original article

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Global Lung Oncology Branch trial 3 (GLOB3): final results of a randomised multinational phase III study alternating oral and i.v. vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer

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Background: The study compared the efficacy of a first-line treatment with day 1 i.v. vinorelbine (NVBiv) and day 8 oral vinorelbine (NVBo) versus docetaxel (DCT) in a cisplatin-based combination in advanced non-small-cell lung cancer, in terms of time to treatment failure (TTF), overall response, progression-free survival (PFS), overall survival (OS), tolerance and quality of life (QoL).

Methods: Patients were randomly assigned to receive cisplatin 80 mg/m^2 with NVBiv 30 mg/m^2 on day 1 and NVBo 80 mg/m^2 on day 8 every 3 weeks, after a first cycle of NVBiv 25 mg/m^2 on day 1 and NVBo 60 mg/m^2 on day 8 (arm A) or cisplatin 75 mg/m^2 and DCT 75 mg/m^2 on day 1 every 3 weeks (arm B), for a maximum of six cycles in both arms.

Results: From 2 February 2004 to 1 January 2006, 390 patients were entered in a randomised study and 381 were treated. The patient characteristics are as follows (arms A/B): metastatic (%) 80.5/84.8; patients with three or more organs involved (%) 45.3/40.8; median age 59.4/62.1 years; male 139/146; squamous (%) 34.2/33.5; adenocarcinoma (%) 41.6/39.3; median TTF (arms A/B in months) [95% confidence interval (CI)]: 3.2 (3.0–4.2), 4.1 (3.4–4.5) ($P = 0.19$); overall response (arms A/B) (95% CI): 27.4% (21.2% to 34.2%), 27.2% (21.0% to 34.2%); median PFS (arms A/B in months) (95% CI): 4.9 (4.4–5.9), 5.1 (4.3–6.1) ($P = 0.99$) and median OS (arms A/B in months) (95% CI): 9.9 (8.4–11.6), 9.8 (8.8–11.5) ($P = 0.58$). The median survival for squamous histology was 8.87/9.82 months and for adenocarcinoma 11.73/11.60 months for arms A and B, respectively. Main haematological toxicity was grade 3–4 neutropenia: 24.4% (arm A) and 28.8% (arm B). QoL as measured by the Lung Cancer Symptom Scale was similar in both arms.

Conclusions: Both arms provided similar efficacy in terms of response, time-related parameters and QoL, with an acceptable tolerance profile. In the current Global Lung Oncology Branch trial 3, NVBo was shown to be effective as a substitute for the i.v. formulation. This can relieve the burden of the i.v. injection on day 8 and can optimise the hospital's resources and improve patient convenience.

Key words: advanced NSCLC, chemotherapy, navelbine oral, platinum based, phase trial study

introduction

Lung cancer is the leading cause of cancer death, with 165 280 and 58 574 deaths among men and women, respectively, reported in Europe in 2002 [1].

First-line treatment of advanced non-small-cell lung cancer (NSCLC) primarily consists of platinum cisplatin (CDDP)-based doublets that include camptothecin analogues, docetaxel (DCT), gemcitabine (GEM), paclitaxel or vinorelbine (NVB). In randomised phase III trials, these regimens have produced remission rates of 17%–44%, median progression-free survival (PFS) of 3–5 months and median overall survival (OS) of 7–11 months [2–7].

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Cancer treatment has traditionally been dominated by i.v. drug therapy [8]. There has, however, been a steady increase in the number of oral anticancer agents available during recent years, offering obvious benefits in terms of convenience and ease of administration, as well as addressing patients' preference for oral therapy [9].

Oral vinorelbine (NVBo) is a new formulation with evidence of single-agent activity in first-line chemotherapy of advanced NSCLC, reported in a randomised phase II study versus i.v. vinorelbine (NVBiv) [10]. Several phase II studies have been completed to investigate the efficacy and safety of NVBo in combination with cisplatin in the first-line treatment of advanced NSCLC [11]. The activity was comparable to that of the full NVBiv regimen used in the Southwest Oncology Group (SWOG) trials [12, 13].

Gebbia et al. [14] compared NVBiv delivered on days 1 and 8 in combination with CDDP, both agents repeated every 3 weeks with the SWOG NVBiv/CDDP doublet and reported an advantage for the days 1 and 8 NVBiv/CDDP schedule over the SWOG weekly NVBiv/CDDP in terms of tolerability, toxicity and delivery of the scheduled dose, by keeping the same efficacy.

Taking advantage of the new oral formulation of NVB, we decided to implement a randomised phase III study in chemotherapy-naive patients with stage IIIB or IV NSCLC to compare the effect of alternating NVBiv and NVBo plus cisplatin (NP) with one of the accepted standard regimens, DCT and CDDP (DP).

patients and methods

This was a multicentre, multinational, prospective, open-label, randomised phase III study carried out in 19 participating countries and 42 centres. The list of participating investigators is reported in the acknowledgements.

eligibility criteria

Patients were required to be between 18 and 75 years, with histologically or cytologically (fine needle aspiration) proven NSCLC, stage IIIB (with supraclavicular nodal metastases or pleural effusion), stage IV or relapsing (locally or distant) after a local treatment; Karnofsky performance status of 80% or more; life expectancy >12 weeks; previously untreated with chemotherapy or immunotherapy; adequate bone marrow, hepatic and renal function; neutrophils $\geq 2.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; haemoglobin >11 g/dl or 6.8 mmol//l; total bilirubin ≤1× upper limit of normal value (ULN); transaminases <2.5× ULN; alkaline phosphatases <5× ULN; creatinine ≤ULN or creatinine clearance ≥60 ml/min; with the presence of at least one measurable indicator lesion (RECIST criteria) not previously irradiated and assessed by conventional computed tomography (CT) scan: longest diameter ≥20 mm, spiral on CT scan or ≥10 mm on magnetic resonance imaging. The patient had to give written informed consent before completing any study-related procedure. Male or female patients with reproduction potential had to use an approved contraceptive method during and for 3 months after the end of study treatment. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and subsequent amendments and in compliance with Good Clinical Practice Guidelines.

stratification and treatment plan

Patients were stratified according to disease stage (IIIB/IV) and centre by using computer-generated list and randomly assigned to NP or DP.

Patients in the NP arm received as a first cycle NVBiv on day 1 and NVBo on day 8 at 25 mg/m^2 and 60 mg/m^2, respectively; in the absence of grade 3–4 haematological toxicity, the doses then increased to NVBiv 30 mg/m^2 on day 1 followed by NVBo 80 mg/m^2 on day 8. CDDP 80 mg/m^2 was administered i.v. on day 1, with adequate hydration according to the routine practice of each centre. Cycles were repeated every 3 weeks. Preventive antiemetic treatment (using an oral 5-HT_3 antagonist) was recommended before each treatment on days 1 and 8, chosen according to the investigational centre's routine. NVBo softgel capsules of 20 or 30 mg (from three to six at each administration) were to be rapidly swallowed with a glass of water without chewing or sucking. It was recommended that NVBo be administered after a light meal.

Patients in the DP arm received DCT 75 mg/m^2 in combination with CDDP 75 mg/m^2 on day 1 every 3 weeks. A total of six doses of dexamethasone 8 mg were given orally to all patients in the DP arm as prophylaxis against fluid retention and hypersensitivity reactions. Antiemetic prophylaxis was given routinely and patients receiving CDDP also received adequate hydration according to the centre's routine practice.

Treatment was modified in case of haematological and/or non-haematological toxic effects evaluated on days 1 and 8 of each cycle in both arms. All dose adjustments were made according to the system showing the greatest degree of toxicity. In the NP arm, the presence of grade 3–4 haematological toxicity resulted in NVBo doses being delayed, up to 1 week, and eventually decreased to and maintained at 60 mg/m^2. In the DP arm, DCT doses were modified for neutropenia and thrombocytopenia. If day 1 of the next cycle of DCT was delayed due to haematological toxicity, CDDP was also to be delayed and administered without dose reduction when DCT was resumed. CDDP doses were not to be modified for haematological toxicity in either arm. If the study treatments could not be administered after an additional 2 weeks delay (cycle duration >5 weeks) because of any toxicity, patients were definitively discontinued. After two cycles, tumour response was assessed. Patients showing disease progression (PD) were removed from the study. Patients showing stabilisation (no change) or complete or partial response continued the treatment to six courses. In case of documented PD before the first disease evaluation, the treatment was discontinued and the response to treatment was assessed as early progression. Second-line chemotherapy was offered at the time of relapse at the investigator's choice. The nature of any second-line therapy was recorded.

When appropriate, colony stimulating factors could be given to patients who experienced febrile neutropenia, grade 4 asymptomatic neutropenia lasting >7 days or neutropenic infection.

response, survival, quality of life and clinical benefit

Response was determined in comparison with baseline assessment of measurable disease or evaluable disease and confirmed 4 weeks later using the RECIST criteria [15]. An independent radiologists' panel was organised for all patients having a response or stable disease approaching partial remission in the range of 20%–25% according to the investigator assessment. The radiologist was kept blinded to the treatment received by the patient. Time to treatment failure (TTF) was calculated from the date of randomisation up to the date of failure (defined as progression, relapse, death, withdrawal due to adverse event, patient's refusal, loss to follow-up or start of new anticancer therapy). Duration of response was calculated from the time that measurement criteria were met for complete or partial response until the documentation of progression or death or start of new anticancer therapy. PFS was calculated from the date of randomisation until the date of progression or the date of death. OS was measured from the date of randomisation up to death or last follow-up. Toxic effects were graded according to the National Cancer Institute—Common Toxicity Criteria (NCI-CTC, version 2.0). The quality of life (QoL) was assessed using the Lung Cancer Symptom Scale (LCSS) [16] at baseline, at the end of each cycle just before the

administration of next cycle and at the end of the study. Clinical benefit was assessed taking into account four clinical parameters (performance status score, weight, lung cancer-related symptoms and analgesic score) measured at baseline, at the end of each cycle just before the administration of next cycle and at the end of the study. A clinical benefit responder was defined as any patient who demonstrated improvement of at least one parameter without deterioration of any other parameter for at least 3 weeks.

statistical analysis

The clinical hypotheses were calculated on previous experiences reporting a median TTF for NP and DP of 3.8 and 2.8 months, respectively [11]. Assuming an accrual time of 24 months, a follow-up time after the last inclusion of 12 months, an estimated sample size of 175 patients in each treatment arm was required. To accommodate an anticipated 10% loss of patients to follow-up, 386 patients had to be included to allow the detection of a TTF superiority between NP and DP arms with a type I error rate of 5% and a power of 80%, using a two-sided log-rank test adjusted on stage. TTF was chosen as a primary end point because, assuming that both doublets were able to produce similar efficacy, the evaluation of this parameter was able to differentiate patient's compliance to treatment. The statistical analysis was carried out using the SAS® system software version 8.2 for Windows®. All statistical tests were two sided at a 5% level of significance. The χ^2 test was carried out to compare proportions or replaced by Fisher's exact test if the expected frequency in one cell of the contingency table was <5. The 95% confidence interval (CI) for proportions was computed. Comparisons between the treatment arms were provided for ordinal data using the nonparametric Wilcoxon rank sum test. The distributions of quantitative data were examined by the Kolmogorov–Smirnov test. In case of Gaussian distribution, the comparison between the treatment arms was made with a Student's *t*-test, otherwise the nonparametric Wilcoxon test was carried out. For time-dependent parameters, the Kaplan–Meier curves and life tables by treatment arm were provided. CIs on the median were calculated. Log-rank test adjusted on stage was carried out to compare the two arms for TTF. All randomised and treated patients were included in the intention to treat (ITT) population and analysed in the arm they were assigned by randomisation. The assessable population was a subset of the ITT population. To be included in the assessable population, the patients had to be eligible, assessable and treated in the arm assigned by randomisation. To be assessable, patients should have received a minimum of two cycles of treatment as required by the protocol unless PD or death from PD documented before the second cycle. In this case, the patient was considered as assessable with early progression.

results

patients and treatment administration

From 2 February 2004 to 1 January 2006, 390 patients with unresectable or metastatic NSCLC were entered in a randomised study at 42 investigational centres in 19 countries. The cut-off date for the analysis was 31 August 2006. Baseline characteristics of patients were balanced across the treatment groups. The demographic data at baseline for the ITT population are presented in Table 1.

Of 390 patients, four and five patients were not treated in the NP and DP arms, respectively. Of 381 treated patients included in the ITT analysis, 157 patients in NP and 171 in DP were assessable for response, with 33 and 20 patients excluded from the analysis in NP and DP arms, respectively. The reasons for nonevaluability are reported in Figure 1.

Table 1. Patients' characteristics at baseline—ITT population

	NP		DP	
	n	%	*n*	%
Number of patients	190	100	191	100
Median age (range), years	59.4 (38.4–75.8)		62.1 (36.5–75.1)	
Age category				
<50	24	12.6	24	12.6
(50–65)	110	57.9	89	46.6
≥65	56	29.5	78	40.8
Sex				
Male	139	73.2	146	76.4
Female	51	26.8	45	23.6
Karnofsky PS[a]				
80	72	37.9	72	37.7
90	80	42.1	73	38.2
100	37	19.5	46	24.1
Histology at diagnosis				
Squamous/ epidermoid	65	34.2	64	33.5
Adenocarcinoma	79	41.6	75	39.3
Large cell	8	4.2	18	9.4
Bronchial alveolar	2	1.1	–	–
Giant cell	1	0.5	1	0.5
Unknown	35	18.4	33	17.3
Extent of disease at study entry				
Locoregional (with pleural effusion)	37 (18)	19.5 (50)	29 (13)	15.2 (46)
Metastatic	153	80.5	162	84.8

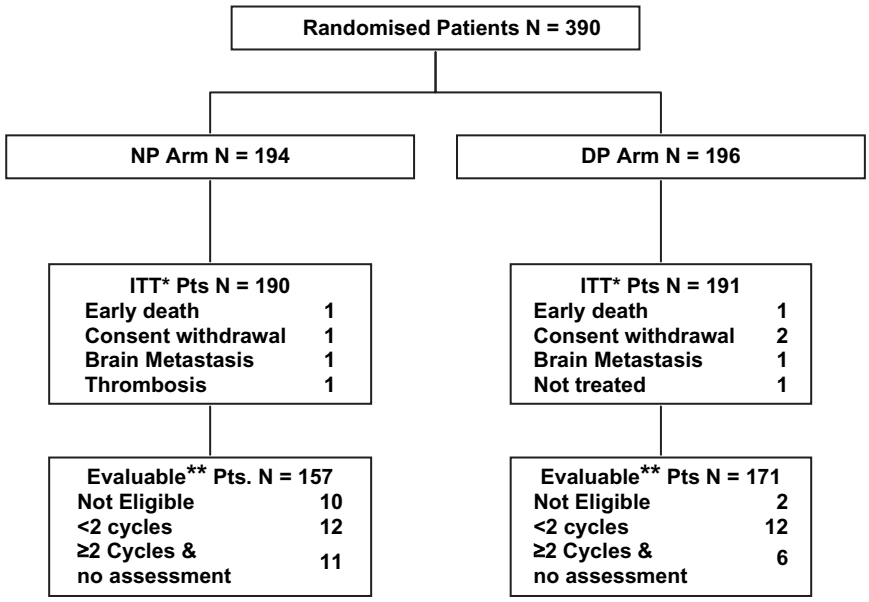
[a]one patient PS 70 in NP.

NP, i.v. vinorelbine and oral vinorelbine plus cisplatin; DP, docetaxel and cisplatin; PS, performance status.

efficacy

Concerning the primary efficacy analysis, the median TTF was 3.22 (95% CI 2.96–4.24) and 4.11 (95% CI 3.45–4.50) months in the NP and DP arms, respectively ($P = 0.20$), hazard ratio (HR) 0.872 (95% CI 0.710–1.072) (Figure 2). TTF by histology in the NP arm was 3.22 months for squamous cell carcinoma (95% CI 2.76–4.63) and 3.05 (95% CI 2.33–4.27) for adenocarcinoma, while in the DP arm TTF was 4.22 (95% CI 3.81–4.57) and 3.94 (95% CI 2.23–6.08) for squamous cell carcinoma and adenocarcinoma, respectively.

Concerning the other end points, overall response (OR) was evaluated in the ITT and assessable population. In the ITT population, after panel review, the objective response rates were similar in both arms (Table 2). In the assessable population, after independent panel review, a similar response rate was reported, with 31.2% (NP) (95% CI 24% to 39%) and 29.6% (DP) (95% CI 22.8% to 37%) ($P = 0.75$). OR was achieved with a similar median time to response of 1.7 (range 1.2–4.6) and 1.4 (range 1.0–4.4) months in the NP and DP arms, respectively. Response rates by histology in the NP arm were 24.6% for squamous histology and 29.1% for adenocarcinoma, while in the DP arm 28.1% and 22.7% response rates were reported in squamous histology and adenocarcinomas,



*Patients evaluable for ITT evaluation; **Patients evaluable for Response evaluation

Figure 1. Consort diagram. *Patients assessable for ITT evaluation; **patients assessable for response evaluation.

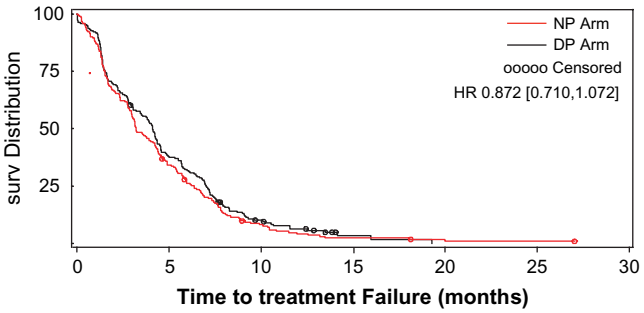


Figure 2. Time to treatment failure—ITT population.

respectively. PFS was 4.9 (95% CI 4.44–5.95) and 5.1 (95% CI 4.34–6.14) months in the NP and DP arms, respectively ($P = 0.99$). At the cut-off date for analysis, 131 patients had died in the NP arm and 137 in the DP arm, with 59 and 53 patients alive in the NP arm and DP arm, respectively. The main cause of death in both arms was progressive disease (90.1% NP; 83.2% DP). The median survival was 9.9 (NP) (95% CI 8.41–11.6) and 9.8 (DP) (95% CI 8.80–11.5) months ($P = 0.58$) (Figure 3). The median survival for squamous histology was 8.87 (NP) (95% CI 6.44–12.81) and 9.82 (DP) (95% CI 8.41–12.19) months and for adenocarcinoma 11.73 (NP) (95% CI 8.67–16.46) and 11.60 (DP) (95% CI 9.72–15.74) months. The 1-year survival was 39.4% and 40.9% in the NP arm and DP arm, respectively.

After discontinuation or progression, approximately one-third of patients received second-line therapy, mainly single agent. In the NP arm, the most common second-line therapies were DCT (16 patients), pemetrexed (14 patients) and a tyrosine kinase inhibitor (TKI) (30 patients). In the DP arm, GEM (15 patients), pemetrexed (16 patients) and TKI (31 patients) were commonly used.

quality of life

One hundred and forty-nine patients in the NP arm (78.4%) and 152 patients in the DP arm (79.6%) were assessable for the QoL LCSS questionnaire. The global analysis of LCSS did not show any significant difference between the two arms for appetite, asthenia, cough, dyspnoea, haemoptysis and pain. The average symptom burden as assessed by the LCSS was similar in the two arms. The global score was similar in the two arms, showing a worsening from baseline to cycle 6 relative to the disease evolution (Figure 3).

There were 115 and 117 patients assessable for clinical benefit in the NP and DP arms, respectively. There were 19.1% responders in the NP arm and 19.7% in the DP arm ($P = 0.92$) (22 and 23 patients, respectively). Median time in weeks to deterioration did not differ between arms when assessed for weight [NP 25 weeks; DP 24 weeks ($P = 0.93$)], Karnofsky performance status [NP 25.6 weeks; DP 20 weeks ($P = 0.68$)] and pain and analgesic consumption [NP 7.1 weeks; DP 8.7 weeks ($P = 0.87$)].

cumulative doses and dose intensity

Overall, 807 and 845 cycles were delivered in NP and DP arms, respectively, without delay in 81.3% and 90.5% of cycles in each of the two arms. The reasons for cycle delays for haematological/non-haematological toxicity were reported in 48.3%/6.6% and in 8.8%/20.0% of cycles in NP and DP arms, respectively.

In the NP arm, 708 cycles of NVBo were delivered on day 8 with or without delay for 97.7% of them. The reason for the day 8 delay was haematological toxicity in 9 of 16 affected cycles (56.3%).

At least one dose reduction during the trial was reported in 37 (19.5%) and 30 (15.7%) patients in the NP and DP arms, respectively. The number of doses reduced for related

Table 2. Response rate according to panel review—ITT population

	NP		*P*	DP	
Number of patients	190	%		191	%
Complete remission	–	–		2	1.0
Partial remission	52	27.4		50	26.2
Objective response (95% CI)	52	27.4 (21.2–34.2)	0.97	52	27.2 (21–34.2)
SD	83	43.7		78	40.8
Disease control (CR + PR + SD) (95% CI)	135	71.1 (64–77.4)	0.52	130	68.1 (61–74.6)
Progressive disease	35	18.4		43	22.5
Nonevaluable	20	10.5		18	9.4

NP, i.v. vinorelbine and oral vinorelbine plus cisplatin; DP, docetaxel and cisplatin; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

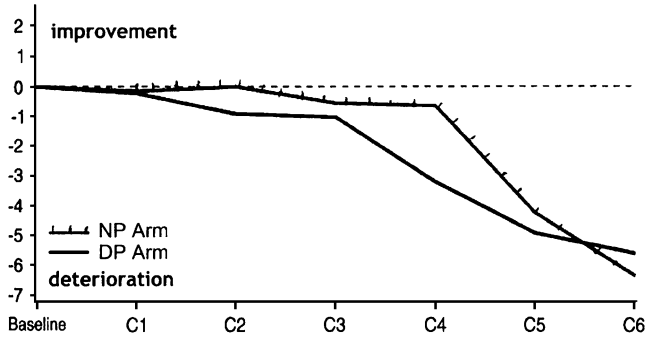


Figure 3. Lung Cancer Symptom Scale—global score.

haematological toxicity on day 1 of the cycle was similar in both arms. Among the 172 patients receiving the second cycle, 122 cycles (70.9%) were given with escalated doses. The main reason for not escalating the dose was recorded as clinical error.

The planned six cycles of treatment during the study period were delivered in 85 of 190 patients in the NP arm and in 98 of 191 patients in the DP arm; the mean numbers of cycles were 4.2 and 4.4 cycles, respectively, with 124 and 129 patients having completed four cycles in both arms. The relative dose intensity in the NP arm was 92% for NVBiv, 83.6% for NVBo and 93.7% for CDDP. In the DP arm, the relative dose intensity was 96.3% for DCT and 96.6% for CDDP.

toxicity

The summary of the worst NCI-CTC toxicity per patient for either arm is presented in Table 3. Two patients were not assessable for haematological toxicity in the NP and DP arms, respectively. Overall, haematological toxicity was similar between the two arms except for the number of episodes of febrile neutropenia, affecting 17 (8.9%) and eight (4.2%) patients in the NP and DP arms, respectively. Despite that, in both arms, grade 4 neutropenia (one of the criteria entering in the definition of febrile neutropenia) was reported in a similar number of patients (NP 71; DP 69). As a whole, the incidence of grade 3/4 neutropenia was less in the NP arm (52.7%) when compared with the DP arm (56.6%). The number and percentage of patients receiving antibiotics was 85 with 44.7% of patients and 81 with 42.4% in the NP and DP arms, respectively. More grade 3/4 anaemia was reported in the NP arm, 26 (13.9%) versus seven (3.7%) patients in the DP arm, with slightly more patients having grade 1/2 anaemia in the DP arm [160 patients (84.7%)] when compared with the NP arm [146 patients (77.7%)]. Regarding non-haematological toxicity, all patients are assessable. Nausea, vomiting and anorexia were more frequent in the NP arm. More diarrhoea, peripheral sensory neuropathy, pyrexia and alopecia were reported in the DP arm.

Death occurred within 30 days of last administration for 19 and 13 patients in the NP and DP arms, respectively, with one patient in the NP arm (grade 4 neutropenia) and three patients in the DP arm (gastrointestinal perforation, septic shock, peritoneal infection) having the reason of death as a drug-related serious adverse event.

discussion

This study demonstrated that the doublet chemotherapy combinations NVBiv/NVBo–cisplatin and DCT–cisplatin produced similar results in terms of response and time-related parameters. Further second-line treatments were given to a similar proportion of patients in both arms without any impact on the final results. The safety profile of these combinations was typical for each of the two combinations, except for haematological toxicity, with a higher number of episodes of febrile neutropenia in the NP arm, despite a similar incidence of grade 3 and grade 4 neutropenia in both arms, and with no further impact on infection. The higher incidence of nausea, vomiting and anorexia in the NP arm can be attributed to both the antiemetic effect of the 3 days of steroid use associated with the DCT administration and the NVBo formulation.

The efficacy analysis by histology in the current study showed similar survival results in both arms. Scagliotti et al. [17] recently reported that patients with lung adenocarcinoma had a clinically relevant improvement in OS when treated with cisplatin and pemetrexed (PP) versus cisplatin and gemcitabine (GP) (PP 11.8; GP 10.04; $P = 0.03$). These results seem to open the door to a novel, tailored approach based on histology type. Nevertheless, this assumption should be carefully evaluated and other CDDP-based doublets should be tested apart from GP. Although the analysis is in a smaller sample size, in the Global Lung Oncology Branch trial 3

Table 3. Common treatment-related adverse events (>5%) in either arm per patient

Event	Overall, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Overall, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
	NP arm (*n* = 188)			DP arm (*n* = 189)		
Neutropenia	148 (78.7)	28 (14.9)	71 (37.8)	145 (76.7)	38 (20.1)	69 (36.5)
Febrile neutropenia[a]	17 (8.9)	–	–	8 (4.2)	–	–
Leucopenia	139 (73.9)	36 (19.1)	23 (12.2)	145 (76.7)	56 (29.6)	10 (5.3)
Haemoglobin	172 (91.5)	24 (12.8)	2 (1.1)	167 (88.4)	7 (3.7)	–
Thrombocytopenia	73 (38.8)	5 (2.7)	–	61 (32.3)	1 (0.5)	–
	NP arm (*n* = 190)			DP arm (*n* = 191)		
Tinnitus	11 (5.8)	–	–	6 (3.1)	–	–
Abdominal pain	19 (10.0)	3 (1.6)	–	18 (9.4)	1 (0.5)	–
Constipation	41 (21.6)	1 (0.5)	–	35 (18.3)	2 (1)	–
Diarrhoea	48 (25.3)	4 (2.1)	–	61 (31.9)	11 (5.8)	–
Dyspepsia	13 (6.8)	–	–	6 (3.1)	–	–
Nausea	127 (66.8)	14 (7.4)	–	114 (59.7)	9 (4.7)	–
Stomatitis	36 (18.9)	3 (1.6)	–	37 (19.4)	–	–
Vomiting	101 (53.2)	17 (8.9)	1 (0.5)	74 (38.7)	11 (5.8)	–
Fatigue	96 (50.5)	8 (4.2)	2 (1.1)	93 (48.7)	12 (6.3)	–
Injection site reaction	15 (7.9)	1 (0.5)	–	3 (1.6)	–	–
Pyrexia	11 (5.8)	–	–	17 (8.9)	2 (1)	–
Weight decreased	47 (24.7)	–	–	34 (17.8)	–	–
Anorexia	86 (45.3)	5 (2.6)	1 (0.5)	70 (36.6)	6 (3.1)	–
Dizziness	6 (3.2)	–	–	14 (7.3)	1 (0.5)	–
Dysgeusia	6 (3.2)	–	–	21 (11)	–	–
Paraesthesia	14 (7.4)	1 (0.5)	–	16 (8.4)	–	–
Peripheral sensory neuropathy	20 (10.5)	–	–	30 (15.7)	–	–
Alopecia	67 (35.3)	–	–	111 (58.1)	–	–

[a]Calculated in 190 and 191 assessable patients in NP and DP arms, respectively.
NP, i.v. vinorelbine and oral vinorelbine plus cisplatin; DP, docetaxel and cisplatin.

(GLOB3), both arms reported similar OS results in squamous (8.87 months for NP; 9.82 months for DP) or adenocarcinoma subtypes (11.73 months for NP; 11.60 months for DP).

Data from the present study make it possible to undertake a reappraisal of the safety and activity data of the different NVB–CDDP combination regimens. The doublet NP used in this trial with NVB on days 1 and 8 was the optimal approach, with a balanced efficacy/safety ratio coupled with optimal dose intensity. Previous trials testing weekly NVB with CDDP every 4 weeks reported the typical efficacy of a third-generation doublet but with a significant difference in terms of safety, treatment cancellations and QoL [4, 14].

Systemic chemotherapy remains the front-line treatment of advanced NSCLC and the choice of combination may be based on factors other than activity such as drug safety profile, expected toxicity, oncologists' familiarity with the drugs, convenience and costs [5, 13]. Intravenous therapy has a considerable impact on patient daily life. Patients spend a substantial amount of time travelling to, waiting for and receiving cancer care, which can be reduced with home-based therapy or even day hospital oral administration [18]. Oral chemotherapy, when effective, may offer major patient convenience and reduction of constraints over standard i.v. chemotherapy [19]. Current research is oriented to developing oral formulations active against NSCLC and several agents are already approved or in development [20, 21]. The availability of an effective oral chemotherapy is advantageous for patients living in remote areas or far from oncology centres [22]. Lastly, oral chemotherapy may reduce anxiety in patients who are afraid of injections [22, 23], and it may be a more appropriate route of administration when venous access is problematic.

Several surveys have shown that most patients prefer oral to i.v. therapy [9, 22, 24], providing that there is similar efficacy. The patient preference of the NVBo formulation over NVBiv has been tested in a randomised trial in advanced NSCLC. NVBo plus platinum salt was preferred by three of four patients because their everyday life was less affected due to the shorter time spent in clinic and the possibility of taking the day 8 dose at home [25]. In the GLOB3, NVBo on day 8 in the days 1 and 8 of the NP schedule reduced the burden of i.v. therapy while maintaining adequate dose intensity.

A simple schedule is also important. Compliance is often influenced by the patient's ability to follow the complexity of the regimen (avoidance of food intake because of risk of decreased systemic exposure) or the dosing schedule when patients have to swallow a large number of tablets every day [26–28]. O'Neil and Twelves [8] reported as acceptable a maximum of six to eight tablets per day. The current NVBo formulation allows optimal compliance since patients have to swallow a mean of four to six capsules per intake, thanks to the two available strengths of 20 and 30 mg. Nevertheless, effective patient education about their therapy is mandatory when a full

home treatment is planned, with written take-home information, diaries, guidelines for dose reduction in case of adverse events and side-effect support kits [29, 30].

A recent meta-analysis aimed at comparing DCT–cisplatin with i.v. navelbine–cisplatin as first-line treatment in NSCLC also included trials with other vinca alkaloids. It reached a significant difference in terms of efficacy and safety for the DCT–cisplatin doublet [31]. This meta-analysis suffers from the heterogeneity of the studies included in the analysis and therefore difficulties arise in resolving the differences among patient population, or among the methods of assessment of the factors. Therefore, the true theoretical HR that we are trying to globally estimate in the meta-analysis from the included studies may vary from one study to another [32]. For instance, based on current available data on a large randomised trial conducted by Fossella et al. [4] comparing platinum-based doublets with NVB or DCT, the differences between these two doublets were mostly related to their safety profile and not conclusively related to any real differences in efficacy.

Based on the currently available drugs for treating NSCLC, where third-generation doublets achieve the same results, the choice in the daily practice should be based on the convenience that the treatment brings together with its efficacy. The GLOB3 is the first large randomised trial using an oral formulation of NVB in a platinum doublet that confirms that oral chemotherapy may be a step forward for the first-line treatment of NSCLC patients since it optimises treatment convenience coupled with efficacy.

Concerning front-line chemotherapy for NSCLC patients, new approaches are under development in patients expressing epidermal growth factor receptor. A recent phase III clinical trial reported that patients treated with cetuximab plus NVB/CDDP achieved significantly improved survival compared with patients treated with NVB/CDDP alone [33].

The oral formulation of NVB is an opportunity for treatment optimisation in combination with new oral targeted therapies and feasibility trials are ongoing to evaluate the safety and efficacy of such an approach.

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