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Multicentre randomised phase III study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced non-small cell lung cancer

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Abstract

This study compares two cytotoxic regimens comprising the same dose and schedule of cisplatin (CP) plus vinorelbine (VNR) or gemcitabine (GEM) administered under the same schedule to patients with advanced non-small cell lung cancers (NSCLC). From April 1998 to February 2003, 285 patients were randomised to receive either VNR 25 mg/m^2 on days 1 and 8 as an intravenous (i.v.) bolus plus CP 75 mg/m^2 on day 1 (regimen A) or GEM 1200 mg/m^2 on days 1 and 8 as an i.v. 30-min infusion plus CP 75 mg/m^2 on day 1 (regimen B). Both treatments were recycled every 21 days. If no progression had occurred after six cycles, the patients continued to receive VNR or GEM monochemotherapy weekly. Cross-over of the two single agents was considered if disease progression occurred. Objective response (OR), time to progression (TTP) and overall survival (OS) were analysed according to the intention-to-treat principle. 272 patients were ultimately eligible (137 on A and 135 on B). Their main characteristics were: male/female ratio 214/58; median age 63 (range 32–77) years; median Karnofsky Performance Status (PS) 80 (range 70–100); stage IIIB 34%, stage IV 61%, recurrent disease 5%; histology – epidermoid 29%, adenocarcinoma 53%, other NSCLC 18%. The characteristics of the patients in the two arms were well matched. The following response rates were observed in regimens A and B, respectively: complete response (CR) 0.7% and 3.7%, partial response (PR) 31.9% and 22.2% ($P = 0.321$). Median CR + PR duration was 8 months in both arms. Clinical benefit represented by an improvement in symptoms was evident in 25.7% and 28.1%, respectively. Median TTP was 5 months in both arms and median OS 11 months in both arms. Grade III–IV neutropenia occurred in 30.7% and 17.7% of the patients in arms A and B, respectively ($P = 0.017$); thrombocytopenia occurred in 0% and 9.3% ($P = 0.004$), respectively. No difference in the incidence of anaemia was observed. Non-haematological toxicity was generally mild: a higher incidence of grade 1–2 peripheral neurotoxicity and grade 1–2 local toxicity with regimen A and grade 1–2 liver toxicity with regimen B was reported. A pharmacoeconomic comparison showed a difference between the two doublets, principally due to the different costs of VNR and GEM. Under the study conditions the combination of VNR or GEM with the same dose and schedule of CP produced similar OR,

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clinical benefits, TTP and OS in advanced NSCLC, and only mild toxicological differences were observed. Pharmaco-economic evaluation favoured the CP + VNR doublet.

Keywords: NSCLC; Vinorelbine; Gemcitabine; Cisplatin

1. Introduction

Two drug regimens containing platinum derivatives are the standard treatments for advanced non-small cell lung cancers (NSCLC) in patients with good performance status [1]. These regimens are represented by the doublets cisplatin (CP) plus gemcitabine (GEM), or vinorelbine (VNR) or paclitaxel or docetaxel, and the doublet carboplatin plus paclitaxel. As any differences in the activity of these regimens are small, their toxicological profiles and pharmaco-economic features may be important in deciding which should be administered in clinical practice.

At present, CP is considered to be the reference drug for advanced NSCLC, but the optimal dose of CP has not yet been determined, as a wide dose range between 60 and 120 mg/m^2 is used. The higher doses are associated with a higher incidence of typical side-effects such as nausea/vomiting, renal impairment and cumulative neurotoxicity.

VNR is a vinca derivative whose activity in advanced NSCLC was demonstrated toward the end of the 1980s. At a weekly dose of 30 mg/m^2, its combination with CP at a dose of 120 mg/m^2 on day 1 proved superior to a combination of vindesine plus CP given at the same dose [2]. In these combinations the dose-limiting toxicity was neuropathy and myelosuppression, necessitating a reduction in the dose of both drugs so that the dose intensity of VNR was reduced by around 30%. Subsequently, the Southwest Oncology Group (SWOG) carried out a trial in which VNR was administered weekly at a dose of 25 mg/m^2 and CP at 100 mg/m^2, and that regimen was compared to single-agent CP [3]. The combination was superior to the single agent in terms of response rate, time to progression and survival. The most important side-effect was again myelosuppression. This CP + VNR regimen became the standard for SWOG and a reference regimen for clinical trials in patients with advanced NSCLC. However, in this combination also the VNR dose was reduced by around 50% on day 15, as was that of CP (a 50% reduction in courses 3 and 4).

Between 1992 and 1996 our group carried out a phase III trial to compare two doublets containing the same dose of CP (60 mg/m^2) and high-dose epirubicin (on day 1) or VNR 25 mg/m^2 (on days 1 and 8) in advanced NSCLC. The cycles were repeated every 21 days [4]. The trial demonstrated the same antitumour activity for both doublets but a better toxicological profile for CP + VNR. In particular, the CP + VNR combination had an overall response rate of 27% in 103 patients, with a median overall survival of 9.6 months and 1-year survival of 39%. On the basis of this trial, the regimen CP + VNR on days 1 and 8 repeated every 21 days became our standard treatment in clinical practice.

By early in 1998 many phase II trials had shown that the combination CP + GEM was very active in advanced NSCLC: the objective response rate ranged from 26% to 54%, with 1-year survival in the range 35–61% and median survival in the range 8–13 months [5–10]. In these trials GEM was administered on a weekly basis for 3 weeks out of every 4 weeks or for 2 weeks out of every 3 weeks.

The present trial was designed to determine whether the experimental regimen of CP + GEM offers any advantages over our standard regimen of CP + VNR. The only difference between the two regimens was the presence of GEM or VNR; the CP dose and schedule (75 mg/m^2 on day 1) and the GEM and VNR timing schedules (days 1 and 8) were identical in both arms. The chief aim was to compare the objective response, the time to progression and the survival.

2. Patients and methods

2.1. Patient population

Patients had to fulfil the following criteria to be candidates for randomisation: histological or cytological diagnosis of NSCLC; stage IIIB, IV or recurrent disease after an operation for primary NSCLC; Karnofsky Performance Status (KPS) $\geqslant 70$; no prior chemotherapy or radiation therapy; adequate marrow (granulocyte count >1500/μl; platelet count of at least 100,000/μl), cardiac, hepatic and renal (serum creatinine <1.5 mg/dl) functions. Patients with the following conditions were excluded: symptomatic brain metastases, previous or concomitant malignancies, with the exception of *in situ* carcinoma of the cervix and adequately controlled, non-melanoma skin cancer. The ethical committee of each participating centre approved the study protocol. All patients gave written informed consent.

2.2. Study plan and treatments

After stratification by stage (IIIB vs. IV/recurrent disease), KPS (70/80 vs. 90/100) and by participating centre, the patients were randomised to receive either

regimen A (CP + VNR) or regimen B (CP + GEM). CP at a dose of 75 mg/m^2 was administered on day 1 in a 1-h intravenous (i.v.) infusion with pre- and post-treatment hydration and standard forced diuresis after the administration of VNR or GEM. VNR was administered by i.v. bolus at a dose of 25 mg/m^2 on days 1 and 8 and GEM was administered by 30 min i.v. infusion at a dose of 1200 mg/m^2 on days 1 and 8. On day 1, antiemetic treatment (including dexamethasone 20 mg i.v. and granisetron 3 mg or other 5-hydroxytryptamine$_3$ receptor antagonists) was administered. On day 8, antiemetic premedication with dexamethasone 12 mg i.v. was scheduled for GEM only.

Both regimens were recycled every 3 weeks for up to six cycles in the absence of progressive disease or intolerance. Single-agent maintenance therapy (regimen A: VNR 25 mg/m^2; regimen B: GEM 1000 mg/m^2) was scheduled on days 1, 8 and 15 within each 28 days if disease progression was not evident after six cycles. Maintenance therapy was continued until there was progression or intolerance. When disease progression occurred, either during the first six cycles or during single-agent maintenance therapy, a second-line single-agent therapy with cross-over of the two drugs was considered after evaluation by the physician in charge. Second-line monotherapy schedules were the same as those described for maintenance therapy. Responding patients with intrathoracic disease were evaluated for surgery or radiotherapy after at least four cycles.

2.3. Dose modification

During the treatment, patients had a complete blood cell count each week. VNR or GEM were not administered on day 8 if neutrophils were <1500/μl and/or thrombocytes were <75.000/μl. If there was grade 4 neutropenia for more than 3 days, or febrile neutropenia or grade 4 thrombocytopenia, then the drug doses were reduced by 25% in the subsequent cycle. The CP dose was reduced by 50% in second or subsequent cycles if the serum creatinine on day 1 was >1.5 and <2.0 mg/dl, and the calculated creatinine clearance was at least 50 ml/min CP was withheld if the calculated creatinine clearance was less than 50 ml/min.

2.4. Evaluation

At entry all patients underwent a complete disease staging according to a standard protocol [physical examination, radiographs and computed tomographic (CT) scans of the chest, bronchoscopy, ultrasonography or CT scans of the upper abdomen, bone scan, blood count, biochemical tests and electrocardiogram]. Other tests were performed if necessary. The physical examination, a complete blood count and biochemical tests were repeated at every cycle. Interim blood counts were made once a week during the treatment. A chest radiograph was scheduled after the first and second cycles, and thereafter every two cycles. A CT scan was scheduled after three or four cycles. The objective response was assessed in accordance with World Health Organisation (WHO) criteria [11]. A clinician and a radiologist carried out the external evaluations of all the objective responses. The duration of any objective remission was calculated as the period from the beginning of treatment to evidence of progression. The suspension of treatment after the first two cycles for reasons other than refusal or toxicity, or events not related to the cancer or interruption of follow-up, was considered as progression.

Time to progression (TTP) was defined as the time from random assignment to the first evidence of progressive disease or death, if progression was not documented. Survival was measured from the time of random assignment to the date of death or the date of the last contact with the patient if lost to follow-up. Toxicity was assessed at every cycle using WHO criteria [11]. In this paper, side-effects are aggregated according to the greatest intensity observed in each patient. Clinical benefit was evaluated by monitoring symptoms such as pain, dyspnoea and cough from the outset, and during subsequent cycles, according to a previously used 3-grade coding system [4]. In particular, the evaluation of pain was based on the level of consumption of analgesics, dyspnoea on clinical manifestations (absent, under exertion and at rest), and cough on the need for antitussic medication.

2.5. Resource utilisation measures

Consistent with the design of the clinical trial, we performed a cost-minimisation analysis from a hospital management perspective [12]. We identified and quantified the immediate medical costs, and turned them into monetary values. For the two chemotherapeutic regimens, we assessed the cost of the drugs alone, because the costs of drug delivery, supportive medications and medical procedures were identical for the two groups and were therefore irrelevant for comparative purposes.

We also assessed the cost of toxicity-related treatments, as these differed between the two arms. These costs concerned blood cell and platelet transfusions and central venous access, granulocyte growth factors and antibiotics. Unit costs are presented in the appendix to Table 6, accrued from the hospital pharmacy.

2.6. Statistical aspects

The trial was designed to verify the results obtained at that time with the CP + GEM regimen, as represented in particular by a high response rate rather than by TTP or survival. For this reason, the main aim concerned the response rate. The number of patients to be enrolled was

calculated on the basis of the expected overall tumour response. An objective response of 27% for the reference treatment (CP + VNR) was assumed on the basis of a previous trial [4] and a 15% difference between the reference treatment and the new regimen (CP + GEM) was considered to be of clinical interest. Given alfadES = 0.05 and power $(1-\beta) = 0.80$, and a one-sided level of significance, a sample size of 130 patients per treatment arm was computed. All the randomised eligible patients were included for analysis of objective response, TTP and overall survival, according to the intention-to-treat principle.

Descriptive statistics were used for the demographic and baseline disease characteristics of the study population. The overall tumour response and incidence of adverse effects were analysed using the appropriate method for ordered or non-ordered categorical data: tabulated data were compared by the Pearson χ^2-test. Confidence intervals (95%) were calculated assuming a binomial distribution. Variables concerning TTP and overall survival were analysed according to the Kaplan–Meyer product-limit method and the differences were assessed by both the log-rank tests.

For the pharmaco-economic analysis, although the costs had a skewed distribution, we present mean not median values, because the mean can easily be transferred and applied across the whole population [12]. We formally tested the difference in direct costs between the two treatments using the Mann–Whitney *U* test. *P*-values <0.05 were considered statistically significant.

3. Results

From April 1998 to March 2003, 286 patients were enrolled on the study and were randomised to receive either regimen A (CP + VNR; 143 patients) or regimen B (CP + GEM; 143 patients). Fourteen non-eligible patients (six in regimen A and eight in regimen B) were excluded from the analysis as they did not comply with the inclusion criteria. The reasons were as follows: six did not have stage IIIB or IV, or recurrent, disease, three had had prior malignant neoplasms, one had non-NSCLC histology, one had low KPS and three had insufficiently documented baseline data. The main characteristics of the eligible patients are reported in Table 1. The two groups were well matched and there was no statistical significant difference in the distribution of sex, age, KPS, histotype or stage. The majority of stage IIIB cases had N3 disease.

3.1. Delivered treatment

A CONSORT flowchart for the progress of patients through the study is shown in Fig. 1 and an outline of the treatment cycling is presented in Fig. 2. 146 (53.7%) patients completed the six cycles; the reasons for non-completion in the remaining patients were as follows: two non-starters, three refusals, 2 toxicity, 4 cardiovascular disease not due to the treatment, three deaths for reasons not due to disease progression, 2 radiotherapy, 10 lost follow-up and 100 progressions. The median number of cycles per patient was six for both arms (ranges 1–10 with regimen A and 1–7 with regimen B). The mean percentages of doses actually administered as compared with the planned dose in the scheduled time intervals during the administration of the CP combinations were 86.8% for VNR, 88.9% for GEM, 96.6% for CP (+VNR) and 98.9% for CP (+GEM). 98 patients (36%) received single-agent maintenance therapy after the completion of six cycles; 93 patients (34.2%) received second-line chemotherapy; 79 (corresponding to 29.1%), received single-agent cross-over treatment. Second-line therapy differing from single-agent cross-over treatment consisted of various regimens, the more frequent of which was taxotere monotherapy.

Table 1
Patient characteristics

	CP + VNR, *n* = 137	CP + GEM, *n* = 135	Total, *n* = 272
Male/female	104/33	110/25	214/58
Median age (range) (years)	62 (32–75)	63 (33–77)	63 (32–77)
Median Karnofsky PS (range)	80 (70–100)	80 (70–100)	80 (70–100)
Histology			
Epidermoid	40 (29%)	38 (28%)	78 (29%)
Adenocarcinoma	71 (52%)	73 (54%)	144 (53%)
Other NSCLC	26 (19%)	24 (18%)	50 (18%)
Stage			
IIIB	44 (32%)	49 (36%)	93 (34%)
IV	90 (65%)	75 (56%)	165 (61%)
Recurrence	3 (2%)	11 (8%)	14 (5%)

Abbreviations: CP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; NSCLC, non-small cell lung cancer; PS, performance status.

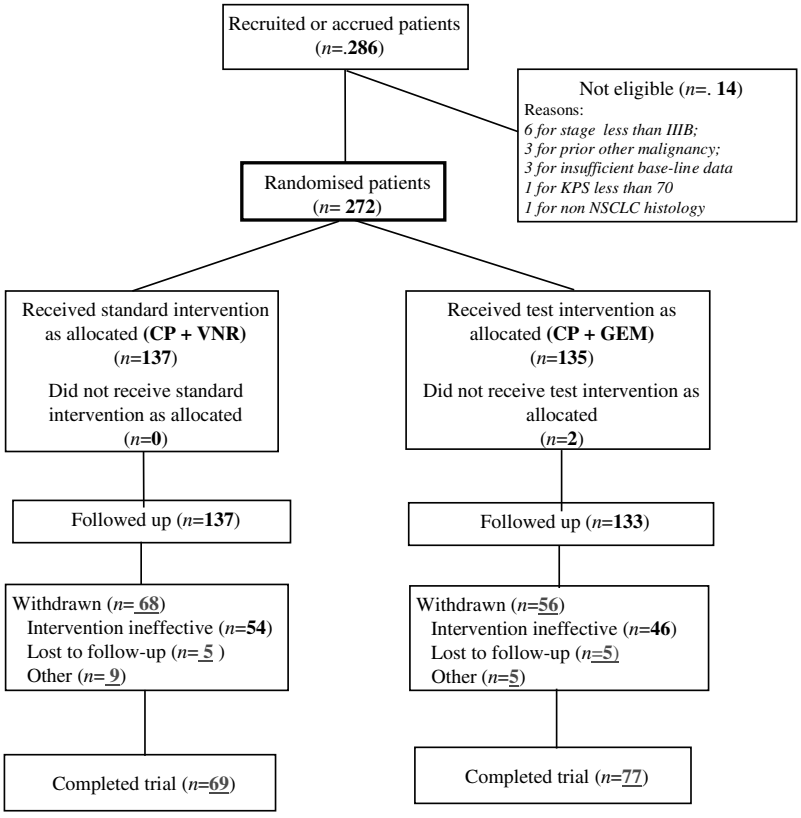

Fig. 1. Flow chart of the progress of patients through the trial (CP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; KPS, Karnofsky PS; NSCLC, non-small cell lung cancer) (adapted from Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996; **276**;637–639).

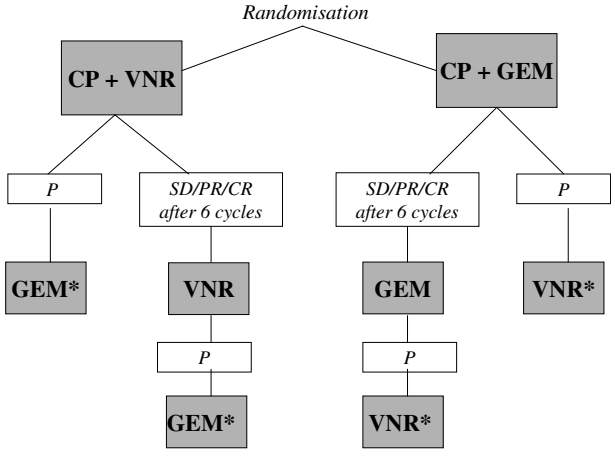

Fig. 2. Outline of the study. SD, stable disease; PR, partial response; CR, complete response; GEM, gemcitabine; VNR, vinorelbine; CP, cisplatin.

3.2. Toxicity

The side-effects are reported in Table 2. The incidence of grade 3–4 neutropenia was higher in regimen A (30.7% vs. 17.7%, $P = 0.017$). Febrile neutropenia was observed in 7 patients on arm A; it was usually treated on an outpatient basis with granulocyte growth factors and antibiotics for a mean duration of 4 days. One of these patients, who had febrile neutropenia and an acute abdomen after the first cycle of CP + VNR, was hospitalised and died within a few days. Grade 3–4 anaemia was observed in 7.1% (regimen A) and 3.9% (regimen B), respectively; in 11 and 9 patients red cell transfusions were administered. Thrombocytopenia was more frequent in regimen B, but only in one instance was a platelet transfusion necessary. Non-haematological toxicity was on the whole moderate: no difference was observed between the two regimens for emesis, stomatitis, fever, alopecia and renal toxicity; mild-to-moderate peripheral neuropathy was higher in regimen A, while grade 1–2 liver toxicity, represented by a moderate increase in transaminases and/or bilirubin, although of low incidence, was more frequent with regimen B; a higher incidence of grade 1–2 local reactions at the site of i.v. injection (pain, erythema, swelling or phlebitis) was observed in arm A (15.2% of patients) than in arm B (1.6%) ($P = 0.000$).

Table 2
Side-effects of the two regimens

Side-effect	CP + VNR			CP + GEM			*P*	
	No. evaluated	G1–4 (%)	G3/4 (%)	No. evaluated	G1-4 (%)	G3/4 (%)	Total	G3/4
Neutropenia	124	57.3	30.7	124	49.2	17.7	ns	0.017
Anaemia	127	52.8	7.1	128	49.2	3.9	ns	ns
Thrombocytopenia	126	4.8	0	128	22.7	9.3	0.000	0.004
Nausea/vomiting	128	57.8	3.1	126	57.9	4.0	ns	ns
Fever	127	18.9	2.4	127	11.8	4.70	ns	ns
Peripheral neuropathy	128	29.7	0	123	17.9	0.8	0.028	ns
Constipation	116	9.5	0	113	9.2	0	ns	ns
Stomatitis	126	7.9	0.8	125	6.4	0	ns	ns
alopecia	126	11.1	4.8	125	19.2	8	ns	ns
Local toxicity[a]	126	15.2	0	127	1.6	0	0.000	–
Renal toxicity	127	3.1	0	126	7.1	0.8	ns	ns
Liver toxicity	128	0.8	0	123	8.1	0	0.039	–

G, grade; ns, non-statistically significant differences; other abbreviations as in Table 1.
[a] Includes pain, swelling, erythema or phlebitis in the arm where the drugs were administered.

Table 3
Objective responses to the two regimens

	CP + VNR		CP + GEM		*P*
	n	%	*n*	%	
Eligible	137	100	135	100	
CR	1	0.7	5	3.7	0.918
PR	43	31.4	31	23.0	0.293
CR + PR	*44*	*32.1*	*36*	*26.7*	0.321
SD	48	35	63	46.7	0.051
P	30	21.9	24	17.8	0.392
Not evaluable[a]	15	10.9	12	8.9	0.719

CR, complete response; PR, partial response; other abbreviations as in Tables 1 and 2.
[a] *Reasons:* 2 patients never began the treatment, 3 refused to continue, 4 presented cardiovascular complications after the 1st or 2nd cycle and were withheld, 3 patients died (1 because of toxicity and 2 for unknown causes), 8 could not be evaluated because lost to follow-up, 2 suspended for toxicity, 2 lacked data and 3 had concurrent radiotherapy to the chest.

3.3. Objective response

The objective-response analysis is reported in Table 3. Complete remission (CR) was observed in 1 (0.7%) and 5 (3.7%) patients in arms A and B, respectively. CR occurred in 2 patients with stage IIIB disease (regimen B), in four with recurrent disease (one in regimen A and three in regimen B). Three of these patients had recurrent intrathoracic disease and one had liver metastases. Partial remission (PR) occurred in 43 (31.4%) and 31 (23%) patients in arms A and B, respectively. The overall objective response (CR + PR) rate was 32.1% (95% confidence limits: 24.5–40.5%) and 26.7% (95% confidence limits: 19.5–35.1%) ($P = 0.321$). The majority of the objective remissions were observed within the fourth cycle. The median duration of remission was 8 months (95% confidence limits: 7–9 months) and 8 months (95% confidence limits: 7–10 months) on arms A and B, respectively ($P = 0.523$). The objective-response analysis by age, histotype, stage and KPS is reported in Table 4; no difference was observed between the treatments in any of the subgroups.

3.4. Clinical benefits

The evaluation of clinical benefits was based on changes in three major symptoms (pain, dyspnoea and cough) after three to four cycles. An improvement in at least one symptom without a worsening or the appearance of another was recorded in 25.7% (regimen A) and 28.1% (regimen B) of patients, respectively. There were no statistically significant differences (Table 5).

3.5. Treatment after chemotherapy

18 patients (nine in arm A and nine in arm B) were operated on after a minimum of four cycles. The operation consisted of the complete resection of the residual disease in 12 patients (six in arm A and six in arm B), incomplete resection in three and an

Table 4
Analysis of objective remissions

	CP + VNR (137 patients)		CP + GEM (135 patients)		*P*
	Total	CR + PR	Total	CR + PR	
Age (years)					
<65	97	30 (30.9%)	85	23 (27.0%)	ns
>66	40	14 (35%)	50	13 (26.0%)	
Karnofsky PS					
70–l80	76	17 (22.4%)	74	16 (21.6%)	ns
90–100	61	27 (44.2%)	61	20 (32.7%)	
Stage					
IIIB	44	20 (45.4%)	49	15 (30.6%)	ns
IV	90	22 (24.4%)	75	16 (21.3%)	
Recurrence	3	2 (66.6%)	11	5 (45.4%)	
Histology					
Adenocarcinoma	71	23 (32.3%)	73	19 (26.0%)	ns
Epidermoid	40	18 (45%)	38	14 36.8%)	
Other NSCLC	26	3 (11.5%)	24	3 (12.5%)	

ns, non-statistically significant differences; all other abbreviations as in Tables 1–3.

Table 5
Clinical benefits of the two regimens

	CP + VNR		CP + GEM		*P*
Evaluable patients	109	100%	103	100%	ns
Improvement	28	25.7	29	28.1	ns
No change	59	54.1	53	51.4	ns
Worsening	22	20.2	21	20.3	ns

ns, non-statistically significant differences; other abbreviations as in Tables 1–4.

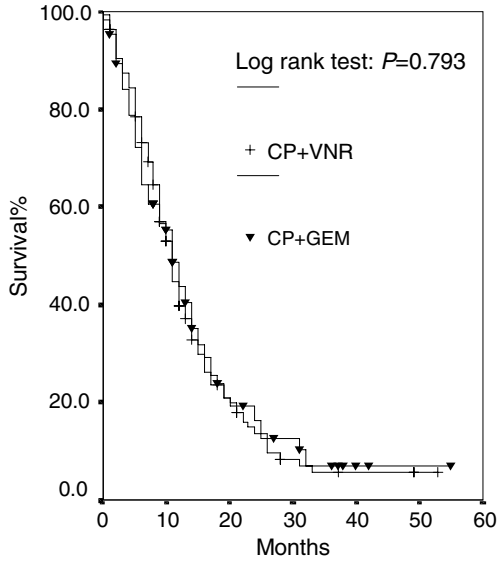

Fig. 3. Time to progression (CP, cisplatin; VNR, vinorelbine, GEM, gemcitabine).

explorative intervention in another three. 22 patients with stage IIIB disease received chest radiotherapy after chemotherapy (11 in arm A and 11 in arm B).

3.6. Time to progression and survival

Median TTP was 5 months (95% confidence limits: 4–6 months) for both arms (Fig. 3). TTP after single-agent cross-over as second-line treatment was 4 months for

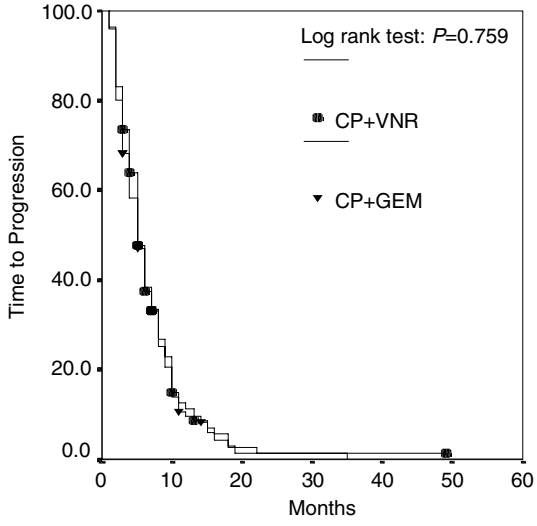

Fig. 4. Overall survival (CP, cisplatin; VNR, vinorelbine, GEM, gemcitabine).

Table 6
Pharmaco-economic analysis of the two regimens

Resources	CP + VNR (n = 87) Mean ± SD	CP + GEM (n = 78) Mean ± SD	P
Chemotherapy cost[a]	839.31 (±371.63)	2877.38 (±981.00)	<0.0001
Toxicity-related treatment cost[b]	42.93 (±84.73)	23.53 (±66.74)	0.048
Total cost per patient	882.24 (±391.66)	2900.91 (±971.20)	<0.0001

[a] Unit cost (in €) per mg: cisplatinum (CP) 0.356, vinorelbine (VNR) 1.898, gemcitabine (GEM) 0.14.
[b] *Antibiotics:* 0.0578€ per mg; granulocyte-colony-stimulating factor: 1.68€ per MU; central venous catheter implantation: 114€; red cell or platelet transfusion (per pack): 139.35€.

GEM (95% confidence limits: 2–6) and 3 months for VNR (95% confidence limits: 2–4) (P = 0.756). Two hundred and twenty five patients (82.4%) had died after a median follow-up of 45 months (range 8–68 months): 113 (82.4%) in arm A and 112 in arm B (82.9%). The survival curve, calculated for all the eligible patients, is shown in Fig. 4. The median survival was 11 months (95% confidence limits: 9–13 months) and 11 months (95% confidence limits: 9–13 months) in arms A and B, respectively. The 12-month survival was 39.7% and 44.4% and the 24-month survival was 13.7% and 16.6% in arms A and B, respectively. None of the differences was statistically significant. Out of 12 completely resected patients, five are still alive: three in arm A after 10, 28 and 37 months and two in arm B after 31 and 38 months, while five have died of disease and two lost to follow-up.

3.7. Pharmaco-economic evaluation

The two regimens were mostly delivered on an outpatient basis. They required the same time for delivery and the same commitment by the medical and nursing staff. They included the same dose and the same modality of CP administration, the same antiemetic prophylaxis; the two protocols differed only in the presence of VNR or GEM on day 1 and day 8. The pharmaco-economic analysis was limited to those patients recruited at the main centre from among those participating in the trial. Table 6 reports the mean costs of the drugs and those related to the treatment of side-effects per patient. The comparison between the two treatments showed that the direct cost of regimen A was significantly lower than that of regimen B (882.24€ vs. 2900.91€).

4. Discussion

The combination CP + VNR was originally studied in two randomised trials in France; the planned weekly administration of VNR was at a dose of 30 mg/m^2 in combination with CP administered on day 1 at a dose of 120 mg/m^2 [2] or 80 mg/m^2 [13], with the cycle restarting on the 28th and 21st days, respectively (Table 7). Subsequently, the SWOG performed two consecutive trials using weekly VNR at a dose of 25 mg/m^2 and CP at 100 mg/m^2 [3,14]. The dose intensity of VNR with weekly administration was always lower than 80% because the adopted dose was reduced or suspended, owing to severe neutropenia, especially by the third week. This regimen has been the standard of reference for the treatment of patients with advanced NSCLC for the SWOG and other international groups.

Owing to the myelotoxicity of regimens that include weekly VNR, we studied and used, more than a decade ago, VNR administered only on days 1 and 8 in combination with CP on day 1 [4]. Another Italian group used this schedule for VNR in three consecutive trials [17–19] (Table 7). The trials that used VNR on days 1 and 8 only showed that, in combination with different doses of CP (60 or 100 mg/m^2), the antitumour activity was similar to that observed with regimens containing weekly VNR, but at the same time the toxicity was reduced. Recently, a phase II study has confirmed these observations [20]. On these grounds, the regimen VNR 1–8 every 21 days was chosen as the standard treatment for the present trial.

Our trial shows no important differences in objective response, clinical benefits, TTP and overall survival between the two regimens, thus refuting our initial hypothesis, which envisaged a possibly greater activity for CP + GEM on the basis of the phase II studies available at the time of the trial design. Subsequent randomised studies using the combination CP + GEM have demonstrated that the objective response rate of the combination may range between 22% and 42% [21–26] (Table 8). The study design provided for the suspension of CP and the continuation of monochemotherapy after six cycles of combination therapy if there was no evidence of disease progression. Nevertheless, in the event of progression, both during the combination therapy and the single-drug maintenance therapy, the trial provided for second-line therapy with cross-over of the two single agents, if the physician in charge deemed that a further treatment was of use for the patient. Second-line treatment was carried out in 34.2% of cases, with cross-over of single drugs in 29.1% of cases. No significant differences emerged between the two single-agent second-line therapies.

Table 7
Results of phase III trials on cisplatin (CP) + vinorelbine (VNR) regimens in advanced non-small cell lung cancer

Authors	Regimens	CpCb dose/day of recycling	2nd Drug dose	No. of patients	Stage IV (%)	Mean no. of cycles	Dose intensity (%)	OR (%)	TTP	mS	Neutropenia	Thrombo-cytopenia	Anaemia	Neurop	na/vo	Renal
The French regimens																
Le Chevalier (1994) [2]	VNR + CP	120/28	30/week	206	49	3	71 (v)	30	–	10	78.7	2.9	–	9.4	58[d]	5.9[f]
	VDS + CP	80		200	54.5	3	98 (vs)	19	–	8	47.6	3.1	–	18	59	4.0
	VNR	–	30/week	206	47	11[c]	83 (v)	14	–	8	53.2	0	–	9.0	12	0.0
Depierre (1994) [13]	VNR + CP	80/21	30/week	116	53	–	–	43[a]	4.5[a]	8	65[g]	0	–	12.2	23	29.7[e]
	VNR	–	30/week	115	56	–	–	16	2.2	8	34	0	–	7.5	5	5
The SWOG regimen																
Wozniak (1998) [3]	VNR + CP	100/28	25/week	206	92	3	48[i] (v)	26	4	8	81[a]	6	24	8	20	5
	CP	100/28	–	209	92	2	50[j] (P)	12[a]	2[a]	6[a]	5.5	2	8	5	20	4.5
Kelly (2001) [14]	VNR + CP	100/28	25/week	202	89	3	65 (v)	28	4	8.1	76[a]	4	17	3	18[a]	?
	PTX + Cb	auc 6/21	225	206	88	4	97 (ptx)	24	4	8.6	57	10	13	13[a]	7	
Scagliotti (2002) [15]	VNR + CP	100/28	25/week	201	81	3.2	77.4 (v)	30.5	4.6	9.5	64.6[a]	0.5	19.2[a]	3	12.6[a]	1.5
	GEM + CP	75/21	1250 Day 1,8	205	81	4.0	90.6 (G)	30	5.3	9.8	38.1	36.6[a]	17.7[a]	0	6.6	0
	PTX + Cb	auc 6/21	225	201	82	4.2	94.7 (P)	31.5	5.5	10.0	50.3	7.7[a]	6.1	7[a]	0.5	0
Fossella (2003) [16]	VNR + CP	100/28	25/week	404	67.1	4	78	24.5[a]	5.7	10.1[b]	79	3.8	24[a]	3.8	16.2[a]	–
	DTX + CP	75/21	75	408	66.9	5	94	31.6[b]	5.5	11.3[b]	74.8	2.7	6.9	3.9	7.0	–
	DTX + Cb	auc 6/21	75	406	67.5	6	93	23.9	5	9.4	74.4	7	10.5	0.7	4.2	–
Regimens with VNR on days 1 & 8																
Colucci (1997) [17]	VNR + CP	100/21	25	53	58	3	–	47[a]	6	9	?	0	10	15[h]	10	20[h]
	IFO + EPI			47	53	3	–	21	4	7	?	2	4	0	15	2
Martoni (1998) [4]	VNR + CP	60/21	25	110	40	4	68 (v)	27	–	9.6	21	0	7	0	4	–
	EPI + CP	60/21	120	102	43	4	68 (E)	32	–	10.5	38[a]	6	8	0	8	–
Gebbia (2002) [18]	VNR + CP	100/28	25	122	45	4	89 (v)	39	4.2	7	–	2	0	2	13	0.1
	MVP	100//28		125	46	4	85 (vs)	42	4.5	8	–	16	0	2	13	0
Gebbia (2003) [19]	VNR + CP	100/28	25	140	53	4.7	91 (v)	44[a]	5.2	9	26	17	14	3	21	–
	GEM + CP	100(day 8)/28	1400 Day 1, 8	138	54	4.3	84 (g)	34	4.9	8.2	21	41[a]	19	2	23	–
Present series	VNR + CP	75/21	25	137	65	6	87 (v)	32	5	11	31[a]	0	7	0	3	0
	GEM + CP	75/21	1200 Day 1, 8	135	56	6	89 (g)	27	5	11	18	9[a]	4	1	4	0

OR, objective response; TTP, time to progression; GEM, gemcitabine; VDS, vindesine; IFO, ifosfamide; EPI, epirubicin; Cb, carboplatin; PTX, paclitaxel; DTX, docetaxel; MVP, mitomycin, vinobesine, cisplatin. Side-effects are of grade 3–4 if not otherwise indicated.

–, Lacking data.

[a] Statistically significant difference.

[b] Pair-wise comparison between VNR + CP vs DTX + CP was marginally statistically significant.

[c] No. of administrations.

[d] Grades 2–4.

[e] Grade 4.

[f] Creatinine >250 μmol/l.

[g] Grade 2–3.

[h] Grade 1–2.

[i] At day 15 of each course.

[j] At course 3 and 4.

Table 8
Results of phase III studies on cisplatin (CP) + gemcitabine (GEM) regimens in advanced non-small cell lung cancer

Authors	CP dose (mg/m^2)/ recycling day	No. of patients	Stage IV (%)	Mean no. of cycles	Dose intensity (%)	OR (%)	TTP	OS	Neutropenia	Thrombo-cytopenia	Anaemia	na/vo	Renal
Regimen with GEM at 1000 mg/m^2 days 1–8 and 15/28													
Sandler (2000) [21]	100/28	260	67	4	80 (g) 97 (p)	30	5.6	9.1	57.0	50.4	25	23	4.8
Schiller (2000) [22]	100/28	288	86	–	–	22	4	8	63	50	28	35	9
Crinò (1999) [23]	100/28 Day 2	155	79	4	70 (g) 87 (p)	38	5.0	8.6	49.7	63.9	30.9	18.4	0.7
Regimen with GEM at 1250 mg/m^2 days 1–8/21													
Cardenal (1999) [24]	100/21	69	52	5	93 (g) 91 (p)	41	6.9	8.7	64	55	22	39	?
Scagliotti (2002) [15]	75/21 Day 2	205	81	4	90.6 (g) 94.7 (p)	30	5.3	9.8	38.1	36.6	17.7	6.6	0
Alberola (2003) [25]	100/21	182	77	4	93 (g) ? (p)	42	6.3	9.3	32	19	11	22	2
Smit (EORTC) 2003 [26]	80/21 Day 2	160	79	5	94.7 (g) 96.4 (p)	37	5.1	8.9	43.1	36.3	11.9	12.5	–

OR, objective response; TTP, time to progression; OS, overall survival; g, gemcitabine; p, cisplatin.
Side-effects are of grade 3–4; –, lacking data.

Some difference did emerge in the toxicological profiles of the two combinations: in particular, CP + VNR was associated with a higher incidence of grade 3–4 neutropenia, grade 1–2 local toxicity and grade 1–2 peripheral neuropathy, while CP + GEM was associated with a higher incidence of thrombocytopenia and grade 1–2 liver toxicity. However, these differences do not significantly compromise the clinical practicability of the two treatments.

CP is still the reference drug in the treatment of advanced NSCLC. Although the only studies that have compared the various doses have not observed a dose-response relation in the dose range 60–120 mg/m^2 [27,28], the tendency to use high doses (100–120 mg/m^2) has for many years prevailed; at such doses CP has an important incidence of grade 3–4 side-effects, principally nausea/vomiting, anaemia, renal toxicity and cumulative neurotoxicity. The most recent phase III studies on the CP + VNR combination [14–16] have used the SWOG regimen (CP 100 + VNR 25 mg/m^2 weekly), comparing it with other doublets containing lower doses of CP (75 mg/m^2) [15,16] or carboplatin [14]. In those studies, the combination containing VNR induced a greater incidence of emesis, anaemia, as well as neutropenia [2]. For the first two toxic effects it is likely that the different doses of CP were critical. In particular, as compared with the combination CP (75 mg/m^2) + GEM, the SWOG regimen was more toxic exclusively because of these side-effects [15]. In a recent study in which the two doublets with the same dose of CP (100 mg/m^2, but administered on day 1 with VNR and on day 8 with GEM) were compared [19], none of the three above-mentioned differences emerged.

The present study is first in which doublets containing the same CP scheduling with the same administration scheme for the second drug (first and eighth day) have been compared. Another 3-arm phase III study had included two regimens with these characteristics [29], but the two combinations were analysed together, having been considered equivalent in terms of activity. Under the conditions in our study none of the differences observed in other studies in relation to emesis and anaemia emerged, thus confirming the importance of the CP dose in determining these effects, while only the differences linked to the different toxicological profiles of VNR and GEM were evident (restricted to greater grade 3–4 neutropenia for VNR and higher thrombocytopenia for GEM). The same toxicological differences have recently been confirmed in a phase III trial comparing VNR and GEM monotherapy in the treatment of elderly patients with advanced NSCLC [30].

There is, however, an evident difference at the pharmaco-economic level: the difference in cost between VNR and GEM strongly affected the overall cost of the treatments. This conclusion is particularly valid for Italy, where VNR is cheaper than in other countries.

A possible objection is that the overall costs of the resources used to perform the treatments have not been compared; we did not make this comparison as the treatments were performed in the same setting (the outpatients clinic), CP was administered at the same dose and with the same pattern, just as VNR and GEM were administered with an equivalent deployment of resources. A specific pharmaco-economic analysis performed on SWOG study S9509 [14] has shown that it is indeed the cost of the cytotoxic drugs that has a major impact on the cost of the whole treatment [31].

A limitation of the design of this trial is the inclusion of maintenance therapy. When this trial was designed it was as yet unclear whether maintenance therapy was useful in patients with advanced NSCLC. As both GEM and VNR were active as single-agent, weekly monotherapies, the original design included this kind of administration as maintenance therapy after six cycles of CP-based doublets. However, more recently, no overall benefits have been observed from extending chemotherapy beyond three or four cycles [32,33] or from the use of VNR maintenance therapy after induction chemotherapy [34].

In conclusion, in this randomised trial a comparison of two doublets containing VNR or GEM and the same dose and timing of CP showed similar objective responses, clinical benefits, TTP and overall survival in advanced NSCLC. Both combinations were well tolerated and only mild toxicological differences were observed. There are published indications that the regimen CP + GEM, containing CP at 75–80 mg/m^2 and GEM administered on days 1 and 8 every 21 days, is better tolerated than those containing higher doses of CP and/or weekly doses of GEM; from our study it now emerges that the combination of VNR at 25 mg/m^2 on days 1 and 8 with CP at 75 mg/m^2 on day 1 every 21 days has a similar activity to regimens that include higher doses of CP and/or weekly administrations of VNR, which have so far been the regimens of reference. The CP + VNR regimen used here is very well tolerated and suited to patients with advanced NSCLC. For chemotherapies that are equivalent in their efficacy and tolerance, albeit with slightly different toxicological profiles, a pharmaco-economic evaluation becomes important in the ultimate choice of treatment.

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