

Prognostic role of a comprehensive geriatric assessment on the management of elderly patients with advanced non-small cell lung cancer (NSCLC): a pooled analysis of two prospective phase II trials by the GFPC Group

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Background: The prognostic role of a comprehensive geriatric assessment (CGA) on the management of elderly patients with advanced-stage non-small cell lung cancer (NSCLC) remains to be established. The objective of this analysis was to determine the prognostic role of each CGA domain on overall survival (OS) among elderly patients with advanced-stage NSCLC.

Methods: We pooled individual data from two prospective, randomized phases II trials in patients over 65 years old with advanced-stage NSCLC, who were considered fit (0405 trial) or no-fit (0505 trial) based on a CGA. Both trials compared first-line chemotherapy followed by second-line erlotinib with the reverse strategy in terms of progression-free survival (PFS) and OS. Factors prognostic of OS were sought by using the Kaplan-Meier method and the log rank test for univariate analysis, and a Cox model for multivariate analysis.

Results: Analysis performed on 194 patients (mean age: 77 years, male gender: 70%, never- or ex-smokers: 56%) showed, in univariate analysis that performance status (PS), smoking status, Charlson, simplified Charlson, nutritional scores, and a mobility score were prognostics of OS. In multivariate analysis, PS [HR: 1.4 (1.02–1.9), P=0.04] and the Charlson score [HR: 1.46 (1.07–1.99), P=0.02] were independently prognostic of OS, while the nutritional score [HR: 0.69 (0.46–1.04), P=0.07] and the mobility score [HR: 0.25 (0.06–1.01), P=0.06] were close to significance.

Conclusions: PS and comorbidities appear to be the main predictors of OS in elderly advanced NSCLC patients selected on the basis of CGA.

Keywords: Elderly; non-small cell lung cancer (NSCLC); geriatric; therapeutic; erlotinib; chemotherapy

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). Eighty-five percent of diagnosed lung cancer patients have non-small cell lung cancer (NSCLC) (1) and 70% of them are diagnosed at an advanced stage when systemic therapy is the standard option. Median age at diagnosis is 70 years (2) and lung cancer is therefore a disease of older adults (3). Age is an important factor in NSCLC management decisions, because of the complex interplay between normal age-related decline and co-morbidities. Elderly patients are under-represented in clinical trials, making it difficult to predict the tolerability and outcome of chemotherapy (4). In the routine clinical setting, physicians generally use a combination of performance status (PS) and organ function to select patients for chemotherapy. PS is a strong predictor of outcomes in older cancer patients, especially those with advanced-stage NSCLC (5). However, successful treatment of elderly patients also depends on their physical, cognitive and nutritional status, mobility, and social support. For this reason, more formal geriatric assessments have been developed (6-12). Although there is no consensus method for identifying frail or pre-frail older patients, a number of clinical screening tests are now available (13). Comprehensive geriatric assessment (CGA) consists of a set of tools for assessing cognitive function, psychological, functional and nutritional status, co-morbidities, and medication. Comorbidities are generally assessed with the Charlson comorbidity index and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Several studies have examined the impact of comorbidities on overall survival (OS), in-hospital mortality, hospitalizations, adverse effects, quality of life, and treatment allocation (14).

In elderly patients with advanced-stage NSCLC, several phase II trials and a large phase III trial failed to show a clear benefit of using the CGA for allocation treatment (5,15-19). In addition, the CGA has been criticised for being time-consuming, cumbersome and not standardised, and its real influence on treatment decisions in clinical practice has been questioned (12).

The aim of this study was to estimate the prognostic role of the different GCA domains on OS in elderly patients with advanced-stage NSCLC, by analyzing individual data from two phase II trials.

Methods

Data

We pooled individual data from two prospective, multicenter,

open-label randomized phase II trials in chemotherapy-naive patients over 65 years old with advanced-stage NSCLC. GFPC 0504 involved fit patients (15) and GFPC 0505 frail patients (16), as identified with a CGA. Both trials compared first-line chemotherapy (gemcitabine plus docetaxel for fit patients, gemcitabine alone for frail patients) followed by second-line erlotinib versus the reverse strategy (erlotinib followed by chemotherapy). In both studies the primary endpoint was the time to second-line progression (PFS2). OS was a secondary endpoint.

CGA

All the patients were assessed at inclusion with a CGA by their regular clinicians. The protocol included no specific interventions to improve health disorders identified by the CGA.

The CGA (*Table 1*) included situational, outdoor, social environments, home ergonomics, cognitive and sensory functions (Folstein MMSE), emotional balance, self-confidence and mood, including a depression scale (GDS 5), a nutritional assessment (mini MNA), a quality-of-life scale (IRIS), pain assessment, activities of daily living (ADL) and instrumental activities of daily living (IADL), sphincter control, and motor skills (including falls in the past year and a get-up-and-go test).

Patients were classified as fit or frail according age, the number of comorbidities, PS (*Table 2*).

Statistical analysis

Standard descriptive statistics were used. Quantitative data were expressed as the population, number, mean, standard deviation and range; qualitative data were expressed as the population, number and frequency. All tests were two-sided, and significance was assumed at $P < 0.05$. Quantitative variables were compared with Student's *t*-test or with Wilcoxon's test when the groups were too small or the data were not normally distributed. Qualitative parameters were compared with the Chi² test for theoretical group sizes above 5, and otherwise with Fisher's test.

The endpoint of this prognostic study was OS, defined as the time between randomisation and death from any cause. Patients who did not die were censored at the date of last follow-up. Survival rates and their 95% confidence intervals were estimated with the Kaplan-Meier method. The log-rank test was used to compare survival curves. Parameters significantly associated with OS in univariate analysis ($P < 0.05$) were further tested in multivariate analysis. Hazard

Table 1 Domains explored by comprehensive geriatric assessment.

Domains	Scales
Functional status	ECOG-Performance Status ADL: Katz basic activities of daily living (ADL) scale IADL: simplified Lawton's instrumental activities of daily living (IADL) scale
Co-morbidities	Charlson's index
Medics	Number, type, indication
Cognitive functioning	Folstein's mini mental status evaluation, Schultz-Larsen mini mental status evaluation
Geriatric syndrome	Fecal and/or urinary incontinence
Depression/mood	Geriatric depression scale 5 (GDS5), emotional questionnaire
Nutrition	Body mass index (BMI) and mini nutritional assessment score
Mobility	Timed up and go test
Situational assessment	Accessibility of services, moving means, social environment, accessibility of the house rooms

Table 2 Geriatric inclusion criteria.

Age [Charlson]	IADL (0–4)	ADL (0–6)	Geriatric syndrome	Co-morbidity (Charlson score)	PS	Decision
65–69	4	6	0	0–2	0–1	Not includable
	4	6	0	0–2	2	Fit
	4	6	0	3–4	0–1	Fit
	3–4	<6	0	3–4	2	Unfit
70–79	3–4	6	0	0–1	0–1	Fit
	0–1–2	<6	0	0–1	2	Unfit
	0–1–2	<6	0	2–4	0–2	Unfit
80–89	4	6	0	0	0–1	Fit
	3–4	<6	0	1–2	0–1	Unfit
	0–1–2	<6	0	1–2	0–2	Unfit

Geriatric syndrome: repeated falls, fecal and/or urinary incontinence. IADL, instrumental activities of daily living; ADL, activities of daily living; PS, performance status.

ratios (95% confidence interval) were estimated with Cox's proportional hazards regression model (multivariate analysis), using the lowest-risk group as reference. All tests were two-sided. SAS software version 8.2 was used (Institute INC, Cary, USA).

The protocol was approved by an independent ethics committee in Marseille (N 05/31 and 05/32, 14/02/2015) on behalf of all participating centers, and the study complied with Good Clinical Practices and the Helsinki Declaration. According to French regulations, all the participants gave informed consent before taking part to the study.

Results

From May 2006 to January 2010, respectively 100 and 94 patients were eligible for trials 0504 and 0505. These 194 patients constituted the sample for the present pooled analysis. Mean age was 77 years (66–88 years), and 135 (70%) of the patients were men. PS was 0 in 71 cases (36%) (Table 3). At CGA assessment, respectively 166 (85.6%) and 176 (90.7%) patients had ADL and IADL scores of 3 and 4, 129 (66%) had a Charlson score of 0 or 1, 175 (90.2%) had a mini mental status (MMS) score of >30, 146 (75%)

Table 3 Characteristics of patients

Characteristics	N=194
Mean age \pm std [range]	77 \pm 4 [66–88]
Gender: men	135 (70%)
Treatment sequence	
Chemotherapy followed by erlotinib	93 (48%)
Erlotinib followed by chemotherapy	101 (52%)
Performance status	
0	71 (36%)
1	100 (52%)
2	23 (12%)
NSCLC histology	
Adenocarcinoma	110 (57%)
Squamous	48 (25%)
Others	36 (18%)
Stage	
IIIb	20 (10%)
IV	174 (90%)
Tobacco status	
Currently smoker	85 (44%)
Ex or non-smoker	109 (56%)
Charlson score	
0	71 (37%)
1–2	103 (53%)
>2	20 (10%)

had a motor score of 0 or 1, and 161 (82.9%) had a normal nutritional score (*Table 4*)

The most frequent co-morbidities, based on the Charlson score, were COPD (29.5%) and peripheral arterial disease (18.1%). Ninety-three patients (48%) received chemotherapy followed by erlotinib, while the remaining 101 (52%) patients received erlotinib followed by chemotherapy. No significant difference between the arms was observed in either trial in terms of PFS2 or OS. In the pooled analysis, PFS2 was respectively 6.1 and 4.9 months in patients who received chemotherapy first and erlotinib first, and the respective OS was 7.1 and 5.9 months. Median OS was 6.3 months in the pooled population. Prognostic factors of OS in univariate analysis were PS ($P=0.01$),

smoking status ($P=0.02$), the Charlson score ($P<0.001$), the simplified Charlson score ($P=0.03$), the nutritional score ($P=0.01$), and the level mobility score ($P=0.009$) (*Table 4*). In multivariate analysis, PS ($P=0.04$) and the Charlson score ($P=0.02$) were independently prognostic of OS, while the nutritional score [HR: 0.69 (0.46–1.04), $P=0.07$] and the mobility score [HR: 0.25 (0.06–1.01), $P=0.06$] were close to significance.

Discussion

In this pooled analysis of two trials involving elderly patients with advanced-stage NSCLC, in which the choice of chemotherapy was guided by a CGA, PS and the Charlson co-morbidity score were prognostic of OS, while nutritional and mobility scores were close to significance. These results confirm that PS is a major prognostic factor for OS in lung cancer, as in other malignancies. The role of PS in this setting was recently confirmed in a large French prospective cohort study (20). As in other advanced cancers (21,22), the number of co-morbidities is also significantly associated with OS in advanced-stage NSCLC. The link between co-morbidities and OS is more readily found in homogeneous elderly NSCLC populations (23–25). A joint analysis of two prospective randomized trials of systemic chemotherapy (adjuvant/palliative setting) in a total of 1,255 patients with NSCLC showed a clear association between the Charlson comorbidity index and OS (14). The high prevalence of smoking among patients with advanced NSCLC may help to explain the impact of co-morbidities, especially cardiovascular disease (13).

This analysis included fit and no-fit patients but there is no consensus on the tools used for the different CGA domains. The cut-off of each tool remains also controversial. Here (15,16) the cut-offs were chosen to select elderly patients with advanced NSCLC able to receive a mono or a doublet of chemotherapy. This explains why for MMS for example the cut off was 30, instead of a cut off of 24 used in another's studies to assess the cognitive function of elderly patients without cancer.

We found no impact of several domains of CGA on OS among patients with advanced NSCLC. One possible explanation is the exclusion of patients with poor functional status, i.e., patients with a geriatric syndrome, PS 3 or 4, poor MMS. Most of the rare studies in this area did not base treatment choices on geriatric criteria but included a geriatric assessment before chemotherapy. In a prospective multicenter study, previously untreated patients over

Table 4 Prognosis factors on overall survival

Factors	Univariate, HR [95%]	Analysis, P value	Multivariate, HR [95%]	Analysis, P value
Gender		0.10	–	–
Female (n=59)	1			
Male (n=135)	1.3 [0.95–1.8]			
PS score		0.01	1.4 [1.02–1.9]	0.04
0 (n=71)	1			
1-2-3 (n=123)	1.5 [1.1–2.0]			
Histology		0.47	–	–
Squamous, others (n=84)	1			
Adenocarcinoma (n=110)	0.9 [0.67–1.20]			
Tobacco status		0.02	–	–
Current smoker (n=85)	1			
No or ex-smoker (n=109)	0.70 [0.52–0.95]			
ADL Score		0.14	–	–
<6 (n=28)	1			
6 (n=166)	0.70 [0.32–1.26]			
IADL score		0.17	–	–
0–1–2 (n=18)	1			
3–4 (n=176)	0.70 [0.42–1.16]			
Charlson score		<0.001	1.46 [1.07–1.99]	0.02
0–1 (n=129)	1			
2–3–4 (n=65)	1.97 [1.44–2.7]			
MMS score		0.55	–	–
<30 (n=19)	1			
30 (n=175)	0.88 [0.62–1.24]			
Emotional assessment		0.24	–	–
≤5 (n=176)	1			
>5 (n=18)	0.58 [0.25–1.44]			
Nutritional assessment		0.01	0.69 [0.46–1.04]	0.07
≤8 (n=33)	1			
8 (n=161)	0.60 [0.42–0.91]			
Mobility score		0.009	0.25 [0.06–1.01]	0.06
0–1 (n=146)	1			
2 (n=48)	0.15 [0.04–0.62]			

PS, performance status; ADL, activities of daily living; IADL, instrumental activities of daily living; MMS, mini mental status.

70 years of age scheduled for first-line chemotherapy for various malignancies were assessed with an abbreviated CGA, including the Mini-Mental State Exam, Timed Get Up and Go (GUG), ADL, IADL, Mini Nutritional Assessment (MNA), Geriatric Depression Scale (GDS15), and a co-morbidities index. A low MNA score and a long GUG (poor mobility) were associated with a higher risk of early death (<6 months), contrary to ADL and IADL (19). A history of falls was associated with a three-fold higher risk of early death. Our results are in keeping with these data, with a non significant tendency for mobility and nutritional status to be associated with OS. We found only one small, open phase II study of 59 untreated patients over 70 years of age with advanced NSCLC showing that ADL and IADL were significantly related to OS in multivariate analysis (24). No biological or clinical markers of nutritional status in oncology or CGA has been identified (26,27). Depression has been independently linked to poorer treatment adherence and poorer outcomes in cancer patients (5). In a retrospective analysis of CGA data for 249 consecutive cancer patients aged 70 years or more, an abnormal score on a geriatric depression scale was an independent predictor of poorer OS, but we found not such relationship (5). More recently (17) in a large multicenter, phase III trial, in elderly patients with advanced NSCLC, management allocation on the basis of CGA failed to improve OS but significantly reduced treatment toxicities.

There is currently no agreed alternative to the CGA for patient selection. It would be prudent to prioritise those tools with the best sensitivity (albeit less specific) and those with which physicians are familiar. With good sensitivity and independent prognostic value for 1-year survival, the G8 questionnaire (20) is currently one of the best screening tools for identifying older cancer patients requiring geriatric assessment, and we believe it should be broadly implemented in daily practice. Research must continue to refine the selection of older cancer patients for potentially life-threatening therapy (20,28).

Our analysis has several strengths. In particular, the geriatric assessment was done prospectively before treatment initiation, by the clinician in charge of the patient, in a real-life clinical situation. In addition, the population was restricted to patients with advanced-stage NSCLC, and only two chemotherapy regimens were used.

One limitation of the study was the selection of the patients able to be randomized on analyzed studies, with for example, very few patients with major cognitive problems, or major disabilities. A second limitation was the

administration of the CGA by the clinician in charge of the patient and not by a geriatric specialist but our group and the clinicians involved in these studies have an important background on this topic (15-17,29,30).

In conclusion, PS and comorbidities were the main predictors of OS among elderly patients with advanced-stage NSCLC assessed by a CGA and treated by chemotherapy. Large prospective cohorts studies are needed to identify the best tools for guiding the management of elderly patients with advanced-stage NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocol was approved by an independent ethics committee in Marseille (N 05/31 and 05/32, 14/02/2015) on behalf of all participating centers, and the study complied with Good Clinical Practices and the Helsinki Declaration and written informed consent obtained from all patients.

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