

Economic evaluation of first-line and maintenance treatments for advanced non-small cell lung cancer: a systematic review

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Abstract: During these last years, there have been an increased number of new drugs for non-small cell lung cancer (NSCLC), with a growing financial effect on patients and society. The purpose of this article was to review the economics of first-line and maintenance NSCLC treatments. We reviewed economic analyses of NSCLC therapies published between 2004 and 2014. In first-line settings, in unselected patients with advanced NSCLC, the cisplatin gemcitabine doublet appears to be cost-saving compared with other platinum doublets. In patients with nonsquamous NSCLC, the incremental cost-effectiveness ratios (ICERs) per life-year gained (LYG) were \$83,537, \$178,613, and more than \$300,000 for cisplatin-pemetrexed compared with, respectively, cisplatin-gemcitabine, cisplatin-carboplatin-paclitaxel, and carboplatin-paclitaxel-bevacizumab. For all primary chemotherapy agents, use of carboplatin is associated with slightly higher costs than cisplatin. In all the analysis, bevacizumab had an ICER greater than \$150,000 per quality-adjusted life-year (QALY). In epidermal growth factor receptor mutated advanced NSCLC, compared with carboplatin-paclitaxel doublet, targeted therapy based on testing available tissue yielded an ICER of \$110,644 per QALY, and the rebiopsy strategy yielded an ICER of \$122,219 per QALY. Compared with the triplet carboplatin-paclitaxel-bevacizumab, testing and rebiopsy strategies had ICERs of \$25,547 and \$44,036 per QALY, respectively. In an indirect comparison, ICERs per LYG and QALY of erlotinib versus gefitinib were \$39,431 and \$62,419, respectively. In anaplastic lymphoma kinase-positive nonsquamous advanced NSCLC, the ICER of first-line crizotinib compared with that of chemotherapy was \$255,970 per QALY. For maintenance therapy, gefitinib had an ICER of \$19,214 per QALY, erlotinib had an ICER of \$127,343 per LYG, and pemetrexed had an ICER varying between \$183,589 and \$205,597 per LYG. Most recent NSCLC strategies are based on apparently no cost-effective strategies if we consider an ICER below \$50,000 per QALY an acceptable threshold. We need, probably on a countrywide level, to have a debate involving public health organizations and pharmaceutical companies, as well as clinicians and patients, to challenge the rising costs of managing lung cancer.

Keywords: lung cancer, costs, economics, cost-effectiveness, evaluation

Introduction

During these last years, the number of oncology-related investigational new drug applications has increased, with a growing financial effect on patients and society. Cancer care costs are escalating at a rate of 15% per year, which is nearly three times the increase in overall health care spending.¹ Lung cancer is a leading cause of cancer-related deaths, with an estimated 219,440 new cases and 159,390 deaths in 2009 in the United States. The economic cost of lung cancer is high, estimated at \$9 billion per year. Non-small cell lung cancer (NSCLC) makes up approximately 85% of lung cancer cases,

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and around 65% of patients are diagnosed with advanced stages, with estimated 2 and 5 year survival rates of 15% and 2%, respectively. The main subtypes of NSCLC are squamous cell carcinoma (33%), adenocarcinoma (61%), and large cell carcinoma (6%). Because of the incidence, severity, and rising costs of this illness, it is becoming increasingly important to deliver consistent, high-quality, cost-effective care for NSCLC.²⁻⁵ The purpose of this article is to review the economics of first-line and maintenance treatments for NSCLC. After recalling the current management of NSCLC, we review the cost-effectiveness of advanced NSCLC treatments with a particular emphasis on more recently approved agents.

Search strategy

In June 2014, we reviewed economic analyses of therapies for NSCLC identified by a MEDLINE, CRD, and HEED database search, using a disease-specific medical subject heading term ("lung neoplasms") and subheading ("economics"). Considering recent changes in practices, we limited this review to studies of patients managed since 2004 and to studies published between 2004 and 2014. We also made the same search, for the same period, in all medical economics publications identified in PubMed, restricted to papers with abstracts published in the English language. Analysis was restricted to chemotherapy drugs currently licensed in Europe and the United States for the first-line and maintenance treatment of patients with metastatic NSCLC. Economic analyses of small-cell lung cancer and other aspects of NSCLC, including smoking, screening, and diagnosis and staging procedures, are not reviewed here. Likewise, we did not select studies on the economic effect of supportive medications (growth factors, antiemetics, erythropoietins, etc). Relevant articles and extracts were selected and reviewed, and the reference lists from these sources were scanned for additional trials, as were the reference lists of relevant review articles. Outcomes were reported as stated in the studies without any yearly increment. The first step of this search strategy identified 2,274 published studies; 1,071 were published before 2004, 256 were in a non-English language, and 458 did not focus on approved chemotherapy drugs.

Clinical guidelines for first-line and maintenance management for advanced NSCLC

Clinical practice guidelines for first-line and maintenance management for advanced NSCLC have been drawn up by health care professionals and authorities in many countries and were recently updated.⁶

In patients with driver mutations (ie, epidermal growth factor receptor [*EGFR*] gene mutations and anaplastic lymphoma kinase [*ALK*] translocations), first-line management recommended the use of an oral tyrosine kinase inhibitors (TKIs) or anti-ALK therapies such as erlotinib, gefitinib, or crizotinib until progression.

In patients with no or unknown driver mutations, good performance status (PS), and an age younger than 70 years, the recommendations were to use a platinum doublet therapy (cisplatin or carboplatin) with a third-generation drug (gemcitabine, docetaxel, paclitaxel, vinorelbine, and in cases with no squamous disease, pemetrexed) for four to six cycles. A meta analysis⁷ showed that there are no statistically significant differences in overall survival (OS) or progression-free survival (PFS) between any of the four third-generation chemotherapy doublets.

For patients with nonsquamous histology, a randomized Phase III trial suggested that cisplatin-pemetrexed (CisPem) increases OS compared with cisplatin-gemcitabine (CisGem).⁷ For patients with no squamous histology, bevacizumab may be associated with carboplatin paclitaxel (CarPac) in the United States and with any platinum doublet in Europe.⁷

For patients with a nonprogressive disease who remain in good health status after first-line chemotherapy, without residual toxicity, maintenance therapy can be proposed: continuous maintenance chemotherapy with bevacizumab or pemetrexed for no squamous cell carcinoma, with erlotinib, gefitinib, and pemetrexed (for no squamous cell carcinoma) as switch maintenance.

In elderly patients (older than 70 years) and patients with a PS of 2 who are unable to tolerate a platinum combination, a carboplatin combination or single-agent chemotherapy can be used.

First-line chemotherapy in unselected advanced NSCLC patients

Two recent reviews^{8,9} have reported on the main relevant results on this topic. We summarize here the main results of these reviews with a focus on the recently approved agents.

Making cost-effectiveness comparisons across available first-line chemotherapy treatments is limited by the comparability of the treatment populations and the short time frames. The majority of the reports have been conducted using a third-party payer perspective, taking into account only direct costs.⁸⁻¹²

When comparing CisGem and carboplatin paclitaxel, Neymark et al¹⁰ did not find any differences in survival

between the two groups, but CisGem may reduce costs by approximately €2,000 per patient. The sensitivity analysis carried out on the base-case scenario did not lead to a change in the cost-effectiveness results.¹⁰ A retrospective cost-minimization analysis for Portugal¹² of five doublet chemotherapy regimens from two Phase III trials in the treatment of advanced NSCLC showed that the least and the most costly chemotherapy regimens were, respectively, CisGem and cisplatin vinorelbine (CisVin). CisGem remained less costly in all sensitivity analyses. In Italy,¹³ the mean total treatment costs per patient were €8,094, €11,203, and €9,320 for the CisGem, CarPac, and CisVin regimens, respectively, and the authors concluded that CisGem was a cost-saving choice. Analyses taking into account the situation in several countries are rare. Schiller et al¹⁴ reported an updated cost-effectiveness of CisGem versus others cisplatin doublets, using the perspective of the national health services of five European countries (France, Germany, Italy, Spain, and the United Kingdom). Differences in total cost among the countries were primarily related to the different costs of chemotherapeutic agents and drug administration. CisGem was associated with lower total costs than CisPac and CarPac in all five countries. Compared with CisDoc, CisGem was associated with similar costs in Germany, France, and the United Kingdom and with lower costs in Italy and Spain. In the sensitivity analysis, inpatient versus outpatient administration had the greatest effect on overall cost differences.

For the CisPem doublet, the more complete study¹⁵ used a semi-Markov model to compare CisPem with CisGem, CarPac, and carboplatin-paclitaxel-bevacizumab (CarbPacBev). Data were extracted from a randomized controlled clinical trial comparing CisPem and CisGem, and as no head-to-head data were available, the authors used a mixed-treatment comparison model for the CisPem to CarPac or CarbPacBev comparisons. Medicare reimbursement rates were used to determine drug costs, and a retrospective claims database analysis was used to estimate other direct NSCLC-related costs. Regardless of histological subtype, using CisPem as first-line chemotherapy led to an incremental cost per life-year gained (LYG) of \$104,577 for CisPem compared with CisGem and \$231,291 for CisPem compared with CarPac. In the prespecified subset of patients with non-squamous cell histology, the incremental cost per LYG was \$83,537 for CisPem compared with CisGem and \$178,613 for CisPem compared with CarPac. The incremental cost per LYG for CarbPacBev compared with CisPem was more than \$300,000. This analysis emphasizes the importance of histology in identifying the appropriate patient for CisPem

first-line chemotherapy. Reasonable changes introduced by undertaking sensitivity analyses do not significantly change the base-case.

In a more recent, retrospective observational study¹⁶ evaluating the cost-effectiveness of first-line treatment of advanced nonsquamous NSCLC, costs for patients receiving CisPem were higher compared with costs for the CarPac doublet (difference, \$21,841 for PFS and \$19,137 for OS; $P \leq 0.05$), and patients receiving CisPem had lower mean costs compared with patients receiving CarbPacBev therapy (difference, \$15,160 for PFS and \$19,946 for OS; $P \leq 0.05$).

In a model-based analysis, for all primary chemotherapy agents,⁹ use of carboplatin was associated with slightly higher costs than use of cisplatin. Outcomes vary between regimens, between docetaxel (best) and vinorelbine doublets (worst). In patients with squamous diseases, vinorelbine yielded the least patient benefit but is not the least expensive option. Paclitaxel doublets were consistently the minimum-cost options, and therefore represent the initial good value. The choice of preferred alternative main agents to paclitaxel generally favors docetaxel over gemcitabine, as docetaxel's greater effectiveness appears to outweigh the additional acquisition cost, although both drugs lie on the efficiency frontier. However, the difference in incremental quality-adjusted life-years (QALYs) gained between the treatments reflects only very marginal differences in benefit; in particular, the sensitivity of the results to the general level of drug prices relating to the choice of platinum compound indicates that in a competitive market, which has driven most generic prices down to very low levels, the price of drugs becomes less important than differences in the cost of drug administration and differences in the relative cost of adverse events.

Studies of doublets without platinum salts were rare.^{17,18} A study done in Greece comparing the docetaxel/gemcitabine combination with docetaxel monotherapy in untreated patients with advanced NSCLC¹⁸ showed an incremental cost per LYG of €9,538 when using the combination. The probability of being cost-effective was 91% at a threshold of €20,000, 97% at €35,000, and 98% at €50,000. The authors stated that the docetaxel/gemcitabine combination was a cost-effective treatment option relative to docetaxel monotherapy for patients with NSCLC in the Greek national health system setting. In contrast, in elderly patients with advanced disease, a recent review¹⁹ suggested that docetaxel monotherapy was cost-effective. In a recently published study based on a randomized trial done 10 years before, comparing CisGem, gemcitabine-vinorelbine, and CisVin,²⁰

gemcitabine-vinorelbine was the most expensive regimen (\$6,868), and CisVin was the cheapest (\$4,650). Diagnostic and administration costs did not differ significantly among regimens; the principal cost drivers were toxicity and administration costs.

Oral treatments also have their place in this setting. A comparative cost-minimization of oral and intravenous chemotherapy for first-line treatment of NSCLC in the United Kingdom, from the National Health Service's point of view, showed that oral vinorelbine allows further hospital resource savings compared with other intravenous chemotherapies.²¹

First-line target therapy in NSCLC patients with driver mutations

NSCLC patients with *EGFR* mutation

Advanced NSCLC patients with *EGFR* mutation had improved PFS with a TKI (erlotinib, gefitinib, and afatinib) treatment compared with platinum doublet therapy.^{22–24} A decision analytic model²⁵ showed that compared with the CarPac doublet, targeted therapy based on testing available tissue yielded an incremental cost-effectiveness ratio (ICER) of \$110,644 per QALY, and the rebiopsy strategy yielded an ICER of \$122,219 per QALY. Probabilistic sensitivity analysis revealed substantial uncertainty around these point estimates. With a willingness to pay of \$100,000 per QALY, the testing and the rebiopsy strategies were cost-effective, respectively, 58% and 54% of the time. Personalized therapy with an *EGFR* TKI was more favorable when the nontargeted chemotherapy regimen was more expensive. Compared with the triplet CarPemBev, ICERs were, respectively, \$25,547 and \$44,036 per QALY for the testing strategy and the rebiopsy strategy. These results appeared to be largely insensitive to varying the probability that a patient was *EGFR*-positive.

Another study developed a decision-analytic model to determine the ICER of *EGFR* testing and first-line treatment with gefitinib for patients who harbor activating *EGFR* mutations versus standard care, which includes first-line treatment with chemotherapy followed by gefitinib as second-line treatment.²⁶ The model uses clinical and outcomes data from randomized clinical trials and societal costs from Singapore cancer centers. *EGFR* testing and first-line treatment with gefitinib is a dominant strategy compared with standard care. Because the primary savings result from not providing gefitinib to those who are not likely to benefit, this finding holds regardless of the prevalence of activating mutations. In a secondary analysis, first-line treatment with gefitinib was also dominant when compared with first-line chemotherapy

in patients with activating *EGFR* mutations. A trial-based cost-effectiveness analysis of erlotinib alone versus platinum-based doublet chemotherapy as first-line therapy for Eastern Asian nonsquamous NSCLC.²⁴ showed that Erlotinib monotherapy is more cost-effective from the Chinese health care system point of view. At a threshold of \$96,884, erlotinib had a 50% probability of being cost-effective.

An indirect treatment comparison and a cost-effectiveness analysis of erlotinib versus gefitinib as first-line treatment of *EGFR* activating mutation-positive NSCLC in Hong Kong, on the basis of four relevant Asian Phase III randomized controlled trials,²⁷ resulted in a statistically significant PFS difference in favor of erlotinib (indirect treatment comparison hazard ratio, 0.33; 95% confidence interval, 0.19–0.58; $P=0.0001$). The ICER per LY and QALY was \$39,431 and \$62,419 for erlotinib versus gefitinib, respectively. For the authors, erlotinib appears cost-effective compared with gefitinib for first-line *EGFR*-mutated NSCLC patients.

NSCLC patients with *ALK* translocation

A recent paper analyzed the cost-effectiveness of echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion testing and first-line crizotinib treatment for patients with advanced *ALK*-positive nonsquamous NSCLC.²⁸ Analysis was conducted using a Markov model from the Canadian Public Health (Ontario) perspective and a lifetime horizon. Molecular testing with first-line targeted crizotinib treatment in this population resulted in a gain of 0.011 QALY compared with standard care. The incremental cost was Canadian \$2,725 per patient, and the ICER was Canadian \$255,970 per QALY gained. Among patients with known *EML4-ALK*-positive advanced NSCLC, first-line crizotinib therapy provided 0.379 additional QALY, cost an additional \$95,043 compared with standard care, and produced an ICER of \$250,632 per QALY gained. The major driver of cost-effectiveness was drug price. The authors conclude that crizotinib treatment for *ALK*-positive NSCLC patients is not cost-effective in the setting of high drug costs and a low biomarker frequency. In this analysis, first-line standard care strategy was CisGem doublet without any maintenance, but the recommendations in this setting also allow pemetrexed as a cisplatin companion, as well as, after patients' selection, bevacizumab combined with a paclitaxel-carboplatin regimen. Continuation maintenance with bevacizumab or pemetrexed and switch maintenance with pemetrexed until progression are also acceptable options. Taking into account these costly drug options affects the costs and outcomes of standard care strategy.²⁹ Unfortunately, in the sensitivity

analysis, the cost of standard care chemotherapy was not tested.

Bevacizumab as first-line and maintenance treatment

Several analyses^{30–33} reported the cost-effectiveness of a bevacizumab-containing regimen with chemotherapy alone, for a maximum of six cycles and with the administration of bevacizumab as maintenance therapy in cases of response or disease stability, until disease progression or unacceptable toxicity.

Isla et al³ analyzed different schemes and observed a reduction of direct costs using bevacizumab. Bischoff et al,³⁴ who focused their attention on the comparison of cisplatin-gemcitabine-bevacizumab with CisPem, obtained similar results. Stanisis et al³⁵ analyzed indirect costs in addition to direct costs. They recorded a gain in terms of increased productivity (reduction of indirect costs) in the group of patients treated with regimens containing bevacizumab. This can be attributed to the increase of PFS and the improvement of quality of life. Klein et al³⁶ analyzed first-line and maintenance regimens containing bevacizumab 15 mg/kg and concluded that these schemes are not cost-effective compared with pemetrexed-based regimens. Giuliani et al³² and Ahn et al³⁰ concluded that schemes based on bevacizumab at a dose of 7.5 mg/kg in combination with CisGem are convenient compared with schemes based on CisPem. Finally, Goulart and Ramsey³¹ analyzed the cost-effectiveness of CisPem alone or in combination with bevacizumab at a dose of 15 mg/kg. They concluded that regimens containing bevacizumab are not cost-effective.³¹ In fact, published studies are heterogeneous for different aspects, such as the dose of bevacizumab (7.5 or 15 mg/kg) and the analysis of the direct costs (cost of drugs, costs related to the management of adverse events and increased survival) and indirect costs (costs related to loss of productivity in terms of work, cost of caregiver, etc).³⁶

Maintenance therapy (other than bevacizumab)

Several economic studies were conducted on maintenance therapy.^{37,38} Maintenance gefitinib significantly prolonged PFS compared with placebo in patients from eastern Asia with locally advanced NSCLC with unknown EGFR mutations after four chemotherapeutic cycles of first-line platinum-based combination chemotherapy without disease progression. The cost-effectiveness of this maintenance strategy,³⁸ from a Chinese health care system

perspective, using a semi-Markov model, was an ICER of \$19,214 per QALY gained. The price of gefitinib is the most significant parameter that could reduce the incremental cost per QALY.³⁹

For erlotinib compared with BSC as a maintenance therapy for advanced NSCLC, there were some disagreements.^{40–44} Two European studies concluded that erlotinib was cost-effective compared with BSC.⁴⁴ Both studies extracted survival information directly from patient-level data in the SATURN (Sequential Tarceva in Unresectable NSCLC) trial, a Phase III clinical trial that compared erlotinib or placebo as first-line maintenance therapy: one was restricted to EGFR-negative patients, and the other was not. In contrast, in a US analysis (in which pemetrexed was the primary drug of interest), using indirect comparison instead of patient-level data, the authors estimated an ICER of \$127,343 per LYG in the comparison of erlotinib versus BSC, which appears as not cost-effective.³⁶

For pemetrexed maintenance strategy, with the exception of the study by Greenhalgh et al,⁴⁵ all studies indicated that pemetrexed is not cost-effective in this setting. From the perspective of the Swiss health care system,⁴⁶ the ICER for pemetrexed maintenance was €106,202 per QALY. Uncertainties about the resource used and costs for BSC had a large influence on the cost-effectiveness calculation. From the perspective of the Chinese health care system, the ICERs of maintenance pemetrexed treatment after a CisPac strategy³⁸ in a 1 or 2 year time horizon were \$183,589 and \$126,353 per QALY, respectively. The most sensitive influential variables were PFS health state utility, followed by proportion of patients with postdiscontinuation therapy in both groups. A paper presenting a summary of the evidence review group reported that ICER for pemetrexed maintenance treatment was £47,000 per QALY.⁵ From a US payer perspective,³⁵ in the prespecified subset of patients with nonsquamous histology only, the ICER per LYG was \$122,371 for pemetrexed to observation and \$150,260 for pemetrexed to erlotinib. In all patients with advanced NSCLC, regardless of histologic subtype, using pemetrexed as maintenance therapy led to an ICER per LYG of \$205,597 compared with observation and \$312,341 compared with erlotinib. An adjusted, matched, indirect cross-market cost comparison of erlotinib versus pemetrexed for first-line maintenance treatment of patients with advanced NSCLC² performed in France showed that acquisition costs was the main driver of total monthly per patient costs. Erlotinib appears to be a cost-saving treatment alternative to pemetrexed, producing comparable survival benefits at a lower cost.

Conclusion

A number of economic analyses of first-line and maintenance therapies for NSCLC have been recently conducted. Differences in patient population, type of analysis, currency, year of valuation, time horizon, type of intervention, and included costs hinder direct comparisons of economic outcomes. The strength of these economic analyses is also limited, to varying degrees, by the retrospective nature of economic data collection in most studies, the lack of information on other health care costs (indirect, nonmedical, and intangible costs), and the limited time horizon, which often excludes terminal care, a costly phase of lung cancer management.

Today, significant advances continue to be made for NSCLC patients, and the treatment has become nuanced and specific for particular histological subtypes, clinical patient characteristics, and specific genetic mutations.^{47,48} This review showed that most recent clinical NSCLC guidelines were based on apparently no cost-effective strategies if we consider as acceptable threshold an ICER below \$50,000 per QALY gained. The limitations were that we need clinically relevant cost-effectiveness studies, probably at the country level, and a large debate involving public health organizations and pharmaceuticals companies, but also clinicians and patients, to challenge the rising of the cancer patient's management costs. Finally, careful assessment of the effect on quality of life of these new target therapies is mandatory.

Disclosure

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