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Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: A double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group

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ABSTRACT

Background: Increased expression of cyclooxygenase-2 (COX-2) is common in non-small cell lung cancer (NSCLC) and has been associated with poor prognosis. Experimental and clinical phase II trials have indicated that the addition of the COX-2 inhibitor celecoxib to palliative chemotherapy might increase survival time in patients with advanced NSCLC.
Methods: We performed a double-blind, placebo-controlled multicentre phase III trial at 13 centres in Sweden. Three hundred and nineteen patients with advanced NSCLC stage IIIB–IV and performance status 0–2 were randomised to receive celecoxib 400 mg b.i.d. or placebo in addition to palliative chemotherapy. The primary objective was to compare overall survival. Other end-points were quality of life, progression-free survival, toxicity, cardiovascular events and biological markers.
The trial is registered with ClinicalTrials.gov, No. NCT00300729.
Findings: Three hundred and sixteen patients were included in the analysis, 158 in each treatment group. Median survival time was 8.5 months. There was no survival difference

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between the treatment arms. Small but not statistically significant differences in global quality of life and pain were seen favouring the celecoxib group. No increased incidence of cardiovascular events was observed in the celecoxib group.

Interpretation: This study failed to demonstrate a survival benefit of the addition of celecoxib to palliative chemotherapy.

1. Introduction

Lung cancer is the leading cause of death from cancer in Europe with an estimated 342,000 deaths (19.9% of total cancer-related deaths) in 2008.[1] The majority of patients has advanced non-small cell lung cancer (NSCLC) in stage IIIB or IV at diagnosis and is treated with palliative intent.[2] Median survival time for patients with advanced NSCLC in performance status 0–2 receiving palliative first-line chemotherapy is 6–10 months.[3–6] New treatment strategies are urgently needed.

There is growing evidence for a link between cancer and inflammation.[7,8] Inflammation in the tumour microenvironment has tumour-promoting effects.[8] The presence of a systemic inflammatory response in patients with inoperable lung cancer seems to be associated with poorer quality of life and shorter survival.[9–11] One target currently studied in the treatment of lung cancer is cyclooxygenase-2 (COX-2), an enzyme expressed in inflammatory and neoplastic tissue.[12,13] COX-2 is reported to interfere with angiogenesis, apoptosis and tumour invasiveness.[13] Increased expression of COX-2 has been found in lung cancer[12,14,15] and has been associated with worse prognosis.[15,16] Preclinical studies have shown that COX-2 inhibitors inhibit the growth of human lung cancer cells as single agents as well as in combination with chemotherapy.[12,17] Clinical phase II studies suggested that a combination of the selective COX-2 inhibitor celecoxib with chemotherapy might have a better effect in NSCLC than chemotherapy alone.[18,19]

These and other observations supported the concept of a clinical trial in order to explore the effects of celecoxib in patients with advanced NSCLC. The aim of the present study was to investigate if the addition of celecoxib to first-line palliative chemotherapy would prolong survival in patients with advanced NSCLC. Further objectives were the effects of celecoxib on quality of life, progression-free survival, toxicity, cardiovascular events, and biological markers.

2. Patients and methods

2.1. Trial design

We performed a multicentre, double-blind, placebo-controlled phase III trial to investigate if addition of celecoxib improves survival in patients with advanced NSCLC treated with palliative first-line chemotherapy. The study protocol was developed by a study committee on behalf of the Swedish Lung Cancer Study Group and approved by the Regional Ethics Committee in Linköping and the Medical Products Agency of Sweden. Thirteen centres in Sweden, seven of which are university hospitals, participated in the study.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before randomisation.

2.2. Patients

Patients with cytologically or histologically confirmed NSCLC stage IIIB or IV, age $\geqslant$18 years, WHO performance status (PS) of 0–2 and whose planned treatment was first-line palliative chemotherapy were eligible. No upper age limit was defined. A white blood cell (WBC) count $\geqslant 3.0 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l, bilirubin <1.5 URL (upper reference limit), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <3× URL (×5 in case of liver metastases) and creatinine clearance (usually calculated by the Cockcroft–Gault formula) $\geqslant$40 ml/min were required.

Exclusion criteria were treatment with NSAID other than acetylsalicylic acid at a daily dose of 50–100 mg, hypersensitivity to NSAID or sulphonamides, serious heart or liver disease, active gastrointestinal ulcer, ongoing gastrointestinal bleeding or inflammatory bowel disease, pregnancy or breast-feeding. All patients had to complete the baseline QoL questionnaire before randomisation.

2.3. Treatments

Patients were randomised to celecoxib 400 mg b.i.d. or placebo. Celecoxib or matching placebo capsules were taken from the first day of chemotherapy for a maximum of 1 year. Treatment with celecoxib/placebo was stopped earlier in case of progression, unacceptable toxicity related to the study drug that could not be ameliorated by supportive treatment or if the patient wished to stop.

Chemotherapy with four cycles of a combination of a platinum compound (carboplatin or cisplatin) and a third-generation drug (primarily gemcitabine or vinorelbine) was recommended. The chemotherapy regimen at each centre was chosen according to the local standard and elective use of non-platinum two-drug combinations or single-drug chemotherapy as well as prolongation of chemotherapy were allowed. Each centre should use the same regimen throughout the study. Guidelines for dose modifications were given in the protocol.

2.4. Treatment allocation and allocation concealment mechanism

Patients were randomised according to the minimisation method as described by Pocock and Simon.[20] The variables

incorporated into the scheme were tumour stage (IIIB versus IV), PS (0–1 versus 2) and institution. The *p*-value was 1.0.

The allocation sequence was generated at the data centre, Oncology Centre, Sahlgrenska University Hospital, Gothenburg, Sweden. The Hospital Pharmacy at the University Hospital Lund, Sweden, was responsible for distribution of the study drug. Trial staff at the data centre, the study committee, the treating staff at the centres and the patients were blinded to the allocation.

2.5. Study end-points

The primary end-point was overall survival. Further end-points were quality of life (QoL), progression-free survival (PFS), toxicity, cardiovascular events and biomarkers (vascular endothelial growth factor (VEGF) and proteomics).

2.6. Baseline investigations

A physical examination, blood analyses (full blood count, sodium, potassium, calcium, albumin, AST, ALT, bilirubin, lactate dehydrogenase, albumin, creatinine and CRP) as well as a chest radiograph were required.

Demographic and clinical data (age, gender, weight, tumour type, disease stage, performance status, smoking status, history of cardiovascular and thromboembolic disease and current use of acetylsalicylic acid before randomisation) were registered.

2.7. Assessments

During concomitant treatment with the study drug and chemotherapy, patients were followed up with a physical examination, blood analyses as detailed at baseline and registration of weight before the administration of each cycle, and 3 weeks after completed first-line chemotherapy. Peripheral blood counts were repeated on days 8 and 15 of each cycle. A chest radiograph was taken at 6 and 12 weeks.

After first-line chemotherapy during treatment with the study drug, clinical assessments (physical examination, chest radiograph, weight, blood analyses) were scheduled every 8 weeks. Patients were followed up within the study for 1 year from randomisation. Second- and third-line treatments as well as radiotherapy were recorded. Beyond 1 year, the interval for follow-up examinations was determined by the treating physician.

2.7.1. Disease response and progression

CT scan of the thorax and the upper abdomen was normally part of the initial evaluation and was repeated at the discretion of the responsible physician. Chest radiographs were performed regularly as stated above. After completed first-line chemotherapy, an evaluation of tumour response and subsequent progression was made by the local physician according to RECIST 1.0.[21] There was no independent radiological review.

2.7.2. Toxicity and cardiovascular events

Toxicities were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.[22]

2.7.3. Quality of life

QoL was evaluated by the European Organization for Research and Treatment of Cancer (EORTC) Core Quality-of-Life Questionnaire C30 (QLQ-C30) version 3[23] and the complementary lung cancer specific module QLQ-LC13.[24] In the present study, dyspnoea, fatigue, pain, pain medication and global QoL were regarded as outcome measures of primary interest.

Questionnaires were completed by all patients prior to randomisation (baseline) and in association with scheduled study visits at 3, 6, 9, 12, 20, 28, and 36 weeks.

2.7.4. Biological parameters

Blood samples for analysis of biomarkers were taken at four university hospitals (Gothenburg, Linköping, Lund, and Uppsala) before treatment and at 6, 12 and 20 weeks. The results of these analyses will be reported separately.

2.8. Statistical analysis

All analyses were performed without knowledge about the randomisation code. The balance of demographic and clinical variables between the groups was tested by Fisher's exact test.

2.8.1. Efficacy

Overall survival (OS) was measured from the date of randomisation to death from any cause. Deaths until 15th September 2010 were included in the analysis. The follow-up time was defined as the time from the date for randomisation until the last observation on 15th September 2010. The study was designed to detect an increase in median survival from 7.5 to 9.5 months. With a type I error of 5% and a power of 80% (two-sided test), 760 patients were required, 380 in each treatment group. The time for inclusion of patients was calculated to be 3 years.

The Kaplan–Meier method was used to plot survival curves. Stratified Cox-regression was used to estimate hazard ratios (HR) and assess differences between the treatment groups. PFS was measured from randomisation to documented progression or death in cases where no progression was reported.

The intention-to-treat principle was applied in all analyses.

2.8.2. Toxicity

Regarding chemotherapy-related haematological side-effects, the maximum toxicity ever experienced during treatment was taken into account. Cardiac, vascular and gastric toxicities are reported as summary outcomes.

2.8.3. Quality of life

Four different approaches were used: (1) group comparisons of scale scores at each time point, (2) score changes from baseline, (3) area under the curve (AUC) and (4) rates of symptom palliation defined as improvement, control or prevention, death counted as non-palliation.[25]

Improvement of symptoms was defined as a change in reported baseline symptom levels from moderate or severe (67–100 points) to none or little (0–33 points),[26] or from little to no symptoms without subsequent deterioration by the time of group comparison. Control of symptoms was defined

as stable symptom levels between 1 and 33 points. Prevention of symptoms was assumed when the patients did not report symptoms during the study period.

Here, QoL results up to 20 weeks will be reported, with group comparisons at 12 and 20 weeks being considered to be of primary interest. Non-parametric tests were used for group comparisons. Group differences that were consistent across methods of analysis or detected with a p-value of 0.01 or less were interpreted as probable treatment effects.

2.8.4. *Ancillary analyses*

These analyses were not prespecified in the protocol but were planned and performed prior to unblinding of treatment. Exploratory comparisons of the treatment groups were performed to generate new hypotheses, not to reach definitive conclusions. OS was analysed according to chemotherapy regimen, smoking status, stage and gender. The log-rank test was used to compare survival.

Statistical analysis was performed using the software package Stata version 11.1.

3. Results

3.1. *Patients*

Between May 2003 and May 2006, 319 patients were enrolled. In accordance with the original time schedule, inclusion of patients was discontinued after 3 years, although the stipulated number of patients was not reached. Statistical analysis of the primary outcome is based on 316 patients (Fig. 1).

The celecoxib and placebo groups were well balanced with regard to baseline characteristics (Table 1). Concurrent medication with ASA 50–100 mg was reported in 28 and 22 cases, respectively. Treatment with chemo- and radiotherapy is displayed in Table 2. Four patients did not receive any chemotherapy.

The median time of study medication was 4.0 months (95% CI 2.7–4.9) for patients receiving celecoxib, and 4.5 months (95% CI 3.6–5.1) in the placebo group ($p = 0.5$). Twelve patients were excluded from this analysis due to lack of information on the last dose of the study drug.

3.2. *Efficacy*

At the time of analysis, 287 patients (90%) had died. The median follow-up time was 36 months (range, 16–52 months). The median survival time was 8.5 months. Fig. 2 shows OS and PFS by study treatment. There was no significant difference in OS between the two treatment groups (celecoxib: 8.9, 95% CI 7.3–10.9 months versus placebo: 7.9 months, 95% CI 7.2–10.0). The HR for OS was 1.00 (95% CI 0.79–1.26, $p = 0.97$). Median progression-free survival was 6.1 months for patients receiving celecoxib and 6.5 months for the placebo group and the HR was 1.01 (95% CI 0.77–1.33, $p = 0.94$).

The overall response rate (complete and partial responses) was 36% with celecoxib and 31% with placebo ($p = 0.4$). The proportion of patients with stable disease was 42% and 43%, respectively.

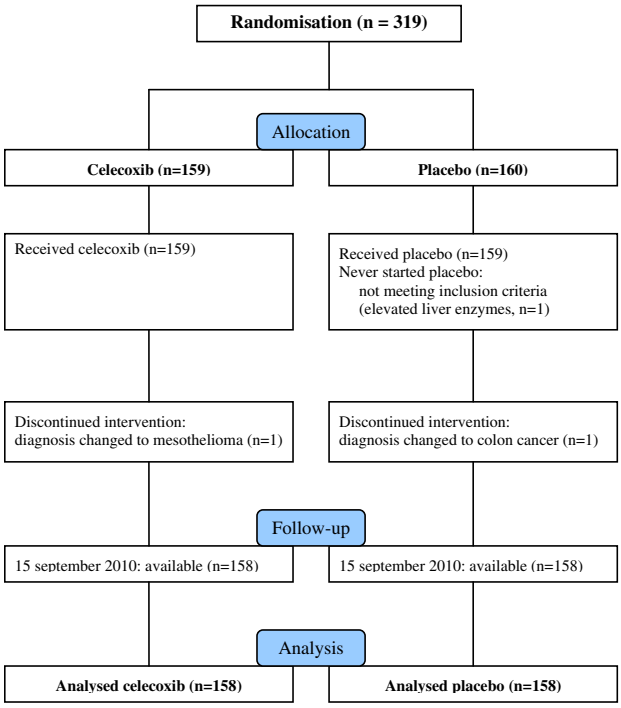

Fig. 1 – Patient flow according to CONSORT statement.

3.3. *Ancillary analyses*

Survival curves for patients receiving carboplatin + vinorelbine or carboplatin + gemcitabine were virtually identical. OS was better for current non-smokers (former smokers + never-smokers) than for current smokers (median survival 9.0 versus 7.9 months, $p = 0.02$). Similarly, survival was superior in patients with stage IIIB disease, with a median survival time of 10.7 months, compared with 7.9 months in stage IV ($p = 0.04$).

OS was superior in women, with a median survival time of 10.3 months (95% CI 7.5–11.3) compared with 7.7 months in men (95% CI 7.0–8.8, $p = 0.04$).

The effect of celecoxib/placebo on survival was also analysed by gender. In women, survival was shorter with placebo than with celecoxib (HR 1.16, 95% CI 0.83–1.62, median survival 7.4 versus 11.3 months; Fig. 3A), while the opposite was seen in men (HR 0.79, 95% CI 0.57–1.09, median survival 8.8 versus 6.4 months; Fig. 3B). In neither subgroup analysis the survival difference reached statistical significance ($p = 0.39$ and $p = 0.14$, respectively).

3.4. *Quality of life*

Compliance with QoL assessments (completed/planned assessments, missing questionnaires due to deaths excluded) during the first 20 weeks of the study was on average 80% in both study groups, ranging between 93% at baseline and 72–79% during follow-up. The numbers of completed QoL questionnaires and mean scores for global QoL and selected symptoms are shown in Table 3. There were no significant score differences between the two treatment arms in any of the measures, neither at baseline nor during follow-up (all p-values above 0.05). Also, AUC from baseline to 20 weeks

Table 1 – Patient characteristics (n = 316).

	Celecoxib (n = 158)		Placebo (n = 158)	
	No.	%	No.	%
Gender				
Male	73	46	87	55
Female	85	54	71	45
Age in years, median (range)	66 (38–85)		65 (37–85)	
Performance status				
0	30	19	30	19
1	87	55	94	59
2	41	26	34	22
Tumour type				
Adenocarcinoma	77	49	94	59
Squamous cell carcinoma	38	24	27	17
Large cell carcinoma	11	7	17	11
Other or not further classified	32	20	19	12
Stage				
IIIB	37	23	38	24
IV	121	77	120	76
Smoking status[a]				
Current smoker	65	41	58	37
Former smoker	77	49	84	53
Never-smoker	16	10	16	10
History of cardiovascular disease				
Yes	35	22	30	19
No	123	78	128	81
History of venous thromboembolism				
Yes	15	10	8	5
No	143	91	149	94
Missing data	0	0	1	1

[a] Current smoker: a person who smoked every week or who had stopped smoking within the last 12 months. Former smoker: a person who had stopped smoking ≥12 months prior to the start of the treatment.

follow-up was similar across the treatment groups (data not shown).

Mean score changes from baseline to 3, 6, 9, 12 and 20 weeks are shown in Fig. 4A–D. Global QoL score changes suggested an improvement over time in favour of the celecoxib arm, but the group differences were not significant (Fig. 4A). Changes in pain scores over time suggested a decrease of pain in the overall study population (Fig. 4B). Pain score changes were in favour of the celecoxib group at all points of time, with borderline statistical significance at 3 weeks ($p = 0.049$). Dyspnoea score changes indicated a symptom improvement in the overall study population up to 9 weeks (Fig. 4C), but no significant group differences were seen. The mean scores for fatigue increased at all time points during follow-up, indicating deterioration in the study population, but no significant differences were seen across the two treatment groups (Fig. 4D).

Palliation rates for pain, dyspnoea and fatigue are displayed in Fig. 5A–C. The best palliation was seen in the pain scores, with palliation rates of around 65% at 6 weeks in both treatment groups. No significant group differences were seen with regard to palliation rates for any of the selected symptoms.

3.5. *Toxicity*

Haematological toxicity is displayed in Table 4. A higher frequency of grade 3–4 leukopenia was observed in the celecoxib group.

The frequency of cardiovascular events is shown in Table 5. The incidence of gastrointestinal ulcers was low with one event in the celecoxib group (grade 4) and three events in the placebo group (one patient of grade 2 and two patients of grade 3). The total number of cardiovascular and gastric events was low and no statistical calculations were performed.

The number of patients in whom serious adverse events (SAE) were reported was similar in both groups with 54 patients in the celecoxib group and 56 patients in the placebo group.

4. Discussion

The addition of celecoxib to first-line chemotherapy in patients with advanced NSCLC did not improve overall or progression-free survival in this trial. QoL analyses showed a pattern of changes favouring the celecoxib group, but the

Table 2 – Treatment with chemo- and radiotherapy.

	Celecoxib (n = 158)		Placebo (n = 158)	
	No.	%	No.	%
First-line chemotherapy				
Carboplatin + gemcitabine	66	42	65	41
Carboplatin + vinorelbine	90	57	89	56
Other two-drug regimen	1	1	1	1
No. of cycles				
0	1	1	3	2
1	16	10	16	10
2	15	9	13	8
3	14	9	12	8
4 or more	112	71	114	72
Second-line chemotherapy	72	46	81	51
Erlotinib	18	11	17	11
Pemetrexed	38	24	45	28
Docetaxel	12	8	9	6
Other	4	3	9	6
Third-line chemotherapy	30	19	35	22
Erlotinib	22	14	23	15
Pemetrexed	3	2	5	3
Docetaxel	1	1	2	1
Other	4	3	5	3
Radiotherapy	72	46	60	38

differences across the study groups were small and statistically not significant.

A limitation of the study is the number of patients actually included. Of the stipulated 760 patients, only 319 patients had been included when the trial was closed. The study was organised to complete recruitment within 3 years, in order to permit subsequent studies in the same patient group. With the current or a slightly lower inclusion rate, a further 4–5 years would have been required to complete the trial. Fear for cardiovascular side-effects of celecoxib may have made investigators more reluctant to include patients. Our data did, however, not show any significant increase of cardiovascular toxicity. With the current number of patients, the power of the study decreased to 47%. QoL analyses suggested small differences in favour of celecoxib, and with a larger number of patients, a more reliable answer to the question if celecoxib affects QoL could have been given.

There are currently two other published phase III studies on the effect of COX-2 inhibitors in patients with advanced NSCLC receiving palliative chemotherapy. In an open-labelled phase III trial with a 2×2 factorial design, Gridelli et al. studied the effect of rofecoxib and of prolonged constant infusion of gemcitabine in patients with advanced NSCLC, PS 0–1 and age <70 years (GECO study).[27] The rofecoxib groups were closed early due to the withdrawal of the study drug and the statistical analysis was limited to 240 patients. Rofecoxib did not prolong OS or PFS but did improve the overall response rate. Furthermore, treatment with rofecoxib was associated with improved QoL parameters, including global QoL and pain-related items. Interpretation of the results is difficult: (1) there were two main end-points: the effect of rofecoxib and the effect of prolonged infusion with gemcitabine on survival, (2) the two treatment groups with rofecoxib

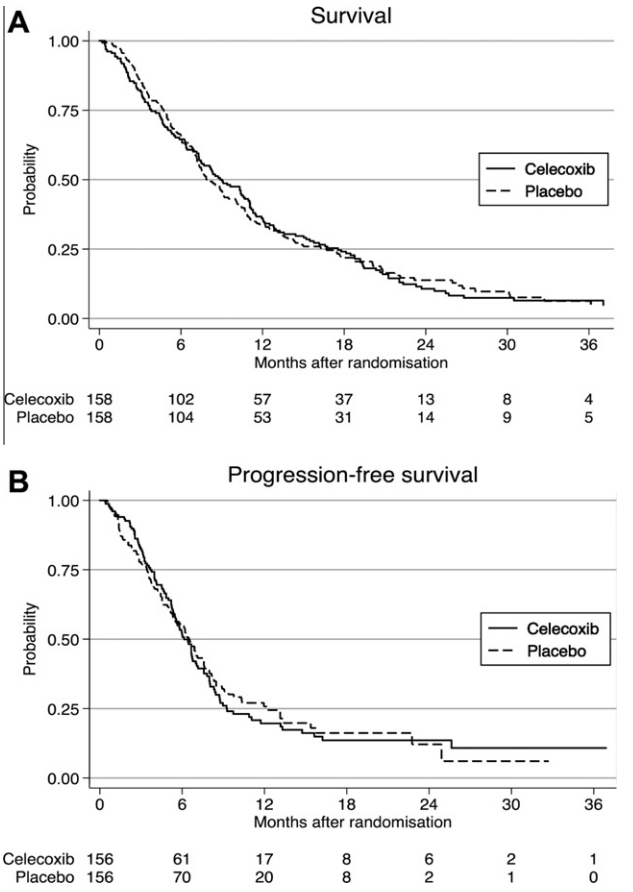

Fig. 2 – (A) Overall survival and (B) progression-free survival according to treatment arms (n = 316).

were closed early which resulted in an imbalance between the groups, and (3) the study was not placebo-controlled.

A randomised placebo-controlled Dutch phase III study of docetaxel/carboplatin with celecoxib 400 mg b.i.d. in patients with advanced NSCLC was presented at the 2009 American Society of Clinical Oncology (ASCO) meeting.[28] Five hundred and sixty-one patients were randomised, 281 to celecoxib and 280 to placebo. Overall and progression-free survival were 8.3 and 5.5 months, respectively, with no differences between the arms. The overall response rate in evaluable patients was higher with celecoxib (p = 0.05).

Our results confirm the results of the Dutch study which did not show any survival benefit of adding celecoxib in patients with advanced NSCLC to palliative chemotherapy. In contrast to our study, response rate was improved in patients who were treated with a COX-2 inhibitor in both Gridelli's and Groen's trials. We could not find any significant differences in QoL. However, a pattern of changes in some of the same items as in Gridelli's study – global QoL and pain – favouring celecoxib was found. No quality of life data were presented in the Dutch study.

We found a higher incidence of grade 3–4 leukopenia in the patients treated with celecoxib, compared to placebo (59 versus 39 patients, respectively, p = 0.02). Altorki et al. observed grade 3 or 4 neutropenia in 18 of 29 patients (62%) with NSCLC who were preoperatively treated with a combination of celecoxib 400 mg × 2 and paclitaxel/carboplatin.[18] An

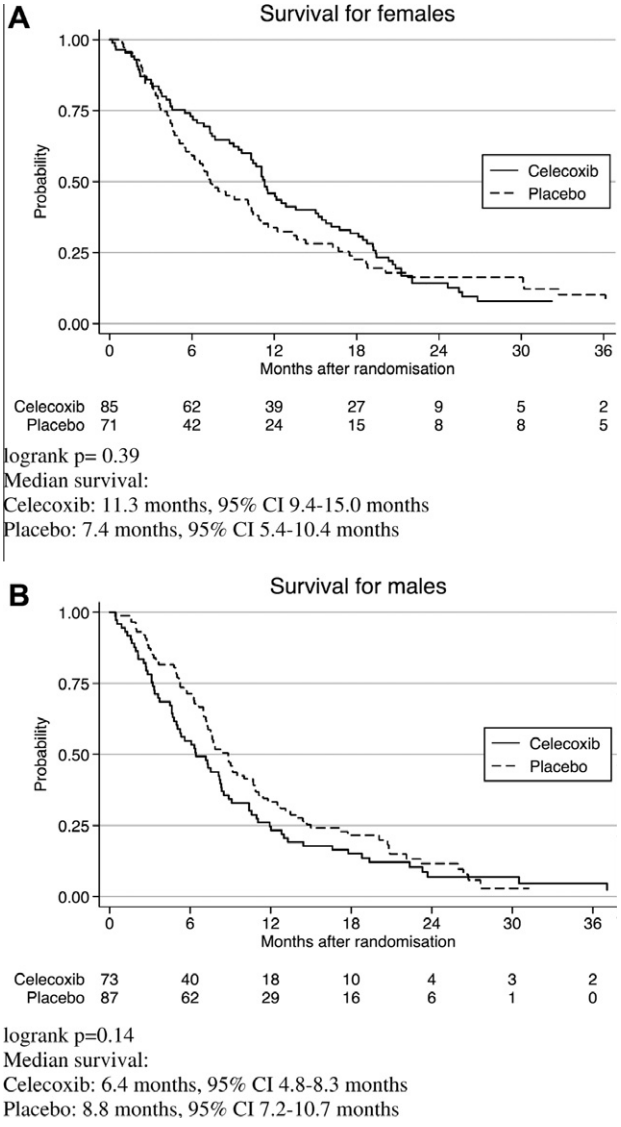

Fig. 3 – Kaplan–Meier survival curves for females (A) and males (B) according to treatment with celecoxib and placebo.

experimental study suggested that COX-2 might play a role in the recovery of the bone marrow after chemotherapy,[29] which could be a possible explanation for a higher frequency of leukopenia. However, no similar observation was made in any of the other randomised trials and it is not possible to draw any definitive conclusions about the clinical importance of this finding.

A comparison of the three randomised trials should be performed with some caution. Rofecoxib and celecoxib differ in their ability to selectively inhibit COX-2 and different chemotherapy regimens were used in the three trials. We did not stipulate a specific type of chemotherapy as there were two different regimens (gemcitabine + carboplatin and vinorelbine + carboplatin) mainly used in Sweden. No survival differences were seen when we compared the two regimens. Nevertheless, neither of the studies showed any survival benefit of adding COX-2 inhibitors to palliative chemotherapy in patients with advanced NSCLC. The pattern of QoL differences in the present study, although not statistically significant, suggested a potential benefit with celecoxib in the same dimensions as in the Italian study (i.e. global QoL, fatigue, and pain).

Recent data suggest that COX-2 expression might have predictive value for treatment with celecoxib. In a three-armed randomised phase II trial comprising 134 patients, subgroup analyses suggested that patients who did not express COX-2 had worse outcome when treated with celecoxib.[16] If so, this could explain the negative results in studies where both COX-2 positive and negative patients are treated. In the present study, a retrospective analysis of COX-2 expression in existing histopathological material has been initiated, but is feasible only in a limited number of patients. Evaluation and quantification of COX-2 expression, however, are challenging.[30] Furthermore, recent data suggest that anticarcinogenic effects of celecoxib are also mediated by COX-2-independent mechanisms.[31,32]

In conclusion, the addition of celecoxib to chemotherapy did not prolong survival in patients with advanced NSCLC in this trial. A small, but statistically insignificant improvement of some QoL parameters was found in the celecoxib group.

Principal investigators

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Table 3 – Mean scores for primary quality of life (QoL) outcome dimensions at 0, 3, 6, 9, 12 and 20 weeks by treatment group (C = celecoxib, P = placebo).

	0 weeks		3 weeks		6 weeks		9 weeks		12 weeks		20 weeks	
	C	P	C	P	C	P	C	P	C	P	C	P
No. of questionnaires	146	147	119	124	114	119	100	111	98	103	81	80
Global QoL	55	57	58	55	57	55	58	56	59	55	57	57
Pain	28	26	22	28	22	24	18	23	21	20	23	31
Pain medication[a]	52	53	60	55	49	53	42	52	51	54	45	58
Fatigue	42	41	45	46	43	44	41	43	41	40	42	44
Dyspnoea (QLQ-C30)	46	40	45	39	46	39	39	38	42	40	40	41
Dyspnoea (QLQ-LC13)	32	29	32	29	32	29	30	31	30	29	30	30

All scale ranges are from 0 to 100. For global QoL, a higher score indicates better QoL, while for the symptom measures, a higher score indicates more pronounced symptoms.

[a] Per cent of patients taking pain medication.

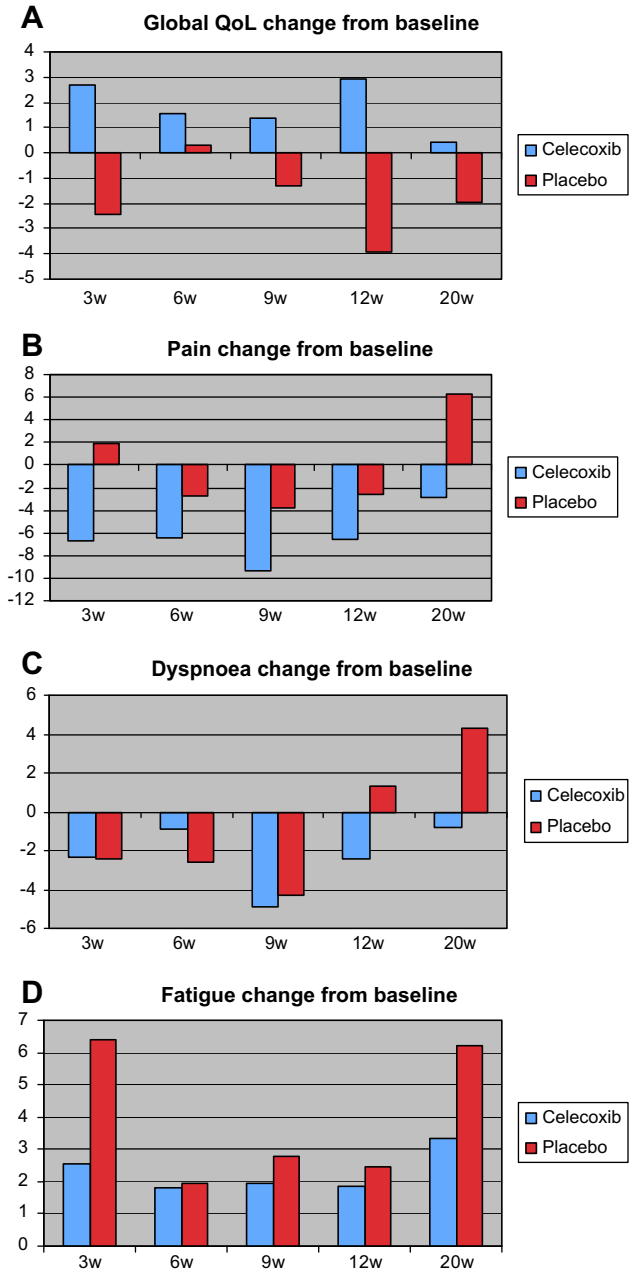

Fig. 4 – Mean score changes from baseline to follow-up points at 3, 6, 9, 12 and 20 weeks for (A) global QoL, (B) pain, (C) dyspnoea and (D) fatigue. For global QoL score, changes >0 indicate improvement, while for symptom scores, changes >0 indicate deterioration.

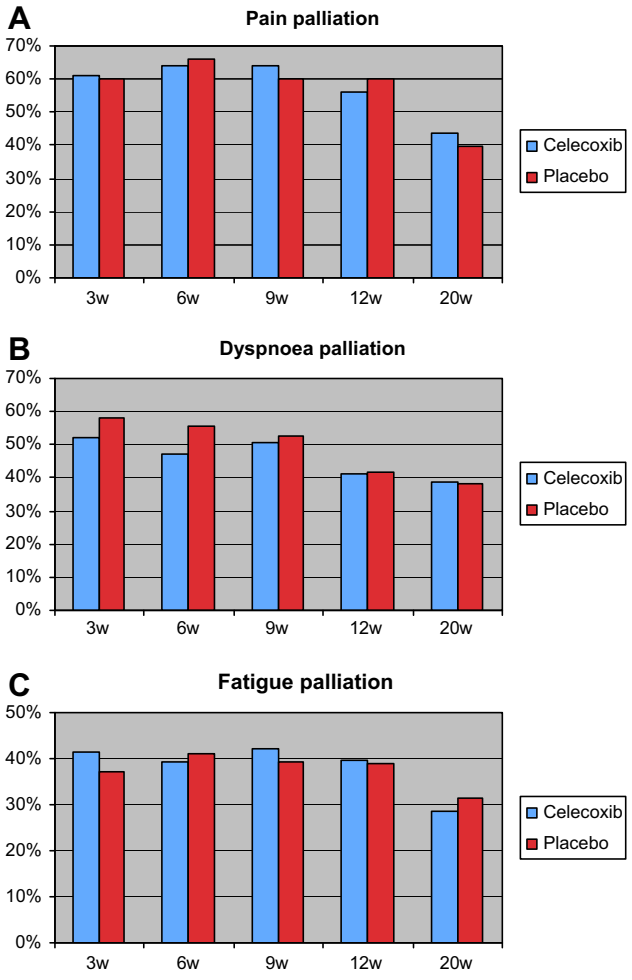

Fig. 5 – Palliation rates in (A) pain, (B) dyspnoea and (C) fatigue.

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Table 4 – Haematological toxicity. Number of patients in each treatment arm experiencing toxicity by worst Common Terminology Criteria for Adverse Events (CTCAE) grade. Four patients did not receive any chemotherapy.

Adverse event	Celecoxib (n = 157)		Placebo (n = 155)		p-Value, Fisher's exact test
Grade	0–2	3 + 4	0–2	3 + 4	
Haemoglobin	152	5	153	2	0.45
Leukocytes	98	59	116	39	0.02
Platelets	120	37	127	28	0.27

Table 5 – Cardiovascular events. Number of patients in each treatment arm experiencing events by worst Common Terminology Criteria for Adverse Events (CTCAE) grade.

Adverse event	Celecoxib (n = 158)		Placebo (n = 158)	
Grade	3 + 4	5	3 + 4	5
Cardiac ischaemia/infarction	2	0	0	1
Thrombosis/thrombus/embolism	17	0	12	0
Cerebrovascular ischaemia	4	0	1	0

Role of the funding sources

The funding sources and supplier of celecoxib/placebo had no role in the study design, collection of data, data analysis, data interpretation, or in the writing of this article. A.K., S.S. and E.H. had full access to all the raw data. The corresponding author had full access to all the data and had the final responsibility for the decision to submit the report for publication.

Contributors

A.K., S.S., B.B. and C.S. designed and planned the trial and wrote the study protocol.

A.K. and S.S. coordinated the trial.

A.K., S.S., B.B. and E.H. analysed the data.

A.K., S.S., B.B. and E.H. wrote the report.

B.B., L.E., J.K., K.L., C.S., S.O.Y. and S.S. enrolled patients, collected data and revised the manuscript.

All authors had full access to the final version of the report and agreed to the submission.

Conflict of interest statement

None declared.

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