

Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study

K. V. Mattson^{1*}, R. P. Abratt², G. ten Velde³ & K. Krofta⁴

¹Department of Internal Medicine, Division of Respiratory Diseases, Helsinki University Central Hospital, Helsinki, Finland; ²Department of Radiation Oncology, Groote Schuur Hospital, Cape Town, South Africa; ³Academic Hospital, Maastricht, The Netherlands; ⁴Faculty Hospital, Prague, Czech Republic

Received 30 November 2001; revised 10 July 2002; accepted 18 July 2002

Background: Docetaxel (Taxotere[®]) is a potent anticancer agent, with proven efficacy as first-line therapy in non-small-cell lung cancer (NSCLC). The aim of this large randomised multicentre phase III study was to evaluate docetaxel in the neoadjuvant (pre-operative) setting.

Patients and methods: Patients with stage IIIA or locally treatable IIIB NSCLC were randomly assigned to receive neoadjuvant docetaxel ($n = 134$) or no chemotherapy ($n = 140$) before surgery/curative-intention radiotherapy. Patients received up to three 3-weekly cycles of docetaxel (100 mg/m²) as 1-h intravenous infusions.

Results: Median survival was 14.8 months in the docetaxel group and 12.6 months in the control group. Median times to disease progression were 9.0 months (docetaxel arm) and 7.6 months (control arm). There were three complete responses and 25 partial responses in patients treated with docetaxel who were evaluable for response ($n = 101$). Docetaxel was well-tolerated: 103 patients (77%) received all three planned cycles. The major toxicity was grade 4 neutropenia (69 patients, 55%) and neutropenic fever (eight patients, 6%). Radiotherapy was well-tolerated after docetaxel administration.

Conclusions: Neoadjuvant docetaxel is generally well-tolerated and shows a promising trend towards longer survival in patients with NSCLC.

Key words: docetaxel (Taxotere[®]), induction, neoadjuvant, non-small-cell lung cancer

Introduction

Induction (neoadjuvant) chemotherapy is being used ever more frequently for the treatment of stage III non-small-cell lung cancer (NSCLC). Cisplatin-based and other combination chemotherapies before or concurrent with thoracic radiation therapy or surgery have consistently reduced mortality and improved survival in clinical trials [1–8]. Neoadjuvant therapy allows delivery of chemotherapy to the tumour through an intact vasculature, as well as the possible eradication of distant micro-metastases [9–11]. Other potential advantages include increased efficacy of chemotherapy early in the course of the disease, a decreased incidence of positive surgical margins, a reduction in the extent of local surgery, and smaller radiation fields, resulting in less damage to normal tissue and loss of function. Importantly, it also has the potential to decrease the size of tumours, thereby facilitating resection or enhancing control with radiation therapy [10]. Although neoadjuvant therapy can be beneficial, it has certain drawbacks and limitations: the toxicity associated with

cisplatin and other older neoadjuvant regimens can be significant.

In clinical studies, docetaxel has been shown to be one of the most effective drugs in advanced NSCLC [12–15]. It has shown consistent activity against platinum-refractory NSCLC [16–18] as well as, more recently, an additive or synergistic effect when combined with other chemotherapeutic drugs [19–23]. Docetaxel has also recently been shown to improve the quality of life for cancer patients [13, 24–28].

Previous studies of stage IIIA NSCLC patients undergoing neoadjuvant therapy before maximum locoregional treatment have not differentiated between N2 and T3 disease [4, 6]. This is important because stage III N2 patients have a worse prognosis than stage III T3 patients who do not have N2 disease. In this study, confirmation of TNM disease classification was based on computed tomography (CT) scans only (i.e. mediastinoscopy was not mandatory) before randomisation, and the efficacy analysis was also carried out according to clinical disease stage. The primary objective of this study was to evaluate the effect of docetaxel before local treatment on the survival of patients with stage IIIA or locally treatable stage IIIB NSCLC. Secondary objectives were to assess the response rate to docetaxel and time to disease progression. Preliminary results have been reported previously [29, 30]; here we report the final results of the study.

*Correspondence to: Dr K. V. Mattson, Department of Internal Medicine, Division of Respiratory Diseases, Helsinki University Central Hospital, FIN 00290 HUS, Finland. Tel: +358-9-471-72270; Fax: +358-9-241-8717; E-mail: Karin.Mattson@hus.fi

Patients and methods

Patients

Patients with stage IIIA N2, IIIA T3 or IIIB NSCLC who were considered suitable for systemic neoadjuvant chemotherapy and local treatment (either radiotherapy or surgery) were enrolled from 15 countries. For patients to be included in the study, they had to have: histologically or cytologically confirmed previously untreated NSCLC; stage IIIA N2 (T0–3) or T3 (N0–1) disease according to TNM classification (based on CT scans only, i.e. mediastinoscopy was not mandatory), or locally treatable stage IIIB (T4, N3) disease; age ≥ 18 years with a World Health Organisation (WHO) performance status of two or more; total white blood cell count $\geq 4.0 \times 10^9/l$; absolute neutrophils (including bands) $\geq 1.5 \times 10^9/l$; platelets $\geq 100 \times 10^9/l$; and adequate hepatic and renal function. Locally treatable stage IIIB disease was defined as disease suitable for curative-intention radiation therapy, of tumour stage T4 excluding malignant pleural effusion, or of nodal stage N3, and with the bulk of the tumour mass within a 10×10 cm field with reasonable margins and not compromising vital structures.

Pregnant or lactating women were excluded, as were women of child-bearing potential unless using an acceptable contraceptive method during the study. Patients with aspartate aminotransferase (AST) $>3 \times$ upper normal limit, alanine aminotransferase (ALT) $>3 \times$ upper normal limit, or alkaline phosphatase $>6 \times$ upper normal limit, symptomatic peripheral neuropathy, previous or current malignancies, uncontrolled infection or other serious medical conditions were also excluded.

Study protocol

Patients were recruited to this randomised multicentre phase III study between 1995 and 1999. Patients meeting the eligibility criteria were randomly assigned to one of the two study groups, docetaxel or control. Docetaxel (Taxotere[®]) was administered as a 1-h intravenous infusion every 3 weeks at a dose of 100 mg/m². Patients received a maximum of three cycles before local surgery or curative-intention irradiation. Surgery or radiation was scheduled to commence within 6 weeks of day 1 of the third treatment cycle. Patients in the control group did not receive neoadjuvant chemotherapy before local surgery or curative-intention irradiation. The decision as to whether a patient would undergo local surgery or curative-intention irradiation was made at baseline by the clinician(s) responsible for the patient's management, based on the extent of tumour dissemination and the patient's ability to withstand local surgery.

All randomly assigned patients were included in the intention-to-treat survival analysis. Patients were also analysed for efficacy in the treatment arm to which they were randomly assigned, and for safety according to the treatment they received. Patients who were randomly assigned to the docetaxel arm, but did not receive docetaxel and proceeded directly to local treatment, were analysed within the docetaxel arm for survival but in the control arm for safety. Patients who received at least two cycles of docetaxel were eligible for response assessment.

The study was performed in accordance with the Declaration of Helsinki (Hong Kong Amendment, 1989). Patients gave written informed consent before enrolment. The approved study protocol and the informed consent statements were reviewed by the ethics committee at each participating institution.

Efficacy parameters

The primary efficacy parameter was survival, defined as the interval between the date of random assignment and the date of death from any cause. Patients were censored at the date of last contact if there was no documentation of death.

Secondary efficacy parameters were time to disease progression and response rate in the docetaxel group. Time to progression was defined as the

interval between the date of random assignment and the date of documented progression (or death due to malignant disease). Response was based on the WHO criteria for assessment of response.

Progressive disease was defined as $>25\%$ increase in the size of at least one bi-dimensionally or uni-dimensionally measurable lesion (in comparison with the measurements at nadir) or the appearance of a new lesion. The occurrence of a malignant pleural effusion (confirmed by cytology) was also considered progressive disease, although such effusions are usual after thoracic surgery. Patients who progressed before the second cycle of docetaxel were considered to have early progressive disease.

Safety assessments

The population analysed for safety consisted of all patients in the docetaxel group who had started at least one infusion of the drug, and all patients in the control arm who had started treatment. Safety and tolerability were assessed according to the type and frequency of adverse events, the haematological toxicity rate and the severity of febrile neutropenia, and laboratory parameters. Haematological toxicity was evaluated from measurements of haemoglobin, platelets, white blood cells and neutrophils. Laboratory parameters included alkaline phosphatase, AST, ALT, total bilirubin and serum creatinine.

Statistical considerations

Efficacy was evaluated in the intention-to-treat population. An analysis of all patients who completed treatment according to the protocol was also carried out. Confidence intervals for the response rates were calculated at the 95% level. Survival time was calculated using Kaplan–Meier analysis, and *P* values were calculated using the log-rank test.

Sample size calculations, based on the Bernstein and Lagakos method [31], indicated that 292 patients were required to allow detection of a 50% increase in median survival with 85% power and a 5% level of significance. This was based on recruitment over a 24-month period with a minimum follow-up period of 12 months, and assumed that equal numbers of patients would be recruited to each of the three stage subgroups and that 5% of patients would be non-evaluable for the primary efficacy analysis.

Results

Patient characteristics

The desired sample size of 292 could not be achieved because of difficulties recruiting patients; instead 274 patients entered the trial. Multidisciplinary treatment for operable NSCLC was a new approach in the mid-1990s when this trial started, but neoadjuvant chemotherapy was well-established by the late 1990s and many centres were therefore reluctant to enrol patients in a study with no chemotherapy in the control arm.

One hundred and thirty-four patients were randomly assigned to receive docetaxel, and 140 to the control group. Patient characteristics (Table 1) were well-balanced between the two arms, and there were only a few patients (13% in the docetaxel arm, 11% in the control arm) with a WHO performance status of two. In the docetaxel arm there were 30 (22%), 57 (43%) and 46 (34%) patients with stage IIIA T3, IIIA N2 and IIIB disease, respectively. Similarly, in the control arm, the corresponding values were 32 (23%), 64 (46%) and 44 (31%), respectively. Of the 134 patients in the docetaxel arm, 89 (66%) completed the whole treatment protocol—docetaxel and local treatment. Reasons for discontinuing docetaxel treatment before receiving any local

Table 1. Baseline patient characteristics

	Docetaxel, <i>n</i> (%)	Control, <i>n</i> (%)
No. of patients	134 (100)	140 (100)
Sex		
Male	103 (77)	117 (84)
Female	31 (23)	23 (16)
Performance status (WHO)		
0–1	115 (86)	125 (89)
2	18 (13)	15 (11)
Not defined	1 (1)	0 (0)
Age, years [median (range)]	61 (37–78)	62 (32–81)
Tumour stage		
IIIA T3	30 (22)	32 (23)
IIIA N2	57 (43)	64 (46)
IIIB	46 (34)	44 (31)
Not defined	1 (1)	0 (0)
Tumour histology		
Squamous cell carcinoma	81 (60)	89 (64)
Adenocarcinoma	27 (20)	27 (19)
Large cell carcinoma	10 (7)	10 (7)
Other	16 (13)	14 (10)
Local treatment received		
Surgery	19 (14)	25 (18)
Curative-intention irradiation	78 (58)	102 (73)
Explorative surgery	3 (2)	1 (1)
Explorative surgery + radiotherapy	0 (0)	3 (2)
None	35 (26)	9 (6)

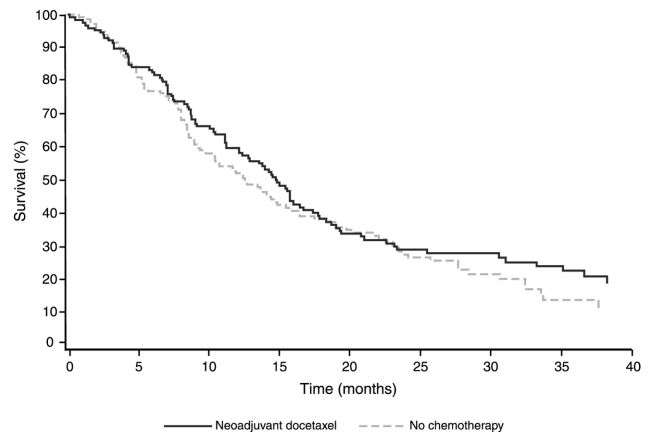
therapy were progressive disease ($n = 14$), adverse events ($n = 4$), consent withdrawal ($n = 6$), death ($n = 7$), lost to follow-up ($n = 1$) and other ($n = 3$). Local treatments for each group are detailed in Table 1.

Treatment administration

A total of 348 cycles of docetaxel were administered, with a median of three cycles per patient. Neoadjuvant therapy with docetaxel was well-tolerated with 103 patients (77%) receiving all three planned cycles. Of the nine patients in the neoadjuvant arm who discontinued treatment due to an adverse event, four did so before receiving the local treatment. Of these, one withdrew due to an adverse haematological event judged possibly or probably related to the treatment.

Efficacy

The primary efficacy parameter, median survival time in the intention-to-treat population (follow-up data were not available for one patient in the docetaxel arm), was 14.8 months in the docetaxel group and 12.6 months in the control group (Table 2). This difference was not statistically significant. When the data

**Figure 1.** Overall survival (intention-to-treat population).

were analysed by disease stage, there were no statistically significant differences in survival for any of the stage subgroups, although median survival was numerically greater in the IIIA T3 and IIIB subgroups in the docetaxel arm, compared with the control arm (Table 2).

Of the secondary efficacy parameters, median time to disease progression in the intention-to-treat population was numerically, but not significantly, better in the docetaxel group (9.0 months) than in the control group (7.6 months) (Figure 1 and Table 2). Among patients treated with docetaxel who were evaluable for response, three (3%) had a complete response and 25 (25%) had a partial response, giving an overall response rate of 28%. Only 19 patients (14%) in the docetaxel arm and 25 (18%) in the control arm underwent surgery (excluding explorative surgery). Of these surgical patients, 11 of 19 in the docetaxel arm and 14 of 25 in the control arm had stage IIIA N2 disease; five (docetaxel arm) and 11 (control arm) had stage IIIA T3 disease; and only three patients in the docetaxel group had stage IIIB disease. In the peri-operative assessments of tumour resectability, 77% of resectable tumours in the docetaxel arm and 76% in the control arm were completely resected; 9 and 10% of tumours were partially resected in the docetaxel and control arms, respectively (Table 2). Most patients (66%), however, underwent radiotherapy.

Safety and tolerability

Toxicity and safety were evaluable in 127 patients in the docetaxel arm and 131 in the control arm. Seven patients in the docetaxel arm and nine patients in the control arm were not treated.

Haematological toxicity is shown in Table 3. The major toxicity was grade 4 neutropenia, which occurred in 69 (54.8%) of docetaxel-treated patients. Febrile neutropenia was observed in eight patients (6%). In the docetaxel group, of the 10 patients (8%) who developed grade 3/4 infections, two (2%) died. Two of the infections occurred during local treatment. In the control arm, five patients suffered grade 3 infections.

Non-haematological toxicity is shown in Table 4. One of the three cases of grade 3 oesophagitis that occurred in the docetaxel group after local treatment was possibly or probably related

Table 2. Efficacy parameters (intention-to-treat population)

	Docetaxel (<i>n</i> = 134)	Control (<i>n</i> = 140)
Median survival, months (95% CI)	14.8 (12.2–16.7)	12.6 (9.7–16.0)
Median survival by disease stage, months		
IIIA N2	15.7 (<i>n</i> = 57)	15.5 (<i>n</i> = 64)
IIIA T3	17.4 (<i>n</i> = 30)	13.6 (<i>n</i> = 32)
IIIB	12.8 (<i>n</i> = 46)	9.0 (<i>n</i> = 44)
One-year survival, % (95% CI)	59.1 (50.4% to 67.7%)	50.5 (41.9% to 59.1%)
Median time to progression, months (95% CI)	9.0 (7.0–11.9)	7.6 (6.4–9.7)
Response rate, % (95% CI) ^a	28 (19% to 38%)	–
Postoperative tumour resectability, number (% of operable patients)		
All	22 (100)	29 (100)
Complete	17 (77)	22 (76)
Partial	2 (9)	3 (10)
Explorative surgery	3 (14)	4 (14)

^aResponse rate in the population evaluable for response to docetaxel (*n* = 101).
CI, confidence interval.

to treatment. One case, which was not treatment-related, was observed in the control group. There was no increase in radiation-related pulmonary toxicity (radiation pneumonitis) in the patients who received neoadjuvant docetaxel.

Mild to moderate fluid retention was observed in 22 patients in the docetaxel arm and eight in the control arm. Elderly patients with chronic obstructive pulmonary disease and heart disease would be expected to suffer some degree of fluid retention. This may have been exacerbated by docetaxel treatment, but fluid retention was only ever mild and of no clinical significance.

Two of the seven deaths which occurred in the docetaxel group were judged to be docetaxel-related as they arose from the infections mentioned above. No National Cancer Institute grade 4 laboratory abnormalities (alkaline phosphatase, creatinine, AST, ALT, total bilirubin) occurred.

Discussion

This is the first reported large phase III study of neoadjuvant treatment using a new non-platinum drug, single-agent docetaxel, in NSCLC. The main reasons for selecting docetaxel for this neoadjuvant trial were its proven activity against NSCLC, and the fact that it has been shown to be safe and well-tolerated.

A trend toward longer survival was noted in the docetaxel group (14.8 versus 12.6 months in controls), although there was no statistically significant difference. Median survival was numerically greater for all the disease substage groups in the docetaxel arm than in the control arm, but the differences did not reach statistical significance. A trend toward a longer time to disease progression in the docetaxel group was apparent in the intention-to-treat population. More patients in the docetaxel arm than in the control arm were unable to have local treatment (26 versus 6%). It is to be expected that a proportion of patients will progress during the 2-month delay in local treatment, while docetaxel is

being administered, given the aggressive nature of locally advanced disease. However, as already mentioned, the overall survival figures in the intention-to-treat analysis favoured the patients receiving neoadjuvant docetaxel.

The majority of neoadjuvant studies in NSCLC have involved combination chemotherapy rather than single-agent chemotherapy. Interestingly, the neoadjuvant use of single-agent docetaxel has been studied more extensively in patients with metastatic breast cancer. Preliminary results from these studies are favourable and indicate that neoadjuvant single-agent chemotherapy with docetaxel induces high clinical and pathological response rates in this disease [32–34]. Previous studies of combination chemotherapy in NSCLC have consistently shown that neoadjuvant chemotherapy improves survival compared with surgery alone [4–7]. These trials, however, included only stage IIIA patients (both IIIA T3 and IIIA N2 disease, all of whom underwent surgery), and have been criticised because they were small, the stage IIIA disease substages were not properly defined pre-

Table 3. Haematological toxicity in the neoadjuvant therapy group (*n* = 127). The population analysed for haematological toxicity consisted of patients with at least one blood count between day 2 and the subsequent infusion of docetaxel. Two (1.6%) treatment-related deaths occurred

	Grade 3		Grade 4	
	<i>n</i>	%	<i>n</i>	%
Leukopenia	46	36.5	10	7.9
Neutropenia	27	21.4	69	54.8
Thrombocytopenia	1	0.8	1	0.8
Anaemia	2	1.6	1	0.8
Infection	6	4.7	4	3.1

Table 4. Numbers of most common grade 3/4 non-haematological adverse events by patient (regardless of treatment)

Adverse event by National Cancer Institute term	Docetaxel (<i>n</i> = 127)		Control (<i>n</i> = 131)	
	Grade 3	Grade 4	Grade 3	Grade 4
Asthenia	8	1	3	0
Cardiac dysrhythmias	0	0	4	0
Diarrhoea	3	1	0	0
Fever	1	0	0	0
Haemorrhage (clinical)	2	1	0	2
Neurocortical	0	4	0	0
Neuromotor	3	2	2	0
Oesophagitis	3	0	1	0
Nausea	1	0	1	0
Pain	8	0	4	0
Pneumonia	1	2	1	0
Pulmonary	6	7	6	3
Skin	4	1	0	0
Stomatitis	2	0	1	0
Taste loss	0	0	0	0

operatively, and the known prognostic factors were inadequately balanced. Several trials of induction chemotherapy followed by conventional radiotherapy in inoperable stage III disease, including stage IIIA N2, have reported similar survival figures to ours. Dillman and co-workers [2] reported a median survival of 13.7 months in patients receiving induction therapy with cisplatin and vinblastine, versus 9.6 months for those treated with standard radiation therapy alone ($P = 0.012$). Updated results from this Cancer and Leukaemia Group B trial indicate median survival times of 13.7 months for patients treated with cisplatin/vinblastine induction chemotherapy versus 11.4 months for those given standard radiation ($P = 0.04$) [35, 36]. A French group reported a median survival of 12 months for patients receiving therapy with vindesine, lomustine, cisplatin and cyclophosphamide before and after radiation therapy, compared with 10 months for radiation therapy alone ($P = 0.02$) [37]. It is noteworthy that all of these studies involved patients with inoperable stage III disease (including IIIA N2 disease) but with excellent performance status and minimal weight loss, unlike the patients in our study.

We were unable to attain the goal of enrolling 292 subjects with mostly operable stage III disease (IIIA T3) into our study. We were therefore obliged to include patients with stage IIIB disease, which is not normally considered operable, and is associated with a worse prognosis. A total of 77% of patients from both arms were inoperable, and 80% of all the patients underwent radiotherapy. This suggests that careful pre-selection of patients is necessary in order to have homogeneous, comparable groups and to identify those who will benefit from neoadjuvant therapy. Indeed, one of the aims of our study was to examine whether survival depended on disease stage, and therefore indirectly on operability. Unfortunately, possibly as a result of the small

sample size, no significant differences between disease stages were observed.

Although neoadjuvant chemotherapy has been shown to be beneficial in many studies such as the ones cited here, before either surgery or radiotherapy, toxicity is frequently a problem when cisplatin-based regimens are used [35, 36]. The present study was undertaken because of the known effectiveness of docetaxel in advanced NSCLC, its significant activity against platinum-refractory NSCLC and its synergy in combination with other drugs [12, 14–16] suggested that it should be useful for neoadjuvant therapy of this disease. These attributes of docetaxel have since been confirmed in more recent studies [13, 19–23]. In our study, neoadjuvant docetaxel therapy was well-tolerated, with 103 patients (77%) completing all three planned cycles. Only nine docetaxel patients (7%) discontinued treatment because of an adverse event, whether or not related to treatment. Neutropenia and other haematological toxicities were within acceptable limits. Grade 4 neutropenia was the most common toxicity, which is consistent with other studies of docetaxel, but the number of episodes of neutropenic fever was relatively small and acceptable. Docetaxel did not have a deleterious effect on definitive therapy compared with the control arm. The incidence of oesophagitis and pneumonitis was similar in both the treatment and control arms (16 versus 10 patients).

In three phase II trials now in progress, docetaxel is being studied in combination with platinum agents as induction therapy in stage III patients [38–41]. The neoadjuvant regimens involve doses of docetaxel ranging from 60 to 100 mg/m² every 3 weeks, administered together with carboplatin (AUC 5–7.5) or cisplatin at 40 mg/m². High response rates of 68–82% have been reported, with complete resections possible in 69–79% of cases.

In conclusion, the results of our study are satisfactory, and similar to those seen in other studies in locally advanced, mainly inoperable NSCLC, and were achieved with relatively low toxicity. This suggests that docetaxel may be a useful non-platinum option for neoadjuvant chemotherapy, now standard treatment for stage III NSCLC. If the encouraging preliminary results of trials investigating neoadjuvant combinations of docetaxel and platinum agents are maintained [38–41], these combinations will also merit further investigation. Because of the heterogeneity of stage III NSCLC and inter-patient variability, further studies are needed in clearly comparable subsets of patients with stage III disease for whom a certain type of combined modality treatment should be recommended. It is particularly important that operable and inoperable patients should not be included in the same studies. Combinations of docetaxel with other drugs, with which it has additive or synergistic effects, should also be studied in the neoadjuvant setting.

Acknowledgements

The authors would like to acknowledge the participation of the following investigators: H. Alume (Hospital General de Agudos F. Tornu, Buenos Aires), C. Blajman (Clinica Especializada Isis, Santa Fe), E. Mickiewicz (Hospital de Oncologia Angel H. Roffo, Buenos Aires), C. Mosca (Instituto de Tisioneumonologia, Buenos Aires) and O. Rivero (Instituto de Investigaciones, Buenos Aires), Argentina; G. Esguerra, J. Godoy (Oncologia

Clinica, Bogota) and G. Marquez (Clinica San Pedro Claver, Bogota), Columbia; K. Krofta (Faculty Hospital Videnska, Prague, Czech Republic); K. Mattson (Helsinki University Central Hospital, Helsinki), V. Nikkanen (Turku University Central Hospital, Turku), A. Ojala (Tampere University Hospital, Tampere), M. Pekkanen (Savonlinna Hospital, Savonlinna), M-L. Romppainen (Oulu University Central Hospital, Oulu) and M. Viren (Kuopio University Hospital, Kuopio), Finland; G. Panagos (Agiii Anargyroi General Hospital of Oncology, Athens, Greece); G. Boszormenyi (National Koranyi Institute of Pulmonology, Budapest, Hungary); H. Hayat (E. Wolfson Medical Centre, Holon), A. Cyjon (Rabin Medical Centre, Petach-Tikva) and R. Borovik (Carmel Hospital, Haifa), Israel; G. ten Velde (Academic Hospital, Maastricht, The Netherlands); E. Cisarz, T. Orłowski (Centrum Onkologii, Wrocław), W. Miłnarczyz (Katedra 1 Klinika Chirurgii Klatki, Wrocław) and J. Tujakowski (Regionalne Centrum Onkologii, Bydgoszcz-Fordon), Poland; H. Queiroga (Hospital de Sao Joao, Porto) and J. Seada (Hospital Eduardo Santos Silva, Oporto), Portugal; M. Gershanovich (N. N. Petrov Research Institute of Oncology, St Petersburg, Russia); P. Kasan (Institute of Tuberculosis and Respiratory Diseases, Bratislava, Slovakia); R. Abratt (Groote Schuur Hospital, Cape Town) and D. Hacking (Durban Oncology Centre, Durban), South Africa; J. Lopez-Lopez (Hospital San Pablo, Barcelona, Spain); J. Carmichael (University of Nottingham, Nottingham), P. Clark (Clatterbridge Hospital, Merseyside), N. Davidson (North Middlesex Hospital, London), D. Dunlop (Glasgow Royal Infirmary, Glasgow), J. Mann, D. Fairlamb (New Cross Hospital, West Midlands), S. Falk (Bristol Oncology Centre, Avon), D. Ferry (Birmingham Heartlands Hospital, Birmingham), A. Price (University of Edinburgh, Edinburgh), J. T. Roberts, J. Bozzino (Newcastle General Hospital, Newcastle), P. Harper (Guy's Hospital, London) and H. Newman (Royal United Hospital, Bath), UK.

This study was supported by a grant from Aventis Pharmaceuticals, Antony, France.

References

- Goldberg M, Burkes RL. Induction chemotherapy for stage IIIA unresectable non-small cell lung cancer: the Toronto experience and an overview. *Semin Surg Oncol* 1993; 9: 108–113.
- Dillman RO, Seagren SL, Propert KJ et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990; 323: 940–945.
- 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.
- 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: 153–158.
- Rosell R, Gomez-Codina J, Camps C et al. Pre-resectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999; 26: 7–14.
- 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: 673–680.
- Roth JA, Atkinson EN, Fossella F et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998; 21: 1–6.
- Shepherd FA, Johnston MR, Payne D et al. Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study. *Br J Cancer* 1998; 78: 683–685.
- Rosell R, Font A, Pifarre A et al. The role of induction (neoadjuvant) chemotherapy in stage IIIA NSCLC. *Chest* 1996; 109 (Suppl 5): 102S–106S.
- Tonato M. The role of neoadjuvant chemotherapy in NSCLC. *Chest* 1996; 109 (Suppl 5): 93S–95S.
- Pastorino U. Benefits of neoadjuvant chemotherapy in NSCLC. *Chest* 1996; 109 (Suppl 5): 96S–101S.
- Cerny T, Kaplan S, Pavlidis N et al. Docetaxel (Taxotere) is active in non-small-cell lung cancer: a phase II trial of the EORTC early clinical trials group (ECTG). *Br J Cancer* 1994; 70: 384–387.
- 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. The TAX 320 non-small cell lung cancer study group. *J Clin Oncol* 2000; 18: 2354–2362.
- Francis PA, Rigas JR, Kris MG et al. Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. *J Clin Oncol* 1994; 12: 1232–1237.
- Miller VA, Rigas JR, Francis PA et al. Phase II trial of a 75-mg/m² dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. *Cancer* 1995; 75: 968–972.
- Fossella FV, Lee JS, Shin DM et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995; 13: 645–651.
- Gandara DR, Vokes E, Green M et al. Activity of docetaxel in platinum-treated non-small-cell lung cancer: results of a phase II multicenter trial. *J Clin Oncol* 2000; 18: 131–135.
- 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: 2095–2103.
- Belani CP. Docetaxel (Taxotere) in combination with platinum-based regimens in non-small cell lung cancer: results and future developments. *Semin Oncol* 1999; 26 (Suppl 10): 15–18.
- Belani CP, Einzig A, Bonomi P et al. Multicenter phase II trial of docetaxel and carboplatin in patients with stage IIIB and IV non-small-cell lung cancer. *Ann Oncol* 2000; 11: 673–678.
- Miller VA, Krug, LM, Ng KK et al. Phase II trial of docetaxel and vinorelbine in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2000; 18: 1346–1350.
- Millward MJ, Zalberg J, Bishop JF et al. Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1997; 15: 750–758.
- Ornstein DL, Nervi AM, Rigas JR. Docetaxel (Taxotere) in combination chemotherapy and in association with thoracic radiotherapy for the treatment of non-small-cell lung cancer. *Thoracic Oncology Program. Ann Oncol* 1999; 10 (Suppl 5): S35–S40.
- Dancey J, Shepherd F, Ramlau R et al. Quality of life (QOL) assessment in a randomized study of Taxotere (TAX) versus best supportive care (BSC) in non-small cell lung cancer (NSCLC) patients (pts) previously treated with platinum-based chemotherapy. *Proc Am Soc Clin Oncol* 1999; 18: 491a (Abstr 1896).
- Miller VA, Fossella FV, DeVore R et al. Docetaxel (D) benefits lung cancer symptoms and quality of life (QoL) in a randomized phase III study of non-small cell lung cancer (NSCLC) patients previously treated with platinum-based therapy. *Proc Am Soc Clin Oncol* 1999; 18: 491a (Abstr 1895).
- Roszkowski K, Pluzanska A, Krzakowski M et al. Multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naïve patients with metastatic or

- non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* 2000; 27: 145–157.
27. Lokich J, Anderson N. Paclitaxel hypersensitivity reactions: a role for docetaxel substitution. *Ann Oncol* 1998; 9: 573.
 28. Moon C, Verschraegen CF, Bevers M et al. Use of docetaxel (Taxotere) in patients with paclitaxel (Taxol) hypersensitivity. *Anticancer Drugs* 2000; 11: 565–568.
 29. Mattson KV, ten Velde G, Krofta K et al. Taxotere as neoadjuvant therapy for radically treatable stage III NSCLC. Preliminary results of an international phase III study. *Proc Am Soc Clin Oncol* 2000; 19: 483a (Abstr 1890).
 30. Mattson K, Abratt R, ten Velde G et al. Docetaxel as neo-adjuvant therapy for radically treatable stage III non-small cell lung cancer: early results of an international phase III study. *Lung Cancer* 2001; 34 (Suppl 4): 21–23.
 31. Moussa MA. Planning the size of survival time clinical trials with allowance for stratification. *Stat Med* 1988; 7: 559–569.
 32. Amat S, Bougnoux P, Penault-Llorca F et al. Primary chemotherapy for operable breast cancer: high pathological response rate induced by docetaxel. *Proc Am Soc Clin Oncol* 2000; 19: 128a (Abstr 500).
 33. Gradishar WJ, Loh K, Erban J et al. Docetaxel as neoadjuvant chemotherapy in patients with stage III breast cancer. *Oncology* 1997; 11 (Suppl 8): 15–18.
 34. Hutcheon AW, Ogston KN, Heys SD et al. Primary chemotherapy in the treatment of breast cancer: significantly enhanced clinical and pathological response with docetaxel. *Proc Am Soc Clin Oncol* 2000; 19: 83a (Abstr 317).
 35. Komaki R, Scott CB, Sause WT et al. Induction cisplatin/vinblastine and irradiation vs. irradiation in unresectable squamous cell lung cancer: failure patterns by cell type in RTOG 88-08/ECOG 4588. Radiation Therapy Oncology Group. Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1997; 39: 537–544.
 36. Sause W, Kolesar P, Taylor S et al. A. Five-year results; phase III trial of regionally advanced unresectable non-small cell lung cancer, RTOG 8808, ECOG 4588, SWOG 8992. *Proc Am Soc Clin Oncol* 1998; 17: 453a (Abstr 1743).
 37. Le Chevalier T, Arriagada R, Quoix E et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991; 83: 417–423.
 38. Griesinger F, Baum RP, Paul J et al. Correlation of metabolic and morphometric tumor response after induction chemotherapy with docetaxel (D) and carboplatin (C) in stage III NSCLC. *Proc Am Soc Clin Oncol* 2000; 19: 548a (Abstr 2160).
 39. 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 (Abstr 1824).
 40. Katakami N, Okazaki M, Nishimura T et al. Phase II trial of induction carboplatin (CAR) and docetaxel (DOC) with concurrent radiation (RT) in early-stage non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000; 19: 524a (Abstr 2060).
 41. Nishimura T, Ikeda A, Katakami N et al. Phase II study of induction carboplatin (CAR) and docetaxel (DOC) with concurrent thoracic radiation (CTRT) followed by surgical resection in stage IB, IIA and IIB non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2001; 20: 254b (Abstr 2767).