Vinorelbine *versus* Paclitaxel for Patients with Advanced Non–small Cell Lung Cancer (NSCLC) and a Performance Status of 2

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Abstract. *Aim: The purpose of this study was to compare two single agents paclitaxel (intravenous) versus vinorelbine (oral) in non-small cell lung cancer (NSCLC) patients with performance status (PS):2. Patients and Methods: The patients were randomized to receive either oral vinorelbine 60 mg/m^2 on days 1, 8, 15 every 4 weeks for 4 cycles (group A) or paclitaxel 90 mg/m^2 intravenously for 1 h on days 1, 8, 15 every 4 weeks for a total of 4 cycles (group B). Results: Among the 74 eligible patients (36 in arm A and 38 in arm B) in arm A, two (6%) had a partial response (95% CI, 0.7-18.7) and 5 (14%) had stable disease (95% CI, 4.7-29.5). In arm B, five (13%) had a partial response (95% CI, 4.4-28.1) and 7 (18%) had stable disease (95% CI, 7.7-34.3). No significant difference was found in terms of clinical benefit between the two groups after two cycles of treatment except for appetite in favour of paclitaxel (p=0.01). Median survival was 3.1months (95% CI, 2.2-4.0) for arm A and 5.1 months (95% CI, 2.7-7.6) for arm B (p=0.95). Toxicity was mild and only alopecia was more profound in the patients of arm B (p=0.008). Conclusion: No significant difference was found in clinical benefit between PS:2 NSCLC patients treated with either vinorelbine or paclitaxel.*

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More than a million new cases of lung cancer are diagnosed annually worldwide (1). About 80% of these cases are tumors of non-small cell type, including adenocarcinomas as well as squamous cell and large cell carcinomas (2). Non-small cell lung cancer (NSCLC) remains the leading cause of malignancy-related mortality (3), with five-year survival across all stages of about 12% (4). Surgery is the treatment of choice, although potentially curative resection of the tumor is feasible only in 20% of the cases (5). A small proportion of patients, usually presenting with locally advanced disease, undergoes radical thoracic radiotherapy along with chemotherapy whilst most patients with advanced stage disease are treated in a palliative way.

The management of patients with advanced NSCLC has improved during the last decade. Compared with best supportive care, chemotherapy offers improvement in overall survival and substantial palliation (6-8) and a meta-analysis has shown that cisplatin-based chemotherapy can prolong median survival by 1.5 months and 1-year survival by 10%(9). Further improvements have been made with the addition of newer agents when restricted to patients with good performance status (PS) (10-13).

In several studies, a PS of 2 was proven to be the most important negative prognostic factor(14-18) and was related to chemotherapy intolerability; thus, these patients were excluded from clinical research and the potential benefit of chemotherapy in daily practice. A 2001 analysis of the ECOG 1594 trial refuted this claim. The analysis of this trial and others concluded that the shorter survival time was disease related and not treatment related (17-19).

As single agents, vinorelbine and gemcitabine (G) proved to be superior to best supportive care in median survival and quality of life (20, 21). Nevertheless, trials comparing single-agent *versus* combination chemotherapy offered conflicting results (22-24).

In the study of our group in which gemcitabine was compared to the combination gemcitabine-carboplatin, no difference was found between the two arms in terms of efficacy. However toxicity was worse in the combination arm (25).

In this study were compared two single agents, vinorelbine and paclitaxel with known activity in NSCLC and a convenient schedule in an effort to eliminate toxicity.

The primary end-point of this study was clinical benefit, which evaluated pain, cough, dyspnea, anorexia, hemoptysis, fatigue, weight loss and general feeling. Secondary end-points were response, survival, time to disease progression (TTP) and toxicity.

Patients and Methods

Eligibility criteria. Chemonaïve patients were required to be at least 18 years of age with histologically confirmed, inoperable, recurrent or metastatic stage IIIb NSCLC with pleural effusion or stage IV NSCLC (American Joint Committee on Cancer criteria) (26). An ECOG PS of 2 was required. Prior radiotherapy was allowed. Patients were required to have completed radiotherapy at least 4 weeks before chemotherapy and to have a life expectancy of at least 12 weeks. Other requirements included measurable or assessable disease in nonirradiated fields, unless subsequent disease was documented. Patients with stable brain metastasis were eligible. In addition, patients had to have adequate bone marrow reserve, kidney and liver functions.

Patients with active infection or a history of other neoplasms (except for basal cell carcinoma of the skin or *in situ* carcinoma of the cervix) were excluded from the study. Patients with active cardiac disease or preexisting grade 3 or 4 motor or sensory neuropathy (World Health Organization [WHO] criteria) (27) were also excluded. Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki and the Hellenic Cooperative Oncology Group institutional policies. All the patients provided informed consent before receiving study treatment.

Treatment plan. Eligible patients were randomly assigned to either arm A or arm B. Arm A received oral Navelbine 60 mg/m^2 on days 1, 8 and 15 every 4 weeks for a total of 4 cycles. H2 blocker anti-emetics were given orally prior to vinorelbine. The patients in group B received paclitaxel 90 mg/m^2 (*i.v.*) for 1 h on days 1, 8 and 15 every 4 weeks for a total of 4 cycles. In both arms, the treatment was repeated every 28 days for two cycles; if the patients had a partial response, stable disease or clinical benefit, they received two more cycles. Reasons for early discontinuation of treatment were progressive disease, intolerable or unacceptable toxicity and volunteer withdrawal from the study. All the patients received ondansentron as an antiemetic.

If patients had hematological toxicity (platelets <100,000/mm^3 and neutrophils <1500/mm^3) or nonhematological toxicity grade 3/4 on the day of chemotherapy, their treatment was postponed until recovery. If a delay was more than 15 days, the patient was taken off the study. If patients had grade 3 or 4 toxicity, their doses were reduced by 25% for subsequent cycles. If, after the first dose reduction, the grade 3 or 4 toxicity persisted, then the patient was taken off the study.

Treatment evaluation. All the eligible patients who received at least two cycles of chemotherapy were evaluated for efficacy. Using the intent-to-treat (ITT) principle, response was evaluated according to standard WHO criteria (27). All the eligible patients who received at least one cycle of chemotherapy were evaluable for toxicity. Toxicity was evaluated according to WHO criteria.

Evaluation of clinical benefit. The primary end-point of this study was clinical benefit, which was based on three measurements. The first measurement was the Lung Cancer Symptom Scale, which consists of six symptoms: dyspnea, cough, hemoptysis, weakness, appetite and pain; these symptoms were scored on a visual analogue scale ranging from 0 to 10 (28-29). The second measurement was of general feeling which was reported as very good/good and moderate/poor. The third measurement was nausea and vomiting which were also scored from 0 to 10. The worst level was 10.

After randomization, the patients recorded their symptoms and general feeling on a special diary card. After cycle 2, the patients completed the visual analogue scale of symptoms and general feeling, expressing positive or negative changes during the last 8 weeks in comparison to their baseline assessment. Similar procedures took place two weeks after cycle 4, which was the end of treatment. In all cases, any new symptoms were recorded in the patient's diary card.

Statistical analysis. All the end-points except toxicity and treatment characteristics were analyzed according to the ITT principle. The treatment characteristics and safety analyses were based on the actual treatment administered.

The sample size was calculated on the assumption that a 0.6 standardized difference in quality of life existed between the two arms. For an alpha and beta error of 0.05 and 0.80, respectively, 45 patients were required per group. The total number of patients was estimated to be 92, taking into consideration a 3% withdrawal. Interim analysis was not planned for this study. Because of the low accrual rate the study ended prematurely when 75 patients randomized.

Summary statistics were calculated for all the parameters. The categorical data were summarized by frequencies and corresponding percentages, while the continuous data were summarized by median and range. Exact confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of the response rates. Differences between groups were evaluated by Fisher's exact test for categorical variables and Mann-Whitney *U*-test for continuous variables. For paired samples Wilcoxon signed-rank test and McNemar test were used where appropriate.

Survival was calculated from the randomization date to the date of death or of last contact. Progression free survival (PFS) was defined as the time interval between randomization and disease progression, secondary neoplasm, death from the disease, or death from any other cause (in cases of unknown date of disease

progression). The median survival and PFS time were estimated with the Kaplan–Meier method, whereas the log-rank test was used to compare time to event (30). All the tests were two-sided and the level of significance was set at a=5%. Statistical comparisons for the secondary end-points between the two groups are presented in the manuscript as indications. The SPSS 15.0 software was used for the statistical analysis.

Results

Baseline patient characteristics. From July 2004 to January 2008, 75 patients entered this study. Seventy four of them were eligible. Thirty six were allocated to arm A (vinorelbine) and 38 to arm B (paclitaxel).

In group A, one patient had missing data whereas in group B, one patient did not start treatment and a second had also missing data. By the end of this analysis, 36 patients in group A and 35 in group B, had died.

The baseline patient and tumor characteristics are presented in Table I. There were no statistically significant differences between the two groups.

Response. There was no statistically significant difference between the two groups. Two patients (6%) had a partial response in group A and 5 (13%) in group B. The disease was controlled in 20% of the patients in group A and 31% in group B (Table II). The median treatment duration was 8 weeks (1-38) and 9 weeks (1-26) for groups A and B respectively. The relative dose intensity was 1.0 (0.4-1.4) for group A and 0.9 (0.7-1.3) for group B.

Survival. The disease free survival for patients in group A was 2.1 months (95% CI: 1.8-2.4) and 2.6 months (95% CI: 1.7-4.7) for group B (p=0.49). The overall survival was 3.1 months (95% CI: 2.3-3.9) for group A and 5.1 months (95% CI: 2.7-7.9) for group B (p=0.95).

The one year survival was 13.9% for group A and 21.0% for group B. There was no statistically significant difference between the groups.

Toxicity. In 65 patients (32 group A, 33 group B) toxicity data was available (Table III). No toxic deaths were seen.

Overall, the treatments were well tolerated by both arms. Grade 3/4 toxicity was rare and only neutropenia was present in 25% of the evaluated patients in group A and 6% in group B. However, this was not statistically significantly different. The only toxicity which was more prominent and statistically significant was alopecia in group B (p=0.008).

No hospitalization was required for neutropenic infection or bleeding. Vomiting was more common in the vinorelbine arm but not significantly.

Clinical benefit analysis. The clinical benefit assessment at baseline was equal in both groups. Following the second cycle of chemotherapy the only statistically significant difference between the two groups was appetite in favor of paclitaxel. However, overall, the improvement in clinical benefit was limited. As a matter of fact appetite was worse in the Navelbine group compared to baseline. In the same group only cough improved (Table IV).

Table I. *Baseline patient and tumor characteristics*.

	Navelbine (N=36)	Paclitaxel (N=38)
Age (yr)		
Median	68.5	70
Range	51-84	48-83
Gender, n (%)		
Male	30 (83)	32 (84)
Female	6 (17)	6 (16)
Stage, n (%)		
IIIa	1 (3)	1 (3)
IIIb	1 (3)	3 (8)
IIIbwet	3 (8)	3 (8)
IV	31 (86)	31 (82)
Stage, n (%)		
IIIa-bwet	5 (14)	7 (18)
IV	31 (86)	31 (82)
Histology, n (%)		
Squamous cell	11 (31)	16 (42)
Adenocarcinoma	19 (53)	11 (29)
Large cell	0 (0)	3 (8)
Mixed	0 (0)	1 (3)
Undifferentiated	2 (5)	2 (5)
Unclasified	1 (3)	0 (0)
MD	3 (8)	5 (13)
Metastatic sites, n (%)		
Lymph nodes	19 (53)	22 (58)
Pleural effusion	11 (31)	8 (21)
Liver	6 (17)	7 (18)
Bones	16 (44)	14 (37)
Brain	3 (8)	7 (18)
Adrenal glands	7 (19)	7 (18)
Number of metastatic sites, n (%)		
1	8 (22)	9 (24)
2	19 (53)	13 (34)
≥3	8 (22)	13 (34)
Unknown	1 (3)	3 (8)
Prior radiotherapy		
Yes	10 (28)	13 (34)
No	26 (72)	25 (66)

There were no statistically significant differences between the groups.

Discussion

Patients with advanced NSCLC and PS 2 are a unique group and have attracted recently the interest of investigators.

Vinorelbine and paclitaxel have known efficacy and a good toxicity profile in patients with NSCLC and PS 0, 1 or

Table II. *Best response*.

	Navelbine (N=36) N (%)	95% Exact CI for the response rate	Paclitaxel (N=38) N (%)	95% Exact CI for the response rate
PR	2 (6)	0.7-18.7	5 (13)	4.4-28.1
SD	5 (14)	4.7-29.5	7 (18)	7.7-34.3
PD	14 (39)	23.1-56.5	11 (29)	15.4-45.9
Early tumor death	4 (11)	3.1-26.1	7 (18)	7.7-34.3
Non-evaluable	2 (6)	0.7-18.7	1 (3)	0.1-13.8
Treatment discontinuation prior to evaluation	5 (14)	4.7-29.5	6 (16)	6.0-31.2
MD	3 (8)	1.7-22.5	1 (3)	0.1-13.8
CR-PR	2 (6)	0.7-18.7	5 (13)	4.4-28.1
All other	34 (94)	81.3-99.3	33 (87)	71.9-95.6

There was no statistically significant difference between the groups.

Table III. *Toxicities*.

	Navelbine (N=32)				Paclitaxel (N=33)			
	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Anemia	9 (28)	9 (28)	1 (3)		14 (42)	5 (15)		
Leucopenia	4 (13)	3 (9)	5 (16)		4 (12)	5 (15)		
Neutropenia	2 (6)	2 (6)	7 (22)	1 (3)	2 (6)	2 (6)	2 (6)	
Thrombocytopenia	3 (9)				1 (3)			
Lymphopenia		2 (6)				2 (6)		
Gastrointestinal	7 (22)	3 (9)			8 (24)			
Vomiting	6 (19)	4 (13)	1 (3)		3 (9)	3 (9)		
Constitutional	1 (3)	1 (3)	1 (3)		7 (21)	3 (9)	1 (3)	
Fever	3 (9)	2 (6)			5 (15)	1 (3)		
Hepatotoxicity	3 (9)	2 (6)	1 (3)		1 (3)	5 (15)	1 (3)	
Diarrhea	4 (13)	1 (3)	1 (3)		5 (15)			
Metabolic	4 (13)	2 (6)			1 (3)	2 (6)	1 (3)	
Alopecia*					6 (18)	2 (6)		
Neurological	5 (16)	1 (3)			8 (24)	2 (6)	1 (3)	
Pain	4 (13)	5 (16)			4 (12)	1 (3)		
Pulmonary		3 (9)	1 (3)	1 (3)	2 (6)	1 (3)		1 (3)
Infection		1 (3)	1 (3)		4 (12)	1 (3)		
Hemorrhage	1 (3)				3 (9)			
Pruritus		1(3)			2 (6)			
Rash	1 (3)				1 (3)			
Cardiac					2 (6)			
Lymphatic	1 (3)					1 (3)		
Vascular							1 (3)	
Allergic reaction						1 (3)		
Stomatitis		1 (3)						
Ocular					1 (3)			

Percentages were calculated on the 65 patients (32 Navelbine, 33 Paclitaxel) for whom we had data on toxicities. Difference between the groups was found only in alopecia (p=0.008).

2 . In the present study, the toxicity was well tolerated in both arms, and no toxic deaths occurred. The incidence of grade 3/4 toxicity was low in both arms. The lack of serious infections and bleeding support the low toxicity profile of both regimens, especially in this group of patients in whom palliation and quality of life are the main goals. Certainly, the low dose intensity of both drugs given to this group of patients with poor PS could explain the low toxicity.

Table IV. *Clinical benefit response*

	Clinical benefit assessments at baseline			Clinical benefit assessments after 2nd cycle			Difference between 2nd Cycle and baseline per group	
	Navelbine (N=32)	Paclitaxel (N=31)		Navelbine (N=14)	Paclitaxel (N=16)		Navelbine (N=14)	Paclitaxel (N=16)
Symptoms	Median (range)	Median (range)	*P*-values[1]	Median (range)	Median (range)	*P*-values[1]	*P*-values[3]	*P*-values[3]
Pain	3 (0-9)	3 (0-9)	0.64	3 (1-7)	1 (0-7)	0.10	0.72	0.75
Cough	1.5 (0-7)	3 (0-8)	0.08	0.5 (0-4)	2 (0-7)	0.11	0.02	0.07
Dyspnea	3 (0-9)	0 (0-10)	0.45	2.5 (0-8)	2 (0-10)	0.67	0.61	0.14
Hemoptysis	0 (0-7)	0 (0-6)	0.76	0 (0-7)	0 (0-3)	0.63	0.18	0.34
Nausea	0 (0-4)	0 (0-2)	0.27	0 (0-7)	0 (0-8)	0.67	0.92	0.10
Vomiting	0 (0-1)	0 (0-3)	0.14	0 (0-2)	0 (0-8)	0.95	0.10	0.71
Weakness	5 (0-9)	5 (0-9)	0.72	4 (2-9)	5 (0-8)	0.56	0.73	0.17
Appetite	4 (0-8)	5 (0-10)	0.71	5 (0-9)	2.5 (0-6)	0.01	0.03	0.01
General feeling	N (%)	N (%)	*P*-values[2]	N (%)	N (%)	*P*-values[2]	*P*-values[4]	*P*-values[4]
Very good/good	7 (22)	4 (13)	0.33	4 (29)	8 (50)	0.45	1.00	0.12
Moderate/poor	23 (72)	27 (87)		9 (64)	8 (50)			
Unknown	2 (6)	0 (0)		1 (7)	0 (0)			

The above *p*-values were derived by the following test-statistics. [1]Mann-Whitney *U*-test; [2]Fisher's exact test; [3]Wilcoxon T; [4]McNemar test.

Although the response rate was higher in the B arm (13%) in comparison with the A arm (6%), the difference was not statistically significant. Even when the response rate was combined with stable disease (31% in the B arm, 20% in the A arm), the difference was not statistically significant between the two arms. Also the time-to-event measurements, there were no statistically significant differences in survival (p=0.95) or TTP (p=0.49).

In the MILES phase III trial, the combination vinorelbine – gemcitabine was associated with more thrombocytopenia and hepatotoxicity than with single-agent vinorelbine. Measures of quality of life were similar in all arms (31).

In the CALGB 9730 phase III trial, among the patients with PS 2, the median survival (4.7 *versus* 2.4 months) and 1-year survival (18% *versus* 10%) were statistically significant in favor of the combination paclitaxel – carboplatin (32).

In an ECOG trial (E1599) evaluating two combination regimens: disease-control rates, median survival and TTP were similar in both arms. Thrombocytopenia was more pronounced in the cisplatin – gemcitabine arm, whereas neurotoxicity was more common in the paclitaxel – carboplatin arm (33).

Evaluation of activity of Erlotinib and gefitinib has been reported by subgroup analysis of the IDEAL 1 and 2 and BR21 trials (34-36).

This has led CALGB to launch a trial comparing erlotinib with chemotherapy in chemonaıve PS2 patients (37). The results showed a superior response rate and progression-free survival (PFS) for patients treated with up-front combination chemotherapy. Patients selected on the basis of clinical and/or molecular markers may fare better than unselected patients when treated with erlotinib. The impressive high median survival in chemotherapy arm could be attributed to selection bias inherent to second-line treatment with erlotinib (45% females, 63% adenocarcinoma) with a positive impact of salvage erlotinib on outcome. The addition of cetuximab(38) or celecoxib (39) to chemotherapy did not seem to improve the outcome.

Clinical benefit analysis cannot substitute for quality-of-life measurement. There is a distinction between the two assessments, and improvement of clinical benefit may have only a modest impact on overall quality of life. Nevertheless, in this group of patients with poor performance status, short survival, very limited social activity, low response rate and increased incidence of progressive disease, frequent assessments are difficult and the drop out rate is high. Also, the amount of missing data in a multiple-endpoint instrument, combined with a small group of patients, may jeopardize the results and were all considered when the use of clinical benefit as the symptomatic dimension of quality of life, was selected.

The majority of patients who answered the clinical benefit questionnaire had no significant improvements of symptoms and general feelings after cycle 2. The difference between the two arms was not statistically significant. Except for appetite which was better in the paclitaxel group. Following

subsequent cycles, the number of evaluated patients was getting too small to reach any conclusions.

The subgroup of NSCLC with PS:2 is still not a homogeneous group of patients for whom treatment is not well defined. Some patients may be treated with only supportive care, some with single agents and some others by doublets with decreased doses(40-42). No solid recommendations are available from any major oncology society so far. Efforts to individualize the treatment based on frailty, concomitant diseases, histology and evaluation of CGA are very important. The present trial confirms that large phase III studies are necessary.

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