available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984)

B. Biesma[a,], C. Manegold[b], H.J.M. Smit[c], L. Willems[d], C. Legrand[e], A. Passioukov[e], J.P. van Meerbeeck[f], G. Giaccone[g], for the EORTC Lung Cancer Group*

[a]*Afdeling Longziekten, Jeroen Bosch Ziekenhuis, Nieuwstraat 34, 5211 NL 's-Hertogenbosch, The Netherlands*
[b]*Thoraxklinik Heidelberg, Germany (previously at Heidelberg University Medical Centre, Mannheim, Germany)*
[c]*Rijnstate Ziekenhuis, Arnhem, The Netherlands*
[d]*Leiden University Medical Centre, Leiden, The Netherlands*
[e]*EORTC Data Centre, Brussels, Belgium*
[f]*Universitair Ziekenhuis Gent, Belgium (previously at Erasmus University Medical Centre, Rotterdam, The Netherlands)*
[g]*Vrije Universiteit Medical Centre, Amsterdam, The Netherlands*

ARTICLE INFO

Article history:
Received 6 January 2006
Accepted 25 January 2006
Available online 8 June 2006

Keywords:
Stage IIIA non-small cell lung cancer
Induction chemotherapy
Docetaxel-cisplatin

ABSTRACT

The objective of this phase II study was to document activity and toxicity of docetaxel and cisplatin as induction chemotherapy in patients with stage IIIA N2 non-small cell lung cancer (NSCLC) before definitive local treatment. Forty-six chemotherapy-naïve patients (median age 60 years) were included. Treatment consisted of 3 cycles of docetaxel (85 mg/m^2 on day 1), followed by cisplatin (40 mg/m^2/day on days 1 and 2) every 21 days. Grade 3–4 leukopenia and neutropenia occurred in 45.7% and 65.2% of the patients, respectively. Among 8 cases of febrile neutropenia (17.4%), one (2.2%) resulted in early death. Common grade 3–4 non-haematological toxicities were nausea (17.4%) and vomiting (13%). Eighty-five percent of the patients received three courses; six stopped prematurely due to toxicity, one due to protocol violation. Response rate was the primary endpoint of this study. Considering eligible patients (n = 40), 18 responses (1 complete and 17 partial responses) were observed (response rate 45%; 95% Confidence interval (CI): 29.3%–61.5%). In stage IIIA-N2 NSCLC patients, docetaxel-cisplatin could be administered and demonstrated manageable toxicity with modest efficacy.

1. Introduction

Patients with stage IIIA N2 non-small cell lung cancer (NSCLC) have a 5-year survival rate of less than 15% when treated with only surgery or radical radiotherapy. These poor results are mainly due to the occurrence of distant metastases which occur in many cases shortly after initial treatment.[1] Interest in combined-modality treatment was generated when a 1995

* *Corresponding author*: Tel.: +31 73 6992615; fax: +31 73 6992614.
E-mail address: b.biesma@jbz.nl (B. Biesma).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.01.049

meta-analysis demonstrated improved survival in stage III patients if radical radiotherapy was combined with chemotherapy.[2] Results of several recent trials have supported the use of combination therapy in this subset of patients. In particular the practice of chemotherapy administration prior to radical treatment has become a standard of care following the publication of two small phase III studies.[3,4] This approach of neo-adjuvant chemotherapy is based on several considerations: chemotherapy may shrink the loco-regional macroscopic disease, making it more amenable to surgery, radiotherapy or both and at the same time chemotherapy may prevent development of distant metastases or eradicate micro-metastases.[5] Both the combination of chemotherapy followed by surgery[3,4,6] and the combination of chemotherapy followed by radiotherapy[7] have demonstrated superior survival compared to surgery or radiotherapy alone. However, data from a more recent French phase III randomised study using neo-adjuvant chemotherapy in stage IB-IIIA patients did not demonstrate superior survival in the stage IIIA subset of patients, although a significant reduction in the development of distant metastases was observed in the chemotherapy group.[8] This study provided evidence that newer, more effective drug combinations are required to further improve survival rates in this patient population.

The use of the so called third generation chemotherapeutic drugs (gemcitabine, paclitaxel, vinorelbine, docetaxel) in combination with platinum drugs in stage IIIb/IV NSCLC has resulted in an (albeit small) increase in response rates (RR) and median survival (MS).[9] Subsequently these two-drug combinations have become subject of investigation in combined modality treatment.[10,11]

As a single agent, docetaxel has demonstrated anti-tumour activity both in first-line[12,13] and second-line[14,15] treatment of NSCLC. Docetaxel has also demonstrated efficacy as a (neo)adjuvant drug in combination with surgery or chemoradiotherapy.[16,17] Platinum-based combination chemotherapy is recommended as a standard of care in good performance status patients with advanced NSCLC.[9] Docetaxel-cisplatin regimens have demonstrated to be amongst the most effective in this patient group, as demonstrated in several phase III trials.[18–20] Furthermore, preliminary data from a Swiss study by Dr Betticher and colleagues with docetaxel-cisplatin combination chemotherapy showed a promising response rate in patients with stage IIIA NSCLC.[21]

As a consequence of these findings, the European Organization for the Research and Treatment of Cancer Lung Cancer Group (EORTC-LCG) initiated a phase II trial to define the activity and safety of the docetaxel-cisplatin combination as an induction regimen for patients with stage IIIA N2 NSCLC. This trial was the third and last of a series of phase II studies using new chemotherapy combinations within the setting of a recently finished randomised phase III trial in patients with stage IIIA N2 disease (EORTC 08941). Results of the two other phase II trials conducted by the LCG were published earlier. In the EORTC 08955 and 08958 studies, gemcitabine-cisplatin and carboplatin-paclitaxel were tested as induction regimens, respectively.[11,10] In the EORTC 08941 trial, patients responding to chemotherapy were randomised between surgery and radical radiotherapy in order to define the optimal definitive local treatment.

2. Patients and methods

2.1. Objectives

The primary objective of this phase II trial was to assess the antitumour activity of docetaxel combined with cisplatin administered as an induction regimen to chemo-naive patients with stage IIIA N2 NSCLC. The secondary objective was to further establish the safety profile of docetaxel-cisplatin as an induction regimen in this patient group.

2.2. Patient selection

Main eligibility criteria for patients entering the study included the following: stage IIIA NSCLC with biopsy proven positive N2 nodes, age > 18 years, World Health Organization (WHO) performance status $\leqslant 2$, adequate baseline organ function defined as an absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, renal and liver function within normal limits. Presence of at least one target lesion that could be accurately measured in at least one dimension as $\geqslant$20 mm with conventional techniques or as $\geqslant$10 mm with spiral CT-scan was requested. Patients had to be considered mentally and physically fit to receive docetaxel-cisplatin chemotherapy, and to undergo a lobectomy or pneumonectomy or radiotherapy following chemotherapy. Patients who had previous therapy for NSCLC, or presence of active infection were excluded, along with patients with pleural or pericardial effusion, superior vena cava syndrome and pre-existing motor or sensory neurotoxicity $\geqslant$ grade 2 National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC).

The study was approved by the EORTC Protocol Review Committee (PRC) and by the ethics committees of the participating centres. All patients gave written informed consent prior to registration.

2.3. Treatment plan

Patients were scheduled to receive 3 courses of chemotherapy every 21 days unless progression of disease or unacceptable toxicity was recorded or patients refused further treatment. Based on the preliminary results of the study conducted by Dr Betticher and colleagues, docetaxel 85 mg/m^2 was administered as a 1-hour intravenous (i.v.) infusion on day 1 and cisplatin 40 mg/m^2 was administered as a 30-minute i.v. infusion on days 1 (directly following docetaxel) and 2.[21] Dexamethasone (or equivalent) at a dose of 8 mg bid was given orally the day prior to chemotherapy (day −1) and the day of chemotherapy (day 1). A $5HT_3$ antagonist was given on days 1–3; the dose and administration route was conducted in accordance with local policy. Adequate hydration was also given according to local practice.

Neither dose reduction or escalation for docetaxel was allowed. The protocol predefined that, if necessary, the next chemotherapy cycle should be postponed until ANC $\geqslant 1.5 \times 10^9$/L and platelet count $\geqslant 100 \times 10^9$/L, liver functions returned to normal as well as creatinine and creatinine clearance $\geqslant$50 ml/min. If febrile neutropenia (FNP) occurred during a cycle, prophylactic use of growth factors was allowed

during the next cycles. If grade 2 neurotoxicity (tinnitus) was observed, treatment was continued with docetaxel alone (no further administration of cisplatin was allowed). Mucositis and diarrhoea had to be fully recovered (grade < 1) before the next cycle. If grade 2 or higher mucositis and diarrhoea occurred during a cycle despite prophylactic treatment, patients were removed from the study. All other toxicities, except for alopecia, occurring during a cycle had to recover to grade $\leqslant 1$ before the next chemotherapy cycle was administered. If a new cycle was delayed for greater than 2 weeks, the patient discontinued from the study.

2.4. Patient evaluation

A complete history, physical examination, complete blood cell count with differential, serum biochemistry, spirometry, bronchoscopy, chest X-ray, computer tomography (CT) of the chest and upper abdomen, bone scan and ECG were obtained at baseline. Patients were monitored throughout treatment by recording history, toxic events, and complete blood cell counts with differential (weekly). Serum chemistry determinations were repeated prior to start of each chemotherapy cycle. All toxicities were coded according to the NCIC-CTC.

Tumour response was evaluated by CT-scan after three cycles of treatment. CT examinations were reviewed by the principal investigator. Subsequently, CT-scans of all reported responders were reviewed by a panel of two independent radiologists. Response was evaluated according to RECIST criteria[22] however confirmation of response after a minimum of 4 weeks was not available: the fact that responding patients were randomised for surgery or radiotherapy precluded a formal 4-week confirmation of response to chemotherapy according to RECIST criteria. The patients with responsive disease, if judged resectable by the local surgeon and multidisciplinary team, were proposed to undergo further randomisation to receive either surgery or radical radiotherapy as part of the EORTC 08941 trial. Repeated mediastinoscopy/tomy was not required in the post-chemotherapy evaluation.

2.5. Statistical considerations

This study was designed according to the Simon one sample two-stage testing procedure.[23] The primary endpoint was response rate and the objective of this study was to select this induction regimen for further study if the results were consistent with a true response rate of 75% or more and to reject it if results were consistent with a true response rate of 55% or less. The type I error was set to 20%, while the power was set to 95%. Under those hypotheses, the total sample size for this trial was 40 evaluable patients. The trial, however, would be discontinued after 24 patients according to the following rule: a first test was to be performed when the first 24 patients were evaluated for response: if $\leqslant 10$ responses were observed, the trial would be stopped with the conclusion that this regimen should not be further investigated. In all other cases accrual would continue until 40 patients were evaluable for response. A second test then would be performed amongst those 40 patients: if $\leqslant 24$ responses were observed, the conclusion would be that the drug combination should not be further investigated. If >24 responses were observed, we would conclude that the drug combination warranted further investigation. Although not foreseen as a secondary endpoint by the protocol, overall survival was measured from the date of registration to the date of death or last follow-up examination and was estimated using the Kaplan-Meier method based on all patients who started protocol treatment.[24]

3. Results

3.1. Patients characteristics

From January 2000 to August 2002, 46 patients were enrolled into the study. Six patients (13%) were subsequently found to be ineligible: three patients had pleural effusion at entry, one patient each had stage IIIB disease (T4 tumour), stage IV disease, and a serious concomitant disease. All patients enrolled were considered evaluable for toxicity; the six ineligible patients were excluded from the response analysis. Baseline characteristics of all patients are shown in Table 1. Median age was 60 years (range 27–74). Approximately two-thirds of patients (65.2%) had a WHO performance status of 1. Major histological tumour subtypes were squamous cell (43.5%) and adenocarcinoma (34.8%). All patients had N2-disease, pathologically proven either by mediastinoscopy or -tomy (44 patients), video-assisted thoracoscopic surgery (VATS, 1 patient) or thoracotomy (1 patient).

3.2. Treatment information

All 46 enrolled patients started chemotherapeutic treatment. The majority of patients (84.8%) received the planned three chemotherapy cycles. One patient (2.2%) received two cycles, while 6 (13.0%) received only one cycle. Median number of administered cycles was three (range 1–3). A total of 125 cycles of docetaxel-cisplatin was administered. Dose modifications and schedule modifications occurred in 4/125 and 13/125 cycles, respectively. Three patients (6.5%) were reported with at least one dose modification but no schedule modifications (cisplatin reduction in 1 patient, cisplatin escalation in 1 patient, docetaxel and cisplatin reduction in 1 patient), 10 patients (21.7%) were reported with at least one schedule modification but no dose modifications and only one patient (2.2%) was reported with at least one dose modification and one schedule modification (treatment interrupted and not restarted) for the cycles received. The median relative dose intensity (ratio of the observed dose intensity to the dose intensity planned by the protocol) was 100.5% (range 0.6%–106.4%) for docetaxel and 101.2% (range 0%–124.2%) for cisplatin. Five patients (10.9%) were identified with severe protocol violations: undertreatment in three patients, overtreatment in one and other violations (chronic idiopathic intestinal pseudo-obstructive syndrome as pre-existing disease) also in one patient. Three of these 5 patients were also identified as ineligible for the study. A summary of treatment is presented in Fig. 1. Of the 40 eligible patients, 17 were subsequently randomized to additional treatment with surgery (9 patients) or radiotherapy (8 patients) according to EORTC protocol 08941. At the request of one participating centre, the 11 patients it included were not randomized.

Table 1 – Patients' baseline characteristics

Characteristic	N (N = 46)	%
Total eligible	40	87.0
Gender		
Male	37	80.4
Female	9	19.6
Age (years)		
Median (range)	60 (27–74)	
TNM stage		
T1N2M0	3	6.5
T2N2M0	36	78.3
T3N2M0	7	15.2
Histology		
Squamous cell	20	43.5
Adenocarcinoma	16	34.8
Other*	3	6.5
Large-cell	7	15.2
WHO performance status		
0	16	34.8
1	30	65.2

All registered patients.
Abbreviation: TNM: tumour-node-metastasis system.
* Poorly differentiated (1), undifferentiated (1), mixed adeno/squamous (1).

3.3. *Haematologic and non-haematologic toxicity*

Grade 3/4 neutropenia was observed in 65.2% of the patients (Table 2). A total of 8 patients (17.4%) experienced febrile neutropenia. No grade 3/4 anaemia or thrombocytopenia was encountered.

Treatment related non-haematologic toxicity grade 3/4 (Table 3) was observed in only a minority of patients and consisted mainly of nausea (17.4% of patients), vomiting (13.0%), fatigue (8.7%), anorexia (6.5%). Grade 3/4 sensory neuropathy and other neurotoxicity occurred in 2.2% of the patients. One patient experienced a grade 4 hypersensitivity reaction during first cycle docetaxel infusion, and further treatment was stopped. In addition, one patient stopped treatment after experiencing a grade 4 rash and another due to grade 4 vomiting.

There were 2 toxic deaths: one patient died of pneumonia complicated by grade 4 neutropenia and sepsis after cycle 1. The second patient completed 2 cycles of chemotherapy but refused further chemotherapeutic treatment due to toxicity. He received additional radiotherapy and died due to radiation pneumonitis. Seven patients died of other not tumour-related reasons: cardiovascular disease (1), infection not due to protocol treatment (1), pulmonary embolism (2), acute cardiac failure (1), cachexia (1), and sepsis (1).

3.4. *Response to induction chemotherapy and additional treatment*

In total, CT-scans of 24 patients were reviewed, including 4 patients reported by the principal investigators to have no response and one reported not evaluable for response. Among the 40 eligible patients, six were not evaluable for response because of early treatment discontinuation due to toxicity (5 patients) or missing baseline measurements (1 patient). Overall response rate for the 40 eligible patients who started protocol treatment was 45.0% (95% CI: 29.3–61.5%). Of 18 responding patients, one reached a complete response (CR), while 17 patients demonstrated a partial response. In addition 14 patients (35.0%) had stable disease. Progressive disease was observed in one patient and early death due to toxicity for another one. Of the 35 eligible patients who received at least 2 cycles of chemotherapy, the response rate was 51.4% (95% CI, 34.0–68.6).

3.5. *Survival*

At the time of this analysis, after a median follow-up period of 27 months, 36 patients (78.3%) had died. In 27 cases (75.0%)

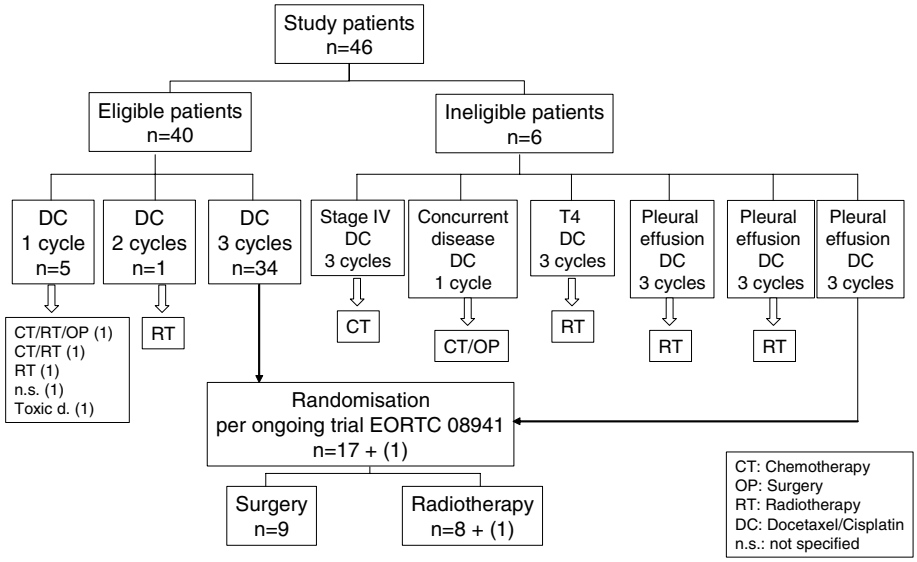

Fig. 1 – Summary of treatment.

Table 2 – Haematologic toxicity

Haematologic Toxicity – Worst grade over all cycles

	Nadir (NCI-CTC)									
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukocytes*	7	15.2	6	13.0	11	23.9	16	34.8	5	10.9
Neutrophils*	7	15.2	2	4.3	6	13.0	7	15.2	23	50.0
Thrombocytes*	40	87.0	4	8.7	1	2.2	–	–	–	–
Hemoglobin*	23	50.0	10	21.7	12	26.1	–	–	–	–

All registered patients (N = 46).
Abbreviation: NCI-CTC: National cancer Institute-Common Toxicity Criteria.
* No lab values available in 1 patient.

Table 3 – Non-haematologic toxicity (main related adverse events)

Number of patients with non-haematologic toxicities* – Worst grade over all cycles

	NCI-CTC Grade					
	0	1	2	3	4	3/4 (%)
Nausea	7	16	15	8	–	17.4
Vomiting	18	14	8	5	1	13.0
Headache	45	1	–	–	–	–
Sensory neuropathy	34	8	3	1	–	2.2
Other neurotoxicity**	40	2	3	1	–	2.2
Alopecia	15	5	26	–	–	–
Fatigue	19	10	13	3	1	8.7
Anorexia	24	11	8	3	–	6.5
Febrile neutropenia	38	–	–	7	1	17.4
Fever without neutropenia	42	1	2	1	–	2.2
Infection	43	1	2	–	–	–
Diarrhoea	27	8	9	2	–	4.3
Constipation	41	2	2	1	–	2.2
Hemorrhage (without G3-4 thrombopenia)	44	1	–	1	–	2.2
Edema	38	3	4	1	–	2.2
Hypotension	43	1	–	2	–	4.3
Trombosis/embolism	45	–	–	–	1	2.2
Shortness of breath	46	–	–	–	–	–
Stomatitis/Pharyngitis	30	10	4	2	–	4.3
Skin (rash/desquamation)	36	9	–	–	1	2.2

All registered patients (N = 46).
Toxic deaths (2): febrile neutropenia (1), pneumonia (1).
* Main related adverse events.
** Other neurotoxicity excludes constipation, headache, and sensory neurotoxicity.

death was related to malignant disease. The median duration of overall survival was 15.8 months (95% CI: 12.2–20.8 months). The estimated 1-year survival rate was 64.5% (95% CI: 50.6–78.5%). The survival curve is depicted in Fig. 2.

4. Discussion

This study reports the activity of a docetaxel-cisplatin induction chemotherapy combination in a multicentre homogenous population of proven stage IIIA-N2 NSCLC. This trial was the third and last of a series of phase II studies using new chemotherapy combinations within the setting of a recently finished randomised phase III trial in patients with stage IIIA N2 disease (EORTC 08941). Our goal was to select a docetaxel-cisplatin combination for further studies if a true response rate of 75% or more was achieved and to reject the combination for further investigation in this patient group if a true response rate of 55% or less was observed. We observed a response rate of 45% among eligible patients with a medium survival of 15.8 months if all included patients were considered. Similar phase II studies in a similar population were conducted by the EORTC Lung Cancer Group with gemcitabine-cisplatin and paclitaxel-carboplatin (Table 4). Based on similar entry criteria, the EORTC study 08955 study, using gemcitabine (1000 mg/m^2 days 1, 8 and 15) and cisplatin (100 mg/m^2 day 2) every 4 weeks, showed a response rate of 70.2% (95% CI 55.1%–82.7%),[11] while the paclitaxel (200 mg/m^2 day 1) and carboplatin (area under the concentration curve of 6) regimen administered every 3 weeks (EORTC 08958) resulted in a response rate of 64% (95% CI 49%–76%).[10] In

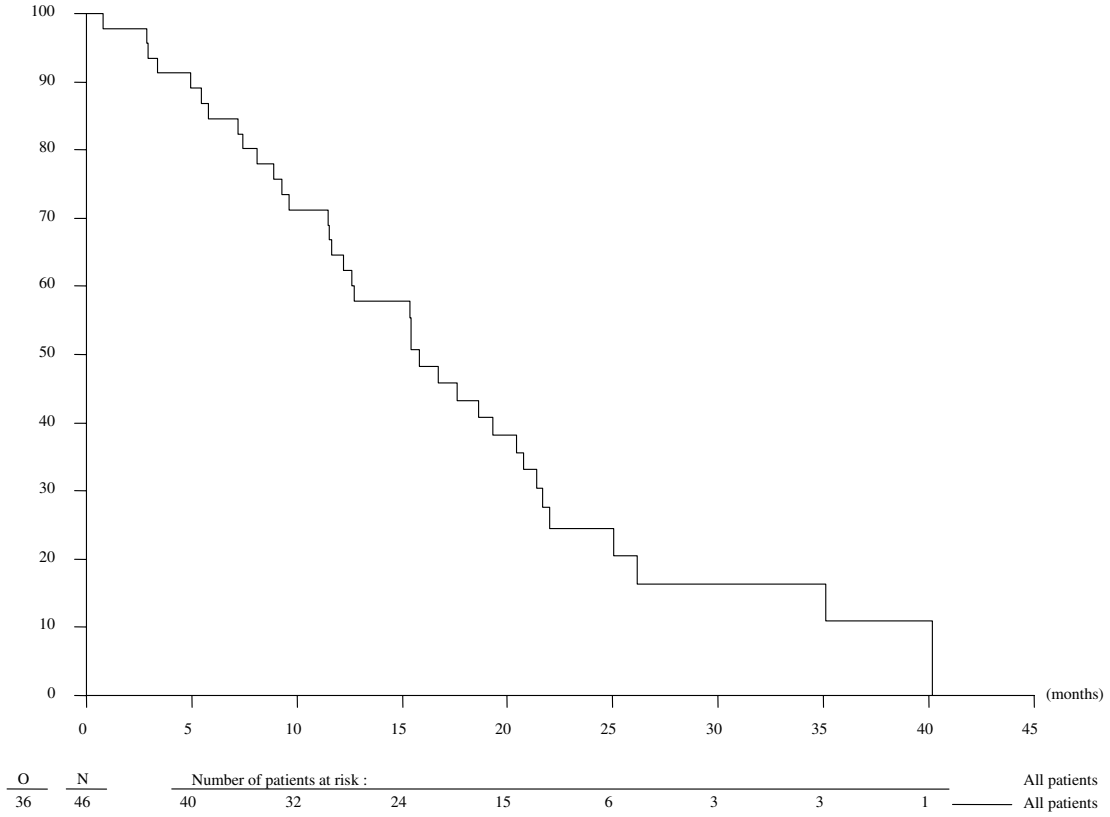

Fig. 2 – Duration of overall survival N = 46 = all patients who started treatment.

comparison to those results, the activity observed in this trial (45%: 95% CI, 29.3–61.5) appears moderate. Examination of patients' characteristics of the three studies shows that, in the EORTC 08955 study, more patients with PS 0 (60%) and slightly less patients with T3N2 tumours (9%) were included compared to the present study. No difference was apparent between the patient characteristics in the EORTC 08958 study and this study. The median survival of this study (15.8 months) was also lower than in the EORTC 08955 study (18.9 months) and the EORTC 08958 study (20.5 months). In our study, 6 (13%) ineligible patients were entered, while in the EORTC 08955 and 08955 study 9% and 11% of the patients were ineligible, respectively. In the Swiss study, one patient (1%) was ineligible. As ineligible patients were included in the survival analysis, this may have affected the outcome. However, both survival results and a comparison of these survival data should be interpreted carefully as they are based on three single-arm phase II studies, each comprised of a limited number of patients.

The combination also appears less active than a recently published schedule examined by Dr Betticher which demonstrated a response rate for docetaxel (85 mg/m^2 day 1) and cisplatin (40 mg/m^2 days 1 and 2) of 66% (95% CI 55%–75%) if administered every 3 weeks for a total of 3 cycles.[25] With 15.8 months, the median survival in the present study appears inferior to the one observed in the Swiss study (27.6 months). In the Swiss study, the cisplatin dose was increased to 50 mg/m^2 days 1 and 2, as Betticher and colleagues observed a high response rate and low toxicity in the first 36 patients. The difference in achieved response rates can not be attributed to the higher cisplatin dose used after the first 36 patients, as the response rate in the first 36 patients in the Swiss trial was also 66%.[20] However, several possible explanations apply for the observed discrepancy in activity. Patient characteristics at study entry, among which some of prognostic significance, were different in both studies and can help to explain the different study outcome. In the present series, 35% of the patients had PS 0, compared to 59% in the Swiss study. In contrast, a higher percentage T3 tumours was included in the Swiss study. Recently, several authors have advocated a sub-classification of N2-disease based on preoperative staging and/or the number of involved mediastinal lymph nodes.[26–28] Based on the available information one can only speculate that this may explain the observed difference in response rate. Of note, disease control (complete response [CR], partial response [PR] and stable disease [SD]) appeared similar for our study and the studies discussed.[10,11,25] Regarding overall survival, results might also have been influenced by the different prognosis of the patients registered.

The observed toxicities are comparable in both series and compare favourably with the toxicities observed in the studies where docetaxel and cisplatin were given on the same day.[29,30] In the Swiss study, increasing the cisplatin dose, did not affect cisplatin-related toxicity. Haematological toxicity mainly consisted of grade 3/4 neutropenia, with 8 patients experiencing febrile neutropenic event and one toxic death. The frequency of grade 3/4 neutropenia was similar to that in the Swiss study. Dr Betticher and colleagues, however, reported no febrile neutropenic events.

Table 4 – Main characteristics of discussed phase 2 trials in stage IIIA-N2 NSCLC

	EORTC 08955 (Ref. 11)	EORTC 08958 (Ref. 10)	EORTC 08984	Betticher (Ref. 25)
Eligible patients (N)	47	52	40	90
Sex (%)				
Male	70	67	80	76
Female	30	33	20	24
Performance status (%)				
0	60	37	35	59
1	40	62	65	39
2	–	2	–	2
Tumour stage (%)				
T1	6	14	7	9
T2	85	67	78	56
T3	9	19	15	36
RR to chemotherapy (%)				
CR	6	2	2.5	8
PR	70	62	42.5	58
SD	6	19	35.0	24
PD	6	17	2.5	10
NE/ED	11		2.5	

RR, Response Rate; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; NE/ED: non-evaluable/early discontinuation.

In conclusion, the present study shows that in stage IIIA-N2 NSCLC patients, docetaxel-cisplatin can be administered, to demonstrate manageable toxicity and modest efficacy. Efficacy was modest compared to other regimens investigated by the EORTC LCG and the same regimen investigated by others in this patient group and, furthermore, did not meet the criteria set up by our statistical design. In comparison with the other EORTC trials and the study published by Dr Betticher and colleagues, this study demonstrated no differences with regard to the patient characteristics. The outcome of this study, we feel can be considered intrinsic to the chemotherapy combination used, and is not likely to be due to patient selection.

Conflict of interest statement

B. Biesma, C. Manegold, H.J.M. Smit, L. Willems , C. Legrand, A. Passioukov, J.P. van Meerbeeck and G. Giaccone, hereby declare not to be engaged in any financial or personal relationships with other people or organisations that could inappropriately influence their work.

Acknowledgement

This publication was supported by grant(s) number 5U10CA11488-29 through 5U10CA11488-35 from the National Cancer Institute (Bethesda, Maryland, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

We are grateful to Aventis Pharmaceuticals, part of the sanofi-aventis group, for the financial support they provided to this study.

The authors would like to acknowledge the contribution to patient accrual of the following investigators: Dr. Stigt (Isala Klinieken, Zwolle - NL); Dr O'Byrne (Royal Infirmary, Leicester - UK; now at St James's Hospital, Dublin - IE); Dr Ardizzoni (Istituto Natzionale per la Ricerca sul Cancro, Genova - IT; now at Azienda Ospedaliera Di Parma, Parma - IT); Dr. van Zandwijk (A. van Leeuwenhoek Ziekenhuis, Amsterdam - NL).

The authors would also like to thank Sonia Dussenne of the EORTC Data Centre for data management. This work was presented in part at the 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, USA, June 2004.

REFERENCES

1. Shields TW. The significance of ipsilateral mediastinal lymph node metastasis (N2 disease) in non-small cell carcinoma of the lung: A commentary. *J Thorac Cardiovasc Surg* 1990;**99**:48–53.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995;**311**:899–909.
3. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994;**86**:673–80.
4. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994;**330**:153–8.
5. Albain KS, Pass HI. Induction therapy for locally advanced non-small cell lung cancer. In: Pass HI, Michell JB, Johnson DH, et al., editors. *Lung Cancer: Principles and Practice (ed 2)*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000. p. 798–820.
6. Pass HJ, Pogrebniak HW, Steinberg SM, et al. Randomized trial of neoadjuvant therapy for lung cancer. Interim analysis. *Ann Thorac Surg* 1992;**53**:992–8.
7. Dillman RO, Herndon J, Seagren SL, Eaton Jr WL, Green MR. Improved survival in stage III non-small cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;**88**:1210–5.

8. Depierre A, Milleron B, Moro-Sibilat D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIA non-small-cell lung cancer. *J Clin Oncol* 2002;**20**:247–53.
9. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;**22**:330–53.
10. O'Brien MER, Splinter T, Smit EF, et al. Carboplatin and paclitaxel (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: an EORTC phase II study (EORTC 08958). *Eur J Cancer* 2003;**39**:1416–22.
11. van Zandwijk N, Smit EF, Kramer GWP, et al. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Group (EORTC 08955). *J Clin Oncol* 2000;**18**:2658–64.
12. Fossella FV, Lee JS, Berille J, Hong WK. Summary of phase II data of docetaxel (taxotere), an active agent in first and second line treatment of advanced non-small cell lung cancer. *Sem Oncol* 1995;**22**(suppl 4):22–9.
13. Miller VA, Rigas JR, Francis PA, et al. Phase II of 75 mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. *Cancer* 1995;**75**:968–72.
14. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;**18**:2095–103.
15. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J Clin Oncol* 2000;**18**:2354–62.
16. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003;**21**:2004–10.
17. Mattson KV, Abratt RP, ten Velde G, Krofta K. Docetaxel as neoadjuvant therapy for radically treatable stage III non-small cell lung cancer: a multinational randomised phase III study. *Ann Oncol* 2003;**14**:116–22.
18. Schiller JH, Harrington D, Bealni CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;**346**:92–8.
19. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;**21**:3016–24.
20. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese taxotere lung cancer study group. *J Clin Oncol* 2004;**22**:254–61.
21. Betticher DC, Hsu Schmitz SF, Gauthier Y, et al. Neoadjuvant chemotherapy with docetaxel (Doc, taxotere) and cisplatin (CIS) in patients (pts) with non-small cell lung cancer (NSCLC), stage IIIA, N2 is highly active with few toxicities. *Proc Am Soc Clin Oncol* 1999;**18**:473a. (abstract 1824).
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Inst* 2000;**92**:205–16.
23. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;**10**:1–10.
24. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
25. Betticher DC, Hsu Schmitz SF, Tötsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicentre phase II trial. *J Clin Oncol* 2003;**21**:1752–9.
26. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol* 2000;**18**:2981–9.
27. Grunenwald D, Le Chevalier T. Re: Stage IIIA category of non-small cell lung cancer: a new proposal. *J Natl Cancer Inst* 1997;**89**:88–9.
28. Vansteenkiste JF, De Leyn PR, Deneffe GJ, Lerut TE, Demedts M. Clinical prognostic factors in surgically treated stage IIIA-N2 non-small cell lung cancer: analysis of the literature. *Lung Cancer* 1998;**19**:3–13.
29. Belani CP, Bonomi P, Dobbs TW, et al. Docetaxel and cisplatin in patients with advanced non-small cell lung cancer (NSCLC): a multicentre phase II trial. *Clin Lung Cancer* 1999;**1**:144–50.
30. Zalcberg J, Millward M, Bishop J, et al. Phase II study of docetaxel and cisplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 1998;**16**:1948–53.