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Assessment of functional status, symptoms and comorbidity in elderly patients with advanced non-small-cell lung cancer (NSCLC) treated with gemcitabine and vinorelbine

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Abstract *Background:* The incidence and prevalence of comorbid conditions in lung cancer patients increase with age. The aim of the study was to determine response and tolerability with the biweekly combination gemcitabine–vinorelbine in elderly non-small-cell lung cancer (NSCLC) patients. In order to characterise the population included in the study well and assess the results achieved properly, an evaluation of the functional status, comorbidity and survival was performed. *Patients and method:* Between June 2001, and December 2003, 59 untreated advanced NSCLC patients over the age of 70 years entered the study. Treatment consisted of gemcitabine 1750 mg/m^2 and vinorelbine 30 mg/m^2 on day 1 every two weeks. The response was evaluated every five cycles (RECIST guidelines). Comorbidity was evaluated according to the Charlson and Kaplan Feinstein scales. To measure functional status, activities of daily living (ADL) and instrumental ADL (IADL) were considered. *Results:* Median age was 74; ECOG performance status was <2 in 59.3%; no dependence in ADL or IADL was found in 24.8% and 42.4% of patients, respectively. A total of 381 courses were administered. Grade 3–4 neutropenia was present in 6.8% of these courses and correlated with IADL. Objective response was 22% (95% CI 12–32). Mean global survival and cause-specific survival were 29 weeks (95% CI 19.9–38.1) and 32 weeks (95% CI 23.4–40.8) respectively. Comorbidity displayed no close correlation with functional status, but comorbidity according to the Kaplan Feinstein index correlated with IADL. Performance status, ADL, IADL and weight loss were significantly related to survival in multivariate analysis. *Conclusions:* This biweekly combination is feasible in elderly lung cancer patients with a high burden of comorbidity and dependence. Toxicity is acceptable, whereas response rate and survival fall in the range of active regimens. ADL and IADL indices allow the identification of elderly patients with a worse prognosis.

Key words Elderly • Lung cancer • Functional status Biweekly • Gemcitabine • Vinorelbine

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Introduction

The standard approach for advanced non-small-cell lung cancer (NSCLC) in elderly patients is a matter of some dispute. Vinorelbine (VRL) is a semi-synthetic vinca alkaloid that has also demonstrated activity for first-line treatment of patients with advanced NSCLC. The ELVIS trial showed an advantage in the median survival time (28 *vs.* 21 weeks) for elderly patients receiving single agent VRL as compared to those treated with supportive care alone [1]. Gemcitabine (GEM) is a nucleoside analogue with a confirmed activity against chemo-naïve NSCLC [2] and has a mild toxicity profile that allows it to be combined easily with other chemotherapeutic agents. Retrospective [3] and prospective studies [4] have also supported the use of GEM in elder-

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ly NSCLC patients, given its tolerability and activity regardless of age.

Among the non-platinum combinations, GEM and VRL are certainly of particular interest because of their essentially non-overlapping toxicities and high activities in chemo-naïve patients. This regimen proved to be safe and easy to administer in an outpatient setting. The Southern Italy Cooperative Oncology Group (SICOG) demonstrated that a combination of GEM plus VRL fared better that VRL alone in elderly patients (MST of 29 *vs.* 18 weeks) [5]. However the main adverse reaction was myelotoxicity. In contrast to this study, the Multicentre Italian Lung cancer in Elderly Study (MILES) showed no survival benefit from GEM plus VRL [6].

The weekly repetition of both drugs is very often accompanied by dose reduction and low dose-intensity [5]. Several other studies [7–9] of the VRL and GEM combination in untreated NSCLC patients, in which doses ranked from 20 to 30 mg/m^2 for VRL and 750 to 1200 mg/m^2 for GEM, were administered on days 1, 8 and 15 every 4 weeks or days 1 and 8 every 3 weeks. In the majority of these studies, doses were reduced and growth factor was added and/or a deferral of drug administration was required because of grade 3–4 myelotoxicity, ranging from 40% to 50%. Some of them even reported death by sepsis [8].

It has been demonstrated that VRL and GEM can be combined with other anti-neoplastic agents given every two weeks with a good clinical and toxicity profile, even in pre-treated patients with advanced breast cancer [10].

The heterogeneity of the population is a prominent feature of the studies with elderly cancer patients. The evaluation of functional status detects individual differences within this heterogeneous population. Few studies have specifically examined the functional status of older cancer patients, however; only by assessing the functional status of patients can we discriminate and compare the results achieved between different studies. The activities of daily living (ADL) and the instrumental ADL (IADL) scales are the most universally utilised measures of functional status [11, 12]. The ADL items cover basic functions that are similar to stages in child development and the IADL covers skills with more cognitive influence [13].

We have conducted a study to evaluate the efficacy and toxicity of the combination of GEM and VRL administered every 2 weeks in untreated elderly patients with advanced NSCLC. A phase I trial of the biweekly combination was published before [14] in patients with advanced or refractory solid tumours younger than 71 years. In this study the recommended doses for phase II was GEM 2500 mg/m^2 and VRL 30 mg/m^2. Nevertheless, due to the patients' characteristics, the dose level of GEM and VRL in the study presented here was based on the dose intensity of both agents achieved in weekly schedules.

The objective of the study was to determine response and tolerability with the biweekly combination GEM–VRL in elderly NSCLC patients. In order to characterise the population included in the study well and assess the results achieved properly, an evaluation of the functional status, comorbidity and survival was performed.

Patients and methods

Patients were eligible if they had histological or cytological diagnosis of advanced NSCLC, stages IIIB (pleural effusion, supraclavicular nodes or where radiotherapy was contraindicated) and IV; age ≥70 years; ECOG performance status of 0, 1 or 2; at least one measurable lesion (pleural effusion, ascites, osteoblastic lesions and lesions previously treated with radiotherapy were not admitted as measurable); life-expectancy >12 weeks; neutrophil count ≥1500/mm^3 and platelet count ≥100 000/mm^3; adequate hepatic and renal function. The study protocol was approved by the ethics committee of participating centres. All patients gave written informed consent.

Exclusion criteria were the presence of symptomatic brain metastases or a second tumour without adequate therapy in the previous five years.

Given the population characteristics and the existing data in the literature at the moment of the study design, it was decided to administer a lower dose of GEM broadly authenticated in combination. Treatment consisted of GEM 1750 mg/m^2 day 1 and VRL 30 mg/m^2 day 1. Courses were repeated every two weeks to a maximum of 15 per patient.

A complete blood count was performed before the beginning of a new course. If the neutrophil count was <1500/mm^3, the platelets <100 000/mm^3 or creatinine >1.5 mg/dl, therapy was deferred for one week. If these figures did not recover after a two-week delay, the patient was withdrawn. The doses of both drugs were reduced by 25% in case of febrile neutropenia, grade IV neutropenia, bleeding grade III–IV thrombopenia or if the last cycle had been delayed two weeks. The prophylactic use of granulocyte colony stimulating factor was not considered. Dose reduction was allowed in cases of hepatic toxicity, peripheral neuropathy or mucositis.

The response was evaluated every five cycles as complete response (CR), partial response (PR), stable disease (SD) or progressive disease in accordance with Response Evaluation Criteria in Solid Tumours (RECIST) guidelines [15]. Toxicities were assessed using National Cancer Institute Common Toxicity Criteria (version 2).

Comorbidity was evaluated according to the Charlson and Kaplan Feinstein scales, which are simple and commonly used in geriatrics [16, 17]. Functional status was measured as ADL and IADL [11, 12]. ADL includes bathing, dressing, using the bathroom, continence, getting up and being able to move around the house, and feeding. For each of the six items, two possible scores were assigned: 0 (dependent) or 1 (independent). IADL included the ability to use the telephone, shopping, meal preparation, housekeeping, transportation/travel, responsibility for own medications and the ability to handle finances. For each item two responses were available: dependent (0 score) and independent 1 (score). Only adroit individual self-

Table 1 Patients' characteristics

Characteristic	Number of patients
Gender male/female	53/6
Age	
70–74/>74	34 (57.6%)/25 (42.4%)
Performance status (ECOG)	
PS0/PS1/PS2	2 (3.4%)/33 (55.9%)/24 (40.7%)
Stage (TNM and AJCC)	
IIIA	5 (8.5%)
IIIB	18 (30.5%)
Pleural effusion, yes/no	7 (38.8%)/11 (61.1%)
IV	36 (61%)
Weight loss	
No	27 (45.8%)
<10%	21 (35.6%)
>10%	10 (16.9%)
Unknown	1 (1.7%)
ADL able to do	
1–4	6 (9.5%)
5	9 (15.3%)
6	42 (71.2%)
Unknown	2 (3.4%)
IADL able to do	
1	1 (1.7%)
3	13 (22%)
4–5	11 (18.7%)
>5	32 (54.2%)
Unknown	2 (3.4%)
Charlson's scale	
No co-morbidity	12 (20.3%)
Co-morbidity	47 (79.7%)
1	18
2	15
3 or more	14
Kaplan Feinstein's score	
No comorbidity	8 (13.5%)
Comorbidity	51 (86.5%)
1	4
2	12
3	9
4	10
5	11
6 or more	5

management was considered, therefore transportation/travel was not included. All questions were phrased to ask about performance and re-phrased to ask about ability.

Statistical analysis

The primary end point of this study was a response rate defined as the proportion of the patients whose best response was CR or PR among all per-protocol patients. Simon's two-stage design was used to determine the sample size. The accrual number was estimated to assume that a response rate in the range of 20–40% in eligible patients would indicate potential usefulness, with α=0.05 and β=0.10. This regimen would be rejected if less than 4 of the first 19 patients had an objective response at the interim analysis. Allowing for an approximate 10% dropout rate, the required number of eligible patients was approximately 59.

Correlation between variables was evaluated by the Spearman's test (two-sided $p \leq 0.05$ as level of significance). Survival was measured from the date of inclusion to the date of death or most recent follow-up; curves were calculated using the Kaplan-Meier method and compared with Log-Rank, Breslow and Tarone-Ware tests. For multivariate analysis, Cox's proportional hazard model was used. Differences were considered statistically significant if the p values were less than 0.05.

Results

Patient characteristics

From March 2001 to December 2003, 59 patients were included in the study. There were 53 men and 6 women. The median age was 74 years (range 70–83). Table 1 shows the patients' characteristics.

Toxicity

A total of 381 courses were administered, with a median of 6 per patient (range 1–15). Treatment was delayed in 53 cycles (13.9%) and reduced to 75% in 19 cycles (4.9%). Grade 3–4 neutropenia appeared in 6.8% of the courses. No thrombocytopenia grade 3–4 was registered. Non-haematological toxicity was mild and mainly consisted of fatigue, nausea and anorexia. Table 2 shows the haematological and non-haematological toxicities, respectively. Although there was no death due to toxicity, dependency in three or more IADL correlated with grade 3–4 neutropenia (Table 3).

Response and survival

Although data to evaluate response were available in 51 patients, the whole group was considered (intent-to-treat analysis). Thirteen patients achieved partial response, for an overall response rate of 22% (95% confidence interval: 12–32%) after chemotherapy. Twenty-two patients (37.3%) had stable disease, whereas 24 patients failed either due to progression (16 patients), refusal to go on therapy or death before response evaluation (8 patients). Overall response according to per-protocol analysis was 25% (95% confidence interval: 13–36.8%). Response did not correlate with comorbidity, ADL or IADL. The median overall survival and median cause-specific survival were 29 weeks (95% confidence interval: 19.9–38.1 weeks) (Fig. 1) and 32 weeks (95% confidence interval 23.4–40.8 weeks) respectively. One-year survival and one-year cause-specific survival were 28.75% and 32.6% respectively. The median time to progression was 24.85 weeks (95% confidence inter-

Table 2 Haematological and non-haematological toxicity (CTC v.2)

Toxicity/grade	Number of cycles (percentage)			
	1	2	3	4
Neutropenia	38 (9.97)	26 (6.82)	19 (4.98)	7 (1.83)
Leukopenia	32 (8.39)	12 (3.14)	7 (1.83)	0
Thrombocytopenia	3 (0.78)	0	0	0
	Number of patients (percentage) (greatest registered per patient)			
Anaemia	9 (15.25)	4 (1.04)	1 (0.26)	0
	Number of cycles (percentage)			
Nausea and vomiting	38 (9.97)	9 (2.36)	2 (0.52)	–
Diarrhoea	5 (1.31)	–	–	–
Renal	21 (5.51)	4 (1.04)	–	–
Fatigue	68 (17.81)	27 (7.08)	24 (6.29)	1 (0.26)
Fever	15 (3.93)	1 (0.26)	–	–
Anorexia	8 (2.09)	10 (2.62)	8 (2.09)	1 (0.26)
Infection	6 (1.57)	1 (0.26)		
Peripheral ischaemia	–	1 (0.26)	–	–
Febrile neutropenia	–	–	1 (0.26)	–

val: 21.47–28.41 weeks). Six patients died from causes different from disease progression: coronary disease, congestive heart failure in two patients, renal dysfunction, gastrointestinal bleeding and chronic lung disease without lung cancer progression. Seven patients received second-line therapy: chemotherapy with taxanes was applied in five of them and tyrosine kinase inhibitors in the other two.

Median survival was significantly better in patients with a performance status <2 (37.71 weeks, 95% CI 22.48–52.9 weeks) *vs.* those with a value of 2 (17.71 weeks, 95% CI 14.47–20.95 weeks). There was a trend towards better survival in patients with fewer co-morbid conditions (Charlson or Kaplan Feinstein scores) or a greater capacity to develop IADL. Variables related to survival and the level of prognostic significance are shown in Table 4. ECOG performance status, ADL, IADL and weight loss were significantly related to survival in multivariate analysis.

Correlation and multivariate analysis

Comorbidity displayed no close correlation with functional status (Table 5), however comorbidity measured according to Kaplan Feinstein correlated with IADL.

Discussion

The assessment of performance status according to the classical Karnofsky or ECOG scales has been shown to be an effective predictor of outcome in several oncological studies. However, its application to patients over 70 years of age has limited utility and may under-represent the degree of functional impairment [18].

Comorbidity and functional status according to ECOG, ADL and IADL have been shown to be independent in older cancer patients [19]. However, some

Table 3 Correlation between neutropenia and instrumental activity of daily living

Spearman's rho	Correlation coefficient	Significance	*N*
PS>1	–0.056	0.672	59
IADL**	0.317*	0.017	56
ADL	0.188	0.162	57

*Correlation is significant at the 0.05 level (two-tailed)
**Dependence in three or more IADL

Table 4 Survival: univariate and multivariate analysis

Variable/test	Univariate analysis		
	Log-rank	Breslow	Tarone-Ware
Stage III vs. IIIB*–IV	0.2376	0.3572	0.2855
PS 0–1 vs. 2	0.0394	0.0090	0.0138
Weight loss	0.0117	0.0324	0.0199
0–10% vs. >10%			
ADL	0.0010	0.0032	0.0018
IADL	0.3477	0.9860	0.6927
Comorbidity			
Charlson	0.1460	0.3355	0.2200
Kaplan Feinstein	0.7111	0.9909	0.8807

IIIB with pleural effusion
p significant <0.05

Variable	Multivariate analysis			
	Standard error	Significance	Regression coefficient	Relative risk
PS 2/0–1	0.4012	0.0074	0.1283	2.92
Weight loss	0.2188	0.0004	0.1824	2.16
Stage III[$]	0.3538	0.4912	0.0000	0.78
ADL*	0.6006	0.0044	0.1393	5.52
IADL[&]	0.3987	0.0025	0.1507	3.33
Charlson index	0.2047	0.8486	0.0000	1.03

I*Dependence in two or more ADL; [&]Dependence in two or more IADL; [$]IIIB without pleural effusion

degree of correlation between comorbidity and IADL has been reported before [20] and, in the same way, IADL correlated with comorbidity in our series according to the Kaplan Feinstein score. Given that the latter score was developed by consensual criteria for use in a longitudinal study of diabetics [17], it could probably reflect some aspects of functional activity not contemplated in ADL or ECOG scores. The Charlson score has already performed similarly to the previous system devised by Kaplan and Feinstein [16]; notwithstanding, it ignores several comorbidities that may be important in lung cancer patients.

Neither Charlson nor Kaplan Feinstein scores revealed prognostic value in this series of elderly patients, nevertheless cause-specific survival was better than survival in the whole group. This result is in accordance with the published literature [20]. Both scores have already performed similarly. It must be taken into consideration that the Charlson score, which was developed empirically and based on the 1-year mortality from an inception cohort study of patients admitted to a medical service, ignores several comorbidities that may be important in lung cancer patients, such as blood diseases or renal dysfunction. However myocardial infarction, cerebrovascular disease and diabetes have not been found to be important predictors of survival in lung cancer patients [21]. Thus, concurrent comorbidities according to these indices probably had no relevant prognostic impact for advanced lung cancer patients, who have low overall survival rates.

In the present study, 24.8% of the patients had a limitation for ADL and 42.4% for IADL baseline. On the

Table 5 Correlation between comorbidity and functional status

Correlation coefficient	ECOG	AVD	IAVD	Charlson	Kaplan Feinstein
ECOG	1	–0.286*	–0.231	–0.023	0.180
ADL	–0.286*	1	0.400**	–0.034	–0.116
IADL	–0.231	0.400**	1	–0.122	–0.385**
Charlson	–0.023	–0.034	–0.122	1	0.575**
Kaplan Feinstein	0.180	–0.116	–0.385**	0.575**	1

Spearman's correlation
*Correlation is significant at the 0.05 level (two-tailed)
**Correlation is significant at the 0.01 level (two-tailed)

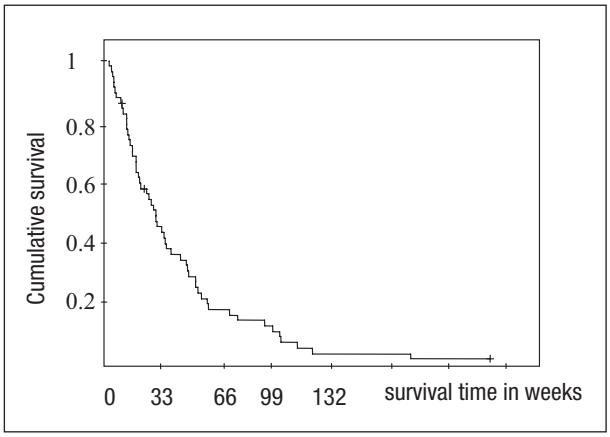

Fig. 1 Median survival of the whole group

other hand, ADL and IADL had an independent prognostic role. ADL has been shown to be particularly associated with survival in previous studies [22] and its prognostic value in the present study contrasts with that reported before in elderly patients with advanced lung cancer [20], perhaps as a consequence of the higher proportion of ADL-dependent patients. On the other hand, the ADL cut-off is especially important although common criteria of frailty include dependence in one or more ADLs [23]. However, account must be taken of the existence of a large number of different and often conflicting criteria for the definition of frail older persons [24]. This datum must be considered when response and survival are evaluated and the weight of the number of ADL and IADL dependencies has to be investigated.

As has been reported before [25], a strong association emerged between PS and presence of ADL and/or IADL limitations. It is clear from these data that the Comprehensive Geriatric Assessment (CGA) may help to identify better the specific needs of each patient with poor PS among the whole set of functional status parameters. ADL and IADL may be more sensitive than PS alone and many aspects of functional impairment are not fully recognised by PS [26].

The importance of activity level as a rudimentary predictor of chemotherapy-related toxicity in an elderly population with NSCLC has already been described [27]. According to the results published before, IADL limitations correlated with grade 3–4 neutropenia. On the other hand, changes in IADL scores have been associated in the literature with an increased risk of chemotherapy complications [28].

Weight loss demonstrated prognostic significance independent of functional status. This fact has been reported previously, but only performance status was considered as a marker of functionality [29]. Weight loss occurs as a result of two main causes: the first is the tumour itself and its treatment, and the second is the body's metabolic/inflammatory response to the tumour. However, functional status may reflect an interactive process between cancer and comorbidity level.

On the basis of this and other studies [22], functional status according to ECOG, PS and ADL-IADL should be scored to ensure comparability between oncological and geriatric studies. Older cancer patients tend to have a wide range of functional ability, so, rather than trying to derive inherent truth that can be generalised to all older cancer patients, doctors must realise the importance of individual assessment of functional status [13]. Functional status can be a helpful guide in discerning which older patients are most vulnerable to the stresses of cancer treatment [13].

With regard to the evaluated scheme, the results achieved in the present study agree with the pre-existing data indicating that the repetition of VRL and GEM on day 8 does not seem to increase the effectiveness but rather enhances grade 3 and 4 myelotoxicity, resulting in dose reduction or treatment delay. In the scheme presented, both drugs were administered at optimal dose intensity once every 2 weeks and the myelotoxicity that usually occurs with the day 1 to 8 administration of a 21-day schedule was obviated. However response (22%) and survival (median of 29 weeks) were similar to that published before [30]. Notwithstanding, at present, such a long treatment would be questionable.

The combination of VRL and GEM administered biweekly produces an acceptable response and survival rates and is well tolerated in elderly NSCLC patients. On the other hand, functional scales such as ADL and IADL seem to allow the identification of elderly patients with a worse prognosis and who probably require individualised cancer management. However, an additional approach, yet to be tested, is whether functional deficits can be corrected prior to initiating cancer treatment, moving more patients to a healthier category. This fact could allow more effective therapy to be used than would have otherwise been applied [13].

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