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Gemcitabine, vinorelbine and cisplatin combination chemotherapy in advanced non-small cell lung cancer: a phase II trial

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Abstract

The purpose of this phase II trial was to investigate the efficacy and safety of a combination chemotherapy with gemcitabine, vinorelbine and cisplatin in the first-line treatment of advanced non-small cell lung cancer (NSCLC). Patients with NSCLC stage IIIB or IV disease received 1000 mg/m^2 gemcitabine and 25 mg/m^2 vinorelbine on days 1 and 8 and 75 mg/m^2 cisplatin on day 2, every 3 weeks. From December 1998 to May 1999, 31 patients (21 stage IV and 10 stage IIIB disease), with a median age of 59 years (range 40–72 years) were enrolled. The overall intent-to-treat response rate was 45% (95% confidence interval (CI): 27–64%) with 2 complete responders (CR) and 12 partial responders (PR), 7 patients had stable disease and 10 progressed. Median survival was 12.8 months (95% CI: 6.5–12.8+ months), median time to progression was 5.1 months (95% CI: 3.5–7.7 months), and the 1-year survival rate was 52.9% (95% CI: 36.7–76.2%). Patients with stage IIIB disease had a significantly longer overall survival than patients with stage IV disease ($P=0.05$). Transient World Health Organization (WHO) grade IV leucopenia, anaemia and thrombocytopenia occurred in 3 (10%), 2 (6%) and 3 (10%) patients, respectively. The predominant non-haematological toxicities were alopecia and nausea/vomiting. 15 patients (48%) had WHO grade II and III alopecia and 14 patients (45%) nausea/vomiting. The combination of gemcitabine, vinorelbine and cisplatin has demonstrated major antitumour efficacy in advanced NSCLC with a manageable toxicity profile.

Keywords: Chemotherapy; Cisplatin; Gemcitabine; Non-small cell lung cancer; Phase II trial; Vinorelbine

1. Introduction

More than 1.3 million new cases of non-small cell lung cancer occur worldwide every year. In Western Europe and in the United States, lung cancer is the most frequent cause of death due to malignant tumours. Treatment of patients with non-small cell lung cancer (NSCLC) is a particular challenge in oncology because more than one-third of patients have distant metastases at diagnosis [1], allowing only palliative treatment. A recent meta-analysis indicates that chemotherapy significantly improves survival and symptom control compared with best supportive care in stage IV NSCLC patients [2]. Chemotherapy achieved a reduction in mortality as well as an improvement in quality of life, particularly during the first 6 months of treatment [3]. The analysis of single agents revealed that of all conventional cytotoxic drugs only cisplatin produces a significant benefit compared with best supportive care, whereas alkylating agents, vinca alkaloids, and etoposide have no or only an insignificant effect on survival [2]. However, substantial toxicity detracted from the advantages obtained in survival rates and symptom control with cisplatin-containing regimens.

Thus, there is a need for at least equally active, but better tolerated agents to optimize the therapy of metastatic

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and advanced NSCLC. Since the 1990s, promising new active cytotoxic agents have been investigated in advanced NSCLC. These novel agents include the nucleoside analogue gemcitabine, the vinca-alkaloid vinorelbine, the taxanes paclitaxel and docetaxel, the camptothecin derivatives irinotecan and topotecan and the benzotriazin derivative tirapazamine.

The new cytotoxic agents have extended the therapeutic approaches available for metastatic NSCLC. Gemcitabine and vinorelbine are two of the most extensively evaluated new cytotoxic agents. Each is characterized by a favourable toxicity profile and are far better tolerated than platinum-based regimens [4-6]. Gemcitabine is generally well tolerated, the most frequent side-effect being myelosuppression which is usually mild. Other uncommon side-effects include rashes, flu-like syndrome, pulmonary toxicity and elevated levels of transaminases [7]. The primary toxicity of vinorelbine is myelosuppression, phlebitis and usually mild and reversible peripheral neuropathy [8].

Gemcitabine and vinorelbine have single-agent response rates of 20–30% with median survival rates of 7–10 months and 1-year survival rates of up to 30% in phase II trials [9–13]. When gemcitabine or vinorelbine were combined with cisplatin in phase II trials [14–16], higher response rates of 26–57% were observed. These phase II trials also yielded higher median survival rates of 8–15 months and 1-year survival rates of up to 60%. The doublet combination of these new cytotoxic agents with cisplatin was more active than either used as single agents, and randomised trials [17,18] showed that combinations such as gemcitabine plus cisplatin and vinorelbine plus cisplatin were preferable compared with cisplatin alone. On the basis of their mild toxicity profile, gemcitabine and vinorelbine can be combined easily in triplets combinations.

As yet, no adequate standard of chemotherapy exists for patients with NSCLC. Thus, in this phase II trial, we evaluated the potential and the toxicity profile of gemcitabine plus vinorelbine plus cisplatin in combination as a first-line treatment in patients with advanced NSCLC before starting a randomized phase III trial which is currently ongoing.

2. Patients and methods

Eligibility criteria included cytologically- or histologically confirmed NSCLC (stage IIIB or IV), and no previous chemotherapeutic treatment. Patients were also required to have objective bidimensionally measurable ($\geqslant 20\times 20$ mm) disease, a life expectancy of at least 12 weeks, a performance status $\geqslant 70$ (Karnofsky Performance scale (KPS)), age between 18 and 75 years, and adequate bone marrow (neutrophils $\geqslant 2.0\times 10^9$ cells/l platelets $\geqslant 100\times 10^9$ cells/l), hepatic (bilirubin $\leqslant 1.5\times$ the upper normal limit [UNL] and alanine aminotransferase (ALT) and asparate aminotransferase AST $\leqslant 3\times$UNL in the absence of liver metastases or ALT and AST $\leqslant 5\times$UNL in the presence of liver metastases), and renal (serum creatinine $\leqslant 1.5\times$UNL) function. Patients with brain metastases were eligible as well.

Patients were excluded from the study if they had previous cancer (except adequately treated basal cell carcinoma of the skin or carcinoma of the cervix), pre-existing sensory or motor neuropathy greater than World Health Organization (WHO) grade I, a history of myocardial infarction, coronary heart disease greater than or equal to grade III (Canadian Cardiovascular Society scale), ventricular cardiac arrhythmias $\geqslant$grade IIIB (Lown scale), cardiac insufficiency $\geqslant$grade III (New York Heart Association scale), and active infections. Exclusion criteria also included pregnancy, breast feeding and inadequate contraceptive precautions. All eligible patients gave informed consent prior to entering this study.

2.1. Treatment schedule

Patients received 1000 mg/m^2 gemcitabine and 25 mg/m^2 vinorelbine on days 1 and 8 and 75 mg/m^2 cisplatin on day 2 every 3 weeks. Gemcitabine was given as a 30-min infusion followed one hour later by vinorelbine (15-min infusion). To protect the vein in which vinorelbine was infused and to prevent the development of phlebitis 250 ml of 0.9% saline was given immediately after the vinorelbine infusion. Cisplatin was given over a 1-h infusion with standard pre- and posthydration on day 2. All three drugs were administered as an intravenous (i.v.) infusion, in 0.9% saline. A combination of metoclopramide and dexamethasone was given on days 1 and 8 and a combination of a HT_3-antagonist and dexamethasone was adminstered on day 2 15–30 min before starting chemotherapy to prevent nausea and vomiting.

Within courses, doses of gemcitabine and vinorelbine were modified as follows: no reduction for neutrophils $\geqslant 1.5\times 10^9$ cells/l and platelets $\geqslant 100\times 10^9$/l; 50% dose reduction for neutrophils 1.0–1.49×10^9 cells/l or platelets 75–99×10^9 cells/l dose delay for neutrophils $<1.0\times 10^9$ cells/l or platelets $<75\times 10^9$ cells/l. When haematological WHO toxicity grade IV or non-haematological WHO toxicity grade III (except for alopecia and nausea/vomiting) occured at any time, a dose reduction of 25% regarding all three cytotoxic drugs was made for the subsequent cycles. The use of granulocyte-colony stimulating factor (G-CSF) and the substitution of red blood cells or platelets was left to the individual decision of the physician.

2.2. Treatment evaluation

Pretreatment evaluation included complete history and physical examination with an evaluation of the

performance status score, chest X-rays in anterior–posterior and lateral view, computed tomography (CT) scan of the chest, sonography or CT of the upper abdomen, fibre optic bronchoscopy with bronchoaspirate and/or brushing and/or bronchial biopsy, complete blood cell count, and serum chemistry analysis. Brain CT scan and radionuclide bone scan were performed only if clinically indicated. All pretreatment imaging procedures were performed within 4 weeks of study entry. The physical examination with evaluation of the performance status score and chest X-ray were repeated every 3 weeks. The indicator lesion(s) were measured with CT scan after every two cycles and, in the event of a response or stable disease, 4 weeks later to confirm the response/stable disease. The responses were reviewed by independent radiologists, but not by a panel.

To detect acute haematological toxicity, blood cell count with differential was performed weekly, and chemistry analysis was performed at the beginning of each cycle. Non-haematological acute toxicity was assessed weekly. Toxicities were evaluated according to WHO criteria. Tumour response was assessed after two cycles of therapy according to standard WHO criteria.

Sample size calculation of patients was based on a modified sequential statistical method for pilot studies of Simon [19]. Response rate, survival and toxicity were assessed for all enrolled patients on an intent-to-treat basis. Median time to progression was calculated from the start of treatment to the first documented disease progression. The Kaplan–Meier method was used to analyse median survival, 1-year survival and median time to progression. The log-rank test was used to compare overall survival and median time to progression by tumour stage.

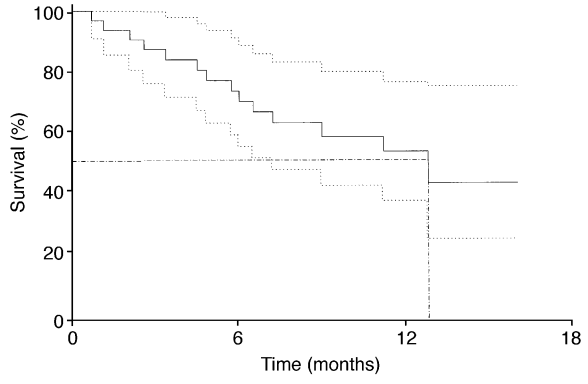

Fig. 1. Kaplan–Meier plot of overall survival ($n=31$) (dotted lines refer to 95% Confidence Interval).

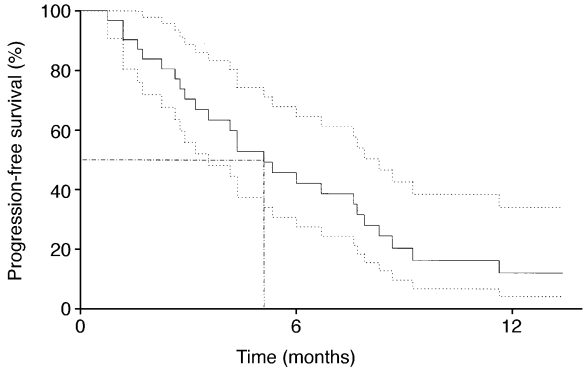

Fig. 2. Kaplan–Meier plot of time to progression ($n=31$) (dotted lines refer to 95% Confidence Interval).

3. Results

3.1. Patient characteristics

From December 1998 to May 1999, 31 patients were enrolled in this study. The majority of patients were men (81%). Patients had a median age of 59 years (range 42–70 years), and a median Karnofsky performance status of 90%. 10 patients (32%) were staged as IIIB and 21 patients (68%) had a stage IV disease at diagnosis. The predominant histological type was adenocarcinoma (48%). Prior tumour-related treatments included 4 patients (13%) with surgery of the chest, 2 patients (6%) with radiotherapy of the chest, 1 patient (3%) with radiotherapy of the bone, and 1 patient (3%) with cranial irradiation.

3.2. Response and survival

The overall intent-to-treat response rate of all 31 patients was 45% (95% confidence interval (CI): 27.3–64%), comprising 2 complete responders (CR) (6%) and 12 partial responders (PR) (39%). 7 patients (23%) had stable disease, and 10 patients (32%) progressed. The response rate of patients with stage IIIB disease was 70% (95% CI: 33–93%) and with stage IV disease 33% (95% CI: 15–57).

The median survival for all 31 patients was 12.8 months (95% CI: 6.5–12.8+ months) (Fig. 1). The median survival for stage IIIB disease was longer than 12.8 months and for stage IV disease was 9.0 months. The overall survival by tumour stage showed a significantly longer survival for patients with stage IIIB disease ($P=0.05$, log-rank test).

Median time-to-progression for all 31 patients was 5.1 months (95% CI: 3.5–7.7 months) (Fig. 2). For patients with stage IIIB disease, the median time-to-progression was 8.4 months (95% CI: 3.5–8.7+months) and with stage IV disease 4.3 months (95% CI: 2.7–7.6 months). The median time-to-progression by stage showed a borderline significantly longer median time-to-progression for patients with stage IIIB disease ($P=0.054$, log-rank test).

The 1-year survival rate for all 31 patients was 52.9% (95% CI: 36.7–76.2%) (Fig. 1). The 1-year survival rate for stage IIIB disease was 78.8% (95% CI: 56.4–100%) and for stage IV disease was 39.3% (95% CI: 21.2–72.7%).

Table 1
Haematological toxicity by cycle ($n = 120$)

Toxicity	WHO grade II	WHO grade III	WHO grade IV
	No. of cycles (%)	No. of cycles (%)	No. of cycles (%)
Leucopenia	17 (14)	17 (14)	3 (3)
Anaemia	30 (25)	5 (4)	2 (2)
Thrombocytopenia	3 (3)	15 (13)	3 (3)

WHO, World Health Organization.

Table 2
Haematological toxicity by patient ($n = 31$)

Toxicity	WHO grade II	WHO grade III	WHO grade IV
	No. of pts (%)	No. of pts (%)	No. of pts (%)
Leukopenia	4 (13)	11 (35)	3 (10)
Anaemia	13 (42)	4 (13)	2 (6)
Thrombocytopenia	3 (10)	10 (32)	3 (10)

WHO, World Health Organization; pts, patients.

Table 3
Non-haematological toxicity by patient ($n = 31$)

Toxicity	WHO grade II	WHO grade III	WHO grade IV
	No. of pts (%)	No. of pts (%)	No. of pts (%)
Neurotoxicity	4 (13)	1 (<1)	1 (<1)
Local phlebitis	4 (13)	1 (<1)	0
Alopecia	11 (35)	4 (13)	0
Nausea/vomiting	9 (29)	5 (16)	0
Fatigue	5 (16)	0	0
Nephrotoxicity	4 (13)	0	0
Cardiac toxicity	0	2 (6)	0
Diarrhoea	0	2 (6)	0

WHO, World Health Organization; pts, patients.

3.3. Toxicity

A total of 120 cycles of gemcitabine, vinorelbine and cisplatin were administered. The mean number of cycles per patient was 4 (range 1–7 cycles). Within courses, seven reductions to 50% according to the dose modification system occurred in the administration of gemcitabine and vinorelbine on day 8. Nine days of therapy (3×day 2; 6×day 8) were omitted and 4 days were delayed by a mean of 7 days. In the course of treatment, a dose reduction of up to 75% of the starting dose for all three drugs was necessary in 6 patients (19%). The predominant cause of dose reduction, as well as omissions and delays, was haematological toxicity, namely neutropenia and thrombocytopenia. Dose intensity was determined according to Hryniuk and colleagues [20]. Based on 120 treatment cycles, 24 days with a reduction to 75%, 7 days with a reduction to 50%, 9 days not given, the average dose intensity regarding all cycles and patients was 624 mg/m^2/week of gemcitabine, 15.6 mg/m^2/week of vinorelbine and 24.4 mg/m^2/week of cisplatin given in combination.

Myelosuppression was the major treatment-related toxicity. Transient WHO grade IV leucopenia, anaemia and thrombocytopenia were observed in 3 (3%), 2 (2%) and 3 (3%) cycles (Table 1), as well as 3 (10%), 2 (6%) and 3 (10%) patients (Table 2), respectively. The duration of leucopenia and thrombocytopenia was brief and occured mainly around day 15 of each cycle. Febrile neutropenia was observed in 3 patients (10%). Only these 3 patients received G-CSF to accelerate the regeneration of their bone marrow function. 15 patients (48%) received a transfusion of red blood cells and 4 patients (13%) of platelets. However, no treatment-induced deaths occurred.

The predominant non-haematological toxicities were alopecia and nausea/vomiting (Table 3). 15 patients (48%) had WHO grade II and III alopecia and 14 patients (45%) nausea-vomiting. Relevant neurotoxicity occurred in 6 patients (19%). 4 patients (13%) developed a peripheral neuropathy WHO grade II and 1 patient (<1%) WHO grade III and IV, respectively. The neurotoxicity was non-cumulative and reversible. Moderate fatigue was observed in 5 patients (16%). 2 patients had a cardiac toxicity WHO grade III. One decompensation of a cardiac insufficiency after standard pre- and posthydration on day 2 and one newly diagnosed atrial fibrillation occurred.

4. Discussion

New cytotoxic agents have broadened the therapeutic approach to advanced NSCLC. The best benefit has been reported for substances such as gemcitabine, vinorelbine, paclitaxel and docetaxel. While combination chemotherapy regimens with conventional cytotoxic drugs produced response rates of up to 25%, median survival from 6 to 8 months and 1-year survival rates of approximately 25% in the early 1990s, new cytotoxic drugs, in combination with cisplatin or

carboplatin, result in response rates from 25 up to 50%, median survival rates from 8 to 10 months and 1-year survival rates of up to 40%. However, the differences between conventional and novel cytotoxic drugs could also be based on different selection criteria and staging procedures.

Gemcitabine and vinorelbine as a doublet combination regimen has demonstrated activity in advanced NSCLC with mild toxicity [21–25]. The favourable efficacy and toxicity profile of the new agents—especially gemcitabine and vinorelbine—makes those new triplet combinations feasible.

In this phase II trial, the triplet gemcitabine plus vinorelbine plus cisplatin demonstrated an overall intent-to-treat response rate of 45%, a median survival of 12.8 months, and a 1-year survival rate of 52.9%. This study also showed—like other studies [26,27]—that locally advanced disease is more chemosensitive compared with metastatic disease. Patients with stage IIIB disease had a response rate of 70% and a significantly longer overall survival than patients with stage IV disease. In our study, 1000 mg/m^2 gemcitabine and 25 mg/m^2 vinorelbine were given on days 1 and 8 in a 3-week cycle. This schedule was identified as the optimal regimen with equal activity as well as less frequent and less severe toxicity in comparison to higher dose levels of gemcitabine and vinorelbine [25].

Up until now, several phase I–II trials with gemcitabine, vinorelbine and cisplatin have been published [28–32]. In these trials, the response rates varied from 33 to 65%, with an average of 50% among 208 patients. The average median survival was 55 weeks (range 26+ to 60 weeks), and the average 1-year survival rate was 53% (range 26–55%), very similar to the result of our study. There were slight differences in the schedules of these trials. Comparable to our study, Ginopoulous and colleagues [32] used 75 mg/m^2 cisplatin in a 3-week cycle, whereas in other studies 100 mg/m^2 cisplatin was given on one day in a 4-week cycle [31] or in a split dose in a 3-week cycle [28,30]. In all of the studies myelosuppression was the major treatment-related toxicity. Comparable to our study, other authors reported similar high rates of WHO grade III and IV leucopenia and anaemia, as well as moderate rates of non-haematological toxicities [28–32]. However, we found the highest rate of WHO grade III and IV thrombocytopenia which we believe can be explained by the fact that we performed our blood cell count weekly. In our study, thrombocytopenia was brief and occurred mainly around day 15 of each cycle. The triplet induced a higher rate of anaemia than the doublet gemcitabine and vinorelbine. The addition of cisplatin to the doublet seems to be responsible for this increase.

The average response rate and survival data of the triplet gemcitabine plus vinorelbine plus cisplatin are nearly identical to that reported in studies of the triplets gemcitabine plus paclitaxel plus platinum [33–36], gemcitabine plus cisplatin plus ifosfamide [37], gemcitabine plus vinorelbine plus ifosfamide [38,39], carboplatin plus ifosfamide plus vinorelbine [40], as well as paclitaxel plus carboplatin plus vinorelbine [41]. Overall, the triplets produced high response and survival rates, but they also induced an increase in haematological WHO grade III and IV toxicities.

Some randomised trials comparing triplets to doublets are published [42–45]. Crino and colleagues [42] observed in their study that mitomycin C plus ifosfamide plus cisplatin versus gemcitabine plus cisplatin had a similar efficacy, but the doublet regimen showed less toxicity. Preliminary results of randomised trials using new triplets indicated an advantage for the three-drug combinations [43–45]. However, these trials are far too small to provide meaningful conclusions. Large randomised trials are indicated to evaluate which triplet is favourable and to determine whether the triplet regimens are more effective than any of the doublet regimens.

In conclusion, this phase II trial of the combination of gemcitabine plus vinorelbine plus cisplatin has demonstrated feasibility and major antitumour activity in advanced NSCLC, with response and survival rates similar to those of other triplets and a manageable toxicity profile. The application of cisplatin on day 2 with a dose of 75 mg/m^2 in a 3-week cycle, as well as a dose modification system on day 8 can avoid the routine application of G-CSF.

Based on our data, we initiated a multicentre randomized phase III trial of gemcitabine plus vinorelbine plus cisplatin versus gemcitabine plus vinorelbine to compare a triplet with a doublet regimen and to investigate the role of cisplatin in the era of the new and well tolerated cytotoxic agents in a palliative treatment situation (stage IIIB with pleural effusion or stage IV disease). Regarding the encouraging results of gemcitabine and vinorelbine and cisplatin in stage IIIB disease, this combination should also be evaluated as a neoadjuvant chemotherapy regimen in stage III disease.

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References

1. Bunn Jr PA, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res* 1998, **5**, 1087–1100.

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 randomized clinical trials. *Br Med J* 1995, **311**, 899–909.
3. Grilli R, Oxmann AD, Julian JA. Chemotherapy for advanced non-small cell lung cancer: how much benefit is enough? *J Clin Oncol* 1993, **11**, 1866–1872.
4. Le Chevalier T, Brisgand D, Douillard JY, *et al*. Randomised study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994, **12**, 360–368.
5. Manegold C. Single-agent gemcitabine versus cisplatin/etoposide in patients with inoperable, locally advanced, or metastatic non-small cell lung cancer. *Semin Oncol* 1998, **25**(Suppl. 9), 18–22.
6. Perng RP, Chen YM, Ming-Liu JM, *et al*. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small cell lung cancer in a phase II randomized study. *J Clin Oncol* 1997, **15**, 2097–2102.
7. Aapro MS, Martin C, Hatty S. Gemcitabine—a safety overview. *Anti-Cancer Drugs* 1998, **9**, 191–201.
8. Johnson SA, Harper P, Hortobagyi GN, *et al*. Vinorelbine: an overview. *Cancer Treat Rev* 1996, **22**, 127–142.
9. Abratt RP, Bezwoda WR, Falkson G, *et al*. Efficacy and safety profile of gemcitabine in non-small cell lung cancer: a phase II study. *J Clin Oncol* 1994, **12**, 1535–1540.
10. Anderson H, Lund B, Bach F, *et al*. Single agent activity of weekly gemcitabine in advanced non-small cell lung cancer: a phase II study. *J Clin Oncol* 1994, **12**, 1821–1826.
11. Depierre A, Lemarie E, Dabouis G, *et al*. A phase II study of navelbine in the treatment of non-small cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115–119.
12. Furuse K, Kubuto K, Kawahara M, *et al*. A phase II study of vinorelbine, a new derivative of vinca alkaloid, for previously untreated non-small cell lung cancer. *Lung Cancer* 1994, **11**, 385–391.
13. Gatzemeier U, Shepherd FA, Le Chevalier T, *et al*. Activity of gemcitabine in patients with non-small cell lung cancer: a multicenter extended phase II study. *Eur J Cancer* 1996, **32**, 243–248.
14. Berthaud P, Le Chevalier T, Ruffie P, *et al*. Phase I-II study of vinorelbine (Navelbine) plus cisplatin in advanced non-small cell lung cancer. *Eur J Cancer* 1992, **28A**, 1863–1865.
15. Crino L, Scagliotti G, Marangolo M, *et al*. Cisplatin-gemcitabine combination in advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1997, **15**, 297–303.
16. Gebbia V, Caruso M, Valenza R, *et al*. Vinorelbine plus cisplatinum for the treatment of stage IIIB and IV non-small cell lung carcinoma. *Anticancer Res* 1994, **14**, 1247–1249.
17. Sandler A, Nemunaitis J, Denham C, *et al*. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 2000, **18**, 122–130.
18. Wozniak AJ, Crowley JJ, Balcerzak SP, *et al*. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1998, **16**, 2459–2465.
19. Simon R. Design, analysis, and reporting of cancer clinical trials. In Peace Marcel KE, ed. *Biopharmaceutical Statistics for Drug Development*. New York, Dekker, 1988, 459–488.
20. Hryniuk WM, Figueredo A, Goodyear M. Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. *Semin Oncol* 1987, **14**(Suppl. 4), 3–11.
21. Isokangas OP, Knuuttila A, Halme M, *et al*. Phase II study of vinorelbine and gemcitabine for inoperable stage IIIB-IV non-small cell lung cancer. *Ann Oncol* 1999, **10**, 1059–1063.
22. Lorusso V, Carpagnano F, Frasci G, *et al*. Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small cell lung cancer. *J Clin Oncol* 2000, **18**, 405–411.
23. Krajnik G, Mohn-Staudner A, Thaler J, *et al*. Vinorelbine-gemcitabine in advanced non-small cell lung cancer (NSCLC): an AASLC phase II trial. *Ann Oncol* 2000, **11**, 993–998.
24. Laack E, Mende T, Benk J, *et al*. Gemcitabine and vinorelbine as first-line chemotherapy for advanced non-small cell lung cancer: a phase II trial. *Eur J Cancer* 2001, **37**, 583–590.
25. Gridelli C, Frontini L, Perrone F, *et al*. Gemcitabine plus vinorelbine in advanced non-small cell lung cancer: a phase II study of three different doses. *Br J Cancer* 2000, **83**, 707–714.
26. Cojean I, Le Chevalier T. Chemotherapy of stage IIIb and IV non-small cell lung cancer. Symposium article. *Ann Oncol* 1995, **6**(Suppl. 3), 41–44.
27. Donnadieu N, Paesmans M, Sculier JP. Chemotherapy of non-small cell lung cancer according to disease extent: a meta-analysis of the literature. *Lung Cancer* 1991, **7**, 243–252.
28. Comella G, Fracsi C, Panza N, *et al*. Cisplatin, gemcitabine, and vinorelbine combination therapy in advanced non-small cell lung cancer: a phase II randomized study of the Southern Italy Cooperative Oncology Group. *J Clin Oncol* 1999, **17**, 1526–1534.
29. Dorta J, Martin G, Constenla M, *et al*. A phase I/II study of gemcitabine, cisplatin and vinorelbine in patients with advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1998, **17**, 482a (abstr 1853).
30. Frasci G, Panza N, Comella P, *et al*. Cisplatin, gemcitabine and vinorelbine in locally advanced or metastatic non-small cell lung cancer: a phase I study. *Ann Oncol* 1997, **8**, 1045–1048.
31. González Barón M, Garcia MJ, Chacón JI, *et al*. A phase II study of gemcitabine, cisplatin and vinorelbine in patients with advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1998, **17**, 469a (abstr 1802).
32. Ginopoulos P, Mastronikolis NS, Giannios J, *et al*. A phase II study with vinorelbine, gemcitabine and cisplatin in the treatment of patients with stage IIIb–IV non-small cell lung cancer (NSCLC). *Lung Cancer* 1999, **23**, 31–37.
33. Greco FA, Burris HA, Hainsworth JD. Gemcitabine, paclitaxel, and carboplatin for advanced non-small cell lung cancer. *Oncology (Huntingt)* 2000, **14**(Suppl. 3), 31–34.
34. Kelly K, Mikhaeel-Kamel N, Pan Z, *et al*. A phase I/II trial of paclitaxel, carboplatin, and gemcitabine in untreated patients with advanced non-small cell lung cancer (NSCLC). *Clin Cancer Res* 2000, **6**, 3474–3479.
35. Frasci F, Panza N, Comella P, *et al*. Cisplatin, gemcitabine, and paclitaxel in locally advanced or metastatic non-small cell lung cancer: a phase I-II study. Southern Italy Cooperative Oncology Group. *J Clin Oncol* 1999, **17**, 2316–2325.
36. Sørensen JB, Stenbygaard LE, Dobernowsky P, *et al*. Paclitaxel, gemcitabine, and cisplatin in non-resectable non-small cell lung cancer (NSCLC). *Ann Oncol* 1999, **10**, 1043–1049.
37. Boni C, Bisagni G, Savoldi L, *et al*. Gemcitabine, ifosfamide, cisplatin (GIP) for the treatment of advanced non-small cell lung cancer: a phase II study of the Italian Oncology Group for Clinical research. *Int J Cancer* 2000, **87**, 724–727.
38. Castellano D, Lianes P, Calzas J, *et al*. Non-cisplatin based chemotherapy for advanced non-small cell lung cancer (NSCLC): a phase II study with gemcitabine (G), ifosfamide (I) and vinorelbine (V). *Proc Am Soc Clin Oncol* 1998, **17**, 480a (abstr 1847).
39. Recchia F, De Filippis S, Rosselli M, *et al*. Ifosfamide, vinorelbine and gemcitabine in advanced non-small cell lung cancer. A phase I study. *Eur J Cancer* 1999, **35**, 1457–1461.
40. Recchia F, Lococo A, Campisi C, *et al*. Carboplatin, ifosfamide and vinorelbine in the treatment of advanced non-small cell lung cancer: a phase II study. *Am J Clin Oncol* 1999, **22**, 57–61.
41. Thompson DS, Hainsworth JD, Scullin Jr DC, *et al*. Paclitaxel-carboplatin alone or with gemcitabine or vinorelbine for stage IV and IIIB non-small cell lung cancer: long term follow up. *Proc Am Soc Clin Oncol* 2000, **19**, 503a (abstr 1967).

42. Crino L, Scagliotti GV, Ricci S, *et al*. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small cell lung cancer: a randomized phase III study of the Italian Lung Cancer Project. *J Clin Oncol* 1999, **17**, 3522–3530.
43. Comella P, Frasci G, Panza N, *et al*. Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group. *J Clin Oncol* 2000, **18**, 1451–1457.
44. Comella P. Interim analysis of a phase III trial. Triple- vs double agent chemotherapy for advanced non-small cell lung cancer. Southern Italy Cooperative Oncology Group. *Oncology (Huntingt)* 2000, **14**(Suppl. 4), 35–40.
45. Hussein A, Birch R, Waller J, *et al*. Preliminary results of a randomized study comparing paclitaxel and carboplatin (PC) with or without gemcitabine (G) in newly diagnosed non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000, **19**, 504a (abstr 1973).