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Keywords:	Targeted therapies, Lung cancer, Reimbursement policy, Interrupted time series

Title Page

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Abstract

Interventions: Targeted therapies have been proven to provide clinical benefits to patients with metastatic non-small cell lung cancer (NSCLC). Gefitinib, a targeted therapy, was initially approved and reimbursed as third-line therapy for advanced NSCLC patients by Taiwan National Health Insurance in 2004; subsequently they became second-line (in 2007) and further first-line (in 2011) therapies for EGFR mutation-positive, advanced NSCLC patients. Another targeted therapy, erlotinib, was initially approved as third-line therapy in 2007, and it became second-line in 2008.

Objectives: This study aims to explore the impacts of above reimbursement policies (removing restriction of reimbursement) on accessibility of targeted therapies.

Design:

Setting: We retrieved 2004-2013 claims data with all patients with lung cancer diagnosis from National Health Insurance Research Database.

Design and Outcome Measures: Using an interrupted time series design and segmented regression, we estimated changes in monthly rate of prescribing rate by patient number and market shares by costs following each modification in the reimbursement policy for gefitinib and erlotinib for NSCLC treatment.

Results: Prescribing rate of targeted therapies relatively increased by 15.58%, decreased by 10.98% and increased by 6.31% at three months following gefitinib as the second line treatment in 2007, erlotinib as the second line treatment in 2008 and gefitinib as the first line treatment in 2011 respectively. Average time to targeted therapies' prescription reduced by 65.84% and 41.59% at 2 years following erlotinib covered by insurance and gefitinib/erlotinib as the second line treatments in 2007-2008 and following gefitinib as the first line treatment in 2011 respectively.

Conclusions: The changes of the reimbursement policies had the significant impacts on the utilization and accessibility of oral targeted therapies for NSCLC treatment. Removing restriction of reimbursement for specific drug would increase its own use but might decrease another drug's use. These interventions also significantly accelerated the prescription of targeted therapies.

Keywords: *Lung cancer, Targeted therapies, Reimbursement policy, Interrupted time series*

Strengths and limitations of this study

- Interrupted time series design and segmented regression were applied.
- Removing restriction of reimbursement had significant impact on drug accessibility.
- Prescribing rate of targeted therapies relatively increased following the policy change.
- Average time to targeted therapies' prescription reduced following the policy change.
- Further studies about how such policies affect the clinical outcomes of treatments and the cost-effectiveness of the policies are needed in the future.

Manuscript

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] In the United States, in 2011, approximately 221,130 new cases of lung cancer (14% of all cancer diagnoses) were predicted, out of which 156,940 deaths (27% of cancer deaths) were estimated to have been due to lung cancer.[2] In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 11,692 new cases of lung cancer (12% of all cancer diagnoses) and 8,587 deaths (20% of cancer death) were expected to occur in Taiwan in 2012.[3] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[4-7]

Since 2004, oral targeted therapies for non-small cell lung cancer have been launched into the market for epidermal growth factor receptor (EGFR) mutation patients. The EGFR molecular targeted drugs (MTD), gefitinib and erlotinib, were firstly approved as third-line or second-line therapy for advanced NSCLC patients because of their therapeutic benefits, as suggested by randomized clinical trials.[8-10] The recent National Comprehensive Cancer Network guideline[11] further suggests MTD as first-line therapy for EGFR mutation-positive, advanced NSCLC patients based on cumulating evidence showing a significant association between mutated EGFR and the clinical benefits of MTD.[12-14] In the light of rapid disease progression, access to pharmaceutical innovations such as MTD on a timely basis is vital to NSCLC patients with the right indications who need it.

According to "Directions for Drug Restricted Benefits for National Health Insurance,"

two targeted therapies, gefitinib and erlotinib, for treatment of lung cancer have been reimbursed in Taiwan since 2004 and 2007, respectively. In the beginning, both were restricted for use as a third-line treatment. Gefitinib could be used as second-line therapy for advanced NSCLC patients after November 2007 and has been further allowed to be used as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2011; erlotinib has been permitted for use as a second-line therapy for advanced NSCLC patients since June 2008 and has been further allowed to be used as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2013.

Little is known about the impacts of changes in targeted therapy-related reimbursement policies (related to removing restriction of reimbursement and broadening eligible patient population) in Taiwan. The aim of our longitudinal analyses was to address this gap by examining the recent trends in utilization and expenditures of targeted therapies (gefitinib and erlotinib) following changes in the reimbursement policy, which involve the accessibility and economic burden of drugs. Furthermore, we also evaluated the changes of time to prescription of NSCLC over time.

Method

Data sources

All monthly claims data, including details of prescription and insurer spending, for antineoplastic agents between 2004 and 2013 were retrieved from Taiwan's National Health Insurance Research Database. The database contains information from a nationwide, mandatory-enrollment, single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled, and this system contracts with 97% of hospitals and clinics throughout the country. The National Health Insurance (NHI) covers a wide range of prescription medicines as well as inpatient and outpatient medical services.[15] NSCLC-related prescriptions were identified using the International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 162). Patients with small cell lung cancer were not included in this study, and patients who had used etoposide and

topotecan were excluded.

Drugs of interest

We used the Anatomical Therapeutic Chemical (ATC) classification system from the World Health Organization. We identified all antineoplastic agents using the ATC code "L01". Targeted therapies included in the analysis were monoclonal antibodies and protein kinase inhibitors (gefitinib and erlotinib). New targeted therapies (afatinib, crizotinib, and ceritinib) were not included in this study because they were not reimbursed by NHI before 2013.

Measurements

To examine the trends in the accessibility of the targeted therapies (gefitinib and erlotinib) following the changes in reimbursement policies, we calculated the monthly number of patients who used each targeted therapy and the related costs from 2004 to 2013. Then, we estimated the proportion of their use by patient number and the market share by cost among total patient numbers and total costs of all antineoplastic agents. The prescribing rate of the targeted therapies by patient number was estimated by using the number of patients who had used the targeted therapies divided by the number of patients who had used antineoplastic agents; the market share of targeted therapies by cost was estimated by using the cost of the targeted therapies divided by the cost of antineoplastic agents. The cost was adjusted using the yearly consumer price index (CPI).[16]

Statistical Analysis

The Interrupted Time Series design[17], a strong quasi-experimental method, was adopted to evaluate the overall changes in drug utilization (prescribing rate and market share of cost) before and after the four modifications to the drug reimbursement policy: (1) erlotinib was covered by NHI in June 2007; (2) gefitinib became available as a second-line treatment in November 2007; (3) erlotinib became available as a second-line treatment in June 2008, and (4) gefitinib became available for first-line treatment in June 2011. For average time to

prescription, we combined the previous three policy changes as one intervention due to the fact that their timing was similar. A segmented linear regression model was used to estimate post-policy changes in both the level and trend of these study outcomes.[18-21] Using baseline trends, we projected rates over time with the assumption that the baseline trend reflected what would have happened without the implementation of the promotion strategies. The basic model included terms to estimate the baseline level for each outcome (intercept), baseline trend (slope), changes in the level immediately after policy implementation, and changes in the trend after the policy change.[17,22] Our models also controlled for autocorrelation.[23] To identify the most parsimonious models, we used backward elimination and excluded non-significant terms (P>0.05). To summarize the results as a single metric, we estimated absolute and relative changes (with 95% confidence intervals, CI)[24] in outcomes 3 months following the interventions compared to projected rates. All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

Patient and Public Involvement

Patients were not involved in this study.

Results

Prescribing rate of targeted therapies by patient number

Table 1 presents the prescribing rate by patient number and the market share by cost of the targeted therapies over time. Overall, the number of patients who had used the targeted therapies (gefitinib and erlotinib) increased from 228 in 2004 to 8,542 in 2013, which accounted for 5.48% of patients who had used antineoplastic agents in 2004 and 58.52% who had used them in 2013. Among these, the number of patients who had used gefitinib increased from 228 (5.48% of patients who used antineoplastic agents) in 2004 to 5,558 (38.08%) in 2013; the number of patients who had used erlotinib increased from 499 (8.44%) in 2007 to 2,984 (20.44%) in 2013.

[Table 1]

Market share of targeted therapies by costs

During the 10-year study period, the estimated market share of targeted therapies by costs increased from US$573,515 in 2004 to US$57,165,899 in 2013, which accounted for 3.85% in 2004 and 62.38% in 2013 of the cost of antineoplastic agents. Among these, the cost of gefitinib increased from US$573,515 (3.85% of cost of antineoplastic agents) in 2004 to US$41,677,315 (45.48%) in 2013; the cost of erlotinib increased from US$2,694,918 (9.13%) in 2007 to US$15,488,583 (16.9%) in 2013.

Effects of multiple changes in reimbursement policies on the use of targeted therapies

Targeted therapies

The prescribing rate of targeted therapies remained steady after erlotinib was covered by NHI in June 2007 (Table 2). There was a relative increase of 15.58% in the prescribing rate of the targeted therapies 3 months after gefitinib became available as a second-line treatment in November 2007, while there was a relative reduction of 10.98% after erlotinib became available as a second-line treatment in June 2008. After gefitinib became available as a first line-treatment in June 2011, it rose relatively by 6.31%. Figure 1 (A) shows the prescribing rate of the targeted therapies by patient number over time.

The market share of targeted therapies by cost remained steady after erlotinib was covered by NHI in June 2007. Gefitinib became available as a second-line treatment in November 2007 and became available as a first line-treatment in June 2011. There was a relative decline of 4.33% in the market share of the targeted therapies by costs 3 months after erlotinib became available as a second- line treatment in June 2008.

[Table 2] [Figure 1]

Gefitinib

The prescribing rate of gefitinib decreased by 20.69% after erlotinib was covered by NHI in June 2007. It increased by 54.32%, decreased by 13.27%, and increased by 21.76% after gefitinib became available as a second-line treatment in November 2007; erlotinib became available as a second-line treatment in June 2008, and gefitinib became available as a first-line treatment in June 2011, respectively. Figure 1 (B) shows the prescribing rate of gefitinib by patient number over time.

There was a relative reduction of 6.59% in market share by cost for gefitinib after erlotinib was covered by NHI in June 2007. This did not change after gefitinib became available as a second-line treatment in November 2007, and erlotinib became a second-line treatment in June 2008. However, the market share by cost increased by 16.63% after gefitinib became available as a first-line treatment in June 2011.

Erlotinib

The prescribing rate of erlotinib declined relatively by 26.79% after gefitinib became available as a second line treatment in November 2007. It increased by 22.62% and decreased by 10.3% after erlotinib became available as a second line treatment in June 2008, and gefitinib became available as a first line treatment in June 2011, respectively. Figure 1 (C) shows the prescribing rate of erlotinib by patient number over time.

There was a relative reduction of 30.33% in market share by cost for erlotinib after gefitinib became available as a second line treatment in November 2007. It increased by 21.66% and decreased by 9.3% after erlotinib became available as a second line treatment in June 2008, and gefitinib became available as a first line treatment in June 2011, respectively.

Time to prescriptions of the targeted therapies

The average time to prescription of the targeted therapies are shown in Table 3, and the estimated changes in time to prescription following changes in the reimbursement policies are presented in Table 4. The average time to prescription of the targeted therapies rapidly

decreased from 802 days (S.D.=654.6) in 2004 to 43 days (S.D.=49.6) in 2013 (Table 3). It reduced by 65.84% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments in 2007 and 2008 and further decreased by 41.59% after gefitinib became available as a first line treatment in 2011 (Table 4). The average time to prescription of gefitinib decreased from 685 days (S.D.=587.4) in 2004 to 33 days (S.D.=33.7) in 2013 (Table 3). There was a relative growth of 39.82% in time to prescription for gefitinib after erlotinib was covered by NHI, and gefitinib/erlotinib became available as second line treatments, while there was a relative decline of 69.57% after gefitinib became a first line treatment (Table 4). The average time to prescription of erlotinib decreased from 1,602 days (S.D.=520.7) in 2004 to 129 days (S.D.=70.8) in 2013 (Table 3). It dropped substantially by 234.37% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments, but it did not change after gefitinib became available as a first line treatment (Table 4).

[Table 3] [Table 4]

Discussion

In this study, the large NHIRD database was taken advantage of to examine 2004-2013 (10 years) of the use of targeted therapies for NSCLC lung cancer. Using a strong quantitative research method (interrupted time series), our findings revealed changes in the accessibility of the targeted therapies, including the prescribing rate, prescription speed, and economic burden, following a series of reimbursement policy modifications.

It was found that four interventions had significant and diverse effects on gefitinib and erlotinib use. To understand the impacts of the drug reimbursement policy of “removing restriction of reimbursement and broadening eligible patient population”, the prescribing rate and prescription speed were used to represent the accessibility of drugs. The results made it possible to determine whether “removing restriction of reimbursement and broadening eligible patient population” actually allowed more patients to have access to the targeted

therapies.

In the case of gefitinib, the prescribing rate has steadily risen since it was first covered by NHI in 2004. Then, the coverage of erlotinib (as a third line) for NSCLC resulted in a drop in gefitinib by 20% (prescribing rate) and 6% (market share by expenditure). A few months later, when gefitinib became available as a second line treatment, this caused the greatest changes in gefitinib use (54.32% reduction). When erlotinib became available as a second-line treatment, gefitinib's use reduced by 13%. Then, gefitinib's prescribing rates and expenditures rose again (21% increase in prescribing rate, 17% in expenditures) when gefitinib became available as a first line treatment.

In the case of erlotinib, three changes in the reimbursement rules had significant effects on prescribing rates and market share by cost. Especially, after gefitinib became available as a second line treatment, the prescribing rate and market share of cost decreased by 27% and 30%, respectively. In addition, the previous rates of erlotinib reduced by 10% and 9%, respectively, after gefitinib became available as a first line treatment. On the other hand, when erlotinib became available as a second line treatment, approximately 23% and 22% increases in prescribing rates and market share by costs were observed, respectively.

The overall use of oral targeted therapies (gefitinib and erlotinib) did not rise following the introduction of erlotinib in June 2007. However, use significantly rose by 15% when gefitinib became available as a second-line treatment in November 2007, while it fell by 10% when erlotinib became available as a second-line treatment in June 2008. When gefitinib became available as a first-line treatment, the overall prescription ratio of oral targeted therapies only increased by 6%. On the other hand, the market share of cost of oral targeted therapies was only slightly diminished when erlotinib became available as a second-line treatment in June 2008, but it was not affected by other interventions. In general, these changes in the reimbursement rules were effective with regard to improving the accessibility of the targeted therapies.

As far as the speed of accessibility of the targeted therapies related to NSCLC treatment, average time to prescription for targeted therapies gradually reduced from 802 days in 2004

to 43 days in 2013. This means the changes in the reimbursement rules (removing restriction of reimbursement and broadening eligible patient population) markedly accelerated the accessibility of targeted therapies.

This study had several limitations. First, the study focused on the effects of removing restriction of reimbursement and broadening eligible patient population related to the accessibility of medicines. We used three indicators: prescribing rate, market share of cost, and time to prescription, as measurements of accessibility of medicine. Due to the lack of clinical test data in the Taiwan NHIRD claims database, this study was not able to identify patients' eligibility to obtain the targeted therapies based on clinical testing (such as pathology or cytological results, and EGFR-TK gene mutation test results, etc.). Secondly, this study analyzed data from the Taiwan NHIRD claims database that did not cover data for payments made by patients themselves. Hence, there may be differences between the estimated prescription rate / costs and the actual value. However, this gap is not believed to be very significant since the proportion of payments made by patients themselves was very small. Third, considering the timing of drug launches, during the study period (2004-2013), only two targeted therapies (gefitinib and erlotinib) could be included, and newer medicines were out of the scope of this study. Finally, this study was aimed toward an examination of the effects of removing restriction of reimbursement and broadening eligible patient population related to accessibility to the targeted therapies. Further studies about how such policies affect the clinical outcomes of treatments and the cost-effectiveness of the policies are needed in the future.

Conclusion

The present study examined how multiple reimbursement policies have changed accessibility, utilization, and clinical outcomes of targeted therapies. Overall, removing restriction of reimbursement and broadening eligible patient population for NSCLC targeted therapies improved the accessibility of such medications. In detail, when a targeted therapy became available for either early or broad use, it increased in terms of utilization but in turn

may have decreased the use of other drugs in a similar class. In addition, the targeted therapies were prescribed earlier once their insurance reimbursement restrictions were lifted. The results of this study can be used as the empirical basis for clinical treatment, to help enhance the content of academic literature on this subject, and can serve as the empirical basis for future targeted therapy studies.

■ Author Contributions

JCH and SCY conceptualized and designed the study. CFW collected data, performed analysis, and drafted the manuscript. JCH and SCY reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

■ Competing Interests

The authors have no competing interests.

■ Funding

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■ Data Sharing Statement

The authors have obtained nationwide, monthly claims data for NSCLC patients, from 2004 to 2013, from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements. No additional data available.

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Table 1. Prescription rate by patient number and market share by costs of targeted therapies over time (2004-2013)

	Prescription rate by patient number							Market share by costs						
	Number of patients who used antineoplastic agents	Number of patients who used gefitinib	(%)	Number of patients who used erlotinib	(%)	Number of patient who used targeted therapies (gefitinib + erlotinib)	(%)	Cost of antineoplastic agents (US$)	Cost of gefitinib (US$)	(%)	Cost of erlotinib (US$)	(%)	Cost of Targeted therapies (gefitinib + erlotinib) (US$)	(%)
2004	4,162	228	5.48	0	0.00	228	5.48	14,887,913	573,515	3.85	0	0.00	573,515	3.85
2005	4,876	872	17.88	0	0.00	872	17.88	22,446,991	8,015,889	35.71	0	0.00	8,015,889	35.71
2006	5,173	1095	21.17	0	0.00	1095	21.17	27,126,263	10,435,769	38.47	0	0.00	10,435,769	38.47
2007	5,909	1413	23.91	499	8.44	1912	32.36	29,531,282	12,265,156	41.53	2,694,918	9.13	14,960,074	50.66
2008	7,130	1975	27.70	1418	19.89	3393	47.59	43,162,957	18,784,869	43.52	11,190,711	25.93	29,975,581	69.45
2009	7,673	1922	25.05	2090	27.24	4012	52.29	48,988,605	17,276,102	35.27	18,099,806	36.95	35,375,908	72.21
2010	8,200	2058	25.10	2445	29.82	4503	54.91	51,384,668	16,242,224	31.61	20,207,860	39.33	36,450,084	70.94
2011	10,254	3440	33.55	2754	26.86	6194	60.41	58,115,193	20,942,858	36.04	19,298,723	33.21	40,241,581	69.24
2012	12,621	5011	39.70	3029	24.00	8040	63.70	76,127,283	36,628,520	48.11	17,785,455	23.36	54,413,975	71.48
2013	14,597	5558	38.08	2984	20.44	8542	58.52	91,642,044	41,677,315	45.48	15,488,583	16.90	57,165,899	62.38

Table 2. Estimated changes in targeted therapies utilization following changes in reimbursement policies using segmented regression models

	Changes of Drug Utilization																	
			Effects of intervention (1) erlotinib covered by NHI (third line) [200706]				Effects of intervention (2) gefitinib as second line treatment [200711]				Effects of intervention (3) erlotinib as second line treatment [200806]				Effects of intervention (4) gefitinib as first line treatment [201106]			
	Intercept	Baseline trend	Level change	Trend change	Absolute change (3 months later)	Relative change (3 months later)	Level change	Trend change	Absolute change (3 months later)	Relative change (3 months later)	Level change	Trend change	Absolute change (3 months later)	Relative change (3 months later)	Level change	Trend change	Absolute change (3 months later)	Relative change (3 months later)
Prescribing rate of targeted therapies	0.0342	0.0041 (0.0021, 0.0060)	--	--	--	--	--	0.0121 (0.0027, 0.0215)	3.63%	15.58%	--	-0.0140 (-0.0226, -0.0054)	-4.20%	-10.98%	0.0264 (0.0037, 0.0491)	--	2.64%	6.31%
Prescribing rate of gefitinib	0.0263	0.0042 (0.0017, 0.0067)	--	-0.0146 (-0.0268, -0.0024)	-4.38%	-20.69%	--	0.0210 (0.0048, 0.0372)	6.3%	54.32%	--	-0.0112 (-0.0211, -0.0013)	-3.36%	-13.27%	0.0215 (0.0026, 0.0404)	0.0072 (0.0032, 0.0113)	4.32%	21.76%
Prescribing rate of erlotinib	0.0099	0.0127 (0.0059, 0.0195)	NA	NA	NA	NA	--	-0.0100 (-0.0173, -0.0026)	-2.99%	-26.79%	0.0228 (0.0060, 0.0396)	--	2.28%	22.62%	--	-0.0076 (-0.0105, -0.0048)	-2.29%	-10.30%
Market share by cost for targeted therapies	0.0446	0.0068 (0.0045, 0.0091)	--	--	--	--	--	--	--	--	--	-0.0062 (-0.0095, -0.0028)	-1.85%	-4.33%	--	--	--	--
Market share by cost for gefitinib	0.1030	0.0043 (0.0014, 0.0072)	--	-0.0064 (-0.0106, -0.0023)	-1.93%	-6.59%	--	--	--	--	--	--	--	--	--	0.0095 (0.0052, 0.0137)	2.85%	16.63%

Market share by cost for erlotinib	0.0194	0.0202 (0.0113, 0.0291)	NA	NA	NA	NA	--	-0.0183 (-0.0278, -0.0088)	-5.49%	-30.33%	0.0302 (0.0077, 0.0527)	--	3.02%	21.66%	--	-0.0074 (-0.0108, -0.0040)	-2.21%	-9.30%

Table 3. Time to prescription of targeted therapies for non-small cell lung cancer treatment over time (2004-2013)

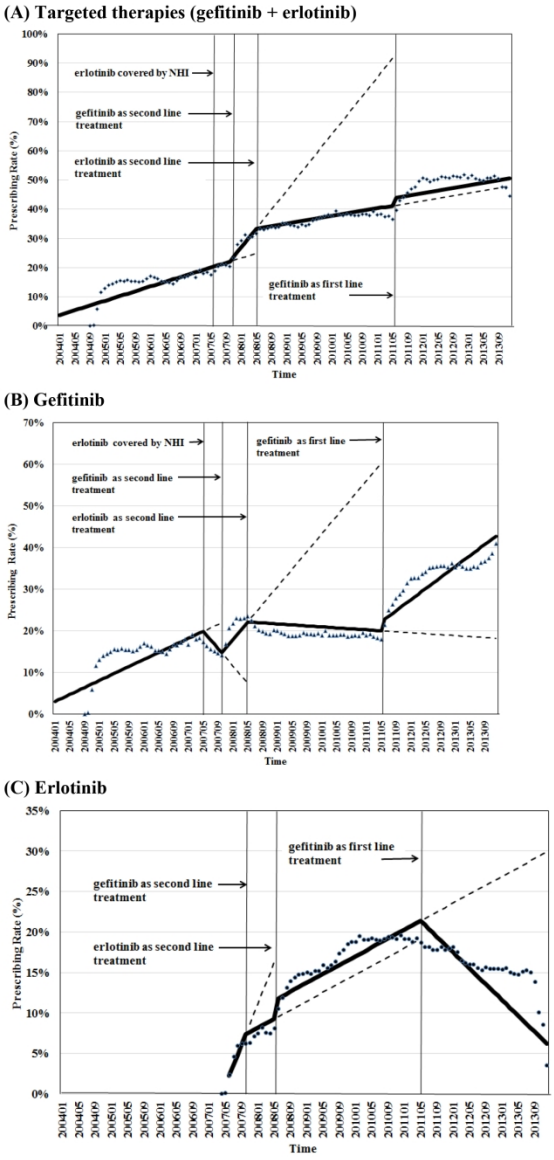
	Time to Prescription (days)					
	Targeted therapies (gefitinib + erlotinib)		Gefitinib		Erlotinib	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
2004	801.7	654.6	685.3	587.4	1,602.0	520.7
2005	683.4	546.2	570.0	497.4	1,128.7	500.4
2006	603.0	471.2	522.1	440.9	743.2	489.4
2007	457.6	397.7	402.4	394.6	524.2	391.4
2008	383.0	343.7	390.1	379.9	377.6	313.1
2009	369.3	315.7	382.1	340.7	359.2	294.2
2010	329.8	242.9	325.6	247.7	333.4	238.8
2011	207.2	207.0	137.9	182.4	313.5	197.2
2012	120.3	137.4	68.5	104.3	249.1	124.7
2013	43.0	49.6	32.5	33.7	128.9	70.8

Table 4. Estimated changes in average time to prescription for NSCLC targeted therapies following changes in reimbursement policies

			Impact of erlotinib covered by NHI and gefitinib/erlotinib as second line treatments in 2007 and 2008				Impact of gefitinib as first line treatment in 2011			
	Intercept	Baseline trend	Level change	Trend change	Absolute change (2 year later)	Relative change (2 year later)	Level change	Trend change	Absolute change (2 year later)	Relative change (2 year later)
Average Time to Prescription (days)										
Targeted Therapies (gefitinib+erlotinib)	922.5246	-116.0248 (-131.6088, -100.4408)	--	67.9176 (41.1362, 94.6990)	-9.20% (-9.65%, -8.75%)	-65.84% (-68.30%, -63.37%)	--	-45.3087 (-72.0901, -18.5273)	-90.62 (-144.18, -37.06)	-41.59% (-57.24%, -25.93%)
gefitinib	759.1598	-83.6959 (-100.3257, -67.0661)	--	51.1611 (23.5177, 78.8045)	102.3221 (47.0363, 157.6080)	39.82% (9.87%, 69.77%)	-182.0687 (-245.2401, -118.8973)	--	-182.0690 (-245.2390, -118.8990)	-69.57% (-81.08%, -58.07%)
erlotinib	1905.0000	-362.5991 (-404.6915, -320.5067)	--	316.5921 (260.7650, 372.4192)	633.1842 (521.5322, 744.8362)	-234.37% (-318.17%, -150.57%)	--	--	0.00%	0.00%

Figure Legends

Figure 1. Prescribing rate by patient number of targeted therapies over time: (A) targeted therapies (gefitinib + erlotinib), (B) gefitinib, (C) erlotinib.
Prescription rate of targeted therapies by patient number = number of patients who used targeted therapies / number of patients who used antineoplastic agents



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Title Page

Effects of Removing Reimbursement Restrictions on Targeted Therapy Accessibility for Non-small Cell Lung Cancer Treatment in Taiwan

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Abstract

Interventions: Targeted therapies have been proven to provide clinical benefits to patients with metastatic non-small cell lung cancer (NSCLC). Gefitinib was initially approved and reimbursed as a third-line therapy for advanced NSCLC patients by Taiwan National Health Insurance (TNHI) in 2004; subsequently it became a second-line (in 2007) and further a first-line (in 2011) therapy for EGFR mutation-positive, advanced NSCLC patients. Another targeted therapy, erlotinib, was initially approved as a third-line therapy in 2007, and it became second-line in 2008.

Objectives: This study is aimed toward an exploration of the impacts of the TNHI reimbursement policies (removing reimbursement restrictions) related to accessibility of targeted therapies.

Setting: We retrieved 2004-2013 claims data for all patients with lung cancer diagnoses from

the National Health Insurance Research Database.

Design and Outcome Measures: Using an interrupted time series design and a segmented regression, we estimated changes in the monthly prescribing rate by patient number and market shares by cost following each modification of the reimbursement policy for gefitinib and erlotinib for NSCLC treatment.

Results: The prescribing rate of the targeted therapies increased by 15.58%, decreased by 10.98%, and increased by 6.31% following the introduction of gefitinib as a second line treatment in 2007, erlotinib as a second line treatment in 2008, and gefitinib as as first line treatment in 2011, respectively. The average time to prescription reduced by 65.84% and 41.59% following coverage of erlotinib by insurance and gefitinib/erlotinib as second line treatments in 2007-2008 and following gefitinib as a first line treatment in 2011.

Conclusions: The changes in the reimbursement policies had significant impacts on the accessibility of targeted therapies for NSCLC treatment. Removing reimbursement restrictions will increase use of that specific drug but may decrease use of other drugs. These interventions also significantly accelerate the time to prescription of targeted therapies.

Keywords: *Lung cancer, Targeted therapies, Reimbursement policy, Interrupted time series*

Strengths and limitations of this study

- This study confirmed that removing reimbursement restrictions for targeted therapies successfully improved drug accessibility.
- In addition to improving the prescription rate, the speed (time to prescription) was also used to measure drug accessibility.
- An interrupted time series design, a strong quasi-experimental method, was applied.
- This study focused on two targeted therapies with similar clinical roles, and it was found that the policy also would tend to decrease use of other drugs.
- During the study period (2004-2013), only first-generation drugs were included, but newer drugs were not.

Manuscript

Effects of Removing Reimbursement Restrictions on Targeted Therapy Accessibility for Non-small Cell Lung Cancer Treatment in Taiwan

Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] In the United States, in 2011, approximately 221,130 new cases of lung cancer (14% of all cancer diagnoses) were predicted, out of which 156,940 deaths (27% of cancer deaths) were estimated to have been due to lung cancer.[2] In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 11,692 new cases of lung cancer (12% of all cancer diagnoses) and 8,587 deaths (20% of cancer deaths) were predicted to occur in Taiwan in 2012.[3] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[4-7]

Since 2004, oral targeted therapies for non-small cell lung cancer have been launched into the market for epidermal growth factor receptor (EGFR) mutation patients. The EGFR molecular targeted drugs (MTD), gefitinib and erlotinib, were firstly approved as third-line or second-line therapy for advanced NSCLC patients because of their therapeutic benefits, as suggested by randomized clinical trials.[8-10] The recent National Comprehensive Cancer Network guideline[11] further suggests MTD as first-line therapy for EGFR mutation-positive, advanced NSCLC patients based on cumulating evidence showing a significant association between mutated EGFR and the clinical benefits of MTD.[12-14] In the light of the rapid disease progression associated with advanced NSCLC, access to pharmaceutical innovations such as MTD on a timely basis is vital to patients with the right indications who need it.

According to "Directions for Drug Restricted Benefits for National Health Insurance," two targeted therapies, gefitinib and erlotinib, used for the treatment of lung cancer have been reimbursed in Taiwan since 2004 and 2007, respectively. When the reimbursement for

gefitinib by health insurance began in November 2004, considering the potential significant impact of its use on the health care drug expenditure budget, it was limited to use only in patients with NSCLC who had previously used platinum and docetaxel or paclitaxel chemotherapy, but who still partially progressed or metastasized (for the third line treatment). Later, clinical studies have confirmed that the efficacy and safety of gefitinib are better than those for chemotherapy drugs, and that clinical treatment guidelines are recommended for second-line treatment. To improve the accessibility of drugs and early use of new drugs, in November 2007, Taiwan National Health Insurance began to pay for gefitinib in patients who had previously used first-line platinum-containing chemotherapy, or patients who had received first-line chemotherapy at 70 years of age or older, but were still partially exacerbated or metastatic, as a second line treatment.[14,15] Finally, for those with EGFR mutation diagnosis, because clinical studies have confirmed that the efficacy of first-line therapy is better than that of posterior therapy, gefitinib has been further allowed to be used as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2011.[12,16,17]

Similarly, considering a limited health care budget, erlotinib has also been limited for use as a third line treatment since June 2007 to patients with NSCLC who had previously used platinum and docetaxel or had undergone paclitaxel chemotherapy, but had still partially progressed or metastasized. Until June 2008, Taiwan National Health Insurance began to pay for erlotinib for patients who had previously undergone first-line platinum-containing chemotherapy, or patients who had received first-line chemotherapy at 70 years of age or older, but were still partially exacerbated or metastatic, as a second line treatment.[18,19] Finally, for those with EGFR mutation diagnosis, because clinical studies have confirmed that the efficacy of first-line therapy is better than that of posterior therapy, it has been further allowed for use as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2013.[20-22]

Little is known about the impacts of changes in targeted therapy-related reimbursement policies (related to removing reimbursement restrictions and broadening the eligible patient

population) in Taiwan. The aim of our longitudinal analyses was to address this gap by examining the recent trends in utilization of and expenditures for targeted therapies (gefitinib and erlotinib) following changes in the reimbursement policy, which involve the accessibility and economic burden of drugs. Furthermore, we also evaluated the changes in time to prescription of NSCLC over time.

Method

Data sources

All monthly claims data, including prescription details and insurer spending, for antineoplastic agents between 2004 and 2013 were retrieved from Taiwan's National Health Insurance Research Database. The database contains information from a nationwide, mandatory-enrollment, single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled, and this system contracts with 97% of hospitals and clinics throughout the country. The National Health Insurance (NHI) covers a wide range of prescription medicines as well as inpatient and outpatient medical services.[23] NSCLC-related prescriptions were identified using the International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 162). Patients with small cell lung cancer were not included in this study, and patients who had used etoposide and topotecan were excluded.

Drugs of interest

We used the Anatomical Therapeutic Chemical (ATC) classification system from the World Health Organization. We identified all antineoplastic agents using the ATC code "L01." Targeted therapies included in the analysis were protein kinase inhibitors (gefitinib and erlotinib). New targeted therapies (afatinib, crizotinib, and ceritinib) were not included in this study because they were not reimbursed by NHI before 2013.

Measurements

To examine the trends in the accessibility of the targeted therapies (gefitinib and erlotinib) following the changes in reimbursement policies, we calculated the monthly number of patients who used each targeted therapy and the related costs from 2004 to 2013. Then, we estimated the proportion of their use by patient number and the market share by cost among total patient numbers and total costs of all antineoplastic agents. The prescribing rate of the targeted therapies by patient number was estimated by using the number of patients who had used the targeted therapies divided by the number of patients who had used antineoplastic agents, and the market share of targeted therapies by cost was estimated by using the cost of the targeted therapies divided by the cost of antineoplastic agents. The cost was adjusted using the yearly consumer price index (CPI).[24]

Statistical Analysis

The interrupted time series design[25], a strong quasi-experimental method, was adopted to evaluate the overall changes in drug utilization (prescribing rate and market share of cost) before and after the four modifications to the drug reimbursement policy: (1) erlotinib was covered by NHI in June 2007; (2) gefitinib became available as a second-line treatment in November 2007; (3) erlotinib became available as a second-line treatment in June 2008, and (4) gefitinib became available as a first-line treatment in June 2011. For average time to prescription, we combined the previous three policy changes as one intervention due to the fact that their timing was similar.

A segmented linear regression model was used to estimate post-policy changes in both the level and trend of these study outcomes.[26-29] Using baseline trends, we projected rates over time with the assumption that the baseline trend reflected what would have happened without the implementation of the promotion strategies. The basic model included terms to estimate the baseline level for each outcome (intercept), baseline trend (slope), changes in the level immediately after policy implementation, and changes in the trend after the policy change.[25,30] Our models also controlled for autocorrelation.[31] To identify the most

parsimonious models, we used backward elimination and excluded non-significant terms (P>0.05).

To summarize the results as a single metric, we expressed the policy intervention by using the relative difference between the actual value and the predicted value after the policy intervention, and we estimated the relative changes in the prescription rates and market shares (with 95% confidence intervals, CI)[32] in outcomes 3 months following the interventions compared to projected rates. We calculated the relative change by using this formula: "The relative changes = (actual value-predicted value) in outcomes 3 months following the interventions / predicted value in outcomes 3 months following the interventions."

In addition, we selected patients who had used the targeted therapies during the study period, and based on the time of newly diagnosed NSCLC, time to prescription was used to represent the length of time required before use of the targeted therapies (representing the speed of drug accessibility). We also calculated the average of the difference between diagnosis date and the date of first use of the targeted therapies for each year over time. The relative changes of the average time to prescription (with 95% confidence intervals, CI)[32] in outcomes 2 years following the interventions compared to projected rates were estimated. The relative changes were calculated using the following formula: "The relative changes = (actual value-predicted value) in outcomes 2 years following the interventions / predicted value in outcomes 2 years following the interventions." All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

Patient and Public Involvement

Patients were not involved in this study.

Results

Prescribing rate of targeted therapies by patient number

Table 1 presents the prescribing rate by patient number and the market share by cost of

the targeted therapies over time. Overall, the number of patients who had used the targeted therapies (gefitinib and erlotinib) increased from 228 in 2004 to 8,542 in 2013, which accounted for 5.48% of patients who had used antineoplastic agents in 2004 and 58.52% who had used them in 2013. Among these, the number of patients who had used gefitinib increased from 228 (5.48% of patients who used antineoplastic agents) in 2004 to 5,558 (38.08%) in 2013; the number of patients who had used erlotinib increased from 499 (8.44%) in 2007 to 2,984 (20.44%) in 2013.

[Table 1]

Market share of targeted therapies by cost

During the 10-year study period, the estimated market share of targeted therapies by cost increased from US$573,515 in 2004 to US$57,165,899 in 2013, which accounted for 3.85% in 2004 and 62.38% in 2013 of the cost of antineoplastic agents, respectively. Among these, the cost of gefitinib increased from US$573,515 (3.85% of cost of antineoplastic agents) in 2004 to US$41,677,315 (45.48%) in 2013; the cost of erlotinib increased from US$2,694,918 (9.13%) in 2007 to US$15,488,583 (16.9%) in 2013.

Effects of multiple changes in reimbursement policies on the use of targeted therapies

Targeted therapies

The prescribing rate of the targeted therapies remained steady after erlotinib was covered by NHI in June 2007 (Table 2). There was a relative increase of 15.58% in the prescribing rate of the targeted therapies 3 months after gefitinib became available as a second-line treatment in November 2007, while there was a relative reduction of 10.98% after erlotinib became available as a second-line treatment in June 2008. After gefitinib became available as a first line-treatment in June 2011, it's usage rose relatively by 6.31%. Figure 1 (A) shows the prescribing rate of the targeted therapies by patient number over time.

The market share of the targeted therapies by cost remained steady after erlotinib was

covered by NHI in June 2007. Gefitinib became available as a second-line treatment in November 2007 and became available as a first line-treatment in June 2011. There was a relative decline of 4.33% in the market share of the targeted therapies by cost 3 months after erlotinib became available as a second-line treatment in June 2008.

[Table 2] [Figure 1]

Gefitinib

The prescribing rate of gefitinib decreased by 20.69% after erlotinib was covered by NHI in June 2007. It increased by 54.32%, decreased by 13.27%, and increased by 21.76% after gefitinib became available as a second-line treatment in November 2007; erlotinib became available as a second-line treatment in June 2008, and gefitinib became available as a first-line treatment in June 2011, respectively. Figure 1 (B) shows the prescribing rate of gefitinib by patient number over time.

There was a relative reduction of 6.59% in market share by cost for gefitinib after erlotinib was covered by NHI in June 2007. This did not change after gefitinib became available as a second-line treatment in November 2007, and erlotinib became a second-line treatment in June 2008. However, the market share by cost increased by 16.63% after gefitinib became available as a first-line treatment in June 2011.

Erlotinib

The prescribing rate of erlotinib declined relatively by 26.79% after gefitinib became available as a second line treatment in November 2007. It increased by 22.62% and decreased by 10.3% after erlotinib became available as a second line treatment in June 2008, and gefitinib became available as a first line treatment in June 2011, respectively. Figure 1 (C) shows the prescribing rate of erlotinib by patient number over time.

There was a relative reduction of 30.33% in market share by cost for erlotinib after gefitinib became available as a second line treatment in November 2007. It increased by 21.66% and decreased by 9.3% after erlotinib became available as a second line treatment in

June 2008, and gefitinib became available as a first line treatment in June 2011, respectively.

Time to prescriptions of the targeted therapies

The average time to prescription of the targeted therapies is shown in Table 3, and the estimated changes in time to prescription following changes in the reimbursement policies are presented in Table 4. The average time to prescription of the targeted therapies rapidly decreased from 802 days (S.D.=654.6) in 2004 to 43 days (S.D.=49.6) in 2013 (Table 3) and reduced by 65.84% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments in 2007 and 2008 and further decreased by 41.59% after gefitinib became available as a first line treatment in 2011 (Table 4). The average time to prescription of gefitinib decreased from 685 days (S.D.=587.4) in 2004 to 33 days (S.D.=33.7) in 2013 (Table 3). There was a relative growth of 39.82% in time to prescription for gefitinib after erlotinib was covered by NHI, and gefitinib/erlotinib became available as second line treatments, while there was a relative decline of 69.57% after gefitinib became a first line treatment (Table 4). The average time to prescription of erlotinib decreased from 1,602 days (S.D.=520.7) in 2004 to 129 days (S.D.=70.8) in 2013 (Table 3). It dropped substantially by 234.37% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments, but it did not change after gefitinib became available as a first line treatment (Table 4).

[Table 3] [Table 4]

Discussion

In this study, the large NHIRD database was taken advantage of to examine 2004-2013 (10 years) of the use of targeted therapies for NSCLC lung cancer. Using a strong quantitative research method (an interrupted time series design), our findings revealed changes in the accessibility of the targeted therapies, including the prescribing rate, prescription speed, and economic burden, following a series of reimbursement policy

modifications.

It was found that four interventions had significant various effects on gefitinib and erlotinib use. To understand the impacts of the drug reimbursement policy of "removing reimbursement restrictions and broadening the eligible patient population," the prescribing rate and prescription speed were used to represent the accessibility of drugs. The results made it possible to determine whether "removing reimbursement restrictions and broadening the eligible patient population" actually allowed more patients to have access to the targeted therapies.

In the case of gefitinib, the prescribing rate has steadily risen since it was first covered by NHI in 2004. Then, the coverage of erlotinib (as a third line) for NSCLC resulted in a drop in gefitinib by 20% (prescribing rate) and 6% (market share by expenditure). A few months later, when gefitinib became available as a second line treatment, this caused the greatest changes in gefitinib use (a 54.32% reduction). When erlotinib became available as a second-line treatment, gefitinib's use reduced by 13%. Then, gefitinib's prescribing rates and expenditures rose again (a 21% increase in prescribing rate and a 17% increase in expenditures) when gefitinib became available as a first line treatment.

In the case of erlotinib, three changes in the reimbursement rules had significant effects on prescribing rates and market share by cost. Especially, after gefitinib became available as a second line treatment, the prescribing rate and market share of cost decreased by 27% and 30%, respectively. In addition, the previous rates of erlotinib reduced by 10% and 9%, respectively, after gefitinib became available as a first line treatment. On the other hand, when erlotinib became available as a second line treatment, approximately 23% and 22% increases in prescribing rates and market share by cost were observed, respectively.

The overall use of oral targeted therapies (gefitinib and erlotinib) did not rise following the introduction of erlotinib in June 2007. However, use significantly rose by 15% when gefitinib became available as a second-line treatment in November 2007, while it fell by 10% when erlotinib became available as a second-line treatment in June 2008. When gefitinib became available as a first-line treatment, the overall prescription rate of oral targeted

therapies only increased by 6%. On the other hand, the market share of cost of oral targeted therapies was only slightly diminished when erlotinib became available as a second-line treatment in June 2008, but it was not affected by other interventions. In general, these changes in the reimbursement rules were effective with regard to improving the accessibility of the targeted therapies.

As far as the speed of accessibility of the targeted therapies related to NSCLC treatment, the average time to prescription for targeted therapies gradually reduced from 802 days in 2004 to 43 days in 2013. This means the changes in the reimbursement rules (removing reimbursement restriction and broadening the eligible patient population) markedly accelerated the accessibility of the targeted therapies.

This study had several limitations. First, the study focused on the effects of removing reimbursement restrictions and broadening the eligible patient population related to the accessibility of medicines. We used three indicators: prescribing rate, market share of cost, and time to prescription, as measurements of accessibility of medicine. Due to the lack of clinical test data in the Taiwan NHIRD claims database, this study was not able to identify patients' eligibility to obtain the targeted therapies based on clinical testing (such as pathology or cytological results and EGFR-TK gene mutation test results, etc.). Secondly, in this study, data from the Taiwan NHIRD claims database was analyzed that did not cover data for payments made by the patients themselves. Hence, there may be differences between the estimated prescription rate / costs and the actual value. However, this gap is not believed to be very significant since the proportion of payments made by patients themselves was very small. Third, considering the timing of drug launches, during the study period (2004-2013), only two first-generation targeted therapies (gefitinib and erlotinib) could be included, and newer medicines were out of the scope of this study. Finally, this study was aimed toward an examination of the effects of removing reimbursement restrictions and broadening the eligible patient population related to accessibility to the targeted therapies. Further studies about how such policies affect the clinical outcomes of treatments and the cost-effectiveness of the policies are needed in the future.

Conclusion

The present study examined how multiple, separate changes in reimbursement policies have changed drug utilization and accessibility of the targeted therapies. Overall, removing reimbursement restrictions and broadening eligible the patient population for NSCLC targeted therapies improved the accessibility of such medications. In detail, when a targeted therapy became available for either early or broad use, utilization increased, but this may have in turn decreased the use of other drugs in a similar class. In addition, the targeted therapies were prescribed earlier once their insurance reimbursement restrictions were lifted. The results of this study can be used as the empirical basis for clinical treatment, to help enhance the content of academic literature on this subject, and can serve as the empirical basis for future targeted therapy studies.

■ Author Contributions

JCH and SCY conceptualized and designed the study. CFW collected data, performed analysis, and drafted the manuscript. JCH and SCY reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

■ Competing Interests

The authors have no competing interests.

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■ Data Sharing Statement

The authors have obtained nationwide, monthly claims data for NSCLC patients, from 2004 to 2013, from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements. No additional data available.

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Table 1. Prescription rate by patient number and market share by costs of targeted therapies over time (2004-2013)

	Prescription rate by patient number							Market share by costs						
	Number of patients who used antineoplastic agents	Number of patients who used gefitinib	(%)	Number of patients who used erlotinib	(%)	Number of patient who used targeted therapies (gefitinib + erlotinib)	(%)	Cost of antineoplastic agents (US$)	Cost of gefitinib (US$)	(%)	Cost of erlotinib (US$)	(%)	Cost of Targeted therapies (gefitinib + erlotinib) (US$)	(%)
2004	4,162	228	5.48	0	0.00	228	5.48	14,887,913	573,515	3.85	0	0.00	573,515	3.85
2005	4,876	872	17.88	0	0.00	872	17.88	22,446,991	8,015,889	35.71	0	0.00	8,015,889	35.71
2006	5,173	1095	21.17	0	0.00	1095	21.17	27,126,263	10,435,769	38.47	0	0.00	10,435,769	38.47
2007	5,909	1413	23.91	499	8.44	1912	32.36	29,531,282	12,265,156	41.53	2,694,918	9.13	14,960,074	50.66
2008	7,130	1975	27.70	1418	19.89	3393	47.59	43,162,957	18,784,869	43.52	11,190,711	25.93	29,975,581	69.45
2009	7,673	1922	25.05	2090	27.24	4012	52.29	48,988,605	17,276,102	35.27	18,099,806	36.95	35,375,908	72.21
2010	8,200	2058	25.10	2445	29.82	4503	54.91	51,384,668	16,242,224	31.61	20,207,860	39.33	36,450,084	70.94
2011	10,254	3440	33.55	2754	26.86	6194	60.41	58,115,193	20,942,858	36.04	19,298,723	33.21	40,241,581	69.24
2012	12,621	5011	39.70	3029	24.00	8040	63.70	76,127,283	36,628,520	48.11	17,785,455	23.36	54,413,975	71.48
2013	14,597	5558	38.08	2984	20.44	8542	58.52	91,642,044	41,677,315	45.48	15,488,583	16.90	57,165,899	62.38

Table 2. Estimated changes in targeted therapies utilization following changes in reimbursement policies using segmented regression models

			Effects of intervention (1) erlotinib covered by NHI (third line) [200706]			Effects of intervention (2) gefitinib became second line treatment [200711]			Effects of intervention (3) erlotinib became second line treatment [200806]			Effects of intervention (4) gefitinib became first line treatment [201106]		
	Intercept	Baseline trend	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)
Prescribing rate of targeted therapies	0.0342	0.0041 (0.0021, 0.0060)	NS	NS	NS	NS	0.0121 (0.0027, 0.0215)	15.58%	NS	-0.0140 (-0.0226, -0.0054)	-10.98%	0.0264 (0.0037, 0.0491)	NS	6.31%
Prescribing rate of gefitinib	0.0263	0.0042 (0.0017, 0.0067)	NS	-0.0146 (-0.0268, -0.0024)	-20.69%	NS	0.0210 (0.0048, 0.0372)	54.32%	NS	-0.0112 (-0.0211, -0.0013)	-13.27%	0.0215 (0.0026, 0.0404)	0.0072 (0.0032, 0.0113)	21.76%
Prescribing rate of erlotinib	0.0099	0.0127 (0.0059, 0.0195)	NA	NA	NA	NS	-0.0100 (-0.0173, -0.0026)	-26.79%	0.0228 (0.0060, 0.0396)	NS	22.62%	NS	-0.0076 (-0.0105, -0.0048)	-10.30%
Market share by cost for targeted therapies	0.0446	0.0068 (0.0045, 0.0091)	NS	NS	0	NS	NS	0	NS	-0.0062 (-0.0095, -0.0028)	-4.33%	NS	NS	0
Market share by cost for gefitinib	0.1030	0.0043 (0.0014,	NS	-0.0064 (-0.0106,	-6.59%	NS	NS	0	NS	NS	0	NS	0.0095 (0.0052,	16.63%

		0.0072)		-0.0023)								0.0137)		
Market share by cost for erlotinib	0.0194	0.0202 (0.0113, 0.0291)	NA	NA	NA	NS	-0.0183 (-0.0278, -0.0088)	-30.33%	0.0302 (0.0077, 0.0527)	NS	21.66%	NS	-0.0074 (-0.0108, -0.0040)	-9.30%

The relative changes = (actual value-predicted value) in outcomes 3 months following the interventions / predicted value in outcomes 3 months following the interventions

NS = not significant; NA=not available

Table 3. Time to prescription of targeted therapies for non-small cell lung cancer treatment over time (2004-2013)

	Time to Prescription (days)					
	Targeted therapies (gefitinib + erlotinib)		Gefitinib		Erlotinib	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
2004	801.7	654.6	685.3	587.4	1,602.0	520.7
2005	683.4	546.2	570.0	497.4	1,128.7	500.4
2006	603.0	471.2	522.1	440.9	743.2	489.4
2007	457.6	397.7	402.4	394.6	524.2	391.4
2008	383.0	343.7	390.1	379.9	377.6	313.1
2009	369.3	315.7	382.1	340.7	359.2	294.2
2010	329.8	242.9	325.6	247.7	333.4	238.8
2011	207.2	207.0	137.9	182.4	313.5	197.2
2012	120.3	137.4	68.5	104.3	249.1	124.7
2013	43.0	49.6	32.5	33.7	128.9	70.8

Table 4. Estimated changes in average time to prescription for NSCLC targeted therapies following changes in reimbursement policies

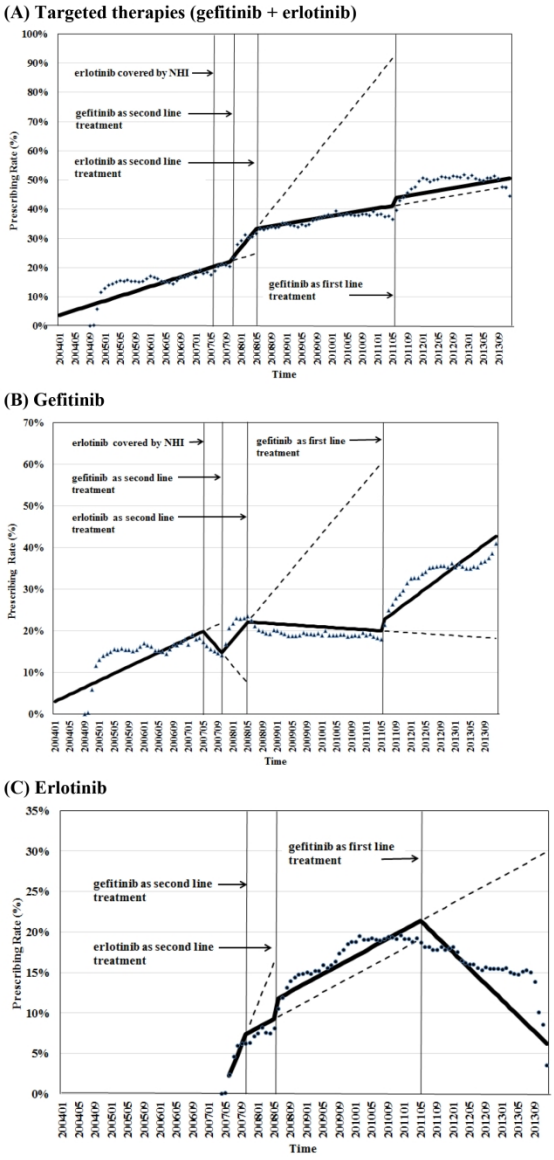
				Impact of erlotinib covered by NHI and gefitinib/erlotinib as second line treatments in 2007 and 2008			Impact of gefitinib as first line treatment in 2011		
		Intercept	Baseline trend	Level change	Trend change	Relative change (2 year later)	Level change	Trend change	Relative change (2 year later)
Average Time to Prescription (days)									
	Targeted Therapies (gefitinib+erlotinib)	922.5246	-116.0248 (-131.6088, -100.4408)	NS	67.9176 (41.1362, 94.6990)	-65.84% (-68.30%, -63.37%)	NS	-45.3087 (-72.0901, -18.5273)	-41.59% (-57.24%, -25.93%)
	gefitinib	759.1598	-83.6959 (-100.3257, -67.0661)	NS	51.1611 (23.5177, 78.8045)	39.82% (9.87%, 69.77%)	-182.0687 (-245.2401, -118.8973)	NS	-69.57% (-81.08%, -58.07%)
	erlotinib	1905.0000	-362.5991 (-404.6915, -320.5067)	NS	316.5921 (260.7650, 372.4192)	-234.37% (-318.17%, -150.57%)	NS	NS	0.00%
Survival Rate (%)									
	One year survival	0.4038	0.0173 (0.0151, 0.0195)	NS	NS	0.00%	NS	NS	0.00%
	Two year survival	0.2243	0.0186 (0.0164, 0.0208)	NS	NS	0.00%	NS	NS	0.00%

The relative changes = (actual value-predicted value) in outcomes 2 years following the interventions / predicted value in outcomes 2 years following the interventions

NS = not significant; NA=not available

Figure Legends

Figure 1. Prescribing rate by patient number of targeted therapies over time: (A) targeted therapies (gefitinib + erlotinib), (B) gefitinib, (C) erlotinib.
Prescription rate of targeted therapies by patient number = number of patients who used targeted therapies / number of patients who used antineoplastic agents



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Title Page

Effects of Removing Reimbursement Restrictions on Targeted Therapy Accessibility for Non-small Cell Lung Cancer Treatment in Taiwan: an Interrupted Time Series Study

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Abstract

Interventions: Targeted therapies have been proven to provide clinical benefits to patients with metastatic non-small cell lung cancer (NSCLC). Gefitinib was initially approved and reimbursed as a third-line therapy for advanced NSCLC patients by Taiwan National Health Insurance (TNHI) in 2004; subsequently it became a second-line (in 2007) and further a first-line (in 2011) therapy for EGFR mutation-positive, advanced NSCLC patients. Another targeted therapy, erlotinib, was initially approved as a third-line therapy in 2007, and it became second-line in 2008.

Objectives: This study is aimed toward an exploration of the impacts of the TNHI reimbursement policies (removing reimbursement restrictions) related to accessibility of targeted therapies.

Setting: We retrieved 2004-2013 claims data for all patients with lung cancer diagnoses from

the National Health Insurance Research Database.

Design and Outcome Measures: Using an interrupted time series design and a segmented regression, we estimated changes in the monthly prescribing rate by patient number and market shares by cost following each modification of the reimbursement policy for gefitinib and erlotinib for NSCLC treatment.

Results: Totally 92,220 patients with NSCLC were identified. The prescribing rate of the targeted therapies increased by 15.58%, decreased by 10.98%, and increased by 6.31% following the introduction of gefitinib as a second line treatment in 2007, erlotinib as a second line treatment in 2008, and gefitinib as as first line treatment in 2011, respectively. The average time to prescription reduced by 65.84% and 41.59% following coverage of erlotinib by insurance and gefitinib/erlotinib as second line treatments in 2007-2008 and following gefitinib as a first line treatment in 2011.

Conclusions: The changes in the reimbursement policies had significant impacts on the accessibility of targeted therapies for NSCLC treatment. Removing reimbursement restrictions can significantly increase the level and the speed of drug accessibility.

Keywords: *Lung cancer, Targeted therapies, Reimbursement policy, Interrupted time series*

Strengths and limitations of this study

- Both prescription rate and speed (time to prescription) was used to measure drug accessibility.
- An interrupted time series design, a strong quasi-experimental method, was applied.
- A segmented linear regression model was used to estimate post-policy changes in both the level and trend of these study outcomes.
- Data from the Taiwan NHIRD claims database was analyzed that did not cover data for payments made by the patients themselves.

Manuscript

Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] In the United States, in 2011, approximately 221,130 new cases of lung cancer (14% of all cancer diagnoses) were predicted, out of which 156,940 deaths (27% of cancer deaths) were estimated to have been due to lung cancer.[2] In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 11,692 new cases of lung cancer (12% of all cancer diagnoses) and 8,587 deaths (20% of cancer deaths) were predicted to occur in Taiwan in 2012.[3] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[4-7]

Since 2004, oral targeted therapies for non-small cell lung cancer (NSCLC) have been launched into the market for epidermal growth factor receptor (EGFR) mutation patients in Taiwan. Two targeted drugs, gefitinib and erlotinib, were firstly approved as third-line therapy for advanced NSCLC patients by Taiwan Food and Drug Administration, based on the results of randomized clinical trials.[8-10] For advanced NSCLC patients with EGFR mutation-positive, two drugs were furtherly suggested to be used as first-line therapy for them by the recent National Comprehensive Cancer Network guideline[11], according to the cumulating evidence showing a significant association between mutated EGFR and their clinical benefits[8,12-14]

According to "Directions for Drug Restricted Benefits for National Health Insurance," gefitinib and erlotinibfor the treatment of lung cancer have been reimbursed in Taiwan since 2004 and 2007, respectively. When the reimbursement for gefitinib by health insurance began in November 2004, considering the potential significant impact of its use on the health care drug expenditure budget, it was limited to use only in patients with NSCLC who had previously used platinum and docetaxel or paclitaxel chemotherapy, but who still partially progressed or metastasized (for the third line treatment). Later, clinical studies have confirmed that the efficacy and safety of gefitinib are better than those for chemotherapy drugs, and that clinical treatment guidelines are recommended for second-line treatment. To improve the

accessibility of drugs and early use of new drugs, in November 2007, Taiwan National Health Insurance began to pay for gefitinib in patients who had previously used first-line platinum-containing chemotherapy, or patients who had received first-line chemotherapy at 70 years of age or older, but were still partially exacerbated or metastatic, as a second line treatment.[14,15] Finally, for those with EGFR mutation diagnosis, because clinical studies have confirmed that the efficacy of first-line therapy is better than that of posterior therapy, gefitinib has been further allowed to be used as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2011.[12,16,17]Similarly, erlotinib has also been limited for use as a third line treatment since June 2007, it has been further allowed for use as a first-line therapy for EGFR mutation-positive advanced NSCLC patients since June 2013. [18-22]

Little is known about the impacts of changes in targeted therapy-related reimbursement policies (related to removing reimbursement restrictions and broadening the eligible patient population) in Taiwan. The aim of our longitudinal analyses was to address this gap by examining the recent trends in utilization of and expenditures for targeted therapies (gefitinib and erlotinib) following changes in the reimbursement policy, which involve the accessibility and economic burden of drugs. Furthermore, we also evaluated the changes in time to prescription of NSCLC over time.

Method

Data sources

All monthly claims data, including prescription details and insurer spending, for antineoplastic agents between 2004 and 2013 were retrieved from Taiwan's National Health Insurance Research Database (NHIRD). The database contains information from a nationwide, mandatory-enrollment, single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled, and this system contracts with 97% of hospitals and clinics throughout the country. The National Health Insurance (NHI) covers a wide range of prescription medicines as well as inpatient and outpatient medical

services.[23] NSCLC-related prescriptions were identified using the International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 162). Patients with small cell lung cancer were not included in this study, and patients who had used etoposide and topotecan were excluded.

Drugs of interest

We used the Anatomical Therapeutic Chemical (ATC) classification system from the World Health Organization. We identified all antineoplastic agents using the ATC code "L01." Targeted therapies included in the analysis were protein kinase inhibitors (gefitinib and erlotinib). New targeted therapies (afatinib, crizotinib, and ceritinib) were not included in this study because they were not reimbursed by NHI before 2013.

Measurements

To examine the trends in the accessibility of the targeted therapies (gefitinib and erlotinib) following the changes in reimbursement policies, we calculated the monthly number of patients who used each targeted therapy and the related costs from 2004 to 2013. Then, we estimated the proportion of their use by patient number and the market share by cost among total patient numbers and total costs of all antineoplastic agents. The prescribing rate of the targeted therapies by patient number was estimated by using the number of patients who had used the targeted therapies divided by the number of patients who had used antineoplastic agents, and the market share of targeted therapies by cost was estimated by using the cost of the targeted therapies divided by the cost of antineoplastic agents. The cost was adjusted using the yearly consumer price index (CPI).[24]

Statistical Analysis

The interrupted time series design[25], a strong quasi-experimental method, was adopted to evaluate the overall changes in drug utilization (prescribing rate and market share of cost) before and after the four modifications to the drug reimbursement policy: (1) erlotinib was

covered by NHI in June 2007; (2) gefitinib became available as a second-line treatment in November 2007; (3) erlotinib became available as a second-line treatment in June 2008, and (4) gefitinib became available as a first-line treatment in June 2011. For average time to prescription, we combined the previous three policy changes as one intervention due to the fact that their timing was similar.

A segmented linear regression model was used to estimate post-policy changes in both the level and trend of these study outcomes.[26-29] Using baseline trends, we projected rates over time with the assumption that the baseline trend reflected what would have happened without the implementation of the promotion strategies. The basic model included terms to estimate the baseline level for each outcome (intercept) (β_0), baseline trend (slope) (β_1), changes in the level immediately after policy implementation (β_2), and changes in the trend after the policy change (β_3) (see the following model).[25,30] Our models also controlled for autocorrelation.[31] To identify the most parsimonious models, we used backward elimination and excluded non-significant terms (P>0.05).

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\_after\_intervention_{t+} e_t$$ [25]

To summarize the results as a single metric, we expressed the policy intervention by using the relative difference between the actual value and the predicted value after the policy intervention, and we estimated the relative changes in the prescription rates and market shares (with 95% confidence intervals, CI)[32] in outcomes 3 months following the interventions compared to projected rates. We calculated the relative change by using this formula: "The relative changes = (actual value-predicted value) in outcomes 3 months following the interventions / predicted value in outcomes 3 months following the interventions."

In addition, we selected patients who had used the targeted therapies during the study period, and based on the time of newly diagnosed NSCLC, time to prescription was used to represent the length of time required before use of the targeted therapies (representing the speed of drug accessibility). We also calculated the average of the difference between diagnosis date and the date of first use of the targeted therapies for each year over time. The relative changes of the average time to prescription (with 95% confidence intervals, CI)[32] in

outcomes 2 years following the interventions compared to projected rates were estimated. The relative changes were calculated using the following formula: "The relative changes = (actual value-predicted value) in outcomes 2 years following the interventions / predicted value in outcomes 2 years following the interventions." All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

Patient and Public Involvement

Patients were not involved in this study.

Results

Prescribing rate of targeted therapies by patient number

Claims data about totally 92,220 patients with NSCLC were collected. Table 1 presents the prescribing rate by patient number and the market share by cost of the targeted therapies over time. Overall, the number of patients who had used the targeted therapies (gefitinib and erlotinib) increased from 228 in 2004 to 8,542 in 2013, which accounted for 5.48% of patients who had used antineoplastic agents in 2004 and 58.52% who had used them in 2013. Among these, the number of patients who had used gefitinib increased from 228 (5.48% of patients who used antineoplastic agents) in 2004 to 5,558 (38.08%) in 2013; the number of patients who had used erlotinib increased from 499 (8.44%) in 2007 to 2,984 (20.44%) in 2013.

[Table 1]

Market share of targeted therapies by cost

During the 10-year study period, the estimated market share of targeted therapies by cost increased from US$573,515 in 2004 to US$57,165,899 in 2013, which accounted for 3.85% in 2004 and 62.38% in 2013 of the cost of antineoplastic agents, respectively. Among these, the cost of gefitinib increased from US$573,515 (3.85% of cost of antineoplastic agents) in 2004 to US$41,677,315 (45.48%) in 2013; the cost of erlotinib increased from US$2,694,918

(9.13%) in 2007 to US$15,488,583 (16.9%) in 2013.

Effects of multiple changes in reimbursement policies on the use of targeted therapies

Targeted therapies

The prescribing rate of the targeted therapies remained steady after erlotinib was covered by NHI in June 2007 (Table 2). There was a relative increase of 15.58% in the prescribing rate of the targeted therapies 3 months after gefitinib became available as a second-line treatment in November 2007, while there was a relative reduction of 10.98% after erlotinib became available as a second-line treatment in June 2008. After gefitinib became available as a first line-treatment in June 2011, it's usage rose relatively by 6.31%. Figure 1 (A) shows the prescribing rate of the targeted therapies by patient number over time.

The market share of the targeted therapies by cost remained steady after erlotinib was covered by NHI in June 2007. Gefitinib became available as a second-line treatment in November 2007 and became available as a first line-treatment in June 2011. There was a relative decline of 4.33% in the market share of the targeted therapies by cost 3 months after erlotinib became available as a second-line treatment in June 2008.

[Table 2] [Figure 1]

Gefitinib

The prescribing rate of gefitinib decreased by 20.69% after erlotinib was covered by NHI in June 2007. It increased by 54.32%, decreased by 13.27%, and increased by 21.76% after gefitinib became available as a second-line treatment in November 2007; erlotinib became available as a second-line treatment in June 2008, and gefitinib became available as a first-line treatment in June 2011, respectively. Figure 1 (B) shows the prescribing rate of gefitinib by patient number over time.

There was a relative reduction of 6.59% in market share by cost for gefitinib after erlotinib was covered by NHI in June 2007. This did not change after gefitinib became available as a second-line treatment in November 2007, and erlotinib became a second-line

treatment in June 2008. However, the market share by cost increased by 16.63% after gefitinib became available as a first-line treatment in June 2011.

Erlotinib

The prescribing rate of erlotinib declined relatively by 26.79% after gefitinib became available as a second line treatment in November 2007. It increased by 22.62% and decreased by 10.3% after erlotinib became available as a second line treatment in June 2008, and gefitinib became available as a first line treatment in June 2011, respectively. Figure 1 (C) shows the prescribing rate of erlotinib by patient number over time.

There was a relative reduction of 30.33% in market share by cost for erlotinib after gefitinib became available as a second line treatment in November 2007. It increased by 21.66% and decreased by 9.3% after erlotinib became available as a second line treatment in June 2008, and gefitinib became available as a first line treatment in June 2011, respectively.

Time to prescriptions of the targeted therapies

The average time to prescription of the targeted therapies is shown in Table 3, and the estimated changes in time to prescription following changes in the reimbursement policies are presented in Table 4. The average time to prescription of the targeted therapies rapidly decreased from 802 days (S.D.=654.6) in 2004 to 43 days (S.D.=49.6) in 2013 (Table 3) and reduced by 65.84% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments in 2007 and 2008 and further decreased by 41.59% after gefitinib became available as a first line treatment in 2011 (Table 4). The average time to prescription of gefitinib decreased from 685 days (S.D.=587.4) in 2004 to 33 days (S.D.=33.7) in 2013 (Table 3). There was a relative growth of 39.82% in time to prescription for gefitinib after erlotinib was covered by NHI, and gefitinib/erlotinib became available as second line treatments, while there was a relative decline of 69.57% after gefitinib became a first line treatment (Table 4). The average time to prescription of erlotinib decreased from 1,602 days (S.D.=520.7) in 2004 to 129 days (S.D.=70.8) in 2013 (Table 3). It dropped substantially by

234.37% after erlotinib was covered by the NHI, and gefitinib/erlotinib became available as second line treatments, but it did not change after gefitinib became available as a first line treatment (Table 4).

[Table 3] [Table 4]

Discussion

The drug accessibility has become a favorite topic for analysis of drug utilization, especially the accessibility of expensive cancer target drugs is the most noticed.[33-35] Although some high-priced drugs have been approved for marketing, the reimbursement restriction from health insurance is an obstacle to drug accessibility.[36,37] In this study, the data from NHIRDwas used to examine the utilization of targeted therapies for NSCLC during 2004-2013 (10 years). Using a strong quantitative research method (an interrupted time series design), our findings revealed changes in the accessibility of the targeted therapies, including the prescribing rate, prescription speed, and economic burden, following a series of reimbursement policy modifications.

It was found that four interventions had significant various effects on gefitinib and erlotinib use. To understand the impacts of the drug reimbursement policy of "removing reimbursement restrictions and broadening the eligible patient population," the prescribing rate and prescription speed were used to represent the accessibility of drugs. The results made it possible to determine whether "removing reimbursement restrictions and broadening the eligible patient population" actually allowed more patients to have access to the targeted therapies.

In the case of gefitinib, the prescribing rate has steadily risen since it was first covered by NHI in 2004. Then, the coverage of erlotinib (as a third line) for NSCLC resulted in a drop in gefitinib by 20% (prescribing rate) and 6% (market share by expenditure). A few months later, when gefitinib became available as a second line treatment, this caused the greatest changes in gefitinib use (a 54.32% increase). When erlotinib became available as a second-line treatment, gefitinib's use reduced by 13%. Then, gefitinib's prescribing rates and

expenditures rose again (a 21% increase in prescribing rate and a 17% increase in expenditures) when gefitinib became available as a first line treatment.

In the case of erlotinib, three changes in the reimbursement rules had significant effects on prescribing rates and market share by cost. Especially, after gefitinib became available as a second line treatment, the prescribing rate and market share of cost decreased by 27% and 30%, respectively. In addition, the previous rates of erlotinib reduced by 10% and 9%, respectively, after gefitinib became available as a first line treatment. On the other hand, when erlotinib became available as a second line treatment, approximately 23% and 22% increases in prescribing rates and market share by cost were observed, respectively.

The overall use of oral targeted therapies (gefitinib and erlotinib) did not rise following the introduction of erlotinib in June 2007. However, use significantly rose by 15% when gefitinib became available as a second-line treatment in November 2007, while it fell by 10% when erlotinib became available as a second-line treatment in June 2008. When gefitinib became available as a first-line treatment, the overall prescription rate of oral targeted therapies only increased by 6%. On the other hand, the market share of cost of oral targeted therapies was only slightly diminished when erlotinib became available as a second-line treatment in June 2008, but it was not affected by other interventions. In general, these changes in the reimbursement rules were effective with regard to improving the accessibility of the targeted therapies.

As far as the speed of accessibility of the targeted therapies related to NSCLC treatment, the average time to prescription for targeted therapies gradually reduced from 802 days in 2004 to 43 days in 2013. This means the changes in the reimbursement rules (removing reimbursement restriction and broadening the eligible patient population) markedly accelerated the accessibility of the targeted therapies.

Past research indicates that the accessibility of a drug is related to the health insurance coverage proportion.[37,38] This study used targeted therapy's accessibility for NSCLC treatment as an example, it further proved that in health insurance, removing reimbursement restrictions can significantly increase the accessibility of drugs and the speed of accessibility

of drugs. Although the accessibility of drugs has increased through changes in health insurance policies, health care resource allocation and health inequalities between various cancer types or diseases are issues that need to be subsequently followed up.

This study had several limitations. First, the study focused on the effects of removing reimbursement restrictions and broadening the eligible patient population related to the accessibility of medicines. We used three indicators: prescribing rate, market share of cost, and time to prescription, as measurements of accessibility of medicine. Due to the lack of clinical test data in the Taiwan NHIRD claims database, this study was not able to identify patients' eligibility to obtain the targeted therapies based on clinical testing (such as pathology or cytological results and EGFR-TK gene mutation test results, etc.). Secondly, in this study, data from the Taiwan NHIRD claims database was analyzed that did not cover data for payments made by the patients themselves. Hence, there may be differences between the estimated prescription rate / costs and the actual value. However, this gap is not believed to be very significant since the proportion of payments made by patients themselves was very small. Third, considering the timing of drug launches, during the study period (2004-2013), only two first-generation targeted therapies (gefitinib and erlotinib) could be included, and newer medicines were out of the scope of this study. Finally, this study was aimed toward an examination of the effects of removing reimbursement restrictions and broadening the eligible patient population related to accessibility to the targeted therapies. Further studies about how such policies affect the clinical outcomes of treatments and the cost-effectiveness of the policies are needed in the future.

Conclusion

The present study examined how multiple, separate changes in reimbursement policies have changed drug utilization and accessibility of the targeted therapies. Overall, removing reimbursement restrictions and broadening eligible the patient population for NSCLC targeted therapies improved the accessibility of such medications. In detail, when a targeted therapy became available for either early or broad use, utilization increased, but this may

have in turn decreased the use of other drugs in a similar class. In addition, the targeted therapies were prescribed faster once their insurance reimbursement restrictions were lifted. The results of this study can be used as the empirical basis for clinical treatment, to help enhance the content of academic literature on this subject, and can serve as the empirical basis for future targeted therapy studies.

■ Author Contributions

JCH and SCY conceptualized and designed the study. CFW collected data, performed analysis, and drafted the manuscript. JCH and SCY reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

■ Competing Interests

The authors have no competing interests.

■ Funding

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■ Data Sharing Statement

The authors have obtained nationwide, monthly claims data for NSCLC patients, from 2004 to 2013, from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements. No additional data available.

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Table 1. Prescription rate by patient number and market share by costs of targeted therapies over time (2004-2013)

	Prescription rate by patient number							Market share by costs						
	Number of patients who used antineoplastic agents	Number of patients who used gefitinib	(%)	Number of patients who used erlotinib	(%)	Number of patient who used targeted therapies (gefitinib + erlotinib)	(%)	Cost of antineoplastic agents (US$)	Cost of gefitinib (US$)	(%)	Cost of erlotinib (US$)	(%)	Cost of Targeted therapies (gefitinib + erlotinib) (US$)	(%)
2004	4,162	228	5.48	0	0.00	228	5.48	14,887,913	573,515	3.85	0	0.00	573,515	3.85
2005	4,876	872	17.88	0	0.00	872	17.88	22,446,991	8,015,889	35.71	0	0.00	8,015,889	35.71
2006	5,173	1095	21.17	0	0.00	1095	21.17	27,126,263	10,435,769	38.47	0	0.00	10,435,769	38.47
2007	5,909	1413	23.91	499	8.44	1912	32.36	29,531,282	12,265,156	41.53	2,694,918	9.13	14,960,074	50.66
2008	7,130	1975	27.70	1418	19.89	3393	47.59	43,162,957	18,784,869	43.52	11,190,711	25.93	29,975,581	69.45
2009	7,673	1922	25.05	2090	27.24	4012	52.29	48,988,605	17,276,102	35.27	18,099,806	36.95	35,375,908	72.21
2010	8,200	2058	25.10	2445	29.82	4503	54.91	51,384,668	16,242,224	31.61	20,207,860	39.33	36,450,084	70.94
2011	10,254	3440	33.55	2754	26.86	6194	60.41	58,115,193	20,942,858	36.04	19,298,723	33.21	40,241,581	69.24
2012	12,621	5011	39.70	3029	24.00	8040	63.70	76,127,283	36,628,520	48.11	17,785,455	23.36	54,413,975	71.48
2013	14,597	5558	38.08	2984	20.44	8542	58.52	91,642,044	41,677,315	45.48	15,488,583	16.90	57,165,899	62.38

Table 2. Estimated changes in targeted therapies utilization following changes in reimbursement policies using segmented regression models

			Effects of intervention (1) erlotinib covered by NHI (third line) [200706]			Effects of intervention (2) gefitinib became second line treatment [200711]			Effects of intervention (3) erlotinib became second line treatment [200806]			Effects of intervention (4) gefitinib became first line treatment [201106]		
	Intercept	Baseline trend	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)	Level change	Trend change	Relative change (3 months later)
Prescribing rate of targeted therapies	0.0342	0.0041 (0.0021, 0.0060)	NS	NS	NS	NS	0.0121 (0.0027, 0.0215)	15.58%	NS	-0.0140 (-0.0226, -0.0054)	-10.98%	0.0264 (0.0037, 0.0491)	NS	6.31%
Prescribing rate of gefitinib	0.0263	0.0042 (0.0017, 0.0067)	NS	-0.0146 (-0.0268, -0.0024)	-20.69%	NS	0.0210 (0.0048, 0.0372)	54.32%	NS	-0.0112 (-0.0211, -0.0013)	-13.27%	0.0215 (0.0026, 0.0404)	0.0072 (0.0032, 0.0113)	21.76%
Prescribing rate of erlotinib	0.0099	0.0127 (0.0059, 0.0195)	NA	NA	NA	NS	-0.0100 (-0.0173, -0.0026)	-26.79%	0.0228 (0.0060, 0.0396)	NS	22.62%	NS	-0.0076 (-0.0105, -0.0048)	-10.30%
Market share by cost for targeted therapies	0.0446	0.0068 (0.0045, 0.0091)	NS	NS	0	NS	NS	0	NS	-0.0062 (-0.0095, -0.0028)	-4.33%	NS	NS	0
Market share by cost for gefitinib	0.1030	0.0043 (0.0014,	NS	-0.0064 (-0.0106,	-6.59%	NS	NS	0	NS	NS	0	NS	0.0095 (0.0052,	16.63%

		0.0072)		-0.0023)									0.0137)	
Market share by cost for erlotinib	0.0194	0.0202 (0.0113, 0.0291)	NA	NA	NA	NS	-0.0183 (-0.0278, -0.0088)	-30.33%	0.0302 (0.0077, 0.0527)	NS	21.66%	NS	-0.0074 (-0.0108, -0.0040)	-9.30%

The relative changes = (actual value-predicted value) in outcomes 3 months following the interventions / predicted value in outcomes 3 months following the interventions

NS = not significant; NA=not available

Table 3. Time to prescription of targeted therapies for non-small cell lung cancer treatment over time (2004-2013)

	Time to Prescription (days)					
	Targeted therapies (gefitinib + erlotinib)		Gefitinib		Erlotinib	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
2004	801.7	654.6	685.3	587.4	1,602.0	520.7
2005	683.4	546.2	570.0	497.4	1,128.7	500.4
2006	603.0	471.2	522.1	440.9	743.2	489.4
2007	457.6	397.7	402.4	394.6	524.2	391.4
2008	383.0	343.7	390.1	379.9	377.6	313.1
2009	369.3	315.7	382.1	340.7	359.2	294.2
2010	329.8	242.9	325.6	247.7	333.4	238.8
2011	207.2	207.0	137.9	182.4	313.5	197.2
2012	120.3	137.4	68.5	104.3	249.1	124.7
2013	43.0	49.6	32.5	33.7	128.9	70.8

Table 4. Estimated changes in average time to prescription for NSCLC targeted therapies following changes in reimbursement policies

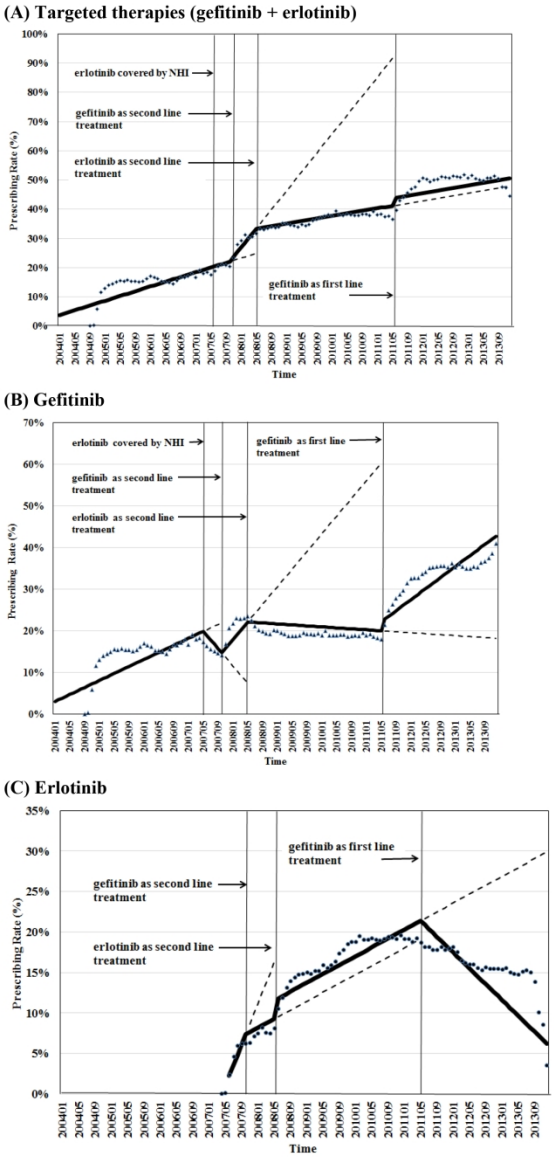
				Impact of erlotinib covered by NHI and gefitinib/erlotinib as second line treatments in 2007 and 2008			Impact of gefitinib as first line treatment in 2011		
		Intercept	Baseline trend	Level change	Trend change	Relative change (2 year later)	Level change	Trend change	Relative change (2 year later)
Average Time to Prescription (days)									
	Targeted Therapies (gefitinib+erlotinib)	922.5246	-116.0248 (-131.6088, -100.4408)	NS	67.9176 (41.1362, 94.6990)	-65.84% (-68.30%, -63.37%)	NS	-45.3087 (-72.0901, -18.5273)	-41.59% (-57.24%, -25.93%)
	gefitinib	759.1598	-83.6959 (-100.3257, -67.0661)	NS	51.1611 (23.5177, 78.8045)	39.82% (9.87%, 69.77%)	-182.0687 (-245.2401, -118.8973)	NS	-69.57% (-81.08%, -58.07%)
	erlotinib	1905.0000	-362.5991 (-404.6915, -320.5067)	NS	316.5921 (260.7650, 372.4192)	-234.37% (-318.17%, -150.57%)	NS	NS	0.00%

The relative changes = (actual value-predicted value) in outcomes 2 years following the interventions / predicted value in outcomes 2 years following the interventions

NS = not significant; NA=not available

Figure Legends

Figure 1. Prescribing rate by patient number of targeted therapies over time: (A) targeted therapies (gefitinib + erlotinib), (B) gefitinib, (C) erlotinib.
Prescription rate of targeted therapies by patient number = number of patients who used targeted therapies / number of patients who used antineoplastic agents



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Prescription rate of targeted therapies by patient number = number of patients who used targeted therapies / number of patients who used antineoplastic agents

134x272mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

Page		Item No	Recommendation
1-2	**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
1-2			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
3-4	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
4	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
4-5	Study design	4	Present key elements of study design early in the paper
4-5	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
4-5	Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
NA			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
5	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
4-5	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
5-7	Bias	9	Describe any efforts to address potential sources of bias
7	Study size	10	Explain how the study size was arrived at
5-7	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
5-7	Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
5-7			(*b*) Describe any methods used to examine subgroups and interactions
5-7			(*c*) Explain how missing data were addressed
5-7			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
NA			(*e*) Describe any sensitivity analyses

Continued on next page

	Results		
7	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
5			(b) Give reasons for non-participation at each stage
NA			(c) Consider use of a flow diagram
7-9	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
7			(b) Indicate number of participants with missing data for each variable of interest
7-9			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
NA	Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
NA			*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
9-10			*Cross-sectional study*—Report numbers of outcome events or summary measures
7-10	Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
NA			(*b*) Report category boundaries when continuous variables were categorized
NA			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
NA	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
10-12	Key results	18	Summarise key results with reference to study objectives
12	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
10-12	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
10-13	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
13	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.