

Update on the treatment of non-small-cell lung cancer: focus on the cost-effectiveness of new agents

A Vergnenègre^{1,4}
I Borget²
C Chouaid^{3,4}

¹Service de Pathologie Respiratoire et d'Allergologie, CHU Dupuytren, Limoges, France; ²Études et Recherche en Économie de la Santé, Institut Gustave Roussy, Villejuif, France; ³Service de Pneumologie, CHU Saint-Antoine, Paris, France; ⁴Inserm, U707, Paris, France

Background: The incidence of lung cancer and the cost of drug treatment have increased dramatically in the last decade. This article examines the costs of new target agents, such as tyrosine kinase inhibitors (TKIs) and anti-angiogenic drugs.

Methods: This study uses PubMed research to focus on the topics of lung cancer, economics, and new targeted therapies.

Results: The published papers only addressed TKIs and anti-angiogenic antibodies. For gefitinib, the results favored a clinical-based selection, despite the low number of studies. Erlotinib was studied in second line and as a maintenance treatment (with the studies reaching opposite conclusions in terms of cost-effectiveness). Economic analyses were not in favor of bevacizumab, but the studies on this topic were very heterogeneous.

Conclusion: The economic impact of a drug depends on the health care system organization. Future clinical trials must include economic analyses, particularly with TKIs in the first line.

Keywords: lung cancer, new target agents, tyrosine kinase inhibitors, anti-angiogenic, bevacizumab

Introduction

Significant progress in the treatment of cancer has been made since the late 1990s, notably with the development of targeted therapies in the first decade of the 21st century. These new treatments have significantly improved the prognosis of some malignancies, including lung cancer, but the cost of treatment has increased in parallel.¹ In 2007, the US National Institutes of Health estimated that the direct costs of care for lung cancer patients totaled US\$ 90 billion, and this figure is predicted to rise to about US\$ 160 billion by 2020.^{2,3}

Cipriano et al reported that initial management costs per lung cancer patient were US\$ 6639 during the first year, with a cumulative total cost of US\$ 164,768.⁴ Costs were slightly lower for patients over 65 years of age.

Overall costs have increased by about 22% during the last decade, while the introduction of new agents has raised drug-related costs by 11% for lung cancer patients.⁵ While chemotherapy (cisplatin-based doublet therapy) has become well standardized, these new drugs have modified the treatment course, leading to longer-term treatment and the need for maintenance therapy. The impact of these new drugs on the overall cost of treatment is far from negligible. The following article examines the cost of new agents used to treat lung cancer, focusing on tyrosine kinase inhibitors (TKIs) and anti-angiogenic agents.

Correspondence: A Vergnenègre
Service de Pathologie Respiratoire
CHU Dupuytren, Hôpital du Cluzeau,
23, av. Dominique Larrey
87042 Limoges cedex–France
Tel +33 555 05 66 29
Fax +33 555 05 68 15
Email alain.vergnenegre@unilim.fr

Methods

We performed a PubMed search with the following keywords: “lung cancer,” “costs,” “targeted therapies,” “erlotinib,” “bevacizumab,” or “gefitinib”. All documents featuring one of three characteristics (lung cancer, costs and targeted therapies) were collected and analyzed by two of the authors (AV and CC).

Results

Economic analyses of TKIs in lung cancer Gefitinib

Gefitinib was the first TKI to be approved for the treatment of non-small-cell lung cancer (NSCLC). Previous data showed an average treatment cost per patient of approximately US\$ 46,000 during the first two years.⁶ The impact of gefitinib is difficult to analyze because of the paucity of studies (Table 1).

Chouaid et al performed a model-based study of compassionate-use gefitinib therapy in France (between 2002 and 2004), based on data from 106 patients.⁷ The total cost for each of these patients was € 40,000 ± € 20,729, with gefitinib representing about 10.7% of the overall cost (€ 4241 ± € 1424). However, this study included only highly selected patients.

A second study conducted in Thailand examined the cost-utility of second-line gefitinib for NSCLC.⁸ The comparators were docetaxel, erlotinib, and pemetrexed. Gefitinib proved to be the most cost-effective second-line treatment. This study adopted the perspective of the Thai health care system, and most of the costs were based on expert estimates.

Horgan et al based their study on the dataset from the INTEREST clinical trial.⁹ In this cost-utility study based on prospective data, the marginal cost-effectiveness of gefitinib versus docetaxel was CA\$ 5161, which was considered acceptable for the North American health care system. Adverse effects and quality of life also favored the use of gefitinib rather than chemotherapy.

Brown et al conducted a study for the UK National Institute for Health and Clinical Excellence (NICE).¹⁰ Patients were not selected for EGFR-R mutations. Costs were considered too high for the British system, despite the fact that this was a selected population (IPASS trial). NICE calculated the costs as ranging from £ 25,000 to £ 65,000 per additional quality-adjusted life year (QALY).

The recently published study by de Lima Lopes et al, adopting the perspective of Asian health systems, analyzed first-line gefitinib use in patients with EGF-R mutations in comparison with chemotherapy.¹¹ The results favored gefitinib, as confirmed by sensitivity analyses.

Erlotinib

Secondline treatment

Erlotinib was first validated in this setting (second line treatment). Among the many studies conducted, only one French study took EGF-R mutation status into account.¹² The use of targeted therapies did not reduce the overall cost of treatment.^{4,13,14}

Bradbury et al conducted an economic analysis of the BR21 registration trial.¹⁵ They showed that marginal cost-effectiveness was close to US\$ 100,000 per year of life saved, which was still just acceptable for the Canadian health care system. Studies of patients' willingness to pay for a portion of their treatment have offered similar results: patients agreed to pay, but only about 5% to 10% of the real cost of these drugs.^{16,17}

Other studies compared erlotinib with chemotherapeutic agents, such as docetaxel and pemetrexed. Carlson et al showed that erlotinib dominated the other two products.¹⁸ Lewis et al compared erlotinib with docetaxel in a cost-utility study.¹⁹ Although the results were very similar, they tended to favor erlotinib. Furthermore, when compared to best supportive care, docetaxel was a better option than erlotinib, as confirmed in other countries, such as Brazil.²⁰ But NICE's recommendations were less favorable from the point of view

Table 1 Economic analyses of gefitinib in NSCLC

Author	Line	Type	Main results	Reference
Chouaid et al	3rd	Modeling of a compassionate-use program. French payer's perspective.	Total costs: € 39,979 ± € 20,279 (10% of total costs).	7
Thongprasert et al	2nd	Model-based comparison: erlotinib, pemetrexed, and docetaxel. Thai payer's perspective.	Gefitinib is better than erlotinib and docetaxel.	8
Horgan et al	2nd	Cost-utility analysis of INTEREST trial, gefitinib versus docetaxel.	ICER CA\$ 5161; gefitinib preferred.	9
Brown et al	1st	Modeling of first-line gefitinib versus chemotherapy.	ICER £ 35,700 for gefitinib versus doublet therapy.	10
de Lima Lopes et al	1st	Modeling of cost-effectiveness of EGF TKIs versus standard care. Asian payer's perspective.	US\$ 2400; dominant strategy.	11

Abbreviation: ICER, incremental cost effectiveness ratio.

of the UK health care system.²¹ Erlotinib did not result in additional costs in an Italian study.²² A recent study conducted in Canada showed that, although the effectiveness was similar with second-line docetaxel was not significant in an unselected population,²³ erlotinib compared well with supportive care in terms of cost effectiveness.²⁴ Borget et al showed that patient selection based on biological and clinical criteria led to lower costs (€ 5020 and € 5815, respectively) than in an unselected population (Table 2).¹²

Maintenance treatment

While most studies have focused on pemetrexed (showing little efficacy),²⁵ recent studies following the Saturn clinical trial have examined the possible place of erlotinib in this setting.²⁶

In a cost-minimization study, erlotinib proved to be less costly than pemetrexed.²⁷ When the manufacturer submitted the dossier to NICE, the UK agency redid the calculations and found that erlotinib was not cost-effective for the British health care system.²⁸ The NICE values were approximately £ 50,000 per QALY.

Vergnenègre et al subsequently performed a cost-effectiveness study for patients with wildtype EGF-R when the disease stabilized after the end of first-line treatment.²⁹ The study was conducted in France, Germany, and Italy. Erlotinib was found to have an acceptable cost-effectiveness ratio per QALY in France (€ 39,783), Germany (€ 46,931), and Italy (€ 27,885). At a threshold of € 50,000, erlotinib had a 50% probability of being cost-effective.

Another recently published study of patients with wild-type EGF-R compared the cost-effectiveness of erlotinib maintenance treatment versus best supportive care.²⁴ The results were € 20,711 in the UK and € 25,124 in Germany. The authors concluded that erlotinib maintenance was medically and economically justified.

First-line treatment

There are no published data on first-line erlotinib. In 2009, Carlson et al conducted an exploratory study, showing that a pharmacogenomic test could reduce the cost per QALY.³⁰

Many clinical trials taking EGF-R mutations into account have now been published,³¹ but economic analyses are still needed. It is very likely that erlotinib will prove to be cost-effective in selected populations.

Anti-angiogenic agents: bevacizumab

Anti-angiogenic therapies have recently been used in patients with lung cancer, but head-to-head comparisons with chemotherapy are rare.³²

Bevacizumab is the most extensively studied anti-angiogenic drug, notably in the phase III trial by Sandler et al.³³ Published articles on the costs associated with this drug have been analyzed in a general review.³⁴

Among the five most interesting articles on the cost-effectiveness of this drug, two showed that bevacizumab had acceptable cost-effectiveness from the standpoint of German and Italian society,³⁴⁻³⁶ while the three studies suggested it was not cost-effective. It must be stressed, however, that all these publications were model-based and did not use real clinical trial data. Giuliani et al³⁵ and Ahn et al³⁶ postulated a dose of 7.5 mg/kg, while the others used 15 mg/kg per day. The models all adopted the payer's viewpoint and not that of society.

Cost analyses should include the overall costs, especially as indirect costs, for patients treated with bevacizumab, could be significantly lower, through earlier return to work.³⁷

Conclusion

New cancer therapeutics are increasingly effective but generate increasingly high costs. Societies must consequently weigh the costs and benefits, using various thresholds (for example, US\$ 100,000 to 150,000 in the United States). Numerous studies have been published, but many are model-based, and their conclusions often differ.⁵ General reviews are helpful but still fail to provide definitive results. Only economic analyses embedded within independently funded clinical trials can serve to inform decision makers. Many previous studies included unselected populations, but it would probably be better to select patient subgroups in which the benefits are likely to be greatest. Such economic studies are needed to ensure each patient receives the most cost-effective treatment.

Disclosure

A Vergnenègre has received honoraria from Roche, Amgen, Lilly and has received funding for clinical research from Astra-Zeneca, Chugai, Lilly, Amgen, Roche and Boehringer Ingelheim. In the past 5 years, Christos Chouaid received fees for attending scientific meetings, speaking, organizing

Table 2 Results of the ERMETIC study¹²

ICER/QALY (euros)	Euros
No selection	43,895
Chemically guided	28,863
Biologically guided	27,209

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

research or consulting from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffman la Roche, Astra Zeneca, Sanofi Aventis, Lilly, Novartis and Amgen.

Isabelle Borget has no conflict of interest in this work.

References

- Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst.* 2008;100:888–897.
- Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst.* 2011;103:117–128.
- Vergnenègre A, Chouaid C. Aspects médico-économiques de la pneumologie [Economic aspects of respiratory disease management]. *Rev Mal Resp.* 2012;4:196–207.
- Cipriano LE, Romanus D, Earle CC, et al. Lung cancer treatment costs, including patient responsibility, by disease stage and treatment modality, 1992 to 2003. *Value Health.* 2011;14:41–52.
- Coate LE, Leighl NB. How affordable are targeted therapies in non-small cell lung cancer? *Curr Treat Options Oncol.* 2011;12:1–11.
- Chouaid C, Atsou K, Hejblum G, Vergnenègre A. Economics of treatments for non-small cell lung cancer. *Pharmacoeconomics.* 2009;27:113–125.
- Chouaid C, Monnet I, Robinet G, Perol M, Fournel P, Vergnenègre A. Economic impact of gefitinib for refractory non-small-cell lung cancer: a Markov model-based analysis. *Curr Med Res Opin.* 2007;23:1509–1515.
- Thongprasert S, Tinmanee S, Permsuwan U. Cost-utility and budget impact analyses of gefitinib in second-line treatment for advanced non-small cell lung cancer from Thai payer perspective. *Asia Pac J Clin Oncol.* 2012;8:53–61.
- Horgan AM, Bradbury PA, Amir E, et al. An economic analysis of the INTEREST trial, a randomized trial of docetaxel versus gefitinib as second-/third-line therapy in advanced non-small-cell lung cancer. *Ann Oncol.* 2011;22:1805–1811.
- Brown T, Boland A, Bagust A, et al. Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer. *Health Technol Assess.* 2010;14(Suppl 2):71–79.
- de Lima Lopes G Jr, Segel JE, Tan DS, Do YK, Mok T, Finkelstein EA. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. *Cancer.* 2012;118:1032–1039.
- Borget I, Cadranet J, Pignon JP, et al. Cost-effectiveness of three strategies for second-line erlotinib initiation in non-small-cell lung cancer: the ERMETIC study part 3. *Eur Respir J.* 2012;39:172–179.
- Chouaid C, Moser A, Coudray-Omnes C, Vergnenègre A. Conséquences économiques de l'erlotinib dans le traitement des cancers bronchopulmonaires non à petites cellules [The economic consequences of erlotinib in the treatment of non-small-cell broncho-pulmonary cancer]. *Rev Mal Resp.* 2008;25:1096–1103. French.
- Isla D, Gonzalez-Rojas N, Nieves D, Brosa M, Finfern HW. Treatment patterns, use of resources, and costs of advanced non-small-cell lung cancer patients in Spain: results from a Delphi panel. *Clin Transl Oncol.* 2011;13:460–471.
- 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.
- Leighl NB, Tsao WS, Zawisza DL, Nematollahi M, Shepherd FA. A willingness-to-pay study of oral epidermal growth factor tyrosine kinase inhibitors in advanced non-small cell lung cancer. *Lung Cancer.* 2006;51:115–121.
- Lang HC. Willingness to pay for lung cancer treatment. *Value Health.* 2010;13:743–749.
- Carlson JJ, Reyes C, Oestreicher N, Lubeck D, Ramsey SD, Veenstra DL. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC). *Lung Cancer.* 2008;61:405–415.
- 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.
- Doral Stefani S, Giorgio Saggia M, Vicino dos Santos EA. Cost-minimisation analysis of erlotinib in the second-line treatment of non-small-cell lung cancer: a Brazilian perspective. *J Med Econ.* 2008;11:383–396.
- McLeod C, Bagust A, Boland A, et al. Erlotinib for the treatment of relapsed non-small cell lung cancer. *Health Technol Assess.* 2009;13(Suppl 1):41–47.
- Schwander B, Ravera S, Giuliani G, Nuijten M, Walzer S. Cost comparison of second-line treatment options for late stage non-small-cell lung cancer: cost analysis for Italy. *Clinicoecon Outcomes Res.* 2012;4:237–243.
- Cromwell I, van der Hoek K, Melosky B, Peacock S. Erlotinib or docetaxel for second-line treatment of non-small cell lung cancer: a real-world cost-effectiveness analysis. *J Thorac Oncol.* 2011;6:2097–2103.
- Cromwell I, van der Hoek K, Malfair Taylor SC, Melosky B, Peacock S. Erlotinib or best supportive care for third-line treatment of advanced non-small-cell lung cancer: a real-world cost-effectiveness analysis. *Lung Cancer.* 2012;76:472–477.
- Bongers ML, Coupe VM, Jansma EP, Smit EF, Uyl-de Groot CA. Cost effectiveness of treatment with new agents in advanced non-small-cell lung cancer: a systematic review. *Pharmacoeconomics.* 2012;30:17–34.
- Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2010;11:521–529.
- Nuijten MJ, de Castro Carpeño J, Chouaid C, et al. A cross-market cost comparison of erlotinib versus pemetrexed for first-line maintenance treatment of patients with locally advanced or metastatic non-small-cell lung cancer. *Lung Cancer.* 2012;76:465–471.
- Dickson R, Bagust A, Boland A, et al. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum-containing chemotherapy: a NICE single technology appraisal. *Pharmacoeconomics.* 2011;29:1051–1062.
- Vergnenègre A, Ray JA, Chouaid C, et al. Cross-market cost-effectiveness analysis of erlotinib as first-line maintenance treatment for patients with stable non-small cell lung cancer. *Clinicoecon Outcomes Res.* 2012;4:31–37.
- Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health.* 2009;12:20–27.
- Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012;13:239–246.
- Nuijten M, Heigener DF, Bischoff HG, et al. Effectiveness of bevacizumab- and pemetrexed-cisplatin treatment for patients with advanced non-squamous non-small cell lung cancer. *Lung Cancer.* 2010;69(Suppl 1):S4–S10.
- Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355:2542–2550.
- Chien CR, Shih YC. Economic evaluation of bevacizumab in the treatment of non-small cell lung cancer (NSCLC). *Clinicoecon Outcomes Res.* 2012;4:201–208.

35. Giuliani G, Grossi F, de Marinis F, Walzer S. Cost-effectiveness analysis of bevacizumab versus pemetrexed for advanced non-squamous NSCLC in Italy. *Lung Cancer*. 2010;69(Suppl 1):S11–S17.
36. Ahn MJ, Tsai CM, Hsia TC, et al. Cost-effectiveness of bevacizumab-based therapy versus cisplatin plus pemetrexed for the first-line treatment of advanced non-squamous NSCLC in Korea and Taiwan. *Asia Pac J Clin Oncol*. 2011;7:22–33.
37. Stanisic S, Bischoff HG, Heigener DF, et al. Societal cost savings through bevacizumab-based treatment in non-small cell lung cancer (NSCLC). *Lung Cancer*. 2010;69(Suppl 1):S24–S30.

ClinicoEconomics and Outcomes Research

Dovepress

Publish your work in this journal

ClinicoEconomics & Outcomes Research is an international, peer-reviewed open-access journal focusing on Health Technology Assessment, Pharmacoeconomics and Outcomes Research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems

organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal>