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A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study)☆

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ABSTRACT

Background: The aim of this randomized phase II trial was to evaluate the feasibility and activity of weekly gemcitabine (G) followed by erlotinib at disease progression (arm A) versus erlotinib followed by G at progression (arm B) in vulnerable elderly patients with advanced non small-cell lung cancer (NSCLC), selected on the basis of a comprehensive geriatric assessment (CGA).
Methods: Vulnerable elderly chemotherapy-naive patients with stage IIIB/IV NSCLC were selected after a CGA (socioeconomic, cognitive and emotional status, depression, nutritional status, ADL and IADL assessments). The primary endpoint was the time to second progression (TTP2). Overall survival (OS), time to first progression (TTP1) and safety were secondary endpoints.
Results: Between May 2006 and January 2010, 21 centers enrolled 100 patients, of whom 94 were eligible. TTP2 was 4.3 and 3.5 months in arm A and arm B, respectively; TTP1 was 2.5 and 2.2 months; and the median OS time was 4.4 and 3.9 months. The respective one-year survival rates were 27.3% and 20%. There was no major unexpected toxicity.
Conclusion: In vulnerable elderly patients with NSCLC not selected for EGFR expression, both strategies were feasible but had modest efficacy. Further studies are needed to identify elderly patients who should receive palliative care only.

1. Introduction

Between 30% and 40% of non small-cell lung cancers (NSCLC) are diagnosed in patients over 70 years of age, raising specific issues of age, comorbidity and toxicity [1]. Most elderly patients are either under-treated or receive non validated schedules [1,2]. In addition, they are largely under-represented in therapeutic trials, and clinical research rarely takes their specificities into account [1]. Yet the value of specific studies in elderly subjects has been clearly demonstrated [2].

The recommended first-line treatment for patients under 65 with metastatic NSCLC and good performance status consists of dual-agent platinum-based chemotherapy. There is no consensus on the management of elderly NSCLC patients, although adapted platinum-based chemotherapy seems feasible in highly selected subjects [3]. Since the ELVIS trial [4], single-agent chemotherapy has been the rule in this setting. However, dual-agent therapy without a platinum salt seems feasible for patients selected on the

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Table 1
Geriatric inclusion criteria.

AGE [Charlson]	Dependence for IADL[a]	Dependence for ADL[b]	Geriatric syndrome[c]	Co-morbidity	Charlson score	PS	Treatment
65–69 [2]	1	0	0	0–2	2–4	0–1	Ineligible[d]
	1	0	0	0–2	2–4	2	Ineligible[e]
	<2	0	0	3–4	5–6	0–1	Ineligible[e]
	<2	0	0	3–4	5–6	2	Eligible[f]
70–79[3]	1	0	0	0–1	3–4	0–1	Ineligible[e]
	<2	0	0	0–1	3–4	2	Eligible[f]
	<2	0	0	2–4	5–6	0–2	Eligible[f]
80–89[4]	1	0	0	0	4	0–1	Ineligible[e]
	<2	0	0	1–2	5–6	0–2	Eligible[f]

[a] Instrumental activities of daily living.
[b] Activities of daily living.
[c] Geriatric syndrome: dementia, urinary or fecal incontinence, falls.
[d] Autonomous.
[e] Fit.
[f] Vulnerable.

basis of a geriatric assessment taking comorbidities into account [1,5]. The EORTC Elderly Task Force considers that vulnerable patients should receive single-agent chemotherapy [1], and several such regimens have been tested. Gemcitabine monotherapy gave acceptable efficacy, with an overall survival time of 5–7 months, with moderate toxicity [6–9]. Targeted therapies have also given promising results in elderly populations. In the pivotal BR21 study, second-line erlotinib had the same efficacy in the subgroup of patients over 70 as in the overall population [10]. Targeted therapies are also a potential first-line option for elderly patients with advanced NSCLC. In an EGFR-non selected population over 70 years of age, erlotinib controlled the disease in 51% of cases, with a median survival time of 10.9 months [11]. Erlotinib was well tolerated, and there was a significant improvement in key symptoms [11].

One difficulty in this setting is the heterogeneity of elderly populations. The use of a co-morbidity score and a comprehensive geriatric assessment (CGA) can help to identify fragile patients and to define a more homogenous group of vulnerable elderly patients [12].

We used a CGA to select a population of vulnerable elderly patients for a multicenter, randomized phase II study of the feasibility and activity of weekly gemcitabine followed by erlotinib at disease progression (arm A), versus the reverse sequence (arm B).

2. Patients and methods

2.1. Study design

This was a multicenter, open-label, phase II study (GFPC 0505). As we wished to evaluate all the active treatment periods, the chosen primary endpoint was the time to second progression (TTP2), as determined with the RECIST method [13]; the secondary endpoints were OS, time to first progression (TTP1), the objective response rate (complete + partial responses), the disease control rate (objective responses + stable disease), safety, and quality of life (QoL). The protocol was approved by an independent ethics committee in Marseille, on behalf of all participating centers, and the study complied with Good Clinical Practices and the Helsinki Declaration. The trial had been registered under NCT number 00419042.

2.2. Eligibility criteria

The geriatric inclusion criteria combined age, the Charlson score [14], comorbidities, performance status (PS) and geriatric items, in order to select a population of vulnerable elderly patients (Table 1). The geriatric non-inclusion criteria were age >89 years and a combined comorbidity-PS score or CGA score incompatible with the values shown in Table 1. Vulnerable elderly patients were unfit patient according to higher comorbidities, age and IADL dependence, without geriatric syndrome (falls, incontinence, dementia)

We applied the following oncologic inclusion criteria: cytologically or histologically proven NSCLC of stage IV or IIIB with T4 stage by neoplastic pleural effusion, not previously treated with chemotherapy, a measurable tumor, life expectancy more than three months, and biological status compatible with chemotherapy (bilirubin < 1.25 ULN, transaminase activity <3 ULN, alkaline phosphatase <2.5 ULN, polynuclear neutrophil count >1.5 G/l, and platelet count >100 G/l). The oncologic non-inclusion criteria were histological status (small-cell lung cancer, bronchioloalveolar carcinoma), prior chemotherapy, symptomatic brain metastases, unstable heart disease, uncontrolled infection, grade >2 neuropathy, a concurrent metastatic malignancy, and permanent contraindications to the use of steroids.

Treatment arm A consisted of a maximum of four cycles with gemcitabine 1250 mg/m^2 on days 1 and 8, repeated every 3 weeks. CT assessments were done after two chemotherapy cycles and then, in case of non progression after 4 cycles, every 6 weeks. Patients who progressed were treated with erlotinib (150 mg/day) and assessed every 6 weeks. In arm B, patients received erlotinib first (150 mg/day), with an assessment every 6 weeks; patients who progressed received the first-line chemotherapy schedule used in arm A.

Patients in both arms systematically received epoietin beta (30 000 units once a week) when the hemoglobin level fell below 11 g/dl. Neutrophil growth factors consisted of curative lenograstim for febrile neutropenia, or secondary lenograstim prophylaxis from days 3 to 5 after chemotherapy. Chemotherapy administration could be postponed for up to 2 weeks if the patient had not fully recovered from the hematological toxicity of the previous cycle, with a 25% dose reduction. Specimen collection for determining EGFR status was not part of the initial study designed in 2005

2.3. Efficacy

Objective tumor responses were assessed at the end of 2 and 4 chemotherapy cycles, every 6 weeks during erlotinib therapy, and every 6 weeks in patients who did not progress after chemotherapy. TTP2 was calculated from the date of randomization to the date of disease progression (after the second line of treatment if the patients received 2 lines, after the first line if the patient progressed and did not receive a second line) or death of any cause, or the last on-trial tumor assessment. OS was calculated from the date

of randomization to the date of death from any cause, or the last date the patient was known to be alive. All responses were centrally reviewed and confirmed by a panel of experts convened by GFPC (Groupe Français de Pneumo-Cancérologie). Patients were monitored for adverse events, biological abnormalities, vital signs and electrocardiographic changes, using NCI-CTC version 2.0 (National Cancer Institute 1999).

2.4. Statistical analysis

In this one-step phase II trial, we assumed that the median TTP2 would be 4 months for the strategy with chemotherapy first (arm A), and 6 months for the strategy with erlotinib first (arm B). A sample size of 47 patients per group would have an 80% power with a type I error of 5% to detect differences between the two arms, based on the log-rank test. This number was rounded up to 50 patients per arm in order to take into account losses to follow-up and ineligibility. The analysis was performed on an intention-to-treat basis. 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 with Fisher's test in other cases. PFS and OS were assessed by means of Kaplan–Meier analysis. Statistical analyses were done with SAS software version 8.02 (Institute Inc, Carry, USA) at study closure. Quality of life was assessed during the initial work-up (intention-to-treat) and at the end of each cycle, using the Spitzer index [15] and the Lung Cancer Symptom Scale (LCSS) [16]. Each item of the Spitzer score is attributed a score of 0–2, with higher values reflecting better health. A mean global score is then calculated. Each item of the LCSS questionnaire is scored from 0 to 10: the higher the score, the more intense the symptom. The LCSS questionnaire yields two scores: a symptom score calculated from the first six items (appetite, fatigue, cough, breathlessness, hemoptysis, and pain), and a global score derived from the last three items (symptom severity, discomfort during routine activities, and quality of life). Quantitative scores are expressed as the mean, median and confidence interval. The groups were compared with Fisher's exact test. Statistical analyses were done with SAS software version 8.02 (Institute Inc, Carry, USA). The sponsors had no role in the study design, study realization, data analysis or manuscript preparation. The results are the property of GFPC. The data were analyzed by the GFPC statistician and interpreted by the authors.

3. Results

Between May 2006 and January 2010, 21 centers enrolled 100 patients in this study (Table 2), of whom 94 patients were eligible. (71% non-squamous, 29% squamous histology) Six patients were excluded, for protocol violations ($n = 4$), consent withdrawal ($n = 1$) or ineligibility ($n = 1$). The patients in the 2 arms were not significantly different: median age was 78.2 years in each arm, and respectively 40% (arm A) and 46% (arm B) of patients were over 80 years old. No significant difference was noted in the Charlson score, co-morbidities, or the geriatric assessment at baseline (Tables 2 and 3). The CGA allowed us to select a population of vulnerable elderly patients: respectively 43% and 38% of patients in arm A and B were dependent in the IADL, and 59.1% and 66% had a Charlson score above 1 (Table 2). We did not find any relationship between PS and geriatric assessment items.

Table 2
Characteristics of the patients; arm A: gemcitabine (G) followed by erlotinib at progression, arm B: erlotinib followed by G at progression.

	ARM A $n = 44$	ARM B $n = 50$
Age, years (mean ± sd)	78.2 ± 3.59	78.2 ± 4.42
Gender: male (%)	37 (84.1%)	39 (78%)
Weight loss >5%	23 (52.2%)	22 (44%)
Smoker		
Current	4 (9.1%)	7 (14%)
Former	36 (81.8%)	34 (68%)
Never smoker	3 (6.8%)	6 (12%)
Unknown	1 (2.3%)	3 (6%)
Performance status		
0	11 (25%)	14 (28%)
1	20 (45.5%)	27 (54%)
2	12 (29.5%)	9 (18%)
Stage		
IIIB	6 (14%)	3 (6%)
IV	38 (86%)	47 (94%)
Histology		
Squamous cell	17 (39%)	10 (20%)
Adenocarcinoma	22 (50%)	31 (62%)
Undifferentied	5 (11%)	9 (18%)
Charlson score		
0	2 (4.5%)	2 (4.5%)
1	16 (36.4%)	15 (30%)
2	18 (40.9%)	26 (52%)
3	8 (18.2%)	7 (14%)
Co-morbidities Age + Charlson (mean + sd) [range]	3.41 (3–4)	3.46 (3–4)
Simplified Charlson score (mean)	5.68 ± 4.07	5.86 ± 3.67

In arm A, all eligible patients received at least one dose of G chemotherapy (83% were assessable) and 48% received second-line erlotinib (90% were assessable) (Fig. 1). In arm B, all eligible patients received at least one dose of erlotinib (86% were assessable) and 46% received second-line G (70% were assessable) (Fig. 1). In arm A the mean number of first-line chemotherapy cycles per patient was 2.9 and the mean duration of second-line erlotinib treatment was 1.7 months. In arm B, the mean duration of first-line erlotinib treatment was 2 months and the mean number of second-line chemotherapy cycles per patient was 2.7. The mean relative G dose intensity was respectively 65% and 51% in arm A (first line) and arm B (second line).

The first objective of the study was not met, as there was no significant difference between the two arms in terms of TTP2 (4.3 and 3.5 months respectively in arms A and B, $p = 0.55$;). TTP1 was respectively 2.5 and 2.2 months ($p = 0.58$); median OS 4.4 and 3.9 months ($p = 0.26$,); and the one-year survival rate 27.3% and 20%. Central review showed no difference in objective responses or disease control (Table 4). There were no significant discrepancies with the investigators' assessments (data not shown). The factors predictive of survival were PS (0 versus 1/2) ($p = 0.0001$), gender (female versus male) ($p = 0.012$) and histology (non squamous versus squamous cell, $p = 0.03$). PS ($p = 0.001$), CGA socioeconomic status ($p = 0.03$) and squamous cell histology ($p = 0.006$) were predictive of TTP1. PS ($p = 0.001$) was predictive of TTP2.

Safety was assessable in all the patients. The most common grade 3–4 adverse events were asthenia in both arms, neutropenia and thrombocytopenia with G, and cutaneous reactions with erlotinib (Table 5). Only 9% of patients in arm A had grade 3–4 anemia, probably because of routine epoietin beta administration. In arms A and B, respectively 75% and 73%, 26% and 78%, and 43% and 38% of patients completed the QoL assessments at baseline, after 8 weeks and after 16 weeks. The median global LCSS score, the median symptom score and the global Spitzer score were similar

Table 3
Comprehensive geriatric assessment; arm A: gemcitabine (G) followed by erlotinib at progression, arm B: erlotinib followed by G at progression.

	Score maximum	Arm A ($n = 44$) Mean score	Arm B ($n = 50$) [Min/max]
Socioeconomic conditions	12	11 [4/12]	11.2 [6/12]
Cognitive assessment	14	13.2 [10/14]	13.1 [9/14]
Emotional status and depression scale	9	1.34 [0/7]	1.46 [0/7]
Sensorial status	4	3.7 [3/4]	3.74 [2/4]
Nutritional risk	14	10.4 [5/14]	9.84 [6/14]
QoL Iris Scale	6	5 [3/6]	5.05 [3/6]
ADL	6	6 [6/6]	6 [6/6]
IADL	4	3.45 [2/4]	3.26 [2/4]
Incontinence scale	4	3.86 [2/4]	3.82 [2/4]
Falls and mobility	10	9.55 [5/10]	9.56 [5/10]
Pain	32	5.84 [0/32]	5.04 [0/24]
Global score (EGSK)	20	17.8 [13.5/20]	17.7 [14.3/20]
MMS de FOLSTEIN	30	29.6 [24/30]	29.1 [24/30]

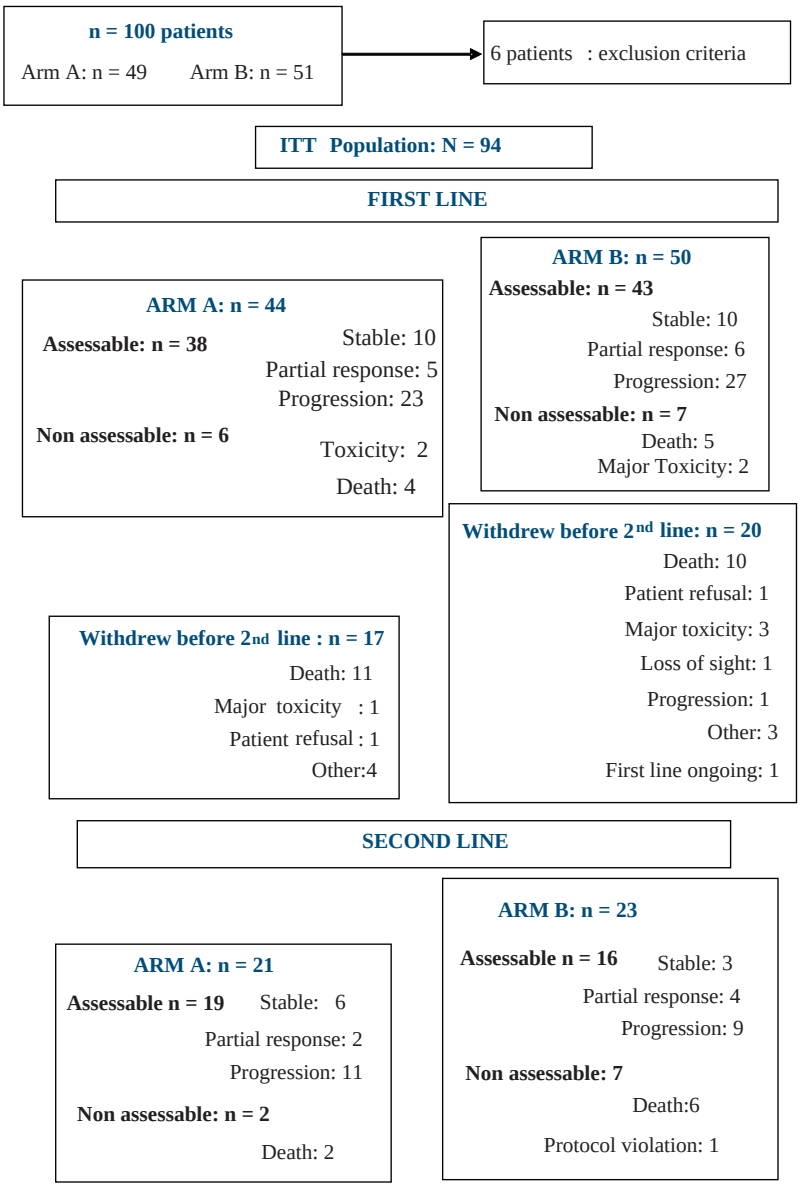

Fig. 1. Flow chart; arm A: gemcitabine (G) followed by erlotinib at progression, arm B: erlotinib followed by G at progression.

Table 4
Efficacy: arm A: gemcitabine (G) followed by erlotinib at progression, arm B: erlotinib followed by G at progression.

	Arm A ($n=44$)	Arm B ($n=50$)
Time to 2nd progression (months, CI 95%)	4.3 (3; 6.2)	3.5 (2.9;5.6)
Time to 1st progression (months, CI 95%)	2.5 (2;4)	2.2 (1.8;3.8)
Median overall survival (months CI 95%)	4.4 (3.1; 7.2)	4 (3; 6)
Objective responses (first line)		
Not assessable	6 (13.6%)	7 (14%)
Progression	23 (52.3%)	27 (54%)
Stable	10 (22.7%)	10 (20%)
Partial response	5 (11.4%)	6 (12%)
Objective responses (second line)		
Not assessable	25 (56.8%)	34 (68%)
Progression	11 (25%)	9 (18%)
Stable	6 (13.6%)	3 (6%)
Partial response	2 (4.5%)	4 (8%)
Complete response	0 (0.0%)	0 (0.0%)

in the two arms and showed little deterioration of quality of life after treatment. These scores did not change significantly during treatment.

4. Discussion

In this phase II randomized trial in vulnerable elderly patients with advanced NSCLC, selected with a comprehensive geriatric assessment, the TTP2 was 4.3 months with weekly gemcitabine followed by erlotinib, and 3.5 months with erlotinib followed by gemcitabine; the respective median times to TTP1 were 2.5 and 2.2 months and the median OS was respectively 4.4 and 3.9 months.

The first originality of this study is that the patients were selected on the basis of geriatric criteria combining age, performance status and comorbidity but also, in keeping with SIOG recommendations, functional, mental, social and nutritional status and daily activities [17]. The Charlson and co-morbidity scales, although they do not correlate with performance status, are an essential complement to the CGA [18].

In order to validate treatments tested in clinical trials, and to make the results of different studies comparable, it seems relevant to use a full geriatric assessment such as CGA, which allows fit patients to be separated from the vulnerable and fragile, pending prospective validation of geriatric screening tools [12,19,20].

The second originality of this study is that the second-line treatment was fixed in each arm, allowing us to evaluate the performance of each treatment sequence. Our results for first-line gemcitabine monotherapy in this population compare well with published data [4,8,21–25], but remain disappointing. However, it is noteworthy that our population included a large proportion of patients with PS = 2 (respectively 29% and 18% in arms A and B) and relatively high comorbidity scores.

Elsewhere, sequential treatment with gemcitabine followed by weekly docetaxel gave a median TTP1 and OS of respectively 4.8 and 8.0 months [26]. A randomized phase II trial [27] comparing pemetrexed monotherapy with pemetrexed followed by gemcitabine gave a very poor median OS of around 5 months in both arms. A more recent phase III trial involving patients over 70 years old showed the superiority of the carboplatin–taxol combination over

Table 5
Adverse events (>5% of patients); arm A: gemcitabine (G) followed by erlotinib at progression, arm B: erlotinib followed by G at progression.

First line toxicity	Arm A Grade 1/2	$n=44$ Grade 3/4	Arm B Grade 1/2	$n=50$ Grade 3/4
Hematologic				
Anemia (%)	24 (54,4)	4 (9.1)	8 (16)	2 (4)
Neutropenia (%)	8 (18,2)	2 (4,5)	1 (2)	1 (2)
Thrombocytopenia (%)	13 (29,6	3 (6.8)	2 (4)	0
Non hematologic				
Cutaneous (%)	4 (9)	1 (2.3)	33 (66)	3 (4)
Pulmonary (%)	14 (31,8)	6 (13.6)	6 (12)	1 (2)
Asthenia (%)	32 (72,7)	5 (11.4)	24 (48)	9 (18)
Diarrhoea (%)	7 (15,9)	0	18 (36)	3 (6)
Constipation (%)	4 (9,1)	0	1 (2)	0
Nausea (%)	6 (13,6)	1 (2,3)	2(4)	0
Vomiting (%)	3 (6,8)	0	5 (10)	0
Renal (%)	4 (9,1)	0	3(6)	1 (2)
Second line toxicity	**Arm A Grade 1/2**	**$n=21$ Grade 3/4**	**Arm B Grade 1/2**	**$n=23$ Grade 3/4**
Hematologic				
Anemia (%)	4 (19)	1 (4,7)	9 (39)	0
Thrombocytopenia (%)	1 (4,7)	0	5 (21)	
Non hematologic				
Asthenia (%)	6 (28,5)	1 (4,7)	8 (34,7)	5 (21)
Pulmonary (%)	4 (19)	2 (9,5)		
Cutaneous (%)	12 (57,1)	2 (9,5)	0	0
Constipation (%)	0	0	4(17)	0
Diarrhoea (%)	6 (28,5)	0	1(4)	0
Nausea (%)	2 (9,4)	0	0	0
Vomiting (%)	0	0	3(13)	1(4)

navelbine or gemcitabine monotherapy [28], but these latter results need to be confirmed, especially with respect to tolerability.

Targeted therapies are a potential option for elderly patients with advanced NSCLC. Jackman et al. tested first-line erlotinib in a phase II study with 80 NSCLC patients over 70 years of age [11]). Erlotinib was well tolerated, giving an encouraging response rate of 10% and disease stabilization in 41% of cases. There was a significant improvement in key symptoms (dyspnea, cough, fatigue and pain) and the median OS was 10.9 months. These results are far better than those obtained here, in terms of both OS and TTP1, but Jackman's population included more women and more patients with adenocarcinoma [11]. In contrast, the same percentage of patients received a second line of treatment. Gefitinib was compared to oral vinorelbine in a phase II randomized trial involving a very similar population (predominantly female elderly patients, most with adenocarcinoma). The median times to first progression were respectively 2.7 and 2.9 months, with median OS times of 5.9 and 8 months [29]. Only 19% of patients in the gefitinib arm received a second-line treatment, compared to 29% of patients in the vinorelbine arm. There were fewer treatment-related grade 3–5 adverse events with gefitinib (12.8%) than with vinorelbine (41.7%). In this latter study a substantially lower percentage of first-line erlotinib-treated patients received second-line chemotherapy. Most patients had a performance status of 2 and more and could not receive chemotherapy, even a non platin doublet. This difference may have contributed to the inferior overall results of this treatment approach. Finally, a more recent study involving unselected elderly patients compared gemcitabine with erlotinib and with the two drugs combined. Median survival was 6.8, 5.8 and 5.6 months respectively [30]. Adding a tyrosine kinase inhibitor to single-agent chemotherapy does not appear to be relevant [30].

In the second-line setting, a retrospective analysis of the BR.21 trial examined the influence of age on erlotinib outcomes [10]. There was no significant age-related difference in PFS or OS in the erlotinib or placebo arm. However, compared with young patients, elderly patients had significantly more overall and severe toxicity (grades 3 and 4) (35% vs 18%; $p < 0.001$), were more likely to discontinue treatment as a result of treatment-related toxicity (12% vs 3%; $p < 0.0001$), and had a lower relative dose intensity (64% vs 82% received >90% of the planned dose; $p < 0.001$). The toxicity of erlotinib in our CGA-selected frail population was acceptable and was not associated with a high rate of treatment withdrawals. Anyway, patients with EFGR mutations and specially elderly must receive erlotinib in first line.

If age alone is not a contraindication to treatment in elderly subjects, another promising approach in this population is to use, in addition to the CGA, genetic selection criteria [31]. Several heritable mutations accelerate the onset of multiple aging phenotypes. The process of normal aging, with the involvement of DNA repair pathways and the impairment of mitotic checkpoint genes, could provide possibilities for customized treatment in elderly patients [31]. Regarding our treatment sequence we do not find the same results that the TORCH trial probably linked to our poor survival [32]

In conclusion, no customized treatment appears as disappointing in this vulnerable elderly population. The use of a CGA is crucial for future trials in this setting. In addition, studies are needed to identify patients who should receive palliative care only. We have started a large national phase III multicenter study involving patients over 70 years of age with advanced NSCLC, in which treatment allocation will be based on a strategy using a simplified geriatric scale (SGS) followed by CGA if abnormal, in comparison with a strategy based on standard criteria (PS and age) and no specific geriatric assessment [33]. One treatment arm for vulnerable elderly patients consists of best supportive care without specific anticancer therapy.

Conflict of interest statement

Supported by an unrestricted educational grant from Roche, Lilly, Sanofi-Aventis and Chugai.

Disclosure

Pr. C. Chouaid has a consultant or advisory relationship, honoraria, research funding to disclose Amgen, Lilly, and Roche.

Pr. A. Vergnenegre has a consultant or advisory relationship with Lilly, Astra Zeneca, GSK and Roche.

Dr. H. LeCaer has honoraria to disclose with Lilly and Roche.

Drs. L. Greillier, R. Corre, H. Jullian, J. Crequit, L. Falchero, C. Dujon, H. Berard have no disclosure.

Contributions

H. LeCaer and C. Chouaid had full control of the study design, data analysis and interpretation, and manuscript preparation. All the authors were involved in planning the analysis and drafting the manuscript. The final draft manuscript was approved by all the authors.

Appendix

The GFPC 0505 team: Prof. A. Vergnenegre, Prof. B. Melloni, CHU Limoges; Dr. Prof. F. Barlesi, Dr. C. Gimenez, Dr. L. Greillier, CHU Marseille; Dr. H. LeCaer, Dr. J.R. Barriere, CH Draguignan; Dr. J. Crequit, CH Creil; Dr. J.B. Auliac, CH Mantes; Dr. R. Poirier, Dr. J. Le Treut, CH Aix; Dr. H. Berard, HIA Toulon; Dr. P. Thomas, Dr. P. Muller, CH Gap; Dr. M. Grivaux, Dr. C. Locher, CH Meaux; Prof. C. Chouaid, Dr. Baud, CHU Paris St Antoine; Dr. D. Paillotin, CHU Rouen BG; Dr. R. Corre, Dr. H. Lena, CHU Rennes; Dr. J.Y. Delhoume, CH Perigueux; Dr. C. Dujon, CH Le Chesnay; Dr. H. Jullian, Dr. J. Simonian, CH Martigues; Dr. P. David, CH Elbeuf; Dr. L. Falchero, CH Villefranche; Dr. I. Monnet, CHI Creteil; Dr. J.A. Silvani, CH Bastia; Dr. R. Gervais, CHU Caen.

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