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Oral vinorelbine given as monotherapy to advanced, elderly NSCLC patients: a multicentre phase II trial

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Abstract

Vinorelbine intravenously (i.v.) demonstrated its efficacy and tolerability in advanced non-small cell lung cancer (NSCLC) patients, including elderly subjects. Since vinorelbine is now available as an oral formulation this phase II open study was designed to evaluate its activity and tolerability in advanced, elderly NSCLC patients. A total of 56 chemonaive patients were recruited from April 2001 through to March 2002. The dosage schedule, already tested in younger NSCLC patients, was 60 mg/m^{2}once a week for three weeks (first cycle), followed by 80 mg/m^2 once a week until disease progression or development of unacceptable toxicity. A limited sampling scheme was used for performing pharmacokinetic analysis on 52 of 56 patients enrolled in the study. Treatment was well tolerated with grade 3/4 neutropenia in 11/17 patients (20/30%) and febrile neutropenia in 1 (2%). Six partial responses (11%) and 25 stable disease responses were recorded, with a disease control rate of 55%. Median overall survival was 8.2 months (95% Confidence Interval (CI) [6.2–11.3]). The clinical benefit response rate was 31% on 32 evaluable patients. Pharmacokinetic profiles appeared quite similar to the historical profiles recorded following i.v. administration. Oral vinorelbine appears to be a reasonable alternative to i.v. vinorelbine, both in terms of activity and tolerability, in advanced, elderly NSCLC patients.

Keywords: Advanced NSCLC; Elderly patients; Vinorelbine; Oral chemotherapy

1. Introduction

Cisplatin-based chemotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC), with different doublets including vinorelbine, gemcita-

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bine, paclitaxel or docetaxel being equivalent in terms of efficacy [1]. Among the third-generation chemotherapy agents, vinorelbine administered by the intravenous (i.v.) route has demonstrated its efficacy, whether used alone or in combination with other agents [2–4]. An oral formulation of vinorelbine has been developed and is now available. Several studies in cancer patients have demonstrated that the key pharmacokinetic parameters of the oral form were largely similar to those of the injectable formulation, so that it appeared feasible to replace i.v. infusions with oral administrations of vinorelbine [5]. Bioequivalence in blood vinorelbine exposure has been demonstrated between 30 mg/m^2 i.v. and 80 mg/m^2 oral, and between 25 mg/m^2 i.v. and 60 mg/m^2 oral treatments. A randomised phase II trial showed that activity of oral and i.v. vinorelbine in advanced NSCLC appears to be comparable and the safety profile qualitatively similar [6].

Substitution of an oral with an injectable form, when feasible, is generally sought in cancer chemotherapy treatments. Patients' preference for the oral route has been noted in a study where of 103 patients likely to receive palliative chemotherapy, 92 patients expressed a preference for the oral over i.v. administration [7]. This is especially true for elderly patients who may not be able to easily visit a medical unit to receive their therapy and who are often reluctant to be treated away from home.

As NSCLC is mainly observed in elderly individuals [8], oral forms of the cytotoxic agents used would be desirable. In view of its activity and relative safety, demonstrated in earlier clinical studies including mainly younger patients, oral vinorelbine appeared to be a good candidate for evaluation in the elderly. Furthermore, single agent i.v. vinorelbine has already shown efficacy and a favourable toxicity profile in randomised trials including advanced, elderly NSCLC patients [9,10].

Our study was therefore designed to evaluate the activity and tolerability of oral vinorelbine given as monotherapy to advanced NSCLC patients aged over 70 years.

2. Patients and methods

This was an open, non-randomised study in which elderly patients presenting with unresectable stage IIIB (with supraclavicular lymph nodes metastases or malignant pleural effusion) or stage IV NSCLC, received oral vinorelbine as first-line chemotherapy.

The primary objective was response rate. Secondary objectives were duration of response, progression-free survival, overall survival, toxicity, clinical benefit, drug pharmacokinetic and inter-individual variability in elderly patients compared with their younger counterparts.

2.1. Patient selection

Criteria for entering the study were: age over 70 years, histologically- or cytologically-proven NSCLC, inoperable stage IIIB with supraclavicular limph nodes metastases or malignant pleural effusion, IV or delayed relapse of any stage becoming unresectable, Karnofsky performance status $\geqslant 80\%$, life expectancy $\geqslant 12$ weeks. The patients were eligible if they had received no prior chemotherapy or immunotherapy. Previous radiotherapy was accepted if measurable lesion(s) were present in non-irradiated areas. Prior surgery for NSCLC was allowed. Patients had to present at least one bi-dimensionally measurable lesion (by World Health Organisation (WHO) criteria) which had not been previously irradiated and measuring at least 10×20 mm. Eligibility criteria also included the following haematological and biochemical criteria: neutrophils $\geqslant 2.0 \times 10^9$/l; platelets $\geqslant 100 \times 10^9$/l, haemoglobin > 110 g/l or 6.8 mmol/l; total bilirubin $\leqslant$1.5× upper normal limit (UNL), aspartate aminotransferase/alanineamino-transferase (ASAT/ALAT) < 2.5× UNL, Alkaline phosphatase < 5× UNL, serum creatinine $\leqslant$UNL. In cases of borderline values of serum creatinine, a 24 h creatinine clearance was required; if this was <0.58 ml/s the patient was not eligible. Patients had to sign an informed consent form prior to any protocol-specific procedure and before registration.

Non-inclusion criteria included: active central nervous system (CNS) disorder or brain metastasis, symptomatic sensory neuropathy > grade 1 by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2 (v2), cardiovascular disease including cardiac failure, myocardial infarction within the previous three months, uncontrolled hypertension or arrhythmia, active infection requiring i.v. antibiotics in the two weeks preceding the initiation of treatment, unstable superior vena cava syndrome, long-term oxygen therapy, unstable pleural effusion or ascites or pericardial effusion, concomitant neoplasm other than *in situ* cervical carcinoma or skin basal cell cancer, radiotherapy within the previous four weeks or previous radiotherapy in the only site used to assess response, concomitant treatment with any other anticancer agent, uncontrolled hypercalcaemia, unstable concomitant disease, known hypersensitivity to drugs with similar chemical structures to the study medication, concomitant treatment with corticosteroids except chronic treatment (> 1 month) at low dosing ($\leqslant$20 mg/day of methylprednisolone or equivalent), significant malabsorption syndrome or disease affecting gastrointestinal tract function, presence of any psychological, familial, sociological or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule. Participation in another clinical trial with any investigational drug study (whatever the use, curative, prophylactic or

diagnostic intent) within 30 days prior to study screening. The protocol was approved by ethical committees at the participating institutions.

2.2. Assessments

Appropriate scanning, or physical assessment to determine tumour involvement was completed within three weeks prior to 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, computerised tomography (CT)-scan of chest and liver; CT-scan of the brain and bone imaging were performed at inclusion. Response assessment was performed every two cycles. Patients responding to therapy had a repeated evaluation at least four weeks later by the same methods. Response rate was the primary criterion to assess the efficacy using WHO criteria: complete response (CR) being the complete disappearance of all known lesions and partial response (PR) a decrease by at least 50% of all bidimensionally measurable lesions, evaluated by two examinations not less than four weeks apart. All patients were followed every three months for survival data until death. Secondary objectives were to determine the duration of response, progression-free survival and survival, the safety profile of oral vinorelbine, to evaluate the clinical benefit and to document the intra-individual pharmacokinetic variability of oral vinorelbine.

Assessment of toxicity by NCI-CTC v2 criteria was made before each three week-cycle. Data for each patient across all cycles of chemotherapy were used, with the most severe result being recorded. Febrile neutropenia was assessed using the Pizzo definition [11]. To determine whether a postponement or reduction in the dose was needed due to haematological toxicity, a complete blood count was performed every week, prior to the administration of the study drug.

In order to assess lung cancer-related symptoms, patients were asked to fill visual analogue scales (VAS) on six symptoms (pain, dyspnoea, cough, haemoptysis, asthenia and anorexia) prior to the initiation of vinorelbine therapy and again at each three week-cycle. Clinical benefit was assessed using VAS, performance status and weight [12]. The clinical benefit reponse rate was calculated for the main measures (e.g., changes in lung cancer symptoms on VAS and PS change from baseline) allowing each patient to be classified as a clinical benefit responder or non-responder. If a patient was classified as stable under the main clinical benefit response, the clinical benefit response rate was calculated using a secondary measure (e.g., change in body weight from baseline). To be evaluable for inclusion in the clinical benefit response rate, a patient had to have a baseline assessment and at least two assessments during the study.

2.3. Treatment

The proposed dosage schedule for oral vinorelbine given to all patients entering the trial was 60 mg/m^2 once a week for the initial three weeks (first cycle) followed by 80 mg/m^2 weekly for the subsequent 3-week cycles. Vinorelbine capsules had to be taken with some food. Anti-emetics, mostly oral 5 HT_3 antagonists, were routinely prescribed for the prevention of nausea and vomiting. They were to be taken in the few hours preceding the intake of vinorelbine capsules and, thereafter, as needed.

Oral vinorelbine treatment was to be administered once a week until evidence of disease progression, development of unacceptable intolerance or patient's refusal. In order to assure full compliance with the protocol requirements, the vinorelbine capsules were taken in hospital, under the supervision of a member of the medical team.

Adjustments in dosage could be made in cases of intolerance and, primarily, in cases of severe neutropenia: if one episode of grade 4 neutropenia or two episodes of grade 3 neutropenia in two consecutive weeks occurred during the first 3 weeks of vinorelbine therapy, the proposed increase from 60 to 80 mg/m^2 did not take place. Similarly, if subsequent grade 4 neutropenia or two episodes of grade 3 neutropenia developed on two consecutive weeks, the 80 mg/m^2 dose was to be reduced to 60 mg/m^2. This flexible schedule was designed to preserve drug activity while taking into account the haematological toxicity. A similar schedule for oral vinorelbine administration had been used previously in the treatment of younger patients with NSCLC [6].

2.4. Statistical methods

Sample size was determined using a two-stage design as described by Fleming in Ref. [13]. With 45 evaluable patients, the null hypothesis tested a true response rate of 10% and an alternative hypothesis of 25%, the type I error α was less than 5% and the type II error β less than 20%.

Continuous data were summarised using median, minimum and maximum values. Categorical data were presented in contingency tables with frequencies and percentages. Confidence intervals (CIs) were calculated at the 95% level. Time-dependent parameters were analysed using the Kaplan–Meier method and the 95% CI for the median reported.

Efficacy analysis were performed on the intent-to-treat and evaluable populations. The primary efficacy parameter was the response rate and included only confirmed CR and PR. The other efficacy parameters were the disease control rate (CR + PR + no change (NC)), duration of response, progression-free survival and

overall survival. A clinical benefit analysis was also performed.

Safety analysis were performed on the population of patients having received at least one dose of study treatment. Worst NCI CTC v2 grades for haematological and non-haematological adverse events were presented.

All statistical analyses were carried out with 8.2 version of SAS® for Windows®.

2.5. Pharmacokinetic assessment

Pharmacokinetic investigations were based on a limited sampling scheme. The scheme was set up and validated by mathematical simulation with a pharmacokinetic population model developed on a database from earlier phase I and phase II data [14]. As a consequence, and despite a limited number of samples (baseline and n=3), a reliable evaluation of each patient's individual pharmacokinetic characteristics could be obtained.

Blood samples were collected on the first administration of oral vinorelbine only, as follows: immediately before the ingestion of the first capsules then 1.5, 3 and 24 h later.

All samples for pharmacokinetic evaluation from the various clinical investigation centres were sent to a single laboratory to assay for vinorelbine. The assay method used was a fully validated LC/MS–MS (liquid chromatography mass spectrometry) method [15].

3. Results

3.1. Patients' characteristics

Between April 2001 and March 2002, 56 patients were enrolled by 11 centres in six European countries. Patients' characteristics are listed in Table 1.

Median age was 74 years(range 70–82 years). Metastases were found in 43 patients (77%): lymph nodes, bone, pleura, and the liver were the most common sites. Co-morbidities, primarily cardiovascular, were present in 87.5% patients, as would be expected in this age range.

The clinical signs recorded at baseline were typical of NSCLC: cough, dyspnoea, chest pain, fatigue, anorexia.

Table 1
Patients' characteristics (n = 56)

Median age (range)		74 (70–82)
Gender: male/female (%)		75/25
Performance status	100	10 (18%)
	90	19 (34%)
	80	27 (48%)
Extent of disease	Stage IIIB	13 (23%)
	Stage IV	43 (77%)
Histology	Squamous cell	18 (32%)
	Adenocarcinoma	23 (41%)
	Large cell carcinoma	4 (7%)
	Bronchial alveolar	2 (4%)
	Undetermined NSCLC	9 (16%)
Number of organs with metastases	1	10 (18%)
	2	26 (46%)
	$\geqslant 3$	20 (36%)
Number of co-morbidities	0	7 (13%)
	1	25 (45%)
	2	14 (25%)
	$\geqslant 3$	10 (18%)

NSCLC, non-small cell lung cancer.

Table 2
Administered doses of oral vinorelbine

Median number of weeks under treatment (range)	9.3 (2.9–31.1)
Median number of doses/patient (range)	7 (1–25)
Median number of cycles administered (range)	3 (1–16)
Median dose intensity (mg/m^2/week) (range)	46.5 (21–77.3)
Median relative dose intensity (%) (range)	65 (34.9–103.1)

3.2. Drug exposure

A total of 471 oral doses (201 cycles) of vinorelbine were administered. The median number of cycles was three per patient (range 1–16) (Table 2). Thirteen patients received six cycles or more. The median dose intensity was 46.5 mg/m^2/week (range 21–77.3 mg/m^2/week) and the median cumulative dose per patient was 439 mg/m^2. Nine patients had at least one administration delayed, but these delays never exceeded nine days. Hundred and twenty six administrations were skipped because of haematological toxicity (73%).

Eleven patients received only one cycle. Out of 45 patients receiving the second cycle, 30 (67%) underwent a dose escalation to 80 mg/m^2. The other 15 patients (33%) remained at the 60 mg/m^2 dose level: due to grade 4 neutropenia (four patients) and one episode of grade 3 neutropenia (four patients). For the remaining seven patients, reasons for not increasing the dose were not specified by the investigator. In addition, in 12 patients, the weekly doses had to be reduced from 80 to 60 mg/m^2.

Anti-emetics, mostly oral $5HT_3$ antagonists, were prescribed routinely for all patients, except for two patients who received no prophylaxis.

3.3. Response

In an intent-to-treat analysis (n = 56), no complete responses were recorded, but six patients (11%) experienced a PR and SD was obtained for 25 patients (45%). The disease control rate was 55%. Median pro-

Table 3
Study results in intent-to-treat ($n = 56$) and evaluable population ($n = 47$)

Population	Intent-to-treat	Evaluable
	n=56 (%) (95% CI)	n=47 (%) (95% CI)
Partial response (PR)	6 (11) (3–19)	6 (13) (3–22)
Stable disease (SD)	25 (45)	25 (53)
Disease control	31 (55) (42–68)	31 (66) (52–80)
Progression-free survival (months)	3.7 (2.5–4.5)	
Duration of response (months)	5.2 (4.3–9.1)	
Median survival (months)	8.2 (6.2–11.3)	

95% CI, 95% confidence interval.

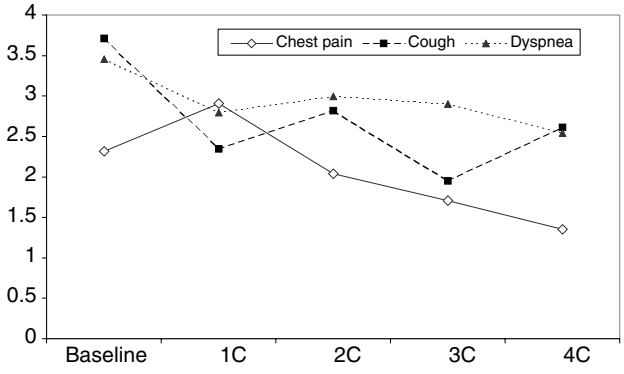

Fig. 1. Evolution of chest pain, cough and dyspnoea. C, chemotherapy cycle.

gression-free survival was 3.7 months and median overall survival 8.2 months (Table 3). In the evaluable population ($n = 47$), the response rate was 13%, with SD observed in 53%, a disease control rate of 66%. Reasons for nine patients being excluded from the analysis were: two non-drug-related deaths after one and two cycles, two withdrawals of consent after one cycle, one had radiotherapy after one cycle and four for non-haematological adverse events, with grade three toxicity observed after one cycle in three patients and after two cycles in one.

3.4. Clinical benefit

Due to the low number of evaluable patients after the fifth cycle, only the first four evaluations were included in the analysis of clinical benefit. As shown on Fig. 1, an improvement was observed for three symptoms: chest pain, cough and dyspnoea. Asthenia, anorexia and haemoptysis remained stable after a slightly increase beyond cycle 1. No weight loss was observed overall during the study period. Out of 32 evaluable patients for clinical benefit, 10 patients (31–95% CI [16–50]) were responders.

3.5. Toxicity

Oral vinorelbine appeared to be quite well tolerated (Table 4).

3.5.1. Haematological toxicity

As expected from previous experience with i.v. as well as oral vinorelbine administrations, neutropenia and leucopenia were the main toxicities recorded in this study. Indeed, grade 4 neutropenia and leucopenia were reported by 30% and 9% of the patients, respectively. By contrast, grade 3 neutropenia, leucopenia and anaemia were reported by 20%, 30% and 4% of the patients, respectively. Neutropenia led to 92 doses in 34 patients being omitted and was the reason for treatment discontinuation in one case. Two cases of febrile neutropenia in a single patient were recorded.

3.5.2. Non-haematological toxicity

Nausea, mostly grades 1 and 2, occurred in 54% of patients. Vomiting occurred in 14 patients, with two patients experiencing grade 3 toxicity, but no cases of

Table 4
Tolerance by patients and by cycles (NCI-CTC v2)

	By patient n=56 (%)			By cycle n=201 (%)		
	Overall	Grade 3	Grade 4	Overall	Grade 3	Grade 4
Haematological						
Anaemia	21 (38)	2 (4)	–	50 (25)	2 (1)	–
Leucopenia	35 (63)	17 (30)	5 (9)	102 (51)	38 (19)	5 (2)
Neutropenia	39 (70)	11 (20)	17 (30)	103 (52)	37 (18)	24 (12)
Thrombocytopenia	3 (5)	–	–	4 (2)	–	–
Non-hematological						
Fatigue	17 (30)	6 (11)	–	88 (44)	8 (4)	–
Nausea	30 (54)	2 (4)	–	70 (35)	5 (2)	–
Vomiting	14 (25)	2 (4)	–	27 (13)	2 (1)	–
Diarrhea	21 (38)	3 (5)	–	42 (21)	3 (1)	–
Infection (PIZZO)	1 (2)	–	1 (1.8)	2 (1)	–	–
Thrombosis	1 (2)	–	1 (1.8)	1 (0.5)	–	1 (0.5)
Neurosensory symptoms	3 (5)	–	–	5 (2)	–	–
Neurosensory constipation	14 (25)	1 (2)	–	23 (11)	1 (0.5)	–

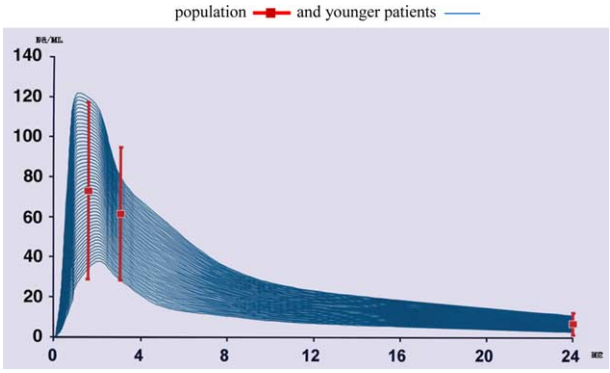

Fig. 2. Pharmacokinetic results: blood exposure and elimination half-life in the elderly population and younger patients —-.

grade 4 vomiting. Diarrhoea was somewhat more common, although again mostly grade 1. Grade 3 fatigue was reported in six patients (11%). Neurosensory symptoms were reported in 3 patients (5%) and 2.5% of cycles, but with no cases of grade 3–4 toxicity. Constipation was observed in 14 patients (25%) with one grade 3 case (2%). There were no relevant changes in the hepatic and renal function tests.

3.6. Pharmacokinetics

Fifty-two of the 56 patients underwent pharmacokinetic sampling. Forty-eight were evaluable for pharmacokinetics, three had missing samples and one had unexploitable concentration data. Individual results are illustrated in Fig. 2. The population pharmacokinetic modelling made it possible to reconstitute, from the limited sampling (three concentration data), the full pharmacokinetic profile and to calculate individual parameters. The time to peak concentration of vinorelbine was short (1.04 ± 0.52 h, mean ± standard deviation (SD)) and similar to previously reported values [5,16,17]. Blood exposure, as well as the elimination half-life, were not significantly different between this elderly population and younger patient populations [18]. Furthermore, the estimates of oral bioavailability and the inter-individual variability were comparable between young and elderly patients [18].

4. Discussion

Although the high prevalence of NSCLC in older people is undisputed, elderly subjects are grossly under-represented in clinical trials. This under-representation may be only a reflection of largely accepted concepts on the low benefit/risk ratio of chemotherapy in elderly patients. It is largely recognised that elderly patients are less likely to be thoroughly screened, that they are less intensively staged, less aggressively treated and, in the end, more likely to be offered no chemotherapy [19]. When they are treated in a non-protocol setting, elderly patients are exposed to frequent dose-reductions, delays and omissions that result in significant reductions in active drug deliveries. In a study involving Medicare patients with NSCLC, Earle and colleagues [20] noted that only 22% of those aged 65 years or over received any chemotherapy. Yet, among the 6232 elderly patients with NSCLC in the Surveillance, Epidemiology and End-Results (SEER) registry of the NCI, used by Earle and colleagues in their survey, median survival was 30 weeks for patients offered chemotherapy, but only 23 weeks for those receiving supportive care alone.

Vinorelbine has already been evaluated in elderly patients with advanced NSCLC in a randomised clinical trial, the ELVIS (Elderly Lung Cancer Vinorelbine Italian Study) trial [10]. In that earlier study, vinorelbine, given i.v. was compared with best supportive care in advanced patients aged 70 years or older. A statistically significant advantage was recorded in terms of overall survival for patients receiving vinorelbine; their median survival was 28 weeks compared with 21 weeks for patients on best supportive care (P=0.03). The one-year survival rate was also in favour of the vinorelbine-treated patients: 32% versus 14% for the other group. An improvement in quality of life was also demonstrated for patients in the vinorelbine group. A subsequent phase III trial conducted by the same group, named Multicenter Italian Lung cancer in the Elderly Study (MILES), and involving approximately 700 advanced, elderly NSCLC patients, compared single agent chemotherapy with vinorelbine or gemcitabine with polychemotherapy with vinorelbine plus gemcitabine [9]. This study confirmed the efficacy of vinorelbine and showed no difference in terms of the response rate, time to progression, survival and quality of life between the single agent and combination chemotherapies.

As expected, given the similarities in the pharmacokinetic profiles between vinorelbine given i.v. and orally, the results of our study confirmed the activity of oral vinorelbine in advanced, elderly NSCLC patients. However, one might anticipate two major differences associated with the oral administration: a higher inter-subject variability reflecting significant differences in the absorption rate from one patient to another and a higher incidence of gastrointestinal side-effects. However, the pharmacokinetic data available from 52 of the 56 patients in this trial indicate that the inter-subject variability is small. Furthermore, no statistical differences in blood exposure levels were observed between young and elderly patients.

In this study, as well as in all earlier studies on vinorelbine, haematotoxicity, specifically neutropenia and, to a lesser extent, leucopenia, are the major dose-limit-

ing factors. It does not appear that changing the route of administration reduced or increased the haematotoxicity of vinorelbine [6]. By contrast, administration by the oral route seems to increase the incidence, but not the severity, of nausea, vomiting and diarrhoea, symptoms that were already seen with the i.v. formulation, and this is why prior administration of anti-emetics is recommended [21].

Recently, Kanard and colleagues [22] reported, in advanced, elderly NSCLC patients, treated by single agent oral vinorelbine, a lower response rate (3.4% Kanard, 11% present study) and superimposible median survival (7.2 months Kanard, 8.2 months present trial). When looking carefully at the doses, schedules and dose reductions used in Kanard's trial, oral vinorelbine was used at lower doses than those recommended in our protocol: 60 mg/m^2 without dose escalation and rounded down to the nearest 10 mg; dose reductions starting from G2 toxicity reaching 75% of the planned doses in cases of haematological/non-haematological toxicity; absence of consecutive dose re-escalation. The patient underdosing was reflected in a lower activity profile, but similar median survival, suggested disease control was obtained using oral chemotherapy in both studies. In their discussion, Kanard and colleagues concluded that the low response rate may have been due to the low doses tested in their trial. As oral chemotherapies are fairly well tolerated, patient tailoring with dose escalation was suggested by these authors [22].

In conclusion, our study supports the option of using oral vinorelbine to treat advanced, elderly NSCLC patients. Dose escalation after the first cycle allows optimisation of the schedule, adapted according to an individual's tolerance.

Conflict of interest statement

C. Gridelli is member of the Pierre Fabre speaker bureau; D. Aubert, J.-P. Burillon and Y. Parlier are Pierre Fabre employees.

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