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ORIGINAL ARTICLE

Economic impact of gefitinib for refractory non-small-cell lung cancer: a Markov model-based analysis

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ABSTRACT

Few data are available on the economics of target therapy for refractory non-small-cell lung cancer (NSCLC).

Objective: To determine the mean global management costs (MC) per patient treated with gefitinib for NSCLC, and the costs of the different management phases.

Method: A Markov approach was used to model treatment costs in a cohort of 106 patients treated with gefitinib as part of a compassionate-use program (third-line treatment) in six public-sector teaching hospitals. The economic analysis adopted the healthcare payer's perspective, and only direct costs were taken into account.

Results: The mean duration of gefitinib treatment was 4.6 ± 5.8 months (1–29 months); median survival was 4 months, 1-year and 2-year survival rates were 12.3% and 4.7%, respectively. The mean total management cost was €39 979 ± 20 279. The model showed that first- and second-line treatments accounted for respectively 29.5% and 44.1% of this cost, while gefitinib periods represented 10.7%, periods of remission 1.25%, and terminal care 14.5%. A sensitivity analysis showed that the price of gefitinib had little influence on the total cost.

Conclusion: The cost of third-line gefitinib therapy for NSCLC appears acceptable from the healthcare payer's perspective, but this needs to be confirmed in dedicated cost–effectiveness studies.

Introduction

Lung cancer is one of the most serious public health problems in industrialized countries. Several studies have underlined the high cost of this malignancy for healthcare systems, especially in the current era of cost rationalization[1,2]. Chemotherapy is an important item of lung cancer management costs. Chemotherapy is the reference first-line treatment for patients with non-small-cell lung cancer (NSCLC) and adequate general health[3]. Current guidelines recommend 4–6 courses of a dual-agent regimen based on platinum[3,4]. It was recently demonstrated that, when this first-line treatment fails, patients whose general health remains adequate may benefit from second-line treatment[5–7]. Target therapies have recently become available in this setting, and include gefitinib and erlotinib, two oral selective epidermal growth factor receptor tyrosine kinase inhibitors (TKI)[8,9]. In phase II trials, at an oral dose of 250 mg/day, gefitinib gave objective responses in 18.4% of patients, stabilized the disease in 30%, and improved symptoms in nearly one in two patients[10–14]. Following these results, gefitinib was approved for the treatment of relapsed NSCLC in several countries. In France, as in other European countries, gefitinib was available for compassionate use between 2001 and 2004,

as a third-line treatment for patients previously treated with platinum-based chemotherapy. The phase III ISEL study of NSCLC patients who were refractory to or intolerant of their last chemotherapy regimen showed a non-significant trend towards a survival benefit with gefitinib, compared with placebo, both in the overall population and in patients with adenocarcinoma[15]. In a pre-planned subgroup analysis of ISEL, a statistically significant increase in survival was observed with gefitinib in patients of Asian ethnicity and in patients who had never smoked. Following the announcement of the ISEL data, gefitinib was withdrawn in European countries and its use was limited in the USA and Canada to those patients already experiencing a benefit from the drug. In the Asia Pacific region, owing to molecular differences in lung cancer, gefitinib has become an established therapy for pre-treated advanced-stage NSCLC, and first-line use for advanced-stage disease is now being studied in a large phase III pan-Asian trial (IPASS study). In contrast, erlotinib has shown a survival advantage in both second- and third-line treatment, and has been available in most western countries since September 2005[16]. As the two drugs have very similar mechanisms of action[9], the observed differences in clinical efficacy are most probably due to a dose effect (possible gefitinib under-dosing at 250 mg) or to a population bias. Both products are simple to administer (one tablet a day) and are relatively well tolerated: grade III–IV toxicity is rare, and few patients need to be hospitalized for adverse effects[10,15,16]. At present, it appears clearly that these drugs will considerably modify the management (and therefore the cost) of NSCLC, but few data are available on the management costs of refractory NSCLC or on the economic impact of target therapy[17].

The aim of this study was to assess, in a sample of patients treated with gefitinib for refractory NSCLC, the mean cost of the clinical management, the costs of the different management phases, and the economic impact of gefitinib therapy.

Methods

A Markov approach was used to model management costs in a cohort of 106 patients treated with gefitinib as part of a compassionate-use program (third-line treatment). The economic analysis adopted the healthcare payer's perspective, and only direct costs were taken into account.

Decision analysis and Markov model

Decision analysis[18] can describe complex clinical problems in *ab* = *n* explicit fashion. To analyze a given strategy, the model has to specify the likelihood of each event in terms of a probability. The resulting multistate transitory model allows patients to make transitions betweeen various health states, at different rates, over extended periods. All clinically important events are modeled as transitions from one state to another. The passage of time is divided into intervals called cycles, and chosen to represent a clinically meaningful time interval. During each cycle, each member of the cohort remains in the same state of health or moves to another state, except when the state is 'absorbing'. The utility associated with spending one cycle in a particular state is referred to as the 'incremental utility'. The net probability of making a transition from one state to another during a given cycle is called a 'transition probability'. The simulation considers a hypothetical cohort of patients beginning the process. Using decision analysis software from TreeAge (TreeAge Software, Inc., Williamstown, MA, USA), we ran a Markov model considering the expected monetary cost of going through the model. The simulation was run as shown in Figure 1: the initial assessment oriented all the patients towards an initial active treatment consisting of various combinations of radiotherapy, chemotherapy and surgery, depending on the case (state L1: first-line treatment). Regular clinical assessment of efficacy and tolerability determines the patients' subsequent management: patients in partial or complete remission pursue the same treatment (state L1) or are simply monitored (state R1), while patients with disease progression receive a second-line therapy (state L2). After this second-line treatment, patients in partial or complete remission may pursue the same treatment (state L2) or receive simple monitoring (state R2). Disease progression after a second treatment indicates

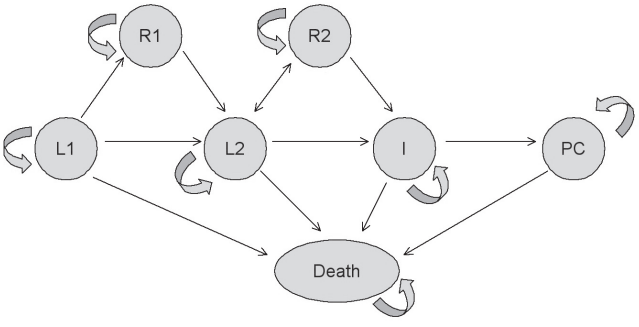

Figure 1. *Model of the management of patients receiving gefitinib therapy as part of a compassionate-use program (third-line treatment) for NSCLC, based on seven mutually exclusive and collectively exhaustive health states: L1: first-line treatment, L2: second- or third-line treatment, R1 and R2: Remission after respectively first- and second-line treatment, I: Gefitinib period, PC: no active treatment; and Death. The arrows represent the possible transitions (arrows drawn to and from a given state denote the possibility of remaining in that state during a cycle)*

gefitinib (state I), and disease progression after gefitinib indicates palliative care (state PC). Between each clinical assessment, each patient is in one of the following seven health states: L1, R1,L2, R2, I, PC or death. In the subsequent cycle (3-month period), the cohort was partitioned between all the states according to the transition probabilities, resulting in a new distribution of the cohort between the seven states. The utility accrued for the cycle is referred to as the 'cycle sum'. Confidence intervals (95%) were obtained by Monte Carlo simulation.

Primary data sources and identification of baseline and transition probabilities

Baseline probabilities and probabilities of transition from one state of health to another over time were established by analyzing the management modalities of all consecutive patients who received gefitinib for at least 1 month as part of a compassionate-use program (third-line treatment) in six public-sector teaching hospitals in France. The aim of this program was to permit early access to gefitinib for patients whose general condition was satisfactory and who were in treatment failure after at least two lines of chemotherapy, at least one of which included cisplatin. In the French healthcare system, there were no administrative or financial obstacles for patients wishing to enter this program. However, the strict conditions and complexity of the administrative process (inclusion of a file providing the patient's entire history, validation of the file by the authorities, and monthly monitoring of outcome with immediate notification of adverse events) favored patients managed in teaching hospitals.

The analysis spanned the period from diagnosis to death and considered all events related to lung cancer that entailed consumption of medical resources, including adverse effects of treatment necessitating hospitalization. Data were collected from the patients' charts by specially trained clinical research technicians. We distinguished the different management phases, for each patient and each 3-month period, as follows: first-line treatment (surgery, chemotherapy and/or radiotherapy), second-line treatment (all other active treatment periods), remission (periods in partial or complete remission), the gefitinib period, and palliative care, defined as a lack of conservative treatment (including palliative radiotherapy, anti-infectives, corticosteroids and pain relief). The patients were classified in each period by one of the authors (CC).

Economic evaluation

The economic analysis[19] adopted the healthcare payer's perspective and took into account only direct costs (i.e. consumption of healthcare resources). Indirect costs (e.g., lost income) and intangible costs (e.g., pain and suffering) were not assessed. Hospitalization costs (administration, security, maintenance, general equipment, central supply, dietetics and social services) were assessed on a *per diem* basis (national unit cost scale for each event) for fixed costs and from drug purchase prices in the establishments concerned. Medical costs (nursing, care, ward supplies, pharmacy, diagnostic tests, laboratory tests and professional services) were determined retrospectively by chart review. Initial diagnostic costs were not taken into account.

Sensitivity analyses

Sensitivity analyses were used to test the relevance of the model by varying the impact of the cost of gefitinib on the mean cost of lung cancer management.

Results

Baseline data

The study involved 106 patients who started compassionate gefitinib therapy between January 2002 and March 2004. Mean age was 55.6 ± 11.8 years and the male–female sex ratio was 2.3. All the patients had a histological or cytological diagnosis of NSCLC. The most common histologic subtype was adenocarcinoma (none of the patients had bronchioloalveolar cell carcinoma). The patients' baseline characteristics are shown in Table 1. At diagnosis, 84% of the patients had locally advanced or metastatic disease. The median number of lines of treatment before gefitinib administration was 2.7 ± 0.8 (range 2–6). The first line of treatment was always a chemotherapy combination (plus surgery in 20 cases and thoracic radiotherapy in 25 cases). In 95% of cases, the chemotherapy regimen was a dual-agent combination including platinum. One hundred and five patients received a second line of chemotherapy (single-agent therapy in 87% of cases, taxan in 74%). One-third of the patients had a subsequent-line therapy, always consisting of a single agent (Table 1). In the model, all chemotherapy regimens administered after the first line of treatment and before gefitinib therapy were considered as second-line treatments.

The mean time between diagnosis and gefitinib therapy was 19.1 ± 13.5 months. Mean performance status at the outset of gefitinib therapy was 1 (range 0–3). The mean duration of gefitinib treatment was 4.6 ± 5.8 months (1–29 months). The median survival time was 4 months, and the 1-year and 2-year survival rates were respectively 12.3% and 4.7% (Figure 2). At

Table 1. *Characteristics of the patients*

	N = 106
Age (years)	55.6 ± 11.8
M/F (%)	70/30
Stages II/III/IV at diagnosis (%)	10/22/68
Tumor histology (%)	
Adenocarcinoma	51 (48.1)
Squamous cell	31 (30.2)
Large cell	18 (17)
Others	5 (4.7)
Previous cancer treatment before gefitinib prescription (%)	
3 chemotherapy regimens	56 (52.8)
4 chemotherapy regimens	32 (30.2)
5 chemotherapy regimens	15 (14.2)
6 chemotherapy regimens	2 (1.9)
7 chemotherapy regimens	1 (0.9)
Gefitinib (months): mean ± SD (range)	4.6 ± 5.8 (1–29)
Survival after gefitinib (median)	4 months

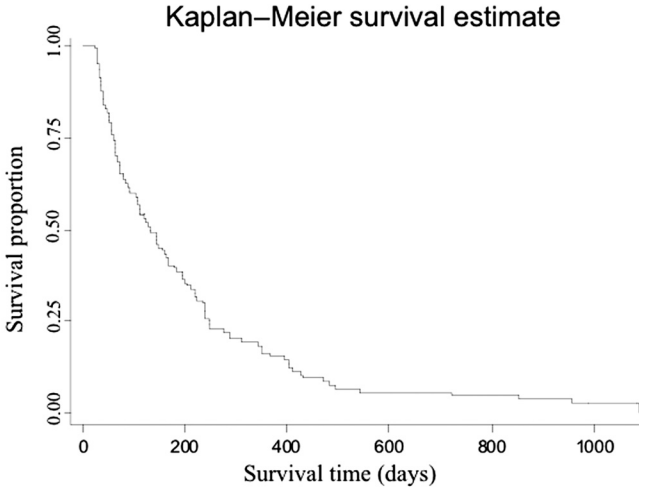

Figure 2. *Survival after the beginning of therapy (days)*

the time of this analysis (March 2006), 104 patients had died and two were still alive, with a follow-up of 33 and 36 months, none on gefitinib. Four patients had a new course of chemotherapy after gefitinib therapy, and these periods were considered as palliative care. This allowed us to classify all the patients, at any given time, in one of the seven health states (L1, R1, L2, R2, I, PC or death). As management was standardized in most cases, this classification was relatively straightforward. The mean cost of each management modality per 3-month period and per patient is summarized in Table 2. The costs of the first- and second-line treatment periods were respectively three and five times higher than the costs of gefitinib treatment periods.

Application of the Markov model

The distribution of the patients in the different health states (in each subgroup and per 3-month period) determined the values of the baseline and transition probabilities and their changes with time (data not shown). On running the Markov model for 20 cycles, and using Monte-Carlo simulation, the mean cost was €39 979 ± 20 279 (95% CI: €16 679–79 858). The costs of the different phases are reported in Table 3. Nearly half the costs were related to second-line management. Gefitinib periods represented 10.7% of the total cost.

Sensitivity analysis

The sensitivity study, in which the price of gefitinib was varied by –25% and –50%, showed only a marginal impact on the mean total NSCLC management cost (Table 4).

Discussion

The advent of tyrosine kinase inhibitors represents an advance in the management of some patients with NSCLC but is raising concerns as to the cost–effectiveness of these drugs. A Markov approach was used to model treatment costs in a cohort of 106 patients treated with gefitinib as part of a compassionate-use program (third-line treatment) in six public-sector teaching hospitals. The results of this program (4.6 months of median gefitinib treatment, 4 months of median survival, respectively 12.3% and 4.7% of 1-year and 2-year survival rates) confirm several previous reports of compassionate-use programs[13,20] in which gefitinib therapy lasted 2–4 months

Table 2. *Mean cost (€) of each management modality, per 3-month period*

	Costs (€)	Chemotherapy (%)	Radiotherapy (%)	Surgery (%)	Complications (%)	Monitoring (%)
L1: First-line therapy	12 476 ± 9718	38.1	18.8	13	26	4.1
R1: Remission after L1	503 ± 402	–	–	–	3	97
L2: Second-line therapy	8555 ± 343	72	10.2	–	10.8	7
R2: Remission after L2	533 ± 412	–	–	–	2	98
I: Gefitinib period	2360 ± 841	78.8	–	–	20.2	1
PC: Palliative care	1860 ± 541	4	4	–	92	–

Table 3. *Global management costs (€) of refractory NSCLC treated by gefitinib (2004)*

	Mean costs ± SD $N = 106$	%
Global costs per patient	39 979 ± 20 729	100
L1: First-line therapy	11 969 ± 5434	29.5
R1: Remission after first-line therapy	138 ± 71	0.3
L2: Second- or third-line therapy	17 494 ± 11 432	44.1
R2: Remission after second-line therapy	376 ± 102	0.9
I: Gefitinib period	4241 ± 1424	10.7
PC: Palliative care	5761 ± 2395	14.5

Table 4. *Sensitivity analysis: influence of the cost of gefitinib (2004)*

Monthly cost of gefitinib (€)	Mean cost (SD)	% variation
Base case: €1860	39 708 ± 20 729	
Variation of –25%	38 872 ± 20 375	–2.1%
Variation of –50%	38 073 ± 19 739	–4.1%

on average with between 5% and 10% of patients treated for more than a year. The global management costs of these heavily-treated patients are particularly high (€39 979), nearly half the costs being related to second-line treatment and 10.7% to gefitinib. Several recent studies[21–24] focus on the economic aspects of NSCLC patient management, but few data are available on target therapies. A recently-published American study[21] of patients treated between 1994 and 1996 showed the importance of chemotherapy in the cost of patient management: costs ranged from US$27 833 for patients not receiving chemotherapy to US$55 959 for those receiving monotherapy and US$78 451 for those treated with a platinum-based dual-agent regimen without a taxan. Management modalities are another important cost determinant. In an analysis of 349 patients with newly diagnosed NSCLC, the average 2-year management cost was US$47 941 (range US$43 758–52 124), and 70% of these costs were due to hospitalization.

Regarding management practices after failure of a first line of treatment, a recently-published study[2] of 2040 patients diagnosed in 2000 and followed for 2 years showed that the mean total cost per patient was US$45 897, and monthly management costs during first-line and second-line treatment and terminal care were respectively US$11 496, US$3733 and US$9399. These results are in keeping with those found in a model-based study of patients managed in France[22] in 1998, when neither target therapy nor taxans were available: the mean cost was US$20 691 (range US$5777–50381), and 62.4% of these costs were related to the first line of treatment, 13.1% to the second line, 1.5% to periods of remission, and 23% to terminal care. It should be noted that these studies involved all patients, analyzed from the time of diagnosis, whereas we only considered those who survived sufficiently long, in adequate general health, to receive a third line of treatment. By definition, these latter patients have higher costs[22,23]. Indeed, Kutikova et al.[2] showed that patients who received a second line of treatment had significantly higher costs than other patients (US$120 650 vs. 45 953). Similarly, a French retrospective analysis of 178 patients showed that the mean cost of relapses was €13 969 and that this cost increased with the number of lines of treatment[24].

One limitation of our study is that it could not analyze the cost-effectiveness of gefitinib in the treatment of NSCLC. It is now clearly established that first-line

chemotherapy for NSCLC is cost-effective and improves survival without markedly diminishing quality of life[25,26]. Data on second-line treatments are less consistent[27]. Drug costs and the cost of hospitalization for adverse effects are major determinants. The cost–effectiveness ratio of second-line treatments is sometimes less positive than that of first-line treatments. With second-line docetaxel, the cost was US$57 000 per year of life gained in the pivotal trial[28], and UK£10 020–32 781 per year of life gained in a model-based study[29]. Medico-economic analysis of gefitinib therapy is hindered by the lack of long-term efficacy data. In the phase III ISEL study, some improvement in survival was seen with gefitinib, although it failed to reach statistical significance, compared with placebo, in the overall population and in patients with adenocarcinoma. A statistically significant increase in survival was observed in the trial of gefitinib in patients of Asian ethnicity and in patients who had never smoked (pre-planned subgroup analysis)[15]. Furthermore, phase II trials have clearly shown the benefits of gefitinib in terms of disease stabilization and symptom relief[10,11]. In contrast, erlotinib showed a survival gain sufficient to support its second-line use[16], warranting preliminary cost–effectiveness studies. From the Canadian healthcare payer's perspective[30], using these data, the cost-effectiveness of erlotinib relative to palliative care was Can$71 018 per QALY. In the same way, also in the second-line treatment setting, taking survival and quality of life as indicators of effectiveness, relative to best palliative care in the UK healthcare system, erlotinib was more cost-effective than docetaxel (respectively, UK£13 175 vs.13 312)[31].

One other limitation of our study is that it focused on the first patients to receive TKI therapy on a compassionate basis in specialized centers, which meant that the results may not be relevant to current practices. Nevertheless, our model clearly shows that periods of TKI therapy generated lower costs than periods of second-line chemotherapy, and that the cost of TKI agents, from the healthcare payer's perspective, had only a modest impact on the global management costs of these patients.

Conclusion

The cost of third-line gefitinib therapy for NSCLC appears acceptable from the healthcare payer's perspective, but this needs to be confirmed in dedicated cost–effectiveness studies.

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