Original Study

Cost Analysis of Erlotinib Versus Chemotherapy for First-Line Treatment of Non–small-Cell Lung Cancer in Frail Elderly Patients Participating in a Prospective Phase 2 Study (GFPC 0505)

Christos Chouaid,[1] Hervé Le Caer,[2] Romain Corre,[3] Jacquy Crequit,[4] Chrystelle Locher,[5] Lionel Falchero,[6] Cecile Dujon,[7] Henri Berard,[8] Isabelle Monnet,[9] Alain Vergnenegre[10]

Abstract

This study assessed the cost-effectiveness (limited to direct medical costs, from the third-party payer perspective) of erlotinib followed by chemotherapy after progression, compared with the reverse strategy, in frail elderly patients with advanced non–small-cell lung cancer (NSCLC). Outcomes and costs were collected prospectively. There was no significant difference between the 2 strategies in term of cost-effectiveness (respectively €47,381 and €44,350 per quality-adjusted life year [QALY]).

Background: A large proportion of elderly patients (>70 years) with newly diagnosed NSCLC are shown to be frail by a comprehensive geriatric assessment. This population is more vulnerable to adverse effects of chemotherapy and might thus benefit more from targeted therapy. The objective of this study was to assess the cost-effectiveness of erlotinib followed by chemotherapy after progression, compared with the reverse strategy, in frail elderly patients with advanced NSCLC participating in a prospective randomized phase II trial (GFPC 0505). **Materials and Methods:** Outcomes (progression-free survival and overall survival) and costs (limited to direct medical costs, from the third-party payer perspective) were collected prospectively until second progression. Costs after progression and health utilities (based on disease states and grade 3-4 toxicities) were derived from the literature. **Results:** Median overall survival, QALYs, and total costs for the erlotinib-first strategy were 3.9 months, 0.33, and €15,233, respectively, compared with 4.4 months, 0.35, and €15,363 for the chemotherapy-first strategy. There was no significant difference between the 2 strategies in term of cost-effectiveness (respectively €47,381 and €44,350 per QALY). **Conclusion:** No difference in cost-effectiveness was found between an erlotinib-first strategy and a chemotherapy-first strategy in frail elderly patients with NSCLC.

Clinical Lung Cancer, Vol. xx, No. x, xxx
Keywords: Cost-utility, Elderly patients, Erlotinib, Phase II trial

Introduction

Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and most patients already have advanced or metastatic disease at diagnosis.[1] Between 40% and 50% of NSCLC cases are diagnosed in patients older than 70 years of age, raising specific issues of age, comorbidity, and toxicity.[2] Comprehensive geriatric assess-

Presented in part at the 2011 European Ispoor meeting in Madrid, Spain

[1]AP-HP Hôpital, St-Antoine, AP-HP, UMPC, Paris
[2]CH de Draguignan, Draguignan
[3]CHU de Rennes, Rennes
[4]CH de Creil-Beauvais, Creil
[5]CH de Meaux, Meaux
[6]CH de Villefranche, Villefranche
[7]CH de Versailles, Versailles
[8]HIA de Toulon, Toulon
[9]CHI de Créteil, Créteil
[10]CHU de Limoges, Limoges, France

Submitted: Feb 12, 2012; Revised: Apr 21, 2012; Accepted: Apr 23, 2012

Address for correspondence: Christos Chouaid, MD, PhD, Service de Pneumologie, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75012 Paris, France
Phone: 33149282516
Fax: +331 49 28 2283; e-mail contact: christos.chouaid@sat.aphp.fr

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2012.04.006

ment (CGA) reveals that a large proportion of these patients are frail.[2,3] Single-agent chemotherapy has been the rule in this setting.[1,4,5] Gemcitabine shows acceptable efficacy and tolerability, with an OS time of 5 to 7 months.[6-9] More recently, targeted therapies have given promising results in elderly populations. In the pivotal BR21 study, second-line erlotinib had the same efficacy in the subgroup of patients who were older than 70 years as in the entire population.[10] Targeted therapies are also a potential first-line option for frail elderly patients with advanced NSCLC. In an epidermal growth factor receptor-non-selected population older than 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]

The objective of the present study was to assess the cost-effectiveness of first-line erlotinib followed by chemotherapy after progression, compared with the reverse strategy, in fit elderly patients with advanced NSCLC, based on a cost analysis of the GFPC 0505 study, a randomized phase II trial.[12]

Patients and Methods

Study Design and Population

The GFPC 0505 study was a multicenter, open-label, randomized phase II trial involving patients with previously untreated stage IIIB or IV NSCLC. It compared first-line erlotinib followed by chemotherapy after progression (gemcitabine 1250 mg/m^2 on days 1 and 8, repeated every 3 weeks) (arm A) with the reverse strategy (arm B). The primary end point was the second progression-free survival time. OS was a secondary end point.

Cost Analysis

Costs were estimated from the French health payer's perspective, from randomization until death. All resources consumed during the first and second lines of treatment were prospectively collected on a per-patient basis. The resources consumed were chemotherapy, erlotinib, supportive treatments (including recombinant human erythropoietin, antiemetics, colony-stimulating factors, antibiotics, management of adverse effects, etc), transfusion, and hospitalization for any reason. The specific unit costs are reported in Table 1.[13-17] Costs incurred after second disease progression were derived from a representative French nationwide sample of 428 patients, using chart review to assess the mean direct monthly costs of the first 18 months of management of patients with NSCLC.[17] Specifically, the costs included outpatient and inpatient services, care provision at skilled nursing facilities, outpatient and inpatient drugs and other medications, nursing care organization, home health visits (including medications), and durable medical equipment. Assuming a yearly increment of 3.5%, 1 month of palliative care cost €2324 (2011 value).

Utilities

Utilities were derived from UK community population-based studies in advanced NSCLC,[13,14] which used the standard gamble interview and visual analog scales to assess quality of life (Table 1[13-17]).

Cost-Utility Analysis

Cost-effectiveness ratios (CERs) were calculated, corresponding to the cost of 1 quality-adjusted life year (QALY) for each strategy.

Table 1 Model Inputs

	Estimates	Low	High	Source
Health State Utilities				
Stable disease during oral therapy	0.673	0.27	0.80	13,14
Stable disease during IV therapy	0.653	0.26	0.78	13,14
Progressive disease	0.473	0.19	0.56	13,14
Death	0			13,14
Cost of Medical Services and Drugs (€)				
Erlotinib 30-day supply (150 mg)	2174.7			15,16
Gemcitabine (mg)	0.2			15,16
Hospitalization at home (day)	368			15,16
Day-ward hospital	422			15,16
G-CSF injection (per cycle)	557.40			15,16
Erythropoietin (per injection)	220.53			15,16
Palliative care after progression (per month)	2324	1627	3021	17

Abbreviation: G-CSF = granulocyte-colony stimulating factor.

Statistical Analysis

Second progression-free survival was calculated from randomization until disease progression (after the second line of treatment if the patient received 2 lines, or after the first line if the patient progressed and did not receive a second line) or death from any cause, or the last on-trial tumor assessment. Overall survival (OS) was calculated from randomization to death from any cause, or the last date the patient was known to be alive. Progression-free survival and OS were assessed by the Kaplan–Meier method. Statistical analyses used SAS software version 9.01 (SAS Institute).

Assessing Uncertainty

The uncertainty in the model was evaluated by using 1-way sensitivity analysis, sequentially varying the estimates for a given model parameter while keeping the other parameters constant, within a range of likely values derived from confidence intervals or reasonable ranges determined from published sources. In addition, a multivariate probabilistic sensitivity analysis was performed, using second-order Monte Carlo simulation, in which the model inputs (time to second progression, OS, utilities, and costs) were drawn from individual data. Specific distributions were assigned to utility data by using published means and standard deviations to specify the normal distribution. A simulation with 10,000 replications of the model was then used to obtain the 95% nonparametric confidence intervals for the cost and effectiveness parameters, and to determine the proportion of replications in each quadrant of the cost-effectiveness plane. The results of multiway sensitivity analysis were presented in radar screen format, where the x-axis showed the difference in effectiveness and the y-axis the difference in costs between the 2 strategies. The 10,000 replications were represented by dots.

Table 2 Characteristics of the Patients

	Arm A (n = 50)	Arm B (n = 44)
Age Mean (years)	78.2 ± 4.4	78.2 ± 3.6
Sex, Male, n (%)	39 (78)	37 (84.1)
Smoker, n (%)		
Current	7 (14.9)	4 (9.3)
Former	34 (72.3)	36 (83.7)
Never smoker	6 (12.8)	3 (7)
Unknown	3 (5.9)	1 (2)
Performance Status, n (%)		
0	19 (39.6)	11 (25.6)
1	24 (50)	23 (53.5)
2	5 (10.4)	9 (20.9)
Stage, n (%)		
IIIB	3 (6.1)	6 (14)
IV	46 (93.9)	37 (86)
Histology, n (%)		
Squamous cell	10 (20)	17 (39)
Adenocarcinoma	31 (62)	22 (50)
Undifferentiated	09 (18)	5 (11)

Arm A: erlotinib followed by gemcitabine after progression; arm B: gemcitabine followed by erlotinib after progression.

Table 3 Costs

	Arm A	Arm B
Total Costs (€, 2011)	**15,233 ± 15,310**	**15,363 ± 11,346**
Hospitalization	1683 ± 3468	4167 ± 3481
Chemotherapy	1020 ± 1713	2893 ± 1439
Erlotinib	6697 ± 7425	2705 ± 5692
EPO	259 ± 621	205 ± 485
Transfusion	14 ± 101	685 ± 3807
Palliative care	5490 ± 11,269	4493 ± 7118
Stable disease	63 ± 347	283 ± 708

Costs of arm A (erlotinib followed by gemcitabine) and arm B (gemcitabine followed by erlotinib). Abbreviation: EPO = erythropoetin.

Results

Between May 2006 and January 2010, 22 centers enrolled 100 patients in this study (Table 2), of whom 94 were eligible. The patients in the 2 arms were not significantly different; median age was 78.2 years in each arm, and, respectively 46% and 40% of patients in arms A and B were older than 80 years old. As already reported, there was no significant difference in the Charlson scores, comorbidities, or geriatric assessment.[12] There was no significant difference between the arms in terms of the time to second progression (3.5 and 4.3 months, respectively, in arms A and B, $P = .55$), or median OS (3.9 and 4.4 months, $P = .26$). QALY values were, respectively, 0.33 ± 0.33 and 0.35 ± 0.34 and costs were €15,233 ± 15,310 and €15,363 ± 11,346. The cost distribution differed between the 2 arms: hospitalization represented, respectively 11% and 27.1% of total costs in arms A and B, respectively; chemotherapy 6.7% and 18.8%; and erlotinib 44% and 29% (Table 3). There was no significant difference in cost-effectiveness (respectively €47,381 and €44,350 per QALY), as confirmed by multivariate probabilistic sensitivity analyses (Figure 1) in which drug costs, utility values, and the cost of palliative care were varied (Table 4).

Discussion

We found no significant difference in the outcomes or costs between an erlotinib-first strategy and a chemotherapy-first strategy for NSCLC in frail elderly patients selected by means of a CGA. The main originality of this study is that the second-line treatment (consisting of the other drug) was fixed in each arm, thus allowing us to evaluate the performance of each entire treatment strategy. Indeed, economic analyses in advanced NSCLC are usually limited to either first- or second-line treatment. In addition, there are few recent economic analyses of the cost-effectiveness of first-line monotherapy in elderly patients with advanced NSCLC.[1]

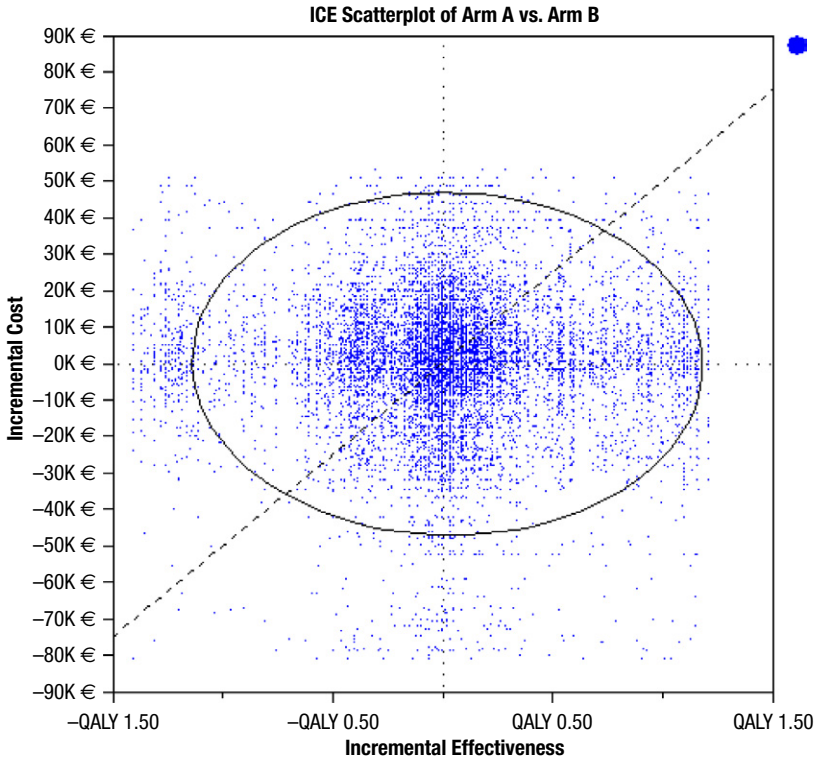
In the second-line treatment setting, the incremental CER of erlotinib versus placebo[18] was explored by using resource utilization determined from individual patient data in the BR.21 trial database (a pivotal trial of second-line treatment). This trial involved 731 patients (488 in the erlotinib arm and 243 in the placebo arm). The erlotinib Incremential CER was US$94,638 per life-year gained (95% confidence interval, US$52,359 to US$429,148). The major drivers of cost-effectiveness included the magnitude of the survival benefit and the cost of erlotinib. Subgroup analyses suggested that erlotinib might be more cost-effective in never-smokers. There was no specific analysis of elderly patients in this study.

The cost-effectiveness of erlotinib has also been compared with that of other agents (docetaxel and pemetrexed) licensed for second-line treatment of advanced NSCLC.[19] In a model-based analysis, second-line treatment with erlotinib, docetaxel, and pemetrexed yielded, respectively 0.42, 0.41, and 0.41 QALY, and total costs were US$37,000, US$39,100, and US$43,800. Again, there was no specific analysis of elderly patients. A more recent cost-utility analysis compared erlotinib and docetaxel for second-line management of advanced NSCLC within the UK National Health Service. The authors used a health-state transition model, based on the 2 pivotal phase III studies of erlotinib versus best supportive care and docetaxel versus best supportive care, to estimate direct costs, QALY, and the subsequent net monetary benefit. Erlotinib was associated with lower total costs (£13,730 vs. £13,956) and with a gain in QALY.[13]

More recently, we analyzed the cost-effectiveness of erlotinib followed by chemotherapy after progression, compared with the reverse strategy, in fit elderly patients with advanced NSCLC. A CGA was used to select elderly patients in good general condition qualifying for doublet chemotherapy without cisplatin. QALY and total costs for the erlotinib-first strategy were, respectively, 0.51 and €27,734, compared with 0.52 and €31,688 for the chemotherapy-first strategy. The incremental CER of the chemotherapy-first strategy was €395,400 per QALY.[20]

One advantage of our study is the prospective cost data collection, at least until second progression. In contrast, management costs after

Figure 1 Multivariate Probabilistic Sensitivity Analysis (Results of 10,000 Replications). Arm A, Erlotinib Followed by Gemcitabine; Arm B, Gemcitabine Followed by Erlotinib



Abbreviations: ICE = incremental cost effectiveness; QALY = quality-adjusted life year.

Table 4 Sensitivity Analysis

	Arm A	Arm B
Base Case	44,350	47,381
Utility of patients treated with erlotinib −20% (0.538)	46,038	52,437
−10% (0.606)	45,079	49,473
10% (0.740)	43,312	44,501
20% (0.807)	42,486	42,372
Post Progression Cost (€)		
1627	39,818	41,854
3021	48,550	51,860

Arm A: erlotinib followed by gemcitabine; arm B: gemcitabine followed by erlotinib.

the end of active treatments were derived from a 2004 national database. In addition, our analysis was limited to direct lung cancer-related medical costs: indirect costs such as lost productivity and caregiver salaries were not included. Also, the way in which we expressed utilities reflects the value from the point of view of society rather than that of the patients concerned. Finally, it is uncertain whether these utilities are fully relevant to our population of elderly patients. However, our sensitivity analyses largely compensated for these limitations, as the conclusions based on the base-case scenario were unaffected when we varied the different model parameters.

Conclusion

In frail elderly NSCLC patients, there is no significant difference in cost-effectiveness between a chemotherapy-first strategy and an erlotinib-first strategy.

Clinical Practice Points

- Few studies are published on frail elderly patients treated for NSCLC.
- This cost-effectiveness analysis showed that, in this population, erlotinib followed by chemotherapy after progression and the reverse strategy are acceptable strategies from the third-party payer perspective. Large phase 3 study is needed to confirm these results.

Acknowledgments

This trial was an academic trial conducted by Groupe Français de Pneumo-Cancérologie and sponsored by Limoges University Hospital (France). Sources of funding included public funding and an unrestricted grant from F. Hoffmann-La Roche Ltd.

Disclosure

C. Chouaid has received consultancy fees (less than US$10,000) from Roche Pharmaceuticals, Amgen, GlaxoSmithKline, AstraZeneca, and Lilly. A. Vergnenegre has received consultancy fees (less than US$10,000) from Roche Pharmaceuticals, AstraZeneca, and Lilly. The other authors have no conflicts of interest.

References

1. Chouaid C, Atsou K, Hejblum G, et al. Economics of treatments for non-small cell lung cancer. *Pharmacoeconomics* 2009; 27:113-25.
2. Pallis AG, Georgoulias V. Is there a standard regimen for first-line treatment of advanced/metastatic non-small-cell lung cancer? What has meta-analyses contributed to today's standard of care. *Lung Cancer* 2012; 75:269-74.
3. Jatoi A, Hillman S, Stella P, et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. *J Clin Oncol* 2005; 23:9113-9.
4. Gridelli C, Maione P, Illiano A, et al. Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non small-cell lung cancer: the MILES-2P studies. *J Clin Oncol* 2007; 25:4663-9.
5. Gridelli C, Kaukel E, Gregorc V, et al. Single-agent pemetrexed or sequential pemetrexed/gemcitabine as front-line treatment of advanced non-small cell lung cancer in elderly patients or patients ineligible for platinum-based chemotherapy: a multicenter, randomized, phase II trial. *J Thorac Oncol* 2007; 2:221-9.
6. Comella P, Frasci G, Carnicelli P, et al. Gemcitabine with either paclitaxel or vinorelbine vs paclitaxel or gemcitabine alone for elderly or unfit advanced non-small-cell lung cancer patients. *Br J Cancer* 2004; 91:489-97.
7. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. *Lung Cancer* 2001; 34(suppl 4):S65-9.
8. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the multicenter Italian lung cancer in the elderly study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003; 95:362-72.
9. Ricci S, Antonuzzo A, Galli L, et al. Gemcitabine monotherapy in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. *Lung Cancer* 2000; 27:75-80.
10. Wheatley-Price P, Ding K, Seymour L, et al. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2008; 26:2350-7.
11. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for non-small-cell-lung advanced cancer. *J Clin Oncol* 2007; 25:760-6.
12. LeCaer H, Greillier L, Corre R, et al; GFPC 0505 Team. A multicenter phase II randomized trial of gemcitabine followed by erlotinib on 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). *Lung Cancer,* Published online March 7, 2012. PMID: 22405570.
13. Lewis G, Peake M, Aultman R, et al. Cost-effectiveness of erlotinib versus docetaxel for second-line treatment of advanced non-small-cell lung cancer in the United Kingdom. *J Int Med Res* 2010; 38:9-21.
14. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 2008. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2579282/pdf/1477-7525-6-84.pdf. Accessed: January 20, 2012.
15. Ministère de la Santé et des Solidarités. Arrêté du 27 février 2007 relatif à la classification et à la prise en charge des prestations d'hospitalisation pour les activités de médecine, chirurgie, obstétrique et odontologie et pris en application de l'article *L.* 162-22-6 du code de la sécurité sociale. Journal Officiel n°50 du 28 février 2007, texte 72.
16. Nomenclature Générale des Actes Professionnels. Union des Caisses Nationales de Sécurité Sociale (UCANSS). Paris. Available at: http://www.ameli.fr/fileadmin/user_upload/documents/NGAP-oct-2009.pdf. Accessed: January 20, 2012.
17. Chouaid C, Molinier L, Combescure C, et al. Economics of the clinical management of lung cancer in France: an analysis using a Markov model. *Br J Cancer* 2004; 90:397-402.
18. Bradbury PA, Tu D, Seymour L, et al. Economic analysis: randomized placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer. *J Natl Cancer Inst* 2010; 102:298-306.
19. Carlson JJ, Reyes C, Oestreicher N, et al. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC). *Lung Cancer* 2008; 61:405-15.
20. Chouaid C, Lecaer H, Crequit J, et al. Cost-effectiveness of erlotinib in first line treatment of non small cell lung cancer (NSCLC) in elderly patients: an economical analysis of a prospective phase 2 study (GFPC 0504). *Value Health* 2010; 13:A267.