al. [12], the weak results of one sequential therapy can possibly be explained by the initial use of ifosfamide and led to rejection of any sequential treatment (Table 4).

As expected, the platinum-free treatment caused significantly less nausea and vomiting in the present study, while other statistically significant differences were not observed for any AE. A favourable toxicity profile for the combination docetaxel/gemcitabine was observed in some recently published large trials [13, 21, 25]. Pujol et al. [21] tested the combination of gemcitabine and docetaxel against cisplatin/vinorelbine in a randomized phase III trial in 311 pts with advanced NSCLC. They found no difference in efficacy (median survival 11.1 months versus 9.6 months, n.s., objective

Table 4 Phase II/III studies including sequential regimens with more than two agents

Author	Phase	Schedule	*n*	RR (%)	Median survival	*p* value
Edelman et al. [7]	II	CARBO + GEM(PAC	37	31	9.5 months	
Feliu et al. [9]	II	PAC(CIS + GEM + VIN	52	54	>14 months	
Perol et al. [20]	rand. II	CIS + VIN altern. DOC	70	11	29 weeks	NA
		CIS + VIN		25	42 weeks	
Hosoe et al. [15]	II	GEM + VIN(DOC	44	48	15.7 months	
Gebbia et al. [12]	III	CIS + GEM	400	30	8.2 months	
		CIS + VIN		42	9.0 months	NS
		IFO + GEM(CIS + VIN		19[a]	n.r.	
		VIN + CIS(IFO + GEM		32[a]	n.r.	
Alberola et al. [1]	III	CIS + GEM	557	42	9.3 months	
		CIS + GEM + VIN		41	8.2 months	NS
		GEM + VIN(VIN + IFO		27	8.1 months	
Edelman et al. [8]	rand. II	CARBO + GEM(PAC	204	21	9 months	
		CIS + VIN(DOC		28	9 months	NA
Grossi et al. [14]	II	CIS + PAC(VIN(GEM	51	43	14.4 months	
Dongiovanni et al. [5]	II	CIS + VIN(PAC + GEM	55	42	10.3 months	
Chiappori et al. [3]	II	CARBO + GEM(DOC	40	24	6.7 months	
Pallis et al. [19]	II	CIS + VIN(DOC + GEM	59	46	12.5 months	

CARBO Carboplatin, *CIS* Cisplatin, *GEM* Gemcitabine, *PAC* Paclitaxel, *DOC* Docetaxel, *VIN* Vinorelbin, *IFO* Ifosfamide, *RR* Response rate, *NS* Not significant, *NA* Not applicable

[a] Interim analysis after 243/400 pts, arms closed

response rate 31% vs. 36%, n.s.), but observed a significantly lower frequency of febrile neutropenia, gastrointestinal toxicity, anaemia for the platinum-free combination, whereas docetaxel/gemcitabine had more pulmonary toxicity. In another study conducted by Georgoulias et al. [13], the same combinations were tested in a randomized phase III trial in 413 pts with advanced NSCLC. The docetaxel-gemcitabine combination demonstrated a response rate of 30% vs. 39% for cisplatin/vinorelbine ($p = 0.05$). No differences in survival were observed (median 9.0 months versus 9.7 months, n.s.). There was less nausea and vomiting, anaemia, neurotoxicity, and neutropenia with docetaxel/gemcitabine. With similar survival in these two large randomized trials, docetaxel and gemcitabine in combination have demonstrated a promising toxicity profile. This is equivalent with the observations made in the present study, where the combination of docetaxel and gemcitabine was well tolerated and revealed comparable survival as the sequential triplet schedule.

We observed three pts suffering from moderate to severe dyspnoea under docetaxel and gemcitabine in combination. In these pts, the symptom was not clearly related to tumour progression, pulmonary infections, exacerbation of obstructive pulmonary disease, pleural effusion, or pulmonary arterial embolism. In the large phase III trials published by Pujol et al. [21] and Georgoulias et al. [13], 5.2 and 0.5% of pts developed grade 3/4 pneumonitis during chemotherapy. This is comparable with the 6% seen in our study. However, other publications reported much higher frequencies of severe or fatal pulmonary AEs [6, 17].

Conclusion

The present study tested the efficacy and tolerability of a sequential regimen comprising cisplatin and gemcitabine followed by docetaxel and a platinum-free combination of docetaxel and gemcitabine. Both schedules were active and well tolerated. The results do not justify further phase III investigation. The platinum-free combination was not clearly inferior in this study and demonstrated a favourable tolerability. As no standardized recommendations are available for the use of platinum-free therapies, decisions should be made individually on the basis of age, performance status, and organ function of the patient.

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