GLOB-1: a prospective randomised clinical phase III trial comparing vinorelbine–cisplatin with vinorelbine–ifosfamide–cisplatin in metastatic non-small-cell lung cancer patients

On behalf of the Global Lung Oncology Branch Group

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Received 6 July 2001; revised 20 November 2001; accepted 12 June 2002

Background: The standard doublet, vinorelbine–cisplatin, was compared with a triplet of vinorelbine–ifosfamide–cisplatin, in terms of survival, in patients with advanced non-small-cell lung cancer (NSCLC).

Patients and methods: From February 1998 to June 1999, 259 chemotherapy patients entered the study and were randomised to receive either vinorelbine–cisplatin (NP; vinorelbine 30 mg/m² on days 1, 8 and 15 with cisplatin 80 mg/m² on day 1) or vinorelbine–ifosfamide–cisplatin (NIP; vinorelbine 25 mg/m² on days 1 and 8, ifosfamide 3 g/m² on day 1 and cisplatin 75 mg/m² on day 1), with both regimens being repeated every 3 weeks. All patients had stage IV or relapsed disease and a performance score of 0 or 1.

Results: The overall response rate was 34.6% for NP and 35.7% for NIP. Median and 1-year survival rates were 10.0 months and 38.4% for NP, and 8.2 months and 33.7% for NIP, respectively. A median of four cycles was administered in each arm. The major World Health Organization grade 3–4 toxicities for NP and NIP, respectively, were: neutropenia (20.3% compared with 9% of cycles), anaemia (4.1% compared with 5% of cycles), nausea and vomiting (22.2% compared with 19.4% of patients) and alopecia (5.6% compared with 29.8% of patients). Four toxic deaths occurred in the NP arm and eight in the NIP arm.

Conclusions: The different schedules of vinorelbine in the two arms led to a greater survival in the NP arm without impairing the tolerance profile, although this is not statistically significant. This confirms that the two-drug combination NP is a reference treatment for metastatic NSCLC. The role of three-drug combinations remains questionable in this subset of patients.

Key words: chemotherapy, doublet, non-small-cell lung cancer, quality of life, stage IV, triplet

Introduction

Lung cancer is the leading cause of cancer mortality in men throughout the world, with >1000000 new cases each year. More than 75% of patients with lung cancer have non-small-cell histology, and 50% present with incurable stage IIIIB or IV disease.

Treatment for patients with advanced or metastatic non-small-cell lung cancer (NSCLC) is usually cisplatin-based chemotherapy, which produces a significant improvement in overall survival as compared with best supportive care. In meta-analyses of randomised trials, cisplatin-based chemotherapy increased the median survival by 1.5 months, and the 1-year survival rate improved from 15% to 25% compared with best supportive care [1].

On the basis of reported response rates in phase II trials several agents appear to have interesting levels of activity; however, response rates are notoriously variable in this disease, and poorly correlated with survival. Vinorelbine (Navelbine®, Pierre Fabre Médicament, Boulogne, France) has undergone some of the most thorough testing in randomised trials performed in NSCLC. Depierre et al. [2] included 231 patients to be treated either with vinorelbine 30 mg/m² weekly, or vinorelbine 30 mg/m² on days 1, 8 and 15 with cisplatin 80 mg/m² on day 1 repeated every 3 weeks. A randomised study conducted by Le Chevalier et al. [3] compared standard cisplatin and...
vindesine with either cisplatin and vinorelbine or with single agent vinorelbine. Patients treated with cisplatin–vinorelbine had a significantly longer median survival of 9.3 months compared with 7.4 months for patients treated with cisplatin and vindesine. In another clinical randomised trial conducted in the USA by the South West Oncology Group (SWOG) [4] vinorelbine–cisplatin resulted in superior survival compared with single-agent cisplatin.

A recently completed phase III SWOG trial [5] comparing two novel doublets, paclitaxel–carboplatin and cisplatin–vinorelbine, demonstrated similar efficacy with a median survival of 32 weeks for both arms and a 1-year survival rate of 38% and 36%, respectively. Survival remains suboptimal for these patients.

Survival improvement is still needed, especially when new combinations remain to be investigated. One strategy is to add an active drug with a different mechanism of action to the active doublet of vinorelbine and cisplatin.

The combination of vinorelbine plus ifosfamide and cisplatin has demonstrated a high response rate and has improved 1-year survival in phase II trials. Several studies [6–11] have reported response rates ranging from 41% to 66%, median survival from 9.8 to 14 months and 1-year survival from 47% to 60%.

We conducted a trial with vinorelbine–ifosfamide–cisplatin (NIP) according to three different schedules: (i) arm A: cisplatin (75 mg/m² on day 1), ifosfamide (3 g/m² on day 1), vinorelbine (25 mg/m² on day 1); (ii) arm B: cisplatin (75 mg/m² on day 1), ifosfamide (3 g/m² on day 1), vinorelbine (25 mg/m² on days 1 and 8); (iii) arm C: cisplatin (75 mg/m² on day 1), ifosfamide (3 g/m² on day 1), vinorelbine (25 mg/m² on days 1 and 8, and 12.5 mg/m² on day 15). Response rates were 32%, 44% and 67% in groups A, B and C, respectively. Median survival was 6.5, 8.8 and 12.8 months for groups A, B and C, respectively. The 1-year survival observed in group C was 54% [7].

The regimen used for group C was apparently more effective than the other two, but this regimen was not easy to manage, requiring protracted hospitalisations.

Tan et al. [8] have included 78 patients with advanced/metastatic NSCLC in a NIP phase II trial: vinorelbine 25 mg/m² on days 1 and 8, ifosfamide/Mesna 3 g/m² on day 1, and cisplatin 50 mg/m² on day 1 were delivered on a 21-day schedule. The overall response rate was 58%, a median survival of 14 months, with 60% of patients alive at 1 year.

From these phase II trials, NIP regimens seem to be safe and active, and consequently we have designed a randomised phase III trial in inoperable NSCLC patients with the aim of determining whether a more intensive treatment (the three-drug regimen NIP) is better than a standard treatment (the two-drug regimen NP) in terms of survival.

**Patients and methods**

**Patients**

The inclusion criteria for patient entry to the study were: (i) histological or cytological evidence of metastatic NSCLC (stage IV disease or NSCLC in relapse after a local treatment) with no prior chemotherapy; (ii) age 18–75 years. Clinical characteristics included: (i) Karnofsky performance score (KPS) ≥80% and life expectancy ≥3 months; (ii) at least one evaluable lesion; (iii) adequate bone marrow function (granulocyte count ≥1.5 × 10⁹/L, platelet count ≥100 × 10⁹/L); (iv) adequate liver function (total bilirubin ≤1.5 × the upper limit of normal [ULN], transaminases ≤2.5 × ULN, unless due to documented liver metastases); and (v) adequate kidney function (creatinine ≤130 µmol/L). Patients were excluded from the trial if they had a local relapse suitable for treatment by radiation therapy. Additional clinical features that precluded entry into the trial were: (i) clinical signs of brain metastasis or leptomeningeal involvement; (ii) second malignancy (except adequately treated basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix); (iii) active infectious disease; (iv) uncontrolled hypercalcaemia; (v) pregnancy; (vi) neurological disorders that could interfere with the evaluation of neurological toxicity; and (vii) mentally incapacitated patients, family, social or environmental conditions impairing adequate follow-up and protocol compliance. Patients had to be willing and able to complete Visual Analogic Scale (VAS) questionnaires and give written informed consent. Local ethics committee approval had to be obtained.

**Treatment**

The treatment schedule was as follows: for arm A, vinorelbine 30 mg/m² on days 1, 8 and 15, and cisplatin 80 mg/m² on day 1, repeated every 21 days; and for arm B, vinorelbine 25 mg/m² on days 1 and 8, and cisplatin 75 mg/m² and ifosfamide 3 g/m² on day 1, repeated every 21 days.

At least two courses of treatment were given unless rapid disease progression was seen after the first course. A full assessment was performed after two courses: patients with complete or partial response received a maximum of six cycles; in case of stable disease, patients received two further cycles and thereafter the treatment was stopped. No consolidation was planned.

Chemotherapy doses were reduced for haematological, neurological, hepatic and renal toxicities. Toxicities were graded according to the World Health Organization (WHO) criteria. Changes in dosage were based on blood count results obtained on day 1 of treatment; if neutrophils were <1.5 × 10⁹/L and platelets were <100 × 10⁹/L, treatment was delayed by 1 week. Treatment on days 8 or 15 had to be cancelled if neutrophil counts were <1.0 × 10⁹/L and platelets were <100 × 10⁹/L. If treatment could not be given after a 3-week interval because of haematological toxicity, it had to be discontinued and the patient withdrawn from the study. Prophylactic use of colony-stimulating factors was not permitted. Neurological toxicity above grade 2 (including paresthesia, muscle weakness or paralytic ileus) resulted in suspension of treatment; otoxicity grade 2 or 3 resulted in a 50% dose reduction of cisplatin.

The following dose modifications of vinorelbine were implemented based on AST/ALT (aspartate aminotransferase/alanine aminotransferase) and bilirubin values on day 1 of treatment: if AST/ALT were between 5.1 and 20.0 × ULN or bilirubin was between 1.5 and 3.0 × ULN, dosing was cancelled and the patient was reassessed 1 week later. If AST/ALT were >20.0 × ULN or bilirubin was >3.0 × ULN, vinorelbine was discontinued. Renal impairment also induced vinorelbine dose modifications based upon serum creatinine and creatinine clearance as follows: if serum creatinine was grade >1, the dose was delayed by 1 week and the test repeated; if serum creatinine was greater than the normal value of the centre, the dose was delayed by 1 week and the test repeated. If after a 2-week delay, the creatinine clearance remained at the normal value of the centre, the patient was taken off the study.
If performance status at the time of the next cycle was KPS <70%, treatment was delayed by 1 week. If there was no improvement in KPS, treatment had to be stopped and the patient withdrawn.

The choice of further treatments was at the investigator’s discretion.

Objectives
The main objective was to compare the effect of a three-drug regimen (NIP) with a two-drug regimen (NP) on 1-year survival in patients with inoperable NSCLC previously untreated by chemotherapy.

The secondary aims were: (i) to compare the effect on other measures of efficacy (response rate, duration of response, time to tumour progression, median survival); (ii) to assess the impact of a three-drug regimen (NIP) compared with a two-drug regimen (NP) on patient benefit, defined as changes in KPS, patient weight and lung cancer-related symptoms (pain, dyspnoea, cough, haemoptysis, asthenia and anorexia); and (iii) to assess the safety of both regimens.

Assessments of safety and efficacy
Assessment of toxicity was made before each cycle of chemotherapy according to WHO criteria [12]. The data for each patient across all cycles of chemotherapy were used, recording the most severe result.

Appropriate scanning, or physical assessment to determine tumour involvement was completed within 2 weeks before study entry. Perpendicular diameters of representative malignant lesions were measured and recorded, and the extent of evaluable disease was assessed. Physical assessments were made by chest X-ray, bronchoscopy, ultrasound and/or computed tomography (CT) scan of chest and liver; CT scan of the brain and bone imaging was undertaken if symptoms were present. Response assessment was performed after patients had completed two cycles.

Patients responding to therapy had a repeated evaluation at least 4 weeks later using the same methods. One-year survival was the primary criterion to assess the efficacy of the two regimens, and the best response was recorded for each patient. All patients were followed up for survival every 3 months until death.

Patient benefit assessment
Each patient was classified as a clinical-benefit responder or non-responder on the basis of the following measures, as described below: (i) main measures of clinical benefit; and (ii) secondary measure of clinical benefit.

Main measures of clinical benefit: change in the lung cancer disease-related symptoms. Symptom improvement was assessed using a VAS, which was given to the patient, taking as baseline the first day of treatment. The intensity of each of the following symptoms was evaluated every 3 weeks: pain, dyspnoea, cough, haemoptysis, asthenia and anorexia. The patient was asked to place a mark along the line to indicate his or her subjective judgement. The score of each VAS was expressed as a percentage.

Main measures of clinical benefit: change in performance status. Performance status was recorded once at baseline, before randomisation, and every 3 weeks as long as the patient remained in the study.

Secondary measure of clinical benefit: change in weight. Patient’s weight was recorded at study entry and every 3 weeks, before each course.

To determine whether a patient was a clinical-benefit responder, the main measures were considered first. A patient was considered as a non-responder if either disease symptoms or performance status worsened. A patient was defined as a responder if either disease symptoms or performance status improved. If both were stable, the patient was considered as stable for main measures.

If a patient was classified as stable for the main clinical-benefit measures, the secondary measure (weight change) was examined. Such a patient was defined to be a clinical-benefit responder if weight change was classified as positive (increase of at least 3% from the baseline). If weight change was not positive, the patient was defined as a clinical-benefit non-responder.

Statistical methods
This study was designed to recruit 250 patients with 125 patients in each arm. The sample size was calculated as follows: for the patients randomised to vinorelbine–cisplatin (arm A), 1-year survival was estimated at 35%. For a suitable additional benefit from the vinorelbine–ifosfamide/Mesna–cisplatin, the objective was to detect an absolute improvement of 20% in 1-year survival. In order to have 90% confidence with a one-sided 5% level test, 230 patients were needed to detect the above difference in survival. Considering the likelihood that patients who were lost to follow-up might account for up to 5% of the total number of subjects, a total sample size of 250 eligible patients (125 patients per group) was required.

All relevant baseline assessment data were both tabulated and summarised by frequency and percentage or qualitative item and by calculating the mean and standard deviation, and median and range for quantitative items.

One-year survival was the main end point of this trial. Overall response rate was the secondary end point and was analysed for the intention-to-treat population. Comparison was performed using the chi-square test.

The analysis of safety was focused on the frequency and severity of unwanted side effects or adverse events. Toxicity was graded according to WHO criteria. The analysis was performed for the worst grade by patients and by cycle for each patient.

Duration of response was assessed using the Kaplan–Meier method for patients who achieved an objective response (complete or partial response) according to WHO criteria.

Survival was calculated from randomisation to patient death, and overall survival curves were derived using the Kaplan–Meier method and were compared using the log-rank test.

Results
Population description
Two hundred and fifty-nine patients from 37 centres in 16 countries were enrolled over 17 months between February 1998 and June 1999, with 133 patients in the NP arm and 126 in the NIP arm. Patients were well matched for pre-treatment characteristics (Table 1): age, gender, KPS, stage, histological subtype and number of metastatic sites, with the exception of liver metastases which were present in 13 patients in the NP arm and 30 patients in the NIP arm (9.8% compared with 23.8%; P = 0.003).

The mean time between diagnosis and entry to the study was 21 days (range 1 day to 43.6 months in the NP arm and 1 day to 52.7 months in the NIP arm). No patient had received previ-
uous chemotherapy for advanced disease. Twenty-four patients (NP, 16; NIP, 8) had undergone only surgery before relapsing, 11 patients (NP, 6; NIP, 5) had been treated with radiation therapy only, and 15 patients (NP, 8; NIP, 7) had received both treatments.

Extent of exposure

Among the 259 patients entered into the study, seven did not receive any treatment; four of them died between randomisation and treatment, two refused treatment after randomisation, and one had a decrease in performance score before randomisation and treatment. Patients allocated to the NP arm received a median of 4 cycles (range 1–14). The median dose intensity was 17.9 mg/m² per week (range 9.3–30.7) [odds ratio (OR) 59.8%; 95% confidence interval (CI) 31% to 102%] for vinorelbine, and 24 mg/m² per week (range 16.9–28.8) (OR 89.9%; 95% CI 63% to 108%) for cisplatin. In the NIP arm the median number of cycles administered was 4 (range 1–11). The median dose intensity was 14.6 mg/m² per week (range 6.7–17.5) (OR 87.8%; 95% CI 40% to 105%) for vinorelbine, 23.3 mg/m² per week (range 15.5–33.6) (OR 93.3%; 95% CI 62% to 134%) for cisplatin and 932 mg/m² per week (range 552–1205) (OR 93.2%; 95% CI 55% to 120%) for ifosfamide.

Four hundred and fifty-two (60.2%) cycles were completed to schedule ±3 days (197 and 255 in the NP and NIP arms, respectively) and 299 (39.8%) were delayed (193 and 106 in the NP and NIP arms, respectively). Treatment delays were mainly due to haematological toxicity (71.9% and 52.9% in the NP and NIP arms, respectively).

**Tolerance**

Assessment of tolerance was performed in 240 evaluable patients (126 and 114 in the NP and NIP arms, respectively) and over 962 courses (497 and 465 in the NP and NIP arms, respectively).

Nineteen patients were not evaluable for tolerance, seven having not been treated and 12 having received only one cycle without evaluation. Among these 12 patients, eight were in the NIP arm: five patients died (acute renal failure, pulmonary dysfunction, septic shock, pneumonia, sudden death at home as reported in the serious adverse event forms); one was lost to follow-up; and two were unevaluable for unclear reasons. Four were in the NP arm: three patients died (neutropenia without fever, pneumonia, severe abdominal pain as reported in the serious adverse event forms); and one was lost to follow-up (refusal to continue after day 1 of the first cycle).

Haematological toxicity is summarised in Table 2. Grade 3–4 anaemia was observed in 41.1% and 5% of cycles in the NP and NIP arms, respectively; thrombocytopenia was very uncommon (two cases of grade 3 in the NIP arm). The total leucocyte count and the number of neutrophils were assessed at day 21.

While 20.8% of patients in the NP arm and 8.9% of patients in the NIP arm developed grade 4 neutropenia, this represented 7.6% of administered courses in the NP arm and 2.7% in the NIP arm; however, seven patients developed fatal infections during periods of neutropenia. Four toxic deaths occurred in the NP arm, and eight occurred in the NIP arm (P = 0.2). Eight deaths (three and five in the NP and NIP arms, respectively) also occurred in the 19 patients unevaluable for tolerance.

Clinical tolerance is reported in Table 2. Gastrointestinal tract toxicities included grade 3–4 nausea and vomiting observed in 22.2% and 19.4% of treated patients in the NP and NIP arms, respectively (7.7% and 7.7% of cycles, respectively), and no grade 4 toxicity was observed in the NP arm; four patients in the NP arm and two in the NIP arm experienced grade 3 diarrhoea. WHO grade 3–4 mucositis was not experienced by any patient in the NP arm, but by five patients in the NIP arm.

In assessable patients, alopecia was observed in 80 patients in the NP arm (seven cases of grade 3) and in 87 patients in the NIP arm (34 cases of grade 3).

No patient showed significant elevation of bilirubin. Rare grade 3–4 elevation of transaminases or serum alkaline phosphatase was observed (0.4% of cycles only in the NP arm for transaminases, and 0.2% of cycles in the NP arm compared with 0.5% in the NIP arm for serum alkaline phosphatase).

**Clinical benefit**

Globally, no difference was apparent between the NP and NIP arms as 70% and 57% of patients for NP and 68% and 62% of patients for NIP can be considered as responders after two and four courses, respectively. The completion of the VAS

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**Table 1. Characteristics of randomised patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NP (n = 133)</th>
<th>NIP (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (34–76)</td>
<td>60 (36–75)</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>95/38</td>
<td>96/30</td>
</tr>
<tr>
<td>Karnofsky performance score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100%</td>
<td>87 (65.4%)</td>
<td>78 (61.9%)</td>
</tr>
<tr>
<td>80%</td>
<td>46 (34.6%)</td>
<td>48 (38.1%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>121 (91%)</td>
<td>110 (87.3%)</td>
</tr>
<tr>
<td>Relapsing</td>
<td>12 (9.0%)</td>
<td>16 (12.7%)</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>53 (49.9%)</td>
<td>60 (47.6%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>47 (35.3%)</td>
<td>43 (34.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (24.8%)</td>
<td>23 (18.3%)</td>
</tr>
<tr>
<td>No. of tumour organ sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (4.5%)</td>
<td>6 (4.8%)</td>
</tr>
<tr>
<td>2</td>
<td>29 (21.8%)</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>98 (73.7%)</td>
<td>100 (79.2%)</td>
</tr>
</tbody>
</table>

NP, vinorelbine–cisplatin; NIP, vinorelbine–ifosfamide–cisplatin.
decreased along the course of treatment; 69% of patients had evaluable VAS scores after two courses, and only 46% had them after four courses.

Overall, in both arms, improvement was noticed in all patients, even after only one course, for pain, cough, dyspnoea and haemoptysis. With respect to asthenia and anorexia, a slight deterioration appeared after the first course in both arms, and more predominantly after the second course.

Survival
At the cut-off date of January 2001, 217 patients had died, 111 in the NP arm and 106 in the NIP arm, and the median follow-up for the 42 living patients was 23.2 months (range 18.6–31.8 months). Survival-related parameters are reported in Table 3.

There was no difference in survival between the two arms (Figures 1 and 2). Median progression-free survival was 5.0 and 4.4 months in the NP and NIP arms, respectively (log-rank test, \( P = 0.87 \)). Median survival was 10.0 months for NP and 8.2 months for NIP (log-rank test, \( P = 0.24 \)). The estimated 1-year survival rate was 38.4% for NP and 33.7% for NIP (log-rank test, \( P = 0.24 \)).

Tumour response
The response data of the 259 patients included in the analysis are summarised in Table 4. Forty-six partial responses were observed in the NP arm, while in the NIP arm, one patient achieved a complete response and 44 patients a partial response, giving objective response rates of 35.7% (95% CI 27% to 44%) and 34.6% (95% CI 27% to 43%), respectively. The median duration of response was 8.1 and 9.4 months for NP and NIP, respectively. Disease control (responders with stable disease) was 64.7% (95% CI 57% to 73%) for the NP arm and 59.5% (95% CI 51% to 68%) for the NIP arm.

No difference was found in terms of response between the two arms (\( \chi^2 \) test, \( P = 0.85 \)).

Discussion
Over the past 10 years, there have been considerable changes in the treatment of NSCLC, especially concerning the management of stage IV disease which comprises more than half of all NSCLC patients.

In 1995, a large meta-analysis confirmed the role of chemotherapy (especially platinum-based chemotherapy) in this
setting [1], with an increased median survival of 1.5 months over best supportive care.

The combination of vinorelbine and cisplatin has been studied in several large phase III studies over the last 10 years, demonstrating high levels of efficacy, achieving an overall response of 30%, median survivals of around 8–9 months, and 1-year survival rates around 35%. These results have established vinorelbine–cisplatin as a standard treatment for NSCLC stage IV disease.

Triplet combinations have been widely developed in the field of NSCLC treatment in order to improve both response and survival. The two most commonly used triplets have been MVP (mitomycin C with vindesine and cisplatin) and MIC (mitomycin C with ifosfamide and cisplatin). Crino [13] has compared these two triplets to cisplatin and etoposide, which was considered to be a standard doublet in the early 1990s. The two triplets offered significant advantages in terms of response rate and survival estimates analysed by the log-rank test, with a slight superiority for MIC. As a result, Crino et al. [14] decided to compare MIC with a newly emerging doublet, gemcitabine–cisplatin. This doublet offered a significant superiority in terms of response but failed to demonstrate any advantage in terms of survival, either assessed as median survival or 1-year survival.

Figure 1. Progression-free survival for all patients (cut-off date 1 January 2001).

Figure 2. Overall survival for all patients (cut-off date 1 January 2001).
Vinorelbine has been studied extensively in triplet combinations with several active agents against NSCLC. Among all vinorelbine-based triplets, the largest experience has been reported with cisplatin and ifosfamide.

The present protocol was designed to detect an absolute improvement of 20% in the 1-year survival of the triplet. Concerning the schedules used, NIP was given every 3 weeks with vinorelbine administered on days 1 and 8, based on the previous phase II experience. In the NP arm, vinorelbine was administered weekly (according to the phase III regimens), but cisplatin was repeated every 3 weeks in order to have an equivalent schedule between both arms, and to avoid any discrepancy in terms of tolerance. The results of the study show that the toxicity profile of the two arms is acceptable. It should be noticed that the toxicities have not been evaluated at the nadir but at day 21; in the NP arm, vinorelbine was able to be administered on day 15 to 54.3% of the patients (34.9% of the cycles).

In terms of efficacy, response rates are similar in both arms, with confirmation for NP of activity around 35%, but results are lower than previously reported phase II trials for NIP at 35.7%. More surprisingly, NP generated superior results compared with NIP, with a 2-month benefit for mean survival, and 38.2% versus 32.7%, respectively, for 1-year survival (although this was not statistically significant). This trend in favour of NP might be explained by the different schedules of vinorelbine (25 mg/m² on days 1 and 8 for NIP, and 30 mg/m² once weekly for NP), which allowed an increased dose-intensity in the NP arm; this would support the suggestion by Banerjee [15] that dosage of vinorelbine correlates with survival.

Due to the arrival of several new cytotoxics, many new triplets have been tested in recent years. Vinorelbine has been combined in several phase II studies with gemcitabine and cisplatin/ifosfamide, leading to response rates of 44–65% and median and 1-year survival of 8.6–13 months and 38–65%, respectively [16–19]. Combinations of gemcitabine, ifosfamide and cisplatin [20, 21], or gemcitabine, paclitaxel (or docetaxel) and a platinum salt are numerous and all provide phase II results in the same range in terms of response and survival, generally at the cost of high haematological toxicity (high rate of transfusion and/or requirement for growth factors). With a 2-week schedule of gemcitabine, paclitaxel and cisplatin, Sorensen et al. [22] reported an overall response rate of 54% in 43 patients, with a mean survival of 10.7 months and 1-year survival of 47%; 77% of the patients experienced grade 3–4 neutropenia and 12 patients had grade 3 neurotoxicity. In a trial involving 71 patients treated with gemcitabine, paclitaxel and carboplatin, Burris et al. [23] found 44% of patients with grade 3–4 thrombocytopenia (nine patients required platelet transfusion), 32% of patients with grade 3–4 anemia, 16% with sepsis, 41% with grade 3–4 fatigue and 26% with grade 3–4 myalgia. With a combination of gemcitabine, docetaxel and carboplatin (supported with growth factors), Pacsides et al. [24] found that of 45 patients in total, 46.6% had neutropenia, 28.8% had thrombocytopenia and 22.2% had neurotoxicity, all grade 3–4.

Comella et al. [25] compared two new doublets, vinorelbine–cisplatin and gemcitabine–cisplatin, with a new triplet vinorelbine–gemcitabine–cisplatin. The triplet showed a significant advantage in terms of survival compared with the doublets, after only 60 patients had been accrued in each arm.

The Eastern Cooperative Oncology Group (ECOG) E 1594 trial [27] has recently demonstrated that four platinum-based doublets provide equivalent efficacy results that are in line with previous published phase III studies; it is obvious that a sort of limit has been reached [28] for the level of effectiveness of treatment

The Eastern Cooperative Oncology Group (ECOG) E 1594 trial [27] has recently demonstrated that four platinum-based doublets provide equivalent efficacy results that are in line with previous published phase III studies; it is obvious that a sort of limit has been reached [28] for the level of effectiveness of treatment.

Cisplatin, despite being considered the ‘key drug’ in NSCLC, is associated with several distressing toxicities in this subset of patients. There is a need for new approaches to both improve the results and to decrease the toxicities. One approach could be to move to consolidation after three or four cycles of cisplatin-based combination, but to administer only the second drug. Another promising approach could be to explore non-platinum combinations. Kosmidis [29] has shown favourable

Table 4. Response by treatment arm

<table>
<thead>
<tr>
<th></th>
<th>NIP, n (%)</th>
<th>NIP, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 133)</td>
<td>(n = 126)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>46 (34.6)</td>
<td>44 (34.9)</td>
</tr>
<tr>
<td>Overall response (CR + PR)</td>
<td>46 (34.6)</td>
<td>45 (35.7)</td>
</tr>
<tr>
<td>95% confidence interval (CI)</td>
<td>27–43</td>
<td>27–44</td>
</tr>
<tr>
<td>No change (NC)</td>
<td>40 (30.1)</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>Disease control (CR + PR + NC)</td>
<td>86 (64.7)</td>
<td>75 (59.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>57–73</td>
<td>51–68</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>47 (35.3)</td>
<td>51 (40.5)</td>
</tr>
</tbody>
</table>

NP, vinorelbine–cisplatin; NIP, vinorelbine–ifosfamide–cisplatin.
results for paclitaxel–gemcitabine compared with paclitaxel–
carboplatin. Based on the above, we have decided to imple-
ment a new phase III trial comparing vinorelbine–
gemcitabine with vinorelbine–
carboplatin. Recruitment is on-going into
this trial.

In conclusion, the place for the use of a classical triplet
combination in metastatic NSCLC is still not resolved. The
classical triplets do not show any survival superiority in large
randomised trials. So it may be necessary to consider new
triplets in which the third compound has a different mechan-
ism of action and toxicity profile. In this setting, agents such as
an epidermal growth factor tyrosine kinase receptor inhibitor,
or monoclonal anti-Her-2 neu antibody might be considered.
Results of ongoing trials are awaited.

Acknowledgements
This study was conducted according to Good Clinical Practice
standards and supported by the Institut de Recherche Pierre
Fabre with their provision of vinorelbine (Navelbine®; Pierre
Fabre Médicament, Boulogne, France), documentation of treat-
ment, data management and statistical analysis.

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Table 5. Comparison of doublet combinations with triplet combinations

<table>
<thead>
<tr>
<th>Schedules</th>
<th>OR (%)</th>
<th>P value</th>
<th>Median survival</th>
<th>One-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>36</td>
<td></td>
<td>42 weeks</td>
<td>–</td>
</tr>
<tr>
<td>CDDP–VP16</td>
<td>23</td>
<td></td>
<td>27 weeks</td>
<td>–</td>
</tr>
<tr>
<td>MIC [13]</td>
<td>40</td>
<td>&lt;0.01</td>
<td>36 weeks</td>
<td>–</td>
</tr>
<tr>
<td>GP</td>
<td>38</td>
<td></td>
<td>8.6 months</td>
<td>33</td>
</tr>
<tr>
<td>MIC [14]</td>
<td>26</td>
<td>0.029</td>
<td>9.6 months</td>
<td>34</td>
</tr>
<tr>
<td>NP</td>
<td>25</td>
<td></td>
<td>35 weeks</td>
<td>34</td>
</tr>
<tr>
<td>GP</td>
<td>30</td>
<td></td>
<td>42 weeks</td>
<td>40</td>
</tr>
<tr>
<td>NGP [25]</td>
<td>47</td>
<td></td>
<td>51 weeks</td>
<td>45</td>
</tr>
<tr>
<td>GP</td>
<td>41</td>
<td></td>
<td>40.8 weeks</td>
<td>–</td>
</tr>
<tr>
<td>NGP</td>
<td>40</td>
<td></td>
<td>34.4 weeks</td>
<td>–</td>
</tr>
<tr>
<td>NG→NI [29]</td>
<td>24.1</td>
<td></td>
<td>44.8 weeks</td>
<td>–</td>
</tr>
<tr>
<td>NP</td>
<td>34.6</td>
<td></td>
<td>10 months</td>
<td>38.4</td>
</tr>
<tr>
<td>NIP</td>
<td>35.7</td>
<td></td>
<td>8.2 months</td>
<td>33.7</td>
</tr>
</tbody>
</table>

OR, odds ratio; MVP, mitomycin C–vindesine–cisplatin; CDDP–VP16, cisplatin-etoposide;
MIC, mitomycin C–ifosfamide–cisplatin; GP, gemcitabine–cisplatin; NP, vinorelbine–cisplatin;
NGP, vinorelbine–gemcitabine–cisplatin; NG, vinorelbine–gemcitabine; NI, vinorelbine–ifosfamide;
NIP, vinorelbine–ifosfamide–cisplatin.