Factorial phase III randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: the GEmcitabine-COxib in NSCLC (GECO) study

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Summary

Background The addition of cyclo-oxygenase-2 (COX-2) inhibitors and prolonged constant infusion (PCI) of gemcitabine to treatment for advanced non-small-cell lung cancer (NSCLC) might improve treatment efficacy. We aimed to assess whether the addition of rofecoxib or PCI gemcitabine could improve overall survival compared with first-line treatment with cisplatin plus gemcitabine given by standard infusion.

Methods Patients with stage IV or IIIb (with supraclavicular nodes or pleural effusion) NSCLC who were under 70 years of age and who had performance status 0 or 1 were eligible for this multicentre, prospective, open-label, randomised phase III trial with 2×2 factorial design. Patients were randomly assigned to one of four treatment groups: group A, gemcitabine 1200 mg/m^2 in a 30-min intravenous infusion on days 1 and 8 and intravenous cisplatin 80 mg/m^2 on day 1, every 21 days for six cycles; group B, the same treatments as group A plus oral rofecoxib 50 mg/day until disease progression; group C, intravenous PCI gemcitabine 1200 mg/m^2 in a 120-min infusion on days 1 and 8 and intravenous cisplatin 80 mg/m^2 on day 1, every 21 days for six cycles; group D, the same drugs as group C plus oral rofecoxib 50 mg/day until disease progression. The primary endpoint was overall survival; secondary endpoints were progression-free survival, response rate, quality of life, and toxicity. Analyses were intention-to-treat. This trial is registered on the clinical trials site of the US National Institutes of Health website http://clinicaltrials.gov/ct/show/NCT00385606.

Findings Between Jan 30, 2003, and May 3, 2005, 400 patients were enrolled. Median age was 60 years (range 29–71). PCI gemcitabine did not improve overall survival (median 47 weeks [95% CI 40–55] *vs* 44 [36–52], with standard gemcitabine infusion, hazard ratio (HR) of death 0·93 [0·74–1·17], p=0·41), progression-free survival, nor any other secondary endpoint. Vomiting and fatigue were significantly worse with PCI gemcitabine. The two rofecoxib groups were closed early (on Oct 1, 2004) due to withdrawal of the drug because of safety issues. With intention-to-treat statistical analyses limited to 240 patients (ie, those randomised before July 1, 2004) who had at least 3 months of treatment, rofecoxib did not prolong overall survival (median 44 weeks [CI 36–55] *vs* 44 [40–54] without rofecoxib, and HR of death 1·00 [0·75–1·34], p=0·85), or progression-free survival, but did improve response rate (41% *vs* 26%, p=0·02), global quality of life, physical, emotional and role functioning, fatigue, and sleeping. Rofecoxib significantly increased the incidence of diarrhoea and decreased constipation, fatigue, fever, weight loss, and pain, and analgesic consumption. Severe cardiac ischaemia was more frequent with rofecoxib than without; however, the difference was not statistically significant in the primary analysis (p=0·06) and became significant when patients who were randomised between July 1, 2004, and Sept 30, 2004, were included in the analysis (p=0·03).

Interpretation Neither PCI gemcitabine nor rofecoxib prolonged survival in the patients in this study. Rofecoxib improved response rate and several quality-of-life items, including pain-related items and global quality of life. Further studies with less cardiotoxic COX-2 inhibitors are needed in NSCLC.

Introduction

Prognosis of patients with advanced non-small-cell lung cancer (NSCLC) is poor. Platinum-based chemotherapy is the worldwide standard treatment, and on the basis of meta-analyses, is associated with a small, but significant survival benefit at 1 year in favour of cisplatin-containing regimens compared with best supportive care.[1] However, the benefit of chemotherapy is small and has to be weighed against substantial toxicity.[2] Platinum-based treatment is associated with higher response rates compared with regimens that do not contain platinum, although, it does not prolong overall survival compared with regimens containing third-generation treatments (eg, taxanes, gemcitabine, and vinorelbine).[3] Direct comparisons in phase III trials suggest that no major differences in efficacy exist between platinum-based treatments.[4,5]

In Italy, the most commonly used treatment regimen is a combination of cisplatin and gemcitabine. Phosphorylation of gemcitabine to the monophosphate by deoxycytidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites.[6] Phase I studies have shown that the ability of mononuclear cells to accumulate gemcitabine triphosphate during treatment is saturable, and the

optimum plasma concentration of gemcitabine that maximised the rate of formation of gemcitabine triphosphate was about 20 μmol/L.[7,8] By the use of dose rates of around 10 mg/m²/min, the target gemcitabine concentration in plasma was achieved, and the rate of gemcitabine triphosphate accumulation by mononuclear cells and leukaemia cells was optimised.[9] In a phase II randomised trial in patients with pancreatic cancer, gemcitabine infused at the fixed-dose rate infusion of 10 mg/m²/min led to a median overall improvement in survival, with unusually high 1-year, 2-year, and 3-year survivorship compared with a dose-intense scheme of gemcitabine (2200 mg/m²) given in a standard 30-min infusion.[10] In patients with NSCLC, the results of a randomised phase II study further showed the feasibility and activity of weekly gemcitabine at the fixed-dose rate of 10 mg/m²/min in combination with cisplatin.[11] In this particular study, median progression-free survival was a promising 8 months, although overall survival was similar to that in the standard group at 13 months. These data suggested that exposure to prolonged concentrations of gemcitabine might improve its efficacy.

Preclinical evidence lends support to the association between COX-2, prostaglandins, and cancer. COX is an important enzyme in the conversion of arachidonic acid to prostaglandins, which are involved in maintenance of the gastric mucosa, regulation of renal bloodflow, platelet aggregation, and immune response.[12–14] Two isoforms of COX exist: COX-1 is constitutionally expressed, and COX-2 is inducible by growth factors, oncogenes, carcinogens, and tumour-promoting phorbol esters.[15] COX-2 is overexpressed in various human malignancies, and this overexpression represents an important early event in the development of some human tumours, including colon and lung cancer, and suggests that COX-2 is linked to the development of cancer.[16,17] In patients with NSCLC, overexpression of COX-2 is associated with worse prognosis and with metastasis.[18,19] Several preclinical studies have shown the in-vitro and in-vivo antitumoral activity of selective COX-2 inhibitors, which block tumour growth through many mechanisms, mainly by antiangiogenic and proapoptotic effects.[20,21] Furthermore, synergistic cytotoxicity has been reported in NSCLC cell lines with combinations of COX-2 inhibitors and several chemotherapeutic agents or radiotherapy.[22–24] Based on these findings, COX-2 inhibitors have been combined with chemotherapeutic agents in cancer treatment and early trials have documented the feasibility, good tolerability, and promising activity of such combinations in patients with advanced colorectal cancer and NSCLC.[25,26] Rofecoxib is a selective COX-2 inhibitor that has ten-times greater biochemical selectivity for COX-2 than does celecoxib.[27] When the current study was planned, published research suggested that a rofecoxib dose of 50 mg/day was feasible for prolonged treatment and was associated with a lower risk of gastrointestinal adverse events compared with non-steroidal anti-inflammatory drugs.[28–30]

The aim of this study was to assess whether the efficacy of cisplatin plus gemcitabine chemotherapy for NSCLC could be improved by the addition of rofecoxib or by a prolonged constant infusion (PCI) of gemcitabine.

Methods

Patients and procedures

This was a multicentre, prospective, open-label, randomised, factorial phase III trial. The study protocol was approved by the Ethics Committee of each participating institution and all patients provided written informed consent.

Patients with histologically or cytologically confirmed NSCLC, stage IV or stage IIIB disease with malignant pleural effusion or supraclavicular nodes, who were under 70 years of age, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and who had not received previous chemotherapy were recruited. Patients who had had previous radiotherapy that was completed at least 4 weeks before enrolment were allowed into the study. Patients with asymptomatic brain metastases were eligible if radiotherapy was not needed concomitantly with chemotherapy. Patients were excluded if they had a history of previous invasive malignancy or inadequate bone marrow function (neutrophils $<2\times10^6$ cell/L, platelets $<100\times10^9$ cells/L, haemoglobin <100 g/L), inadequate hepatic function (alanine aminotransferase, aspartate aminotransferase, or bilirubin >1·25×upper normal limit) in the absence of liver metastases, or alanine aminotransferase and aspartate aminotransferase over 2·5×upper normal limit and bilirubin over 1·5×upper normal limit in the presence of liver metastases; or inadequate renal function (serum creatinine >1·25×upper normal limit). Previous treatment with COX-2 inhibitors or systematic use of aspirin were not reasons for exclusion. Aspirin treatment could be continued during the study.

Patients were randomly assigned to one of four treatment groups: patients randomised to group A received gemcitabine 1200 mg/m² in 30-min intravenous infusions on days 1 and 8, and intravenous cisplatin 80 mg/m² on day 1, every 21 days for six cycles; patients in group B received the same treatment as group A plus oral rofecoxib 50 mg per day until disease progression; patients in group C received PCI gemcitabine 1200 mg/m² over 120-minute infusions on days 1 and 8, and intravenous cisplatin 80 mg/m² on day 1, every 21 days for six cycles; patients in group D received the same treatment as group C plus oral rofecoxib 50 mg per day until disease progression. The study protocol advised that a proton pump inhibitor at standard doses be prescribed for patients receiving rofecoxib to prevent gastrotoxicity. Use of a proton pump inhibitor in the control group was at the investigator's discretion. The proton pump inhibitor could be any of the drugs registered in this class in Italy at standard dose (ie, omeprazole 20 mg/day, lansoprazole 30 mg/day, patoprazole 20–40 mg/day, or rabeprazole 20 mg/day).

Dose reductions of chemotherapy were not planned, but treatment could be delayed for up to 2 weeks when toxicity caused by previous cycles had not resolved completely. The prophylactic use of granulocyte-colony-stimulating factors (G-CSF) and erythropoietin was not allowed. The use of G-CSF (the protocol did not specify which G-CSF was to be used; filgrastim and lenograstim were available in Italy during the study and 5μg/kg/day of either were planned) was recommended for grade 4 neutropenia, even without fever. The use of epoetin alfa (10 000 IU/L three times a week) was allowed for anaemia according to its existing indication (haemoglobin ≤105 g/L). Second-line treatments were not prespecified, but were decided on a case-by-case basis by the treating investigator.

All assessments were planned to be the same across all treatment groups. Patients were assessed at baseline with a complete history and physical examination, routine haematology and biochemistry, electrocardiogram (ECG), chest radiography, and CT scan of the head, chest, and abdomen. Routine haematology, biochemistry, and physical examination were done every 3 weeks, before the administration of successive cycles; haematology was also repeated before administration of chemotherapy on day 8 of each cycle. Chest radiography, CT scans, and ECG were repeated after three and six cycles of chemotherapy. Clinical assessment and routine haematology and biochemistry were done every 2 months after the completion of chemotherapy. All examinations were done by investigators at each participating centre.

Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Response was measured by the use of the Response Evaluation Criteria In Solid Tumors (RECIST). Complete response was defined as the disappearance of all target and non-target tumours and no new tumours, as assessed by radiological tests; partial response was defined as a disappearance or a decrease of at least 30% in the sum of longest diameters of target tumours, combined with the disappearance or no change of non-target tumours; progression was defined as a 20% or greater increase in the sum of longest diameters of target tumours or as a clinically evident increase of non-target tumours or the appearance of a new tumour; all remaining cases were defined as stable disease. No central or independent verification of response was used. No central review of histology was done; histology was assessed according to common practice at each participating centre.

Quality of life was assessed using the European Organization for Research and Treatment (EORTC) QLQ-C30 questionnaire (version 3.0) and the lung cancer specific module (QLQ–LC13). Patients were asked to complete the questionnaires at baseline day 8 cycle 1 and at the end of the first three cycles. Additionally, pain was assessed by the use of a visual analogue scale at baseline and before each chemotherapy administration. Analgesic use was recorded for each patient from baseline through to the end of the first three cycles of chemotherapy.

Statistical analysis

Two comparisons were planned, combining the treatment groups two by two: first, when assessing the efficacy of PCI

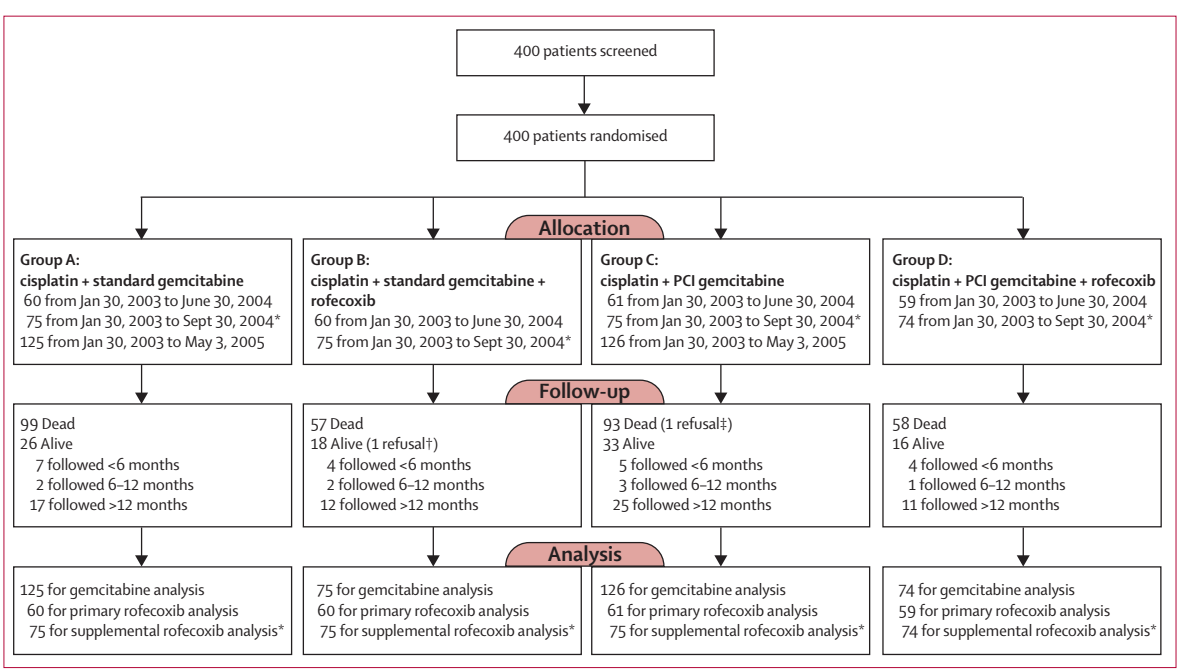

Figure 1: **Study flow according to Consort statement**
*Data reported in webappendix. †Patient was immediately lost to follow-up. ‡Patient received single-agent gemcitabine in standard 30-min infusion.
The three different values reported in the allocation section derive from rofecoxib withdrawal and choice made for statistical analyses (see text for explanation).

Variable	Group A: cisplatin + standard gemcitabine n=125	Group B: cisplatin + standard gemcitabine + rofecoxib n=75	Group C: cisplatin + PCI gemcitabine n=126	Group D: cisplatin + PCI gemcitabine + rofecoxib n=74
Median age, years (range)	59 (37–70)	61 (29–71)	59 (38 –69)	62 (38–70)
Performance status, n (%)				
0	63 (50)	38 (51)	65 (52)	36 (49)
1	62 (50)	37 (49)	61 (48)	38 (51)
Stage of disease, n (%)				
IIIb	13 (10)	10 (13)	15 (12)	11 (15)
IV	112 (90)	65 (87)	111 (88)	63 (85)
Sex, n (%)				
Men	98 (78)	63 (84)	104 (83)	57 (77)
Women	27 (22)	12 (16)	22 (17)	17 (23)
Histology, n (%)				
Squamous-cell carcinoma	28 (22)	25 (33)	25 (20)	22 (30)
Adenocarcinoma	64 (51)	33 (44)	70 (56)	35 (47)
Large-cell carcinoma	6 (5)	4 (5)	5 (4)	1 (1)
Mixed	2 (2)	4 (5)	3 (2)	2 (3)
Undefined	25 (20)	9 (12)	23 (18)	14 (19)
Size of centre, n (%)				
Large (>30 patients)	50 (40)	26 (35)	32 (25)	18 (24)
Medium (11–30 patients)	37 (30)	23 (31)	45 (36)	28 (38)
Small (1–10 patients)	38 (30)	26 (35)	49 (39)	28 (38)

Table 1: **Baseline characteristics of enrolled patients**

gemcitabine, groups A and B (standard gemcitabine) were compared with groups C and D (PCI gemcitabine); second, when assessing the efficacy of rofecoxib, groups A and C (no rofecoxib) were compared with groups B and D (plus rofecoxib). Accordingly, except for baseline values, results have been reported separately for the two comparisons.

The primary endpoint was overall survival defined as the time from the date of randomisation to the date of death from any cause, or the date of last follow-up for living patients. 400 patients and about 200 deaths were required for each comparison to have 80% power of detecting a 0·67 hazard ratio (HR) of death, with two-tailed significance level of 0·05 (East software). This would represent an increase in median overall survival from 8 months in the control groups (similar to that reported in comparable Italian patients enrolled in a previous trial by the same researchers[31]) to 12 months in the experimental groups (supported by a randomised phase II trial of PCI gemcitabine in NSCLC[11]). Patients were randomised to the four treatment groups through an automated straight minimisation procedure that used centre, performance status (0,1), and disease stage (IIIB, IV) as strata; randomisation was done centrally by phone or fax at the coordinating centre (National Cancer Institute, Naples, Italy). Secondary endpoints were progression-free survival (defined as the time from the date of randomisation to the date of progression of disease, date of death from any cause for patients who died without progression, or date of last follow-up for patients without progression and alive at the end of the study), response, quality of life, and toxicity.

All efficacy analyses were done on an intention-to-treat basis. Overall survival and progression-free survival curves were estimated with the Kaplan-Meier method, and tested with a two-sided log-rank test. HR and 95% CI were estimated by use of a Cox proportional hazards model that included treatment, gender, performance status (0, 1), disease stage (IIIb, IV), tumour histology (squamous, adenocarcinoma, other) and centre (three categories according to size: large, with more than 30 patients enrolled; medium, with 11–30 patients enrolled; small, with 1–10 patients enrolled) as covariates.

All enrolled patients were included in the assessment of response, including those who had no measurable tumours at baseline. Contingency tables and the χ^2 test without Yates' correction were applied. The response rate was defined as the number of complete plus partial responses divided by the total number of patients enrolled in each comparison group. An additional descriptive analysis of response limited to target tumours was decided retrospectively for the rofecoxib comparison, driven by the result of the primary response rate analysis.

All patients who received treatment were included in the toxicity analysis. Statistical analysis of toxicity was done in two ways: first, an exact linear permutation test was applied to acknowledge the ordinal nature of toxicity grades (Cytel 7 software); second, an exact χ^2 test was applied that compared severe (grades 3–5) versus not severe (grades 0–2) toxicity. Cardiac and vascular toxic events are usually reported as summary outcomes; however, because of the known toxic effects of rofecoxib, we decided retrospectively

Endpoint	Gemcitabine infusion rate				Rofecoxib			
	Standard (n=200)	PCI (n=200)	HR* (95% CI)	p	Without (n=121)	With (n=119)	HR* (95% CI)	p
Overall survival								
Events, n (%)	155 (78)	150 (75)	..	..	94 (78)	94 (79)	..	..
Median, weeks (95% CI)	44 (36–52)	47 (40–55)	0·93 (0·74–1·17)	0·41†; 0·52‡	44 (40–54)	44 (36–55)	1·00 (0·75–1·34)	0·85†; 1·00‡
6-month probability	0·69	0·76	..	..	0·70	0·73	..	..
1-year probability	0·41	0·45	..	..	0·40	0·42	..	..
Time-to-progression								
Events, n (%)	186 (93)	182 (91)	..	..	108 (89)	111 (93)	..	..
Median, weeks (95% CI)	22 (20–26)	23 (21–26)	0·97 (0·79–1·20)	0·65† 0·80‡	23 (20–30)	25 (22–29)	1·00 (0·76–1·31)	0·98† 1·00‡
6-month probability	0·43	0·42	..	..	0·43	0·47	..	..
1-year probability	0·15	0·12	..	..	0·15	0·14	..	..
Overall objective tumour response								
Responses , n (%)	67 (34)	57 (29)	..	0·28§	32 (26)	49 (41)	..	0·02§
95% CI	27–40	23–35	..	..	19–35	33–50	..	..
Description of tumour response, n (%)								
Complete response	3 (2)	2 (1)	..	..	0	2 (2)	..	..
Partial response	64 (32)	55 (28)	..	..	32 (26)	47 (39)	..	..
Stable disease	51 (26)	62 (31)	..	..	43 (36)	24 (20)	..	..
Progression	59 (30)	47 (24)	..	..	27 (22)	24 (20)	..	..
Not assessed	23 (12)	34 (17)	..	..	19 (16)	22 (18)	..	..

*HR of events for patients in the experimental groups, after adjustment by size of centre, sex, performance status, stage, histological type of tumour, and other treatment factors. †From unadjusted log-rank test. ‡From Cox model including size of centre, gender, performance status , stage, histological type of tumour, and other treatment factors as covariates. §From χ^2 test.

Table 2: **Efficacy outcomes**

to describe and analyse them both as summary outcomes and as specific items to give maximum information.

Quality-of-life data were analysed according to the recommendations of the EORTC QLQ-C30 Scoring Manual. Differences from baseline were calculated for all single items of the questionnaires, global quality-of-life scores, and pain visual analogue scales. Differences in quality-of-life between the treatment groups were compared by the use of the Wilcoxon rank sum test. No previous data on safety of the three innovative treatment combinations were available; therefore, an early analysis of safety, nested within the phase III trial, was planned for the three experimental groups (B, C, and D). The same Simon's optimum two-stage design was applied to each group with unacceptable toxicity as the endpoint: by setting the minimum acceptable proportion of patients with no unacceptable toxicity (p_0) equal to 0·55, the desirable proportion of patients with no unacceptable toxicity (p_0) equal to 0·75, and the error probabilities α and β both equal to 0·10, eight or more cases of unacceptable toxicity in the first 18 patients would have led to halting that treatment group. At the second stage, 41 patients per group were needed, and enrolment would have been stopped for any group with 15 or more cases of unacceptable toxicity. If the second stage was passed, enrolment would continue as planned for the phase III study. Unacceptable toxicity was defined as the occurrence within the first three cycles of any of the following: febrile neutropenia, grade 3–4 neutropenia with infection, any grade 4 anaemia, thrombocytopenia, vomiting, mucositis, diarrhoea, constipation, fatigue, or fever, any other grade 3–4 toxicity, any toxicity inducing a severe worsening of general condition that prevented restaging, or any toxicity that in the judgment of physicians induced early suspension of treatment for reasons other than progression.

Rofecoxib withdrawal

Enrolment into the study began on Jan 30, 2003. On Oct 1, 2004, rofecoxib was withdrawn by the US Food and Drug Administration, European Medicines Agency, and Italian Drug Agency. 299 patients had been randomised up to the date of rofecoxib withdrawal. The two groups that included rofecoxib were closed to further enrolment and the ongoing treatments with rofecoxib were stopped, although chemotherapy plans did not change for these patients. The study continued as planned for the two gemcitabine groups and the last patient was enrolled on May 3, 2005. Due to these changes in enrolment and ongoing treatment, we decided to include only the 240 patients who were enrolled up to June 30, 2004, in the statistical analyses of the rofecoxib groups to allow for data on at least 3 months of treatment with rofecoxib. This choice diminishes the power of the analyses, but decreases the risk of underestimating toxicity and the risk of diluting the possible therapeutic effect of rofecoxib. For the gemcitabine analyses, all randomised patients were considered, without any cut-off date. Patients recruited between Sept 30, 2004, and May 3, 2005, were included in the gemcitabine analyses only.

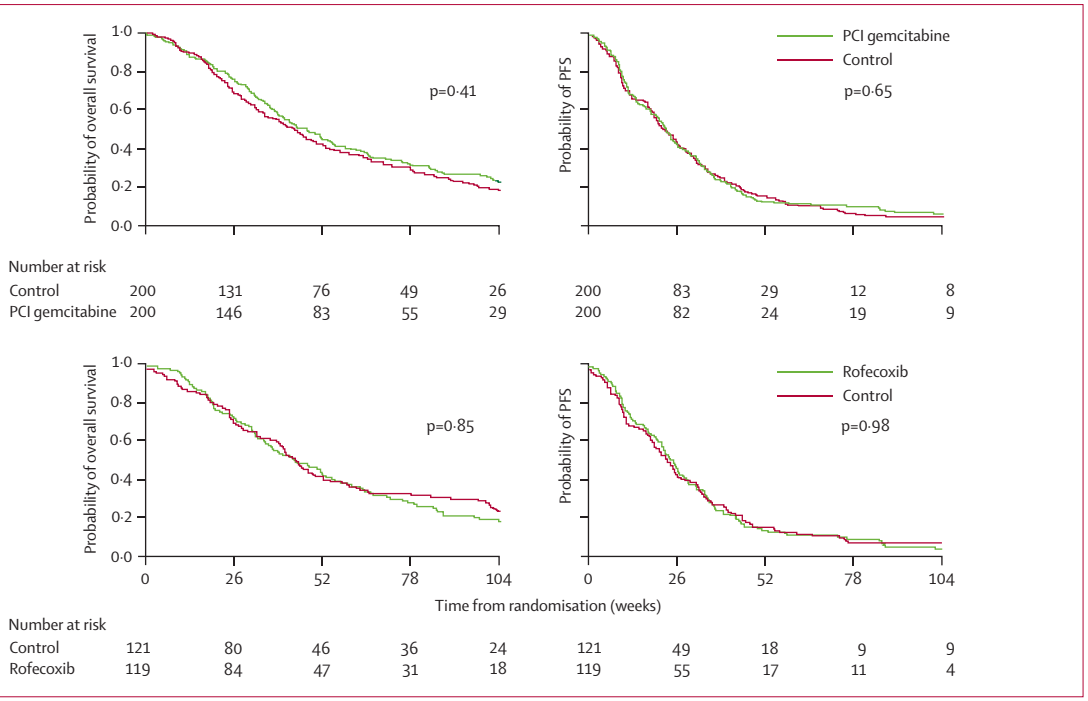

Figure 2: **Overall survival (left panels) and progression-free survival (PFS; right panels) for PCI gemcitabine versus standard gemcitabine (upper panels) and for rofecoxib versus non-rofecoxib (lower panels)**

A complete set of tables and figures reporting results of analyses done on data of all of the 299 patients enrolled up to Sept 30, 2004 is reported in the webappendix.

See Online for webappendix

Role of the funding source

The funding sources and the supplier of rofecoxib had no role in the study design, data collection, data analysis, data interpretation, or in the writing of this report. CGr, CGa, MDM, AM, and FP had full access to all the raw data. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Early safety analysis

The early phase II safety assessment was done according to the protocol plan, and passed the threshold for both stages. The total number of patients with unacceptable toxicity was under the threshold of 15 for all experimental groups. In group B, six patients had unacceptable toxicity consisting of febrile neutropenia (grade 3, one patient), dyspnoea (grade 4, one patient), non-neutropenic infection (grade 3, one patient), epigastralgia (grade 3, one patient), and neurological (grade 3, one patient) and renal (grade 3, one patient) toxic events. In group C, eight patients had unacceptable toxicity consisting of sudden death (grade 5, one patient), ototoxicity (grade 3, two patients), peripheral artherial ischaemia (grade 3, one patient), dyspnoea plus anorexia (both grade 3, one patient), renal (grade 1) and hepatic (grade 3, one patient) toxic effects, physician's decision to stop cisplatin (one patient), and worsening of general condition (one patient). In group D, five patients had unacceptable toxicity consisting of deep venous thrombosis with pulmonary embolism (grade 4, one patient), anaemia (grade 4, one patient), bleeding (grade 4) with consequent anaemia (grade 4) and ischaemic heart attack (grade 4, one patient), thrombocytopenia (grade 3 with mild bleeding, one patient), renal toxic effects (grade 2) with concomitant fatigue (grade 3, one patient).

Overall, 400 patients were randomised into the four groups (figure 1): 125 to group A (standard gemcitabine, cisplatin), 75 to group B (standard gemcitabine, cisplatin, rofecoxib), 126 to group C (PCI gemcitabine, cisplatin), and 74 to group D (PCI gemcitabine, cisplatin, rofecoxib). Two patients refused the assigned treatment after randomisation: one of these patients was assigned to group B and was lost to follow-up; the other was assigned to group C and received single-agent gemcitabine with standard 30-min infusion. Both these patients were removed from compliance and toxicity analyses, but were included in the analyses for the other outcomes according to the intention-to-treat strategy.

Baseline characteristics of all randomised patients were balanced across the four treatment groups (table 1). Median age of patients was 60 years (range 29–71). Performance status was evenly divided between 0 and 1. 351 of 400 (88%) patients had stage IV disease. The study included more than four times as many male patients as female patients. Adenocarcinoma was the most frequent histological cancer type and was recorded in 202 of 400 (51%) patients. 157 of

	Standard gemcitabine (n=199), n (%)						PCI gemcitabine (n=199), n (%)						p	
	0	1	2	3	4	5	0	1	2	3	4	5	WMW	Fisher
Allergy	195 (98)	1 (<1)	3 (2)	0	0	0	196 (98)	2 (1)	1 (<1)	0	0	0	0·65	..
Anaemia	89 (45)	56 (28)	38 (19)	14 (7)	2 (1)	0	91 (46)	35 (18)	48 (24)	21 (11)	4 (2)	0	0·36	0·19
Leucopenia	124 (62)	25 (13)	30 (15)	16 (8)	4 (2)	0	122 (61)	23 (12)	25 (13)	26 (13)	3 (2)	0	0·65	0·22
Neutropenia	106 (53)	17 (9)	29 (15)	35 (18)	12 (6)	0	96 (48)	17 (9)	24 (12)	40 (20)	22 (11)	0	0·14	0·12
Febrile neutropenia	195 (98)	..	..	3 (2)	0	1 (<1)	192 (96)	..	..	5 (3)	1 (<1)	1 (<1)	0·45	0·54
Neutropenic infection	197 (99)	0	1 (<1)	1 (<1)	0	0	194 (97)	0	2 (1)	3 (2)	0	0	0·36	0·62
Non-neutropenic infection	196 (98)	0	1 (<1)	2 (1)	0	0	194 (97)	1 (<1)	0	3 (2)	1 (<1)	0	0·49	0·69
Platelets	131 (66)	14 (7)	17 (9)	33 (17)	4 (2)	0	139 (70)	9 (5)	20 (10)	25 (13)	6 (3)	0	0·44	0·51
Haemorrhage	193 (97)	2 (1)	0	4 (2)	0	0	186 (93)	6 (3)	2 (1)	3 (2)	1 (<1)	1 (<1)	0·13	1·00
Heart rhythm	196 (98)	1 (<1)	2 (1)	0	0	0	198 (99)	1 (<1)	0	0	0	0	0·37	..
Supraventricular arrhythmia	197 (99)	0	2 (1)	0	0	0	199(100)	0	0	0	0	0	0·50	..
Sinus tachycardia	198 (99)	1 (<1)	0	0	..	..	198 (99)	1 (<1)	0	0	..	..	1·00	..
Heart general	186 (93)	0	2 (1)	2 (1)	6 (3)	3 (2)	184 (92)	0	1 (<1)	3 (2)	5 (3)	6 (3)	0·62	0·68
Cardiac ischaemia	196 (98)	0	1 (<1)	1 (<1)	1 (<1)	0	195 (98)	0	1 (<1)	1 (<1)	2 (1)	0	0·75	1·00
CNS ischaemia	195 (98)	..	..	1 (<1)	2 (1)	1 (<1)	197 (99)	..	..	0	1 (<1)	1 (<1)	0·65	0·69
Left ventricular function	199 (100)	..*	..*	0	0	0	198 (99)	..*	..*	1 (<1)	0	0	1·00	1·00
Peripheral arterial ischaemia	199 (100)	..	0	0	0	0	198 (99)	..	0	1 (<1)	0	0	1·00	1·00
Phlebitis (superficial)	198 (99)	..	1 (<1)	..	..	..	199(100)	..	0	..	..	..	1·00	..
Thrombosis or embolism	195 (98)	..	0	1 (<1)	3 (2)	0	195 (98)	..	0	0	2 (1)	2 (1)	0·80	1·00
Sudden death	197 (99)	..	..	..	..	2 (1)	196 (98)	..	..	..	..	3 (2)	..	1·00
Kidney	184 (92)	7 (4)	7 (4)	1 (<1)	0	0	190 (95)	5 (3)	2 (1)	1 (<1)	1 (<1)	0	0·22	1·00
Pulmonary	188 (94)	3 (2)	5 (3)	0	2 (1)	1 (<1)	190 (95)	4 (2)	2 (1)	2 (1)	0	1 (<1)	0·60	1·00
Fatigue	108 (54)	36 (18)	50 (25)	5 (3)	0	0	113 (57)	27 (14)	45 (23)	13 (7)	1 (<1)	0	0·95	0·06
Fever	187 (94)	8 (4)	3 (2)	1 (<1)	0	0	182 (91)	12 (6)	5 (3)	0	0	0	0·39	1·00
Weight loss	189 (95)	6 (3)	3 (2)	1 (<1)	0	0	187 (94)	11 (6)	1 (<1)	0	0	0	0·82	1·00
Hair loss	168 (84)	15 (8)	16 (8)	..	..	..	161 (81)	14 (7)	24 (12)	..	..	..	0·32	..
Skin	194 (97)	2 (1)	3 (2)	0	0	0	195 (98)	2 (1)	2 (1)	0	0	0	0·82	..
Anorexia	177 (89)	11 (6)	9 (5)	2 (1)	0	0	167 (84)	13 (7)	16 (8)	2 (1)	1 (<1)	0	0·13	1·00
Constipation	165 (83)	19 (10)	13 (7)	2 (1)	0	0	173 (87)	17 (9)	9 (5)	0	0	0	0·23	0·50
Diarrhoea	186 (93)	7 (4)	6 (3)	0	0	0	177 (89)	10 (5)	8 (4)	4 (2)	0	0	0·09	0·12
Nausea	109 (55)	36 (18)	51 (26)	3 (2)	0	0	90 (45)	53 (27)	47 (24)	7 (4)	2 (1)	0	0·12	0·14
Stomatitis	184 (92)	6 (3)	6 (3)	3 (2)	0	0	182 (91)	10 (5)	5 (3)	2 (1)	0	0	0·82	1·00
Vomiting	142 (71)	24 (12)	27 (14)	5 (3)	1 (<1)	0	123 (62)	22 (11)	45 (23)	8 (4)	1 (<1)	0	0·02	0·60
Liver	185 (93)	11 (6)	2 (1)	1 (<1)	0	0	181 (91)	11 (6)	5 (3)	2 (1)	0	0	0·41	1·00
Auditory	185 (93)	4 (2)	10 (5)	0	0	..	190 (95)	1 (<1)	6 (3)	2 (1)	0	..	0·38	0·50
Neurological	182 (91)	4 (2)	10 (5)	3 (2)	0	0	178 (89)	17 (9)	4 (2)	0	0	0	0·61	0·25
Other	179 (90)	7 (4)	10 (5)	3 (2)	0	0	183 (92)	9 (5)	6 (3)	1 (<1)	0	0	0·41	0·62
Toxic deaths	194 (97)	..	..	..	..	5 (3)	190 (95)	..	..	..	..	9 (5)	..	0·42

WMW=Wilcoxon Mann Witney exact test. Fisher=Fisher's exact test comparing grade 0–1–2 versus 3–4–5. LVEF=Left ventricular ejection fraction. *LVEF measurement was not planned in asymptomatic patients.

Table 3: **Worst degree of toxic events as defined by NCI-CTC according to gemcitabine groups**

301 (52%) patients for whom we have data received second-line chemotherapy, with large variation in the agent given (docetaxel, paclitaxel, vinorelbine, ifosfamide, carboplatin). In all comparisons, we did not note any statistically significant difference in the numbers of patients receiving second-line treatment.

Evaluation of PCI gemcitabine versus standard gemcitabine

Three patients assigned to PCI gemcitabine crossed to the standard-rate infusion because of toxicity, after one cycle (two patients) and two cycles (one patient). Overall, 831 cycles were initiated with standard and 823 cycles with PCI gemcitabine; gemcitabine treatment on day 8 was omitted in 108 (13%) standard cycles and 139 (17%) cycles with PCI gemcitabine. The median number of cycles administered was five (range 1–6) in both groups. 88 (44%) patients in the standard and 80 (40%) patients in the PCI gemcitabine groups completed six cycles. Treatment with cisplatin and gemcitabine was stopped for disease progression in 62 and 59 patients, for toxicity in 37 and 37 patients, for refusal in six and 12 patients, for death in five and eight patients, and

for protocol violation in one and three patients, in the standard and PCI gemcitabine groups, respectively.

All patients were included in efficacy analyses (table 2). At the time of analysis, with 22 months of median follow-up of alive patients (range 0–40), 305 (76%) patients had died and 368 patients (92%) had disease progression. Overall survival was not significantly different between treatment the groups (p=0·41, figure 2); median overall survival was 44 weeks (95% CI 36–52) with standard gemcitabine and 47 weeks (40–55) with PCI gemcitabine. At multivariate analysis, adjusted for gender, performance status, stage of disease, histotype, size of institution, and addition or not of rofecoxib, the HR of death for patients treated with PCI gemcitabine was 0·93 (0·74–1·17).

The median progression-free survival was 22 weeks (20–26) in the standard groups and 23 weeks (21–26) in the PCI gemcitabine groups (HR 0·97 [0·79–1·20], p=0·65; figure 2). The overall response rate, including complete and partial responders, was 34% (27–40) for the standard groups and 29% (23–35) for the PCI gemcitabine groups (p=0·28). There was no prognostic value of histology in any of the multivariate models applied.

Toxic effects are reported in table 3. Overall, there were 14 toxic deaths that were possibly treatment-related, five in the standard groups (one febrile neutropenia with septic shock, one stroke, one bronchial rupture, and two sudden deaths), and nine in the PCI gemcitabine groups (one febrile neutropenia with septic shock, one massive haemoptysis, one stroke, two pulmonary embolisms, one acute dyspnoea, and three sudden deaths; exact p=0·42).

No significant difference was noted in the occurrence and severity of all considered toxicities, with the exception of vomiting, which was more frequent and severe in the PCI gemcitabine groups; more severe fatigue (not statistically significant) was also found in the PCI gemcitabine groups.

371 (93%) patients completed the baseline quality-of-life assessments; compliance was similar in the two groups at baseline and at subsequent assessments during the treatment, and no statistical significant difference was recorded for compliance in these assessments (data not shown). Baseline mean scores were comparable between the two groups for all the items. Hair loss was the only item for which mean differences from baseline were significantly worse for patients assigned PCI gemcitabine (17, 27, and 27 points after one, two, and three cycles) than for those receiving standard gemcitabine (8, 19, 18 at the same timepoints), with p values of 0·002, 0·02, and 0·03 after one, two and three cycles, respectively.

Evaluation of the addition of refocoxib versus no rofecoxib

As reported above, analyses on rofecoxib are limited to patients enrolled up to June 30, 2004, (240 patients, 119 with and 121 without rofecoxib) to allow for at least 3 months of treatment with rofecoxib. However, a complete set of tables and figures reporting results of analyses done on data of all patients enrolled up to Sept 30, 2004, (299 patients) is reported in the webappendix. No remarkable differences are apparent between the two sets of analyses. Baseline characteristics of patients are balanced between the two groups of the comparison.

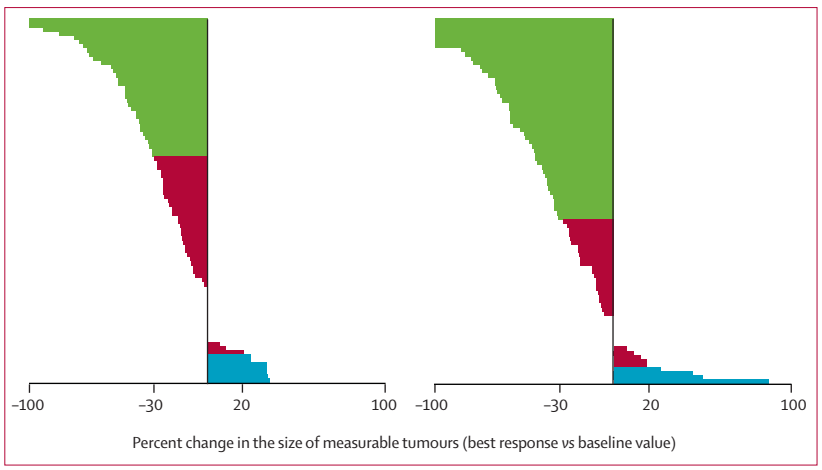

Figure 3: **Description of target tumour best response for rofecoxib (right) and non-rofecoxib (left) groups**
100% change represent a complete response. Green bars indicate objective responses (complete or partial); red bars indicate stable disease; blue bars indicate progressive disease. Plotted data refer to the best response ever recorded in each individual patient who had measurable tumours.

One patient (in group B) refused the assigned treatment after randomisation and was immediately lost to follow-up. Rofecoxib was administered to 118 patients (59 combined with standard chemotherapy and 59 combined with cisplatin plus PCI gemcitabine; figure 1) for a median time of 14 weeks (range 0–64 [95% CI 10–18]). 33 patients received more than 6 months of treatment and one patient received rofecoxib for more than 1 year (64 weeks).

Overall, 497 cycles of chemotherapy were initiated without rofecoxib and 494 cycles were started with rofecoxib; treatment with gemcitabine on day 8 was omitted in 80 (16%) and 67 (14%) cycles in the two groups, respectively. The median number of cycles administered was five (range 1–6) in both groups.

47 (39%) patients completed six cycles of chemotherapy in the groups without rofecoxib and 55 (46%) patients completed six cycles of chemotherapy in the groups with rofecoxib. Chemotherapy was stopped for disease progression in 37 and 27 patients, for toxicity in 25 and 27 patients, for refusal in five and eight patients, for death in six and one patients, and for protocol violation in one and one patient, in the groups without and with rofecoxib, respectively.

240 patients were included in the efficacy analyses (table 2). At the time of analysis, with 23 months median follow-up of alive patients (range 0–40), 188 (78%) had died and 219 patients (91%) had disease progression. Overall survival between treatment groups was not significantly different (p=0·85, figure 2), with median overall survival of 44 weeks in both groups (95% CI 40–54 for the control groups and 36–55 for the rofecoxib groups); in multivariate analysis, adjusted for gender,

	Without rofecoxib (n=120), n (%)						With rofecoxib (n=118), n (%)						P	
	0	1	2	3	4	5	0	1	2	3	4	5	WMW	Fisher
Allergy	117 (98)	2 (2)	1 (<1)	0	0	0	114 (97)	1 (<1)	3 (3)	0	0	0	0·55	..
Anaemia	51 (43)	29 (24)	26 (22)	12 (10)	2 (2)	0	54 (46)	27 (23)	26 (22)	9 (8)	2 (2)	0	0·59	0·67
Leucopenia	72 (60)	14 (12)	15 (13)	17 (14)	2 (2)	0	70 (59)	13 (11)	20 (17)	13 (11)	2 (2)	0	1·00	0·58
Neutropenia	62 (52)	10 (8)	15 (13)	18 (15)	15 (13)	0	55 (47)	7 (6)	20 (17)	25 (21)	11 (9)	0	0·52	0·67
Febrile nutropenia	117 (98)	..	..	2 (2)	0	1 (<1)	114 (97)	..	..	3 (3)	1 (<1)	0	0·68	0·72
Neutropenic infection	119 (99)	0	0	1 (<1)	0	0	115 (97)	0	1 (<1)	2 (2)	0	0	0·37	0·62
Non-neutropenic infection	118 (98)	0	0	2 (2)	0	0	117 (99)	0	0	1 (<1)	0	0	1·00	1·00
Platelets	82 (68)	6 (5)	11 (9)	17 (14)	4 (3)	0	80 (68)	8 (7)	9 (8)	19 (16)	2 (2)	0	1·00	1·00
Haemorrhage	115 (96)	2 (2)	0	3 (3)	0	0	110 (93)	3 (3)	0	4 (3)	1 (<1)	0	0·33	0·50
Heart rhythm	120 (100)	0	0	0	0	0	116 (98)	1 (<1)	1 (<1)	0	0	0	0·24	..
Supraventricular arrhythmia	120 (100)	0	0	0	0	0	117 (99)	0	1 (<1)	0	0	0	0·50	..
Sinus tachycardia	120 (100)	0	0	0	..	..	117 (99)	1 (<1)	0	0	..	..	0·50	..
Heart general	113 (94)	0	1 (<1)	1 (<1)	1 (<1)	4 (3)	108 (92)	0	0	2 (2)	7 (6)	1 (<1)	0·48	0·31
Cardiac ischaemia	120 (100)	0	0	0	0	0	114 (97)	0	0	1 (<1)	3 (3)	0	0·06	0·06
CNS ischaemia	120 (100)	..	..	0	0	0	117 (99)	..	..	0	1 (<1)	0	0·50	0·50
Left ventricular function	120 (100)	..*	..*	0	0	0	117 (99)	..*	..*	1 (<1)	0	0	0·50	0·50
Peripheral arterial ischaemia	119 (99)	..	0	1 (<1)	0	0	118 (100)	..	0	0	0	0	1·00	1·00
Phlebitis (superficial)	119 (99)	..	1 (<1)	..	..	..	118 (100)	..	0	..	..	..	1·00	..
Thrombosis or embolism	117 (98)	..	0	0	1 (<1)	2 (2)	115 (97)	..	0	0	3 (3)	0	1·00	1·00
Sudden death	118 (98)	..	..	..	..	2 (2)	117 (99)	..	..	..	..	1 (<1)	..	1·00
Kidney	110 (92)	5 (4)	3 (3)	1 (<1)	1 (<1)	0	105 (89)	7 (6)	5 (4)	1 (<1)	0	0	0·50	1·00
Pulmonary	116 (97)	0	2 (2)	1 (<1)	0	1 (<1)	108 (92)	4 (3)	4 (3)	0	2 (2)	0	0·12	1·00
Fatigue	58 (48)	22 (18)	32 (27)	7 (6)	1 (<1)	0	78 (66)	13 (11)	23 (19)	4 (3)	0	0	0·008	0·38
Fever	110 (92)	9 (8)	1 (<1)	0	0	0	116 (98)	2 (2)	0	0	0	0	0·03	..
Weight loss	109 (91)	9 (8)	1 (<1)	1 (<1)	0	0	116 (98)	2 (2)	0	0	0	0	0·02	1·00
Hair loss	102 (85)	8 (7)	10 (8)	..	..	..	99 (84)	5 (4)	14 (12)	..	..	..	0·75	..
Skin	117 (98)	0	3 (3)	0	0	0	115 (97)	1 (<1)	2 (2)	0	0	0	1·00	..
Anorexia	101 (84)	9 (8)	6 (5)	4 (3)	0	0	106 (90)	8 (7)	4 (3)	0	0	0	0·16	0·12
Constipation	93 (78)	13 (11)	12 (10)	2 (2)	0	0	105 (89)	12 (10)	1 (<1)	0	0	0	0·009	0·50
Diarrhoea	112 (93)	1 (<1)	7 (6)	0	0	0	100 (85)	11 (9)	6 (5)	1 (<1)	0	0	0·05	0·50
Nausea	62 (52)	23 (19)	31 (26)	4 (3)	0	0	60 (51)	28 (24)	28 (24)	1 (<1)	1 (<1)	0	0·82	0·68
Stomatitis	111 (93)	5 (4)	2 (2)	2 (2)	0	0	111 (94)	5 (4)	2 (2)	0	0	0	0·63	0·50
Vomiting	78 (65)	14 (12)	24 (20)	3 (3)	1 (<1)	0	78 (66)	15 (13)	21 (18)	4 (3)	0	0	0·81	1·00
Liver	109 (91)	7 (6)	3 (3)	1 (<1)	0	0	108 (92)	6 (5)	3 (3)	1 (<1)	0	0	0·93	1·00
Auditory	111 (93)	1 (<1)	6 (5)	2 (2)	0	..	112 (95)	3 (3)	3 (3)	0	0	..	0·39	0·50
Neurological	110 (92)	5 (4)	4 (3)	1 (<1)	0	0	107 (91)	7 (6)	3 (3)	1 (<1)	0	0	0·81	1·00
Other	109 (91)	3 (3)	7 (6)	1 (<1)	0	0	106 (90)	3 (3)	7 (6)	2 (2)	0	0	0·74	0·62
Toxic deaths	114 (95)	..	..	..	..	6 (5)	117 (99)	..	..	..	..	1 (<1)	..	0·12

WMW=Wilcoxon Mann Witney exact test. Fisher=Fisher's exact test comparing grade 0–1–2 versus 3–4–5. LVEF=left ventricular ejection fraction.*LVEF measurement was not planned in asymptomatic patients.

Table 4: **Worst degree of toxic events according to rofecoxib groups**

performance status, stage of disease, histotype, size of institution, and schedule of gemcitabine, the HR of death for patients assigned rofecoxib was 1·00 (0·75–1·34).

Median progression-free survival was 23 weeks (20–30) in the groups not asigned rofecoxib and 25 weeks (22–29) in the groups assigned rofecoxib (p=0·98, HR 1·00 [0·76–1·31]; figure 2). The overall response rate, including complete and partial responders, was 26% (19–35) for the groups not assigned rofecoxib and 41% (33–50) for the groups assigned rofecoxib; this difference was statistically significant using χ^2 test, with p=0·02. In figure 3, the percent change of the size of measurable tumours at the time of best response is reported in the two compared groups, without (left) and with rofecoxib (right). This graphical representation suggests that the positive effect of rofecoxib on response is not limited to a subgroup of patients. There was no prognostic value of histology in any of the multivariate models applied.

Table 4 shows toxic events. We noted seven toxic deaths that were possibly treatment-related, six in the standard

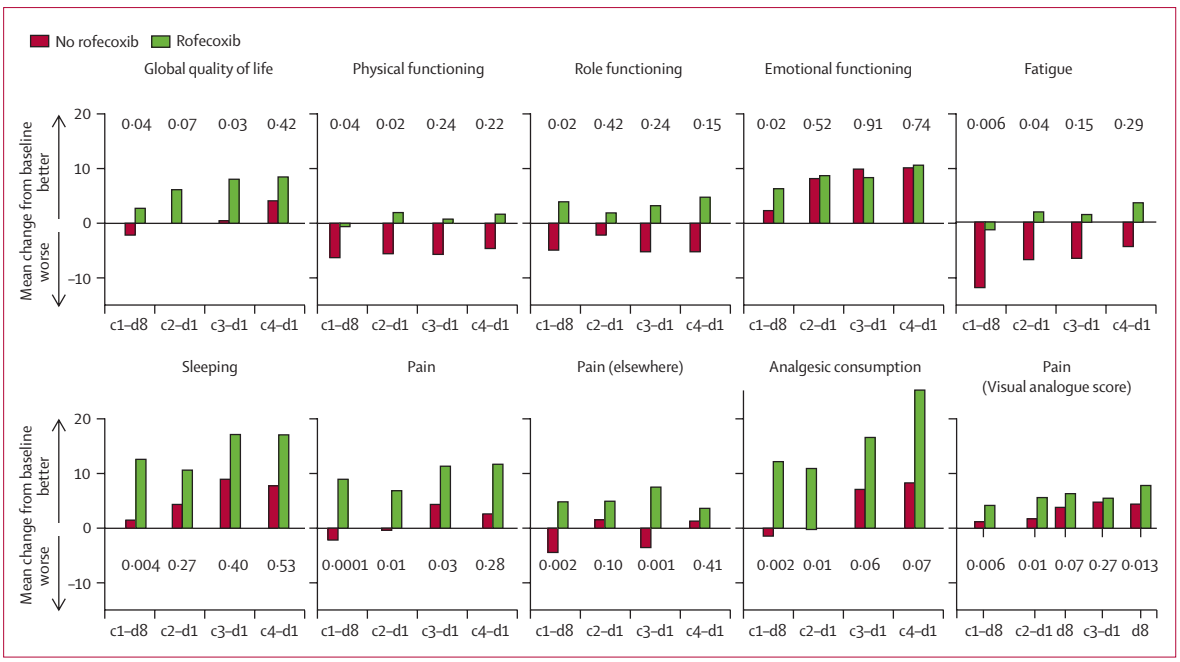

Figure 4: **Quality-of-life and pain analyses for rofecoxib versus non-rofecoxib groups**
Only items for which statistical test was significant in at least one timepoint are reported. Black numbers denote p values from the Wilcoxon rank sum tests. Improvement is indicated by positive changes. Please note that timing of pain assessment with the visual analogue score (box in right lower corner) is different from the EORTC questionnaires (all the other boxes). In the x-axis labels, c denotes cycle, and d indicates day.

groups and one in the rofecoxib groups (exact p=0·12). Patients given rofecoxib had a significantly higher incidence of diarrhoea, which was severe in one patient only, and had a much lower incidence of constipation than those not given rofecoxib. Additionally, patients given rofecoxib had significantly less fatigue, fever, and weight loss. For heart toxicity, summary measures (heart rhythm and heart general) did not show statistically significant differences. However, data scattered by subheadings of Common Toxicity Criteria showed a higher incidence of severe heart ischaemia (exact p=0·06). This comparison was statistically significant (p=0·03 at exact Wilcoxon-Mann-Whitney test and p=0·06 at exact Fisher test) in the analysis done on the dataset including patients randomised up to Sept 30, 2004, in which an additional patient developed ischaemia in the rofecoxib groups (webappendix tables).

221 patients (92%) completed the baseline quality-of-life assessments with no statistical difference in compliance between the two groups at baseline and at subsequent assessments during the treatment (data not shown). Baseline mean scores were not statistically different between the two groups for all the items, except for haemoptysis (p=0·03; data not shown). The most striking differences between groups in changes from baseline were reported in items that studied pain and use of analgesics, which all favoured the rofecoxib group. Less evident, but frequently significant differences were seen for global quality of life, physical, emotional and role functioning, sleeping, and fatigue, again all favouring the rofecoxib groups (figure 4). Some of the changes in quality of life reported above were not more significant in the dataset that included patients randomised up to Sept 30, 2004 (webappendix figure 2).

Discussion

The current study was based on a factorial design with two questions, one regarding the efficacy of a prolonged constant infusion of gemcitabine compared with standard 30-min infusion and the other regarding the effect of adding rofecoxib to chemotherapy with cisplatin and gemcitabine. For both questions, results were negative because a survival difference was not noted in either. The study was not planned to test efficacy interactions in the experimental factors. Overall, because this—to our knowledge—was the first randomised trial with the combination of COX-2 inhibitors and chemotherapy in advanced NSCLC, the trial design was done with an overoptimistic hypothesis (ie, a 0·67 HR of death in the experimental groups) and statistical power might be not sufficient to detect smaller effects.

PCI gemcitabine had previously been proposed as a way to improve the efficacy of this drug in a phase II trial in patients with pancreatic cancer, which showed interesting response and survival.[10] To the best of our knowledge, our study is the first phase III trial to test this hypothesis. Some other trials, also in patients with NSCLC, have been done without a control group or in the framework of a randomised phase II design, not allowing a formal comparison.[11] Therefore, we believe that the results from

our analyses are sufficient to deny the hypothesis that prolonging the infusion time of gemcitabine can produce clinically relevant changes in efficacy in NSCLC.

A notable amount of preclinical and non-experimental research have been published on the possibility that COX-2-inhibiting drugs could be effective in the treatment of cancer. A clinical response of 65% has been reported in a neoadjuvant phase II study,[32] which used the addition of another selective COX-2 inhibitor, celecoxib, to preoperative paclitaxel and carboplatin in 29 patients with stage IB to IIIA NSCLC. In another study, positive results in terms of response (24%, 95% CI 14–37) and 1-year survival (42%) were also reported with the combination of celecoxib and weekly paclitaxel as second-line treatment for NSCLC.[33] In both of these studies, toxicity was apparently not worsened by the addition of celecoxib. Similar data were reported with celecoxib in combination with docetaxel.[34,35] By contrast, celecoxib did not seem to enhance efficacy or improve patient-reported symptoms in a randomised phase II trial[36] when combined with docetaxel and irinotecan or gemcitabine and irinotecan in the second-line treatment of NSCLC. However, that study was not sufficiently powered to detect statistical differences between the regimens tested.

The interest in testing the efficacy of COX-2 inhibitors in advanced cancer was clearly diminished when cardiovascular toxicity was reported in various large trials of chemoprevention.[37–39] In particular, the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial (NCT00282386),[39] which was designed to assess the hypothesis that 3 years of treatment with rofecoxib would decrease the risk of recurrent adenomatous polyps in patients with a history of colorectal adenomas, showed that the use of rofecoxib was associated with an increased risk of confirmed thrombotic events—mainly myocardial infarctions and ischaemic cerebrovascular events. The increased relative risk became apparent after 18 months of treatment.[39] Rofecoxib was consequently withdrawn by the manufacturer and leading drug agencies around the world. Obviously, this finding affected the GECO study, and the enrolment of patients in the rofecoxib groups was halted. Consequently, the final sample for the analysis of the effect of rofecoxib was lower than planned; however, thanks to a longer follow-up, the actual numbers of events were close to the planned numbers needed for the final analysis and statistical power was only slightly decreased to 79%. Unfortunately, prolongation of survival, the primary endpoint, was not reached. However, analyses of secondary endpoints, ie, quality of life, toxicity and response, deserve some comment. Quality-of-life analysis showed a general pattern favouring the addition of rofecoxib, although we should emphasise that some positive changes are dimensionally small and possibly under the thresholds that have been proposed for a difference to be clinically meaningful.[40] Clearly, such positive effects are led by a better control of pain that, reasonably, positively affected global quality of life, physical and role functioning, and fatigue. We have previously shown that pain strongly correlates with global quality of life and functioning scales.[41] Whether the positive effect on pain is simply due to the anti-inflammatory and analgesic effects of rofecoxib or can pertain ultimately to some antineoplastic activity cannot be derived from this analysis. Treatment of pain is often inadequate at the beginning of treatment of lung cancer with chemotherapy, and the use of rofecoxib might have counteracted undertreatment.[41] A weakness of quality-of-life analysis that should be acknowledged is a trial design that did not include a placebo-controlled group. However, this decision was consistent with the fact that survival was chosen as primary endpoint and a placebo was not strictly needed to assess this endpoint. Additionally, the non-profit nature of our trial made the inclusion of placebo groups a complex issue.

Because of cardiovascular events reported in the APPROVe trial,[39] toxicity analysis was especially challenging. The APPROVe trial was run in a completely different context to our trial—ie, a chronic versus a fatal condition. Given the shorter survival of patients with advanced NSCLC, we could presume that our current study would have a very low chance of similar toxicities. But the patients with advanced NSCLC have several concomitant risk factors for cardiovascular morbidity, such as age and cigarette smoking; furthermore, the dose used in our study, which was based on previous reports,[27,28] was double compared with that used in the APPROVe trial.[39] To provide the most toxicity information available, we decided retrospectively not to limit analyses to summary measures (eg, heart general, according to Common Toxicity Criteria) that are commonly applied in cancer trials to report toxicity. Clearly the final analyses can be biased because of the multiple testing of events that are ultimately related, and because of small numbers, which can only be counteracted partially by the application of exact statistical tests. Our data confirm that a slight increase in the risk of ischaemic damage to the heart can be caused by the addition of rofecoxib. Although this did not translate into a significant increment of toxic deaths (which were paradoxically more frequent in the control groups), future studies on COX-2 inhibitors in this population of patients should be done with analogues that are less cardiotoxic than rofecoxib. Furthermore, new information, such as better activity of COX-2 inhibitors in heavy smokers—taking into account that cigarette smoking induces COX-2 overexpression—should be considered.[42]

Our analysis of response suggests that further studies should be done. The current paradigm in clinical research on solid tumours is that whenever a significant decrease of tumour mass occurs it can be attributed to the treatment effect. Therefore, even acknowledging that response is a soft endpoint and its value in advanced NSCLC is limited, our results are the strongest available evidence of an antineoplastic activity of a COX-2-inhibiting drug, to the best of our knowledge. Our finding, however, has some weaknesses. First, the study was not placebo-controlled

and investigators were aware of the assigned treatment; second, objective responses were not monitored independently and the response evaluation is based on measures given tumour-by-tumour by the investigators themselves; third, we did not succeed in collecting a sufficient number of tumour samples to do correlative studies and could not test whether the expression of COX-2 was correlated with chance of response. Accepting that the noted difference is true, we can attempt some interpretation. The analysis of the target tumour response does strongly support the hypothesis that the effect of rofecoxib on tumour size is not limited to a small subgroup of patients (as could be expected for a target-based drug acting through a target that is present in a minority of patients), rather, this effect is shared by all the patients. Such behaviour might be the consequence of a drug that acts in a non-specific way, for example, strengthening the cytotoxic activity of the other associated drugs, or through a target that is almost ubiquitous. Unsurprisingly, the difference in response does not translate into a survival advantage in this study. Johnson and colleagues[43] have recently shown, in an elegant review of 191 trials of lung cancer treatment, that the threshold value in the absolute difference of response that is needed to actually translate into a survival difference is about 30% in a trial the size of the current one.

Our study shows that the prolonged and constant infusion of gemcitabine is not more effective than standard infusion in 30 min, and we believe that further studies on this point are not recommended. Similarly, the addition of rofecoxib to chemotherapy did not improve survival. However, for the latter issue, provocative results of secondary analyses suggest that further trials on the value of COX-2-inhibiting drugs in the treatment of solid tumours should be considered, possibly with drugs that are less cardiotoxic than rofecoxib. By reviewing established trial registries (http://clinicaltrials.gov, accessed May 2, 2007) many clinical trials seem to be ongoing that investigate the role of celecoxib in different tumours (NSCLC, prostate, breast, colorectal, head and neck cancer, sarcomas, brain tumours), as neoadjuvant, adjuvant or metastatic treatment, in combination with chemotherapy, hormone treatment, radiotherapy, or target-based agents. The results of these studies should better define the role of COX-2 inhibitors in the treatment of solid tumours.

Contributors

CGr, CGa, MDM, and FP designed and planned the trial. MDM, AM, and FP coordinated the trial. CGa, MDM, AM, and FP analysed the data. CGr, CGa, FC, MDM, AM, and FP wrote the report. CGr, AC, VB, TG, FC, FC, AF, BD, DG, SB, FR, PM, AR, FC, and AT enrolled the patients, collected data, and revised the manuscript.

Conflicts of interest

CGr is a consultant for, and has received honoraria from, Eli Lilly, the manufacturer of gemcitabine. All other authors declared no conflicts of interest.

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