Evaluation of Erlotinib in Advanced Non-Small Cell Lung Cancer: Impact on the Budget of a U.S. Health Insurance Plan

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ABSTRACT

BACKGROUND: Lung cancer is the most common non-skin cancer and the leading cause of cancer death among men and women in North America. More than half of all patients diagnosed with lung cancer are diagnosed with advanced disease. Most cases of lung cancer are non-small cell lung cancer (NSCLC). Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen.

OBJECTIVE: To assess the budgetary impact, from the health plan perspective, of covering erlotinib for treating patients with NSCLC stage IIIb/IV who have failed at least 1 prior chemotherapy regimen.

METHODS: An Excel-based model was developed to evaluate costs for U.S. Food and Drug Administration-approved and National Comprehensive Cancer Network guideline-recommended treatment options for second- and third-line NSCLC from the perspective of a U.S. health insurer. In particular, the model compares a formulary with erlotinib and a formulary without erlotinib, including the costs of treatment, drug administration, and adverse effects. The incidence of advanced NSCLC is based on the Surveillance, Epidemiology, and End Results Cancer Registry and adverse effects related to treatment (all agents) in published results of clinical trials. Drug and treatment costs were obtained from publicly available sources in 2005.

RESULTS: The base case considers a health plan of 500,000 enrollees. Assuming that erlotinib comprises 30% of second-line treatments and 90% for third-line, total costs of treating stage IIIb/IV NSCLC patients over 1 year are $382,418 with erlotinib and $380,968 without erlotinib (difference: $1,450; 90% confidence interval, -$61,376 to $29,855), less than $0.01 per member per month (PMPM) in 2005. Erlotinib direct cost is offset by reductions in standard chemotherapy-related infusion costs and adverse events.

CONCLUSIONS: Based on the analysis, the inclusion of erlotinib on a formulary appears to have a relatively small impact on the annual health care budget or PMPM expenditures if it is used consistent with the product label indications.

KEYWORDS: Erlotinib, Non-small cell lung cancer, Cost

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With more than 173,000 new cases diagnosed and more than 160,000 deaths projected, lung cancer was the most common non-skin cancer and the leading cause of cancer death among men and women in North America in 2005.[1] Most cases of lung cancer are non-small cell type; more than half of all patients diagnosed with lung cancer are diagnosed with advanced disease. In these cases, platinum-based chemotherapy offers symptomatic relief and modest improvement in survival,[2] yet responses are brief and most patients experience disease progression. Traditionally, second-line chemotherapy with docetaxel has been shown to prolong survival after platinum-based therapy for non-small cell lung cancer (NSCLC).[3,4]

Recently several new agents have been approved for second-line therapy of advanced NSCLC. On November 18, 2004, erlotinib (Tarceva) was approved as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen, i.e., as second-line therapy. Erlotinib is the only epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) therapy shown in a randomized phase III trial to provide a survival benefit to NSCLC patients (hazard ratio [HR] = 0.73).[5] In addition, in a recent Phase III trial of second-line therapy, the novel antifolate pemetrexed showed comparable activity to docetaxel with significantly reduced toxicity.[6]

Although newer agents modestly lengthen overall survival in patients with advanced NSCLC, they are costly, and some have raised concerns about costs to patients.[7] Given the high prevalence of lung cancer, health plan managers may also be concerned about the impact of these novel therapies on their health plan budgets.

We developed a decision model to assess the impact of adding erlotinib to the health plan formulary on total health plan expenditures. The model evaluates patients with advanced NSCLC who have shown disease progression after treatment with chemotherapy and thus are eligible for second- or third-line treatment. The analysis is conducted from the perspective of a private U.S. health insurer.

Methods

The erlotinib budget impact model was developed to assess the budgetary impact of covering erlotinib for the treatment of patients with locally advanced or metastatic (stage IIIb and IV) NSCLC, who have failed at least 1 prior chemotherapy regimen. Treatment options considered for the analysis were based on U.S. Food and Drug Administration (FDA)-approved

indications and practice guidelines recommended by the National Comprehensive Cancer Network (NCCN) for second- and third-line therapy.[8]

The model was developed as a Microsoft Excel workbook.[9] Default estimates are provided for all model inputs based on various public and private data sources. The proportion of patients eligible for treatment with erlotinib were estimated using data from the U.S. Census Bureau and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Registry.[10]

The model considers 2 scenarios. In the first scenario, erlotinib is not a treatment option in either the second- or the third-line treatment situation. Rather, treatment options for patients include 2 chemotherapy regimens, docetaxel and pemetrexed, that have been approved by the FDA for the treatment of advanced NSCLC and that has shown evidence of progression after first-line treatment. In the second scenario, erlotinib monotherapy is a treatment option and is used in place of competing therapies for a proportion of eligible patients. Comparing the total costs of treating patients in these 2 scenarios in the second- and the third-line treatment situation provides an assessment of the economic impact on a health plan's budget of adding erlotinib to the formulary.

TABLE 1 Number of Plan Members With Stage IIIb/IV Non-Small Cell Lung Cancer (NSCLC)

	Plan Members*		Patients With Distant Metastatic Lung Cancer†	
	%	Number	%	Number
Total	100.0	500,000		
Men, age, (years)				
≤44	31.6	158,000	0.0014	2
45-54	7.7	38,500	0.0264	10
55-64	5.1	25,500	0.0998	25
≥65	4.6	23,000	0.2303	53
Women, age, (years)				
≤44	31.7	158,500	0.0014	2
45-54	8.2	41,000	0.0190	8
55-64	5.3	26,500	0.0659	17
≥65	5.8	29,000	0.1289	37
			%	Number
Total number of expected cases			100	156
Patients with NSCLC			80	125
Patients likely to be treated with chemotherapy			78.8	98
Patients receiving second-line therapy			21	21
Patients receiving third-line therapy			11	11

** Proportions in each age group based on Census Bureau records (www.census.gov).*

† Percentages of patients diagnosed with lung cancer and advanced-stage lung cancer are based on cancer incidence data from the Surveillance, Epidemiology, and End Results cancer registry (www.seer.cancer.gov).

Estimation of the Patient Population Eligible for Erlotinib

The number of second- and third-line chemotherapy treatment-eligible patients in a hypothetical private health insurance plan with 500,000 covered lives, including a Medicare-eligible group, is based on a stratification of health plan enrollees by age group and age-specific estimates of the incidence of stage IIIb/IV NSCLC for each group (Table 1).

The age distribution is based on U.S. Census Bureau data.[11] Age- and gender-stratified incidence estimates of advanced lung cancer are based on the incidence for lung cancers listed in the SEER registry as "distant stage." The distant stage designation approximates the American Joint Committee on Cancer (AJCC) stage IIIb/IV designation. The percentage of all metastatic distant stage lung cancer patients with NSCLC pathology is based on the proportion of such cases in the SEER registry.[10]

Treatment Distribution

The model considers treatment options that are (1) FDA approved in the particular indication and (2) recommended by the NCCN guidelines for NSCLC.[8] Thus, patients in the second-line and third-line situations are assumed to receive pemetrexed, docetaxel, or erlotinib. Gefitinib is considered to have minimal use due to recent FDA labeling that severely restricts its use. Off-label treatments for stage IIIb/IV NSCLC are not considered in this model. The distribution of patients estimated to receive the various second- and third-line chemotherapy treatment options in the 2 treatment scenarios described above is based on 2004 market research data for erlotinib, docetaxel, and pemetrexed use in patients with lung cancer; it was derived from a commercially available survey.[13] For the scenario without erlotinib, we assume that 50% of patients receive docetaxel and 50% receive pemetrexed. Under the scenario with erlotinib, we assume that 30% of eligible patients receive erlotinib in the second-line situation (with corresponding equal reductions in use of pemetrexed and docetaxel), and 90% of patients receive erlotinib in the third-line situation.

Drug Utilization and Costs

Drug costs for erlotinib, docetaxel, and pemetrexed are estimated based on the medication dose specified in the product label, expected duration of treatment as reported in the pivotal trials for each product, and national reimbursement surveys of the medications[3,14,15] (Table 2). Dose reductions observed in the clinical trials for each agent were accounted for in the analysis.[3,4,6]

Drug Administration Costs

Erlotinib is a self-administered oral tablet, hence no administration costs are assumed for this medication. The model assumes

TABLE 2 Medication Use* and Costs† of Pemetrexed, Docetaxel, and Erlotinib

	Pemetrexed	Docetaxel
Dose (mg/m^2)	500	75
mg/person	880	132
mg/vial	500	80
Vials/cycle	2	2
Cost/vial ($)	1,999	1,242
Cost/cycle ($)	3,998	2,483
Number of cycles per subject	4	4
Total drug cost per subject ($)	15,990	9,934
	Erlotinib‡	
Cost/monthly prescription ($)		
150 mg	2,330	
100 mg	2,060	
50 mg	750	
Average duration of treatment (weeks)	9.6	
Average number prescriptions/subject	3	
Average drug cost per unit		
Average number of units		
Total drug cost per subject ($)*	6,865	

** From prescribing information.*

† AnalySource Online, selected from National Drug Data File (NDDF) data, included with permission and copyrighted by First DataBank, Inc. Available at: http://www.analysource.com/. Accessed September 22, 2005.

‡ Weighted average of different doses of erlotinib based on dose reduction assumptions.

1 outpatient physician office visit for the first prescription, with refill prescriptions for the remaining prescriptions not requiring additional physician office visits beyond scheduled follow-up evaluations. The total cost of administration for pemetrexed and docetaxel is based on the number of infusions per patient per year and the average cost of administering the infusion. One physician office visit is assumed each time the patient received an infusion. For each infusion, there is assumed to be a fixed cost for the first hour. The cost of the infusion is based on 2005 Centers for Medicare & Medicaid Services (CMS) payment rates for Current Procedural Terminology (CPT) code 96410 (chemotherapy, infusion method).[16] The cost of an outpatient physician visit is based on the 2005 CMS payment rates for CPT 99215 (office or other outpatient visit).[17]

Costs of Adverse Events

The model includes treatment costs for Grade 3 or Grade 4 adverse events (AEs) with an incidence rate of 5% or greater, as listed in the prescribing information for each of the therapies. AEs requiring hospitalizations were included in the model regardless of magnitude of incidence if reported in the pivotal trial publications of the respective therapies (see Table 3 for details on costs of AEs). All patients experiencing Grade 3 or 4 AEs (severe AEs) related to erlotinib were assumed to require 1 outpatient visit.

In clinical trials for erlotinib, rash occurred within 2 weeks of initiating the treatment. Based on treatment recommendations by clinicians, patients experiencing a rash were assumed to receive clindamycin gel for the duration of treatment.[18] Patients experiencing diarrhea while taking erlotinib were assumed to receive treatment with loperamide. Costs of hospitalizations due to severe diarrhea are assumed to include costs of hospitalization as well as costs due to inpatient physician visits.

Febrile neutropenia is assumed to require hospitalization and inpatient physician visits. Patients with severe anemia are assumed to have 1 outpatient visit. In addition, a proportion of patients with anemia are assumed to receive treatment with erythropoietin (Epogen) or a red blood cell (RBC) count transfusion. Proportions of patients receiving erythropoietin or RBC transfusions are obtained from the publication of the pivotal trial that compared pemetrexed with docetaxel in the second-line treatment of NSCLC patients.[6]

Patients with neutropenia (nonfebrile) were assumed to have 1 additional outpatient physician visit. In addition, a proportion of patients are assumed to receive 1 course of granulocyte colony stimulating factors (G-CSF) as prophylaxis for neutropenia. The proportion of patients receiving G-CSF is based on the pivotal trial publication of pemetrexed compared with docetaxel in the second-line treatment of NSCLC patients.[6] Hospitalization rates due to neutropenic fever and other drug-related AEs following treatment with pemetrexed or docetaxel are based on published studies.[6]

Costs for hospitalization were based on Medicare reimbursement rates for the aforementioned complications of interest. Costs for outpatient visits were based on Medicare fee schedules. Drug costs are based on national reimbursement schedules provided by Price-Chek PC, a database published by Medispan/First DataBank.[19]

Analysis

The model was used to estimate the impact of erlotinib on expenditures over 1 year after the drug was made available as a benefit for members of a hypothetical health plan with a total enrollment of 500,000 persons. Analyses of the budget impact of erlotinib focused on comparing costs of treating stage IIIb/IV NSCLC in the second- and third-line treatment situation between scenarios where erlotinib is and is not a treatment option. In addition to aggregate costs to the health plan, an estimate of costs per member per month (PMPM) was computed. The PMPM costs are calculated by dividing the total cost to the plan by the number of members in the plan, then dividing by 12. After analyses were performed using base-case (default) esti-

TABLE 3 Incidence and Costs of Side Effects Related to Use of Docetaxel, Pemetrexed, and Erlotinib

Side Effect*	Incidence (%)	Prior to Erlotinib Expected Cost ($)* to Plan (2nd Line)	Erlotinib Available Expected Cost ($)† to Plan (2nd Line)
Docetaxel			
Neutropenia	65.3	40,017	28,012
Leukopenia	49.4	30,273	21,191
Anemia	9.1	360	252
Febrile neutropenia	6.3	4,190	2,933
Infection	10.2	126	88
Nausea	5.1	63	44
Asthenia	18.2	225	158
Pulmonary AE	21.0	260	182
Hospitalization due to other AE	10.5	4,813	3,369
Expected overall cost to plan ($)		80,328	56,230
Pemetrexed			
Neutropenia	5.0	468	328
Anemia	8.0	287	201
Febrile neutropenia	2.0	1,330	931
Hospitalization due to other AE	6.4	2,934	2,054
Fatigue	16.0	198	139
Anorexia	5.0	62	43
Dyspnea	18.0	223	156
Chest pain	7.0	87	61
Infection without neutropenia	6.0	74	52
Expected overall cost to plan ($)	5,662		3,964
		Expected Cost ($) (2nd Line)	**Expected Cost ($) (3rd Line)**
Erlotinib			
Rash	9.0	106	166
Diarrhea	6.0	46	72
Hospitalization due to diarrhea	3.0	825	1,297
Anorexia	9.0	67	105
Fatigue	18.0	134	210
Dyspnea	28.0	208	327
Expected overall cost to plan ($)	1,385		2,177

** Based on treatment for grade 3 or 4 side effects occurring at higher incidence (>5%) in treatment arm versus control arm in respective pivotal trials of each medication.*

† Proportion of patients receiving docetaxel and pemetrexed decreases once erlotinib is a treatment option, hence the expected cost of side effects changes accordingly.

AE = adverse event.

mates for the parameters, sensitivity analyses were performed on key model parameters to assess the robustness of the model results.

Sensitivity analyses were conducted to evaluate the influence of variation in key parameters such as the percentage of patients receiving erlotinib, treatment costs, rates of AEs on the budget impact in the second-line situation only, and in second- and third-line situations together. Parameters were varied across confidence intervals, when available from clinical studies, or by ±25%, when data were unavailable.

TABLE 4 Treatment Costs to Health Plan by Treatment Situation

Treatment Situation	Scenario 1, Without Erlotinib	Scenario 2, With Erlotinib
Second-line only (n = 21)		
Chemotherapy drug costs ($)	267,084	229,397
Administration costs ($)	24,090	17,606
Cost of side effects ($)	85,991	61579
Total	377,165	308,582
Difference		(68,583)
Second/third-line (n = 32)		
Chemotherapy drug costs ($)	270,758	299,760
Administration costs ($)	24,220	18,902
Cost of side effects ($)	85,991	63,756
Total	380,968	382,418
Difference		1,450

Results

Results Based on Default Parameter Estimates

Based on age-adjusted incidence and observed rates of second- and third-line therapy (21% and 11% of stage IIIb/IV NSCLC patients, respectively), the model estimates that in a hypothetical health insurance plan with 500,000 covered lives, 98 patients with advanced NSCLC will be eligible for second- and third-line therapy during the year of analysis (Table 1). Table 4 lists annual health plan costs of treatment of second- and third-line stage IIIb/IV NSCLC, including drug costs, administration costs, and costs related to AEs. The total expected cost of treating second- and third-line stage IIIb/IV NSCLC is estimated to be $380,968 when erlotinib is not a treatment option. With erlotinib as a treatment option, the treatment cost is increased to $382,418. Similarly, in the second-line situation only, total expected cost is $377,165 when erlotinib is not a treatment option and $308,582 when erlotinib is a treatment option. Expressed as changes in PMPM costs for all members in the health plan, the model estimated that the addition of erlotinib changes these costs by approximately $0.01.

Sensitivity Analyses

Sensitivity analyses demonstrate that estimates of the budget impact of adding erlotinib as a treatment option in second- and third-line treatment situations are most sensitive to (in order of importance) the unit cost of erlotinib, the proportion of patients who are switched from pemetrexed to erlotinib, the proportion of patients switched from docetaxel to erlotinib, and the proportion of patients receiving second- and third-line treatment (Table 5). The cost of managing AE rates for all drugs did not substantially influence the outcome. The expected difference in costs between scenarios is a $1,450 savings with erlotinib available. Using multiway sensitivity analysis, the 90% confidence interval ranges from a $61,376 savings to $29,855 higher costs for the erlotinib scenario.

TABLE 5 One-Way Sensitivity Analyses of the Influence of the Budget Impact of Adding Erlotinib as Available Therapy in the Second- and Third-Line Situations, Expressed as Influence of Changes in the Parameter on Change in Total Plan Costs

Rank	Name	Value*	Sensitivity Correlation†
#1	Erlotinib cost, 150 mg Point estimate: $2,330 High value: $2,913; low value: $1,748	0.335	0.354
#2	% of pemetrexed usage when erlotinib available Point estimate: 35% High value: 43.75%; low value: 26.25%	0.328	0.336
#3	% of docetaxel usage when erlotinib available Point estimate: 35% High value: 43.75%; low value: 26.25%	0.324	0.329
#4	% of patients receiving second-line therapy Point estimate: 21% High value: 26.25%; low value: 15.75%	-0.290	-0.275
#5	Percent patients receiving third-line therapy (% of second line) Point estimate: 11% High value: 13.75%; low value: 8.25%	0.224	0.229
#6	Pemetrexed cycles per subject Point estimate: 4 High value: 5; low value: 3	-0.210	-0.227
#7	Average surface area Point estimate: 1.76 m^2 High value: 2.2; low value: 1.32	-0.207	-0.231
#8	Pemetrexed cost per vial Point estimate: $1,999 High value: $2,498; low value: $1,499	-0.193	-0.190
#9	Pemetrexed dose (mg/m^2) Point estimate: 500 High value: 379; low value: 620	-0.153	-0.152
#10	Erlotinib duration of treatment (weeks) Point estimate: 9.6 High value: 12; low value: 7.2	0.145	0.101

* *Refers to the value of the regression coefficient for the individual parameter in a model that includes all inputs, with the dependent variable of total costs. Negative values refer to parameters where increases decrease total cost.*

† *Refers to the correlation between the individual parameter and the overall budget impact.*

Discussion

The purpose of this erlotinib budget impact model is to estimate the impact on health plan budgets of introducing erlotinib as second- and third-line therapy for patients with advanced

NSCLC. In a health plan of 500,000 enrollees, including erlotinib on the formulary has a modest positive impact on health plan expenditures. The higher direct drug costs of erlotinib are offset by the reduced costs of administration and fewer costs incurred for treatment of severe side effects when compared with pemetrexed and docetaxel. In 1-way sensitivity analysis, the results are relatively insensitive to estimates of the incidence of erlotinib-related AEs. Multiway sensitivity analyses suggest that the difference in costs between the regimens is unlikely to be statistically significant. This decision model suggests that health plans can include erlotinib on their formulary with a relatively low impact on their annual health care budget if erlotinib is used as labeled and in place of rather than in addition to traditional second-line chemotherapy. The budget impact of previous changes in chemotherapy regimens, notably taxanes, has been more substantial than erlotinib.[20] Some chemotherapeutic substitutions may result in cost savings for treating NSCLC patients in certain situations.[21]

The budget impact model follows NCCN-recommended guidelines in the third-line situation, where erlotinib is the only recommended treatment alongside best supportive care. If, in practice, other types of chemotherapy are used in place of erlotinib, then substituting erlotinib for these agents may result in savings in this line of treatment. On the other hand, if other chemotherapy agents are typically added alongside erlotinib as third-line treatment, total treatment costs could be higher than predicted.

Limitations

This model does not consider the other labeled indication for erlotinib—locally advanced pancreatic cancer—nor does it consider "off label" uses, such as head and neck cancer.[22] Although these cancers are relatively uncommon in working-age adults, use of erlotinib in these situations will increase PMPM costs for the health plan because, in these cancers, erlotinib is used in addition to rather than in place of other therapies.

Therapy costs are ultimately influenced by patient adherence to treatment schedules. We assume that patients purchase (and health plans incur) the cost of a full erlotinib prescription, whether or not the patient ultimately takes all the medication as prescribed. This is a conservative assumption; that is, it negatively affects erlotinib relative to the alternatives. In a review of the literature, Lucero and colleagues note that adherence may be similar for both injectable and oral therapies.[23]

This budget impact model does not consider efficacy beyond its immediate impact on expenditures. A more formal evaluation of the cost-effectiveness of erlotinib, with outcomes expressed as years of life gained or quality-adjusted life-years, would provide a more complete picture of the value of this drug as second- and third-line therapy for patients with non-small cell lung cancer.

Conclusion

Erlotinib, a new epidermal growth factor receptor tyrosine kinase inhibitor that has been shown to modestly improve survival for patients with advanced stage non-small cell lung cancer, is expected to replace standard second- and third-line chemotherapy use in these patients. Because erlotinib is costly, we constructed a decision model to estimate the budget impact of adding erlotinib to the formulary. Although drug expenditures increase when erlotinib replaces existing treatments, the net budget impact to health plans of adopting erlotinib is quite modest due to erlotinib's superior side-effect profile. The estimates only consider use that is consistent with product labeling. Off-label use for lung or other cancers, if common, could have more substantial impacts on net health plan expenditures.

DISCLOSURES

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