PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Removing Reimbursement Restrictions on Targeted Therapy Accessibility for Non-small Cell Lung Cancer Treatment in Taiwan: an Interrupted Time Series Study
AUTHORS	Hsu, Jason C.; Wei, Chen-Fang; Yang, Szu-Chun

VERSION 1 - REVIEW

REVIEWER	Chulaporn Limwattananon Faculty of Pharmaceutical Sciences, Khon Kaen University. Thailand
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	General comments The paper used an a quasi-experiment design with quite a lengthy (10 years) time series and appropriate statistical analysis, however, its text and tone have not been carefully crafted and given an insightful thoughts. First, there was lack of policy context and detailed description on the rationale for the three-time (2007, 2008 and 2011) removals of the restricted reimbursement. The authors missed the true meanings of strengths and limitations of the study when they summarized five bullets of these issues. Abstract Conclusions: Page 4, lines 9-11: that “but might decrease another drug’s use” was not evident in the study findings. It was unclear whether ‘another drug’ was chemotherapy or erlotinib. Substitution of chemotherapy with targeted therapy was not examined in the present study. That erlotinib was substituted by gefitinib was unlikely since once gefitinib was shifted up to the second line in 2008 then erlotinib followed on (as the third line in the beginning and as the second line afterwards). Methods Drugs of interest Page 6, line 13: There were no monoclonal antibodies in the analysis. This is mistakenly stated. Measurements Page 6, lines 32-33: Even though estimation of the prescription rate and market share was elaborated, there was no explanation on the measures of key policy effects in terms of absolute change and relative change. The operational definitions and ways to calculate time to prescription were not explained. Results Reduction in time to prescriptions was due to the policy’s permission to use target therapy at an earlier time period without a

	pre-requisite for failure to chemotherapy. To demonstrate an increase in patient access, the paper should tease out if the use of target therapy increased without substitution for chemotherapy or this was just simply therapeutic substitution, of which chemotherapy decreased over time. Tables 2 and 4: A derivation of and connection between four types of changes (in levels, trends, absolute and relative), were unclear since there were no explanations in the Method. It is a burden for readers to figure out the time units for changes (per month in Table 2 or per year in Table 4) and the measure units of changes (as %, percentage points, days) because they were not described in the Table footnotes. It is redundant to present the absolute change which was not mentioned in the main text. In fact, the absolute change is merely a simple sum between changes in levels and changes in trends, then multiplied by number of months (in Table 2) or years (in Table 4). The absolute change in Table 4, column 6 'Impact of erlotinib' for targeted therapies (rows 1-3) was totally wrong (it should be presented as days rather than %). The four decimal points for 'days' were not in a standard format. Conclusion Page 12, line 48: the word 'multiple policies' is unclear if it implied 'multi-faceted' policies or multiple, separated times of policy changes. Page 12, line 50: It was over claimed to conclude that the policies have changed 'clinical outcomes', which were neither the study objective nor measured in the present study.

REVIEWER	Chen, Chung-Yu National Taiwan University Hospital Yunlin Branch, Taiwan
REVIEW RETURNED	05-Aug-2018

GENERAL COMMENTS	This study examined that multiple reimbursement policies have changed the utilization of targeted therapies in Taiwan. However, first-line target therapy including afatinib, erlotinib and gefitinib had became an standard treatment in NSCLC with EGFR mutation. EGFR-TKI in second-line or further treatment has seldom prescribed. Therefore, the better study should analysis the prescribing habit in clinic and change of market sharing among these target agents in NSCLC first-line treatment. Finally, this manuscript may submit to the journal as market economy.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

General comments

1. The paper used an a quasi-experiment design with quite a lengthy (10 years) time series and appropriate statistical analysis, however, its text and tone have not been carefully crafted and given

an insightful thoughts. First, there was lack of policy context and detailed description on the rationale for the three-time (2007, 2008 and 2011) removals of the restricted reimbursement.

We appreciate the reviewer's comments and suggestions. The study now includes a description of the policy decision scenarios and reasons for removing reimbursement restrictions for targeted therapies, including information regarding the results of clinical studies, recommendations for clinical treatment guidelines, and the motivations and expectations for the policy interventions.

"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.1,2 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 2011.3-5" (in Introduction section, para 3)

"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.6,7 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 2013.8-10 "(in Introduction section, para 4)

2. The authors missed the true meanings of strengths and limitations of the study when they summarized five bullets of these issues.

We rethought the strengths and limitations of this study and rewrote the five bullets of these issues as follows (in Title page):

 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.

Abstract, Conclusions

3. Page 4, lines 9-11: that “but might decrease another drug’s use” was not evident in the study findings. It was unclear whether ‘another drug’ was chemotherapy or erlotinib. Substitution of chemotherapy with targeted therapy was not examined in the present study. That erlotinib was substituted by gefitinib was unlikely since once gefitinib was shifted up to the second line in 2008 then erlotinib followed on (as the third line in the beginning and as the second line afterwards).

It refers to another drug that was released between gefitinib and erlotinib. For clarity, we replaced "another drug" with "the other."

When a drug's reimbursement restriction is removed, and it is permitted for use from the third line treatment to the second line treatment, this means that the drug can be used after the second line (including the second line, the third line, etc.)

Therefore, in 2008, gefitinib was permitted for use as the second or third line, and erlotinib could only be used as the third line at that time. Therefore, following the use of traditional chemotherapy as the first line treatment, erlotinib could be used as the second line, and basically gefitinib could still be used later on.

This study did not address the issue of switching or substitution between drugs, but since all treatments in this study were divided into traditional chemotherapeutic drugs and targeted therapies, the patients were also divided into only traditional chemotherapy users and targeted therapy users. The prescription rate of chemotherapies (targeted therapies) = 1 - the prescription rate of targeted therapies (chemotherapies). Therefore, there was an effect of the mutual substitution between targeted therapies and chemotherapies.

Methods

4. Drugs of interest

Page 6, line 13: There were no monoclonal antibodies in the analysis. This is mistakenly stated.

Measurements

Thanks for this correction. We removed the phrase "monoclonal antibodies."

5. Page 6, lines 32-33: Even though estimation of the prescription rate and market share was elaborated, there was no explanation on the measures of key policy effects in terms of absolute change and relative change. The operational definitions and ways to calculate time to prescription were not explained.

Thanks for this valuable suggestion. In this study, changes in the prescription rate and market share were used as indicators of the impacts of policy interventions on drug accessibility. First, we used the trend of these indicators before the policy intervention to predict the indicator after the policy intervention, and then we expressed the policy intervention by using the relative difference between the actual value and the predicted value after the policy intervention [The impacts = (actual value-predicted value) / predicted value]

“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)11 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 Method section, Statistical Analysis, para 3)

“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)11 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).” (in Method section, Statistical Analysis, para 4)

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. We added the description about the way to calculate time to prescription in Method section.

Results

6. Reduction in time to prescriptions was due to the policy’s permission to use target therapy at an earlier time period without a pre-requisite for failure to chemotherapy. To demonstrate an increase in patient access, the paper should tease out if the use of target therapy increased without substitution for chemotherapy or this was just simply therapeutic substitution, of which chemotherapy decreased over time.

We fully agree with the reviewer’s point of view regarding the sentence “Reduction in time to prescriptions was due to the policy’s permission to use target therapy at an earlier time period without a pre-requisite for failure of chemotherapy.”

In terms of the use of traditional chemotherapies before and after policy intervention, since the study defined patients as either targeted therapy users or chemotherapy users, the prescribing rate of the targeted therapies (chemotherapies) by patient number was estimated by using the number of patients who had used the targeted therapies (chemotherapies) divided by the number of patients who had used antineoplastic agents (targeted therapies and chemotherapies). That is, the prescription rate of the chemotherapy drug = 1 - the prescription rate of the targeted therapies. According to Figure 1 (A), the prescription rate of the targeted therapies increased with the policy intervention; in other words, the prescription ratio of the chemotherapies decreased with the policy intervention.

7. Tables 2 and 4: A derivation of and connection between four types of changes (in levels, trends, absolute and relative), were unclear since there were no explanations in the Method. It is a burden for readers to figure out the time units for changes (per month in Table 2 or per year in Table 4) and the measure units of changes (as %, percentage points, days) because they were not described in the Table footnotes.

As mentioned above, we added the following notes in tables 2 and 4. First, we used the trend of the above indicators before the policy intervention to predict the indicator after the policy intervention, and then expressed the policy intervention by using the relative difference between the actual value and the predicted value after the policy intervention [The impacts = (actual value-predicted value) / predicted value]

“The relative changes = (actual value-predicted value) in outcomes 3 months following the interventions / predicted value in outcomes 3 months following the interventions” (in Table 2)

“The relative changes = (actual value-predicted value) in outcomes 2 years following the interventions / predicted value in outcomes 2 years following the interventions” (in Table 4)

8. It is redundant to present the absolute change which was not mentioned in the main text. In fact, the absolute change is merely a simple sum between changes in levels and changes in trends, then multiplied by number of months (in Table 2) or years (in Table 4). The absolute change in Table 4, column 6 ‘Impact of erlotinib’ for targeted therapies (rows 1-3) was totally wrong (it should be presented as days rather than %). The four decimal points for ‘days’ were not in a standard format.

We agree with the committee's suggestion, and we removed “absolute change” from tables 2 and 4. In addition, for consistency, we used four decimal points for “days” everywhere in the Table 2 and 4.

Conclusion

9. Page 12, line 48: the word ‘multiple policies’ is unclear if it implied ‘multi-faceted’ policies or multiple, separated times of policy changes.

We replaced the phrase “multiple reimbursement policies” with “multiple, separated times of reimbursement policy changes.”

“The present study examined how multiple, separate changes in reimbursement policies have changed drug utilization and accessibility of the targeted therapies.” (in Conclusion section)

10. Page 12, line 50: It was over claimed to conclude that the policies have changed ‘clinical outcomes’, which were neither the study objective nor measured in the present study.

Following the reviewer’s suggestion, we removed the phrase “clinical outcomes” from the manuscript.

“The present study examined how multiple, separate changes in reimbursement policies have changed drug utilization and accessibility of the targeted therapies.” (in Conclusion section)

Reviewer #2:

This study examined that multiple reimbursement policies have changed the utilization of targeted therapies in Taiwan. However, first-line target therapy including afatinib, erlotinib and gefitinib had became an standard treatment in NSCLC with EGFR mutation. EGFR-TKI in second-line or further treatment has seldom prescribed. Therefore, the better study should analysis the prescribing habit in clinic and change of market sharing among these target agents in NSCLC first-line treatment. Finally, this manuscript may submit to the journal as market economy.

Many thanks for the reviewer’s valuable recommendation. We agree with the reviewer’s opinions. According to the current clinical treatment guidelines, the first-generation target therapies for non-small cell lung cancer (gefitinib and erlotinib) are recommended for use in the first line, and presently, they are being reimbursed by the National Health Insurance in Taiwan. After 2014 (beyond this study period), afatinib and osimertinib were also approved by Taiwan FDA and have also been used as the first line treatment. Specifically, afatinib is also being reimbursed by the Taiwan National Health Insurance. For manufacturers, understanding the trends in the market share of these target therapies for first-line use is indeed a topic worth exploring, and it is worth publishing in commercial or market economic journals.

However, this study was not done purely from a business perspective but was rather based on academic and historical perspectives. The focus of this study was to review the impacts of the removal of restrictions for reimbursement for targeted therapies using the first generation of targeted therapies (gefitinib and erlotinib) for non-small cell lung cancer as an example. Among them, gefitinib could be reimbursed by health insurance in 2004 (limited to the third line). In 2007 and 2011, reimbursement began for both second line and the first line use, respectively. On the other hand, reimbursement for erlotinib by health insurance began in 2007, and the third and second line uses have been reimbursed since 2008 and 2013, respectively.

Furthermore, two ways to explore the changes in "drug accessibility" were used in this study. The first measurement was the "level" of drug accessibility, which was defined as the proportion of target therapies used for patients with NSCLC (prescription rate = number of people using the target therapies / number of people using the target therapies or only chemotherapy drugs). The second measurement was the "speed" of drug accessibility, which was defined as the interval between the date of diagnosis and the date of first use of the target therapies for newly diagnosed yearly patients. The concept of "drug accessibility" is defined as the proportion and speed of the drug accessibility actually used in a group of patients eligible for the drug. Even if limitations related to use of the all targeted therapies have been removed, and first line use is being reimbursed, the targeted therapies can also be used and reimbursed for any line of treatment. Therefore, we feel that there is no need to distinguish the timing of drug use for a drug accessibility study.

The change in health care payment restrictions is based on multiple aspects of drug efficacy and safety information, clinical treatment consensus, cost-effectiveness, and budget. Nowadays, considering the above factors, all targeted therapies are currently recommended and are reimbursed for first-line treatment use, but if we go back to the time of the policy intervention (2007-2008, 2011-2013), the situation at that time was not the same as it is currently, and the use of targeted drugs for non-first-line use may have also been preferred by many physicians even at that time. If this study had only focused on patients who were eligible for first-line drug use and only used the eligible patients for the first line treatment as the denominator, the results may have been underestimated and inaccurate (biased).

In summary, the purpose of this study was to explore the actual impacts of health insurance policies on "drug accessibility" from an "academic" and "historical" perspective. Therefore, in the context of this study, it was not necessary to point out the timing of drug use, and focusing on the first line treatment only may have led to bias. Therefore, the original research design is still used, and we believe that the purpose and results of this study fall into the scope of BMJ Open.

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VERSION 2 – REVIEW

REVIEWER	Chulaporn Limwattananon Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand
REVIEW RETURNED	07-Oct-2018

GENERAL COMMENTS	Comments for 2018-022293.R1 Introduction Description of the reimbursement policies in paragraphs 4, lines 17-31 and 5, lines 34-52 was repetitively written. Statistical analysis Page 6, line 56 and page 7, line 3: The parsimonious models that the authors eliminated non-significant terms, using backward stepwise methods. This is unclear which variables that have been eliminated. The pre- and post-trend terms should not be eliminated though statistical non-significance since the data were time-series. If the eliminated term was the 0-1 binary variable capturing the immediate change (in level), then this should be explicitly revealed. Discussion Page 10, lines 48-50: There were grammatical errors and NHIRD need to be fully spelled out. Page 11, lines 24-26: the mistake of gefitinib trend, “reduction” should read “increase”.

	Page 13, line 17: the term, “earlier” is ambiguous. Does it mean faster or higher? Table 4 Survival rate was irrelevant because it has not been mentioned in the Method nor the Result sections.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1:

Reviewer Name: Chulaporn Limwattananon

Institution and Country: Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand Please state any competing interests or state ‘None declared’: None declared.

Comments for 2018-022293.R1

Introduction

Description of the reimbursement policies in paragraphs 4, lines 17-31 and 5, lines 34-52 was repetitively written.

Due to the similar change in the health care payment policy of gefitinib and erlotinib, there was duplicate text in the previous version. We removed the similar statements in the two paragraphs to make them more streamlined.

Statistical analysis

Page 6, line 56 and page 7, line 3: The parsimonious models that the authors eliminated non-significant terms, using backward stepwise methods. This is unclear which variables that have been eliminated. The pre- and post-trend terms should not be eliminated though statistical non-significance since the data were time-series. If the eliminated term was the 0-1 binary variable capturing the immediate change (in level), then this should be explicitly revealed.

This study used a segmented linear regression model. Based on Wagner’s (2002) publication7, we added the full formula of model and clearly descripted the variables and their implications.

$Yt = \beta0 + \beta1 * timet + \beta2 * interventiont + \beta3 * time\_after\_interventiont + et$

In this model, β0 estimates the baseline level of the outcome, mean number of prescriptions per patient per month, at time zero; β1 estimates the change in the mean number of prescriptions per patient that occurs with each month before the intervention (i.e. the baseline trend); β2 estimates the level change in the mean monthly number of prescriptions per patient immediately after the intervention, that is, from the end of the preceding segment; and β3 estimates the change in the trend in the mean monthly number of prescriptions per patient after the cap, compared with the monthly trend before the cap.

The full model contains the largest number of covariates and may have the least power to detect significant predictors of the outcome. Therefore, non-significant variables are often removed. Through stepwise backward elimination8, for example, one may select the most parsimonious model, that is, the one that only includes statistically significant predictors (at a predetermined significance level). Table 2 and Table 4 show the variables with significant effects and have not been eliminated.

Discussion

Page 10, lines 48-50: There were grammatical errors and NHIRD need to be fully spelled out.

We added the short term of “NHIRD” in Method section. We corrected the grammatical errors as follows:

“In this study, the data from NHIRD was used to examine the utilization of targeted therapies for NSCLC during 2004-2013 (10 years).” (in Discussion section, para 1)

Page 11, lines 24-26: the mistake of gefitinib trend, “reduction” should read “increase”.

We replaced the word “reduction” with “increase”. (in Discussion section, para 3)

Page 13, line 17: the term, “earlier” is ambiguous. Does it mean faster or higher?

We replaced the word “earlier” with “faster”. (in Conclusion section)

Table 4

Survival rate was irrelevant because it has not been mentioned in the Method nor the Result sections.

We appreciate the reviewer’s correction. The survival rate was removed.

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