Assessing the impact of the Provincial Reimbursement Scheme on the use of Targeted Anticancer Medications in Zhejiang, China: A Controlled Interrupted time-series Analysis

Cong Huang

Peking University School of Pharmaceutical Sciences

Carolina Oi Lam Ung

University of Macau Institute of Chinese Medical Sciences

Haishaerjiang Wushouer

Tsinghua University School of Medicine

Ziyue Xu

Peking University School of Pharmaceutical Sciences

Yichen Zhang

Peking University School of Pharmaceutical Sciences

Xiaodong Guan (✉ guanxiaodong@pku.edu.cn)

Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University <https://orcid.org/0000-0002-1290-3827>

Luwen Shi

Peking University School of Pharmaceutical Sciences

Research

Keywords: Provincial reimbursement, Targeted anticancer medications, Interrupted time-series

Posted Date: March 25th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-18436/v1>

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Abstract

Background: High prices of targeted anticancer medications (TAMs) subject patients to extreme financial burden. To alleviate problems with access and affordability, 6 TAMs were newly listed in the Provincial Reimbursement Drug List (PRDL) in Zhejiang, China in February 2015. To evaluate the implementation of the PRDL policy, this study examined differences in the hospital purchasing volume (HPV) and the hospital purchasing spending (HPS) of 6 listed TAMs pre- and post-enlistment and comparing with 4 other unlisted TAMs.

Methods: Interrupted time-series analysis was employed using the pharmaceutical procurement data of 6 newly listed TAMs (study group) and 4 unlisted TAMs (control group) from 22 tertiary hospitals in Zhejiang, China dated between January 2014 and March 2017.

Results: After February 2015, the average HPV per month increased significantly by 34.6 defined daily doses (DDDs) ($p < 0.001$) and the average HPS per month increased significantly by USD 6614.9 ($p < 0.001$) for the listed TAMs in the study group ($n=6$); neither the average HPV nor the average HPS changed significantly for the unlisted TAMs in the control group ($n=4$). Although only 4 of the 6 listed TAMs exhibited significant decrease in the monthly HPV and HPS individually, the daily cost of each TAM decreased after enlistment.

Conclusions: The PRDL policy has shown positive effect on promoting the access to and improving patients' affordability of TAMs in Zhejiang. The government should conduct further price negotiations and include more TAMs with clinical benefits into reimbursement schemes to relief patients' financial burden and promote access.

Introduction

Cancer has been the leading cause of death and a major public health problem in China with increasing incidence and mortality. (1, 2) In 2015, about 4 million new cancer cases were reported, of which 2.3 million were new cancer deaths, (3) ranking first of major disease mortality. (4) Lung cancer ranks the first in the incidence of cancer in China, followed by gastric cancer, colorectal cancer, and liver cancer. (3)

Anticancer medications are important part of cancer treatment. Although anticancer medications are the key to gains in overall survival for a patient with cancer, their use may subject the patient to an extreme financial burden due to high prices. (5) Especially for targeted anticancer medications (TAMs), high prices have raised major concerns over their affordability. (6) Related studies showed that high medication cost of cancer has caused a serious economic burden on patients in China, especially for the 4 most common cancers (lung cancer, gastric cancer, colorectal cancer, and liver cancer). (4, 7–10)

Adequate health insurance coverage of anticancer medications could promote access and better outcomes for cancer patients. (11–13) By the end of 2018, 94% of the population in China had been covered by Basic Medical Insurance (BMI). (1) In November 2009, the Ministry of Human Resources and Social Security (MOHRSS) issued the National Reimbursement Drug List (NRDL) (2009 Edition) including 102 anticancer medications, marking a crucial step in improving the coverage of anticancer medications in China. (14) Since then, some provinces and cities continued to include expensive anticancer medications into their Provincial Reimbursement Drug List (PRDL) according to local needs and fundraising levels. However, there is a lack of evidence available for decision makers about the impact of the PRDL policy on the use and spending of these medications after enlistment in the provincial reimbursement schemes. (15) In February 2015, Zhejiang Province Human Resources and Social Security (HRSS) department announced the enlistment of 15 expensive medications in the PRDL of Zhejiang after price negotiations. (16) Six of them were TAMs which included rituximab, trastuzumab, imatinib, gefitinib, nimotuzumab and cetuximab. The enlistment allowed the hospitals in Zhejiang to procure the listed medications at the provincially negotiated prices.

In order to evaluate the implementation of the government reimbursement policy, this study examined the differences in the hospital purchasing volume (HPV) and the hospital purchasing spending (HPS) of 6 listed TAMs pre- and post-enlistment and in comparison with 4 other unlisted TAMs in Zhejiang, China.

Method

Study design

We used interrupted time series (ITS), the strongest quasi-experimental design (17) to analyze changes of medication use following the implementation of PDRL policy. The enlistment announcement of 6 TAMs was made on February 5, 2015 and thus we selected February 2015 as the breakpoint. To strengthen our design, in addition to the 6 TAMs newly listed in the PRDL in the study group, we selected 4 other unlisted TAMs in the Zhejiang reimbursement scheme as the control group (bevacizumab, erlotinib, bortezomib, recombinant human endostatin) (see Supplementary Table 1). We hypothesized that the impact on the HPV and the HPS of the listed TAMs in the study group would be different before and after the breakpoint, and from the unlisted TAMs in the control group.

Data Sources

We used the data from China Medicine Economic Information (CMEI), a large database of public hospital medication procurement records in mainland China. (18) We extracted data of the 6 TAMs in the study group and the 4 TAMs in the control group purchased by 22 tertiary hospitals from Zhejiang province between January 2014 and March 2017. Aggregated procurement data included the HPV and the HPS of the TAMs selected in this study, as well as their dosage form, strength, purchase time, the Anatomical Therapeutic Chemical (ATC) code (19) and manufacturer. Detailed information about the 6 listed TAMs in the study group was provided in Table 1. Ethical approval was not required according to the relevant requirements for conducting this type of survey in China.

Table 1
Descriptive information of 4 TAMs unlisted in PRDL of Zhejiang

Generic name	Brand name	Date of NMPA approval	Marketing Authorisation Holder	Strength	DDD †	Thetapeutic Class‡	ATC code
Bevacizumab	Avastin	2010.2.26	Roche Diagnostics GmbH	100 mg/4 ml	50 mg	Metastatic colorectal cancer; Lung cancer	L01XC07
Erlotinib	Tarceva	2006.4.6	Delpharm Milano S.r.l.	100 mg	150 mg	Lung cancer	L01XE03
Bortezomib	Velcade	2005.2.21	BSP Pharmaceuticals S.p.A.	1.0 mg	0.21 mg	Multiple myeloma; Lymphoma mantle cell	L01XX32
Recombinant Human Endostatin	Endostar	2005.9.12	Simcere Pharma	15 mg/3 ml	8.5 mg	Lung cancer	/
†DDD: Defined Daily Dose, is calculated for each product in consideration of the dosage regimen recommended in the manufacturers' instructions of products, as approved by National Medical Products Administration (NMPA).							
‡Therapeutic Class: Summarized from indications in the manufacturers' instructions of products approved by NMPA.							

Outcome Measures

The primary outcomes we included were the average HPV per month and the average HPS per month of the study group and the control group, as well as the HPV per month and the HPS per month for each of the TAMs in the study group. Secondary outcome of interest was the average daily cost (cost of Defined Daily Dose, DDDc) for the 6 TAMs in the study group. The Defined Daily Dose (DDD) in our study referred to the daily amounts based on dosage regimen recommended in the manufacturers' instructions, as approved by National Medical Products Administration (NMPA). (20)The volume in HPV was defined as the numbers of DDD (DDDs). The spending in HPS was indicated by the hospital spending on each medication per month. The HPV per month was reported in the US dollar (US\$1=¥6.1428 based on the 2014 exchange rate (21)) after adjusted to January 2014 using the medical care component of the Consumer Price Index (CPI). (22)

Statistical analysis

We assessed the outcomes over time for the 6 newly listed TMAs in the study group and the 4 unlisted TAMs in the control group. ITS model with a single breakpoint was formulated to estimate the impacts of enlistment on monthly average HPV and HPS. The regression equation is as follows:

$$Y_{it} = \beta_0 + \beta_1 * time_t + \beta_2 * level_t + \beta_3 * trend_t + \varepsilon_{it}$$

Y_t represented the spending or volume at time t . β_0 estimated the level of Y_t at the beginning of the observation period; β_1 estimated the trend of the outcomes in the pre-intervention periods; β_2 estimated the level change of the outcomes immediately following the policy; β_3 estimated the trend change after the intervention; ε_{it} represented the random error at time t . We presented changes in the level or trend of the average HPV per month and the average HPS per month. Total changes by the end of observation (12 months after implementation) of the outcomes were also reported.

The Durbin-Watson statistic was used to test for a serial autocorrelation of the error terms in the regression models. (23) We used the Cochrane-Orcutt auto-regression procedure to correct for first order serially correlated errors when needed. (24) All statistical analysis was performed using STATA/SE V.15.0.

Results

The changes in the average HPV per month and HPS per month of listed and unlisted TAMs

The average HPV per month and the average HPS per month of the 6 listed TAMs in the study group increased significantly after February 2015, while there were no statistically significant changes in the average HPV per month nor the average HPS per month for 4 unlisted TAMs in the control group (Fig. 1; Table 2). The average HPV per month of the listed TAMs in the study group experienced a significant level increase of 34.6 DDDs ($p < 0.001$) following the enlistment while TAMs in control group showed no statistical changes in the HPV level or trend. Similarly, there was a significant increase of \$6614.9 ($p < 0.001$) in the level of the average HPS per month for the listed TAMs in the study group, and no significant changes were observed in the control group. At the end of observation period (12 months after policy implementation), an estimated increase of 50.9 DDDs ($p < 0.001$) in the average of HPV per month and \$8470.1 ($p < 0.001$) in the average of HPS per month of the 6 listed TAMs in the study group was observed.

Table 2
Estimates from ITS models of changes in the average HPV and HPS for two groups

	Baseline level	Baseline trend	Level change	Trend change	Absolute change§
Average Hospital Purchasing Volume (DDD) per month					
Study group†	36.6***	-0.7	34.6***	1.4	50.9***
Control group‡	12.7***	-0.2	-3.1	0.5	2.6
Average Hospital Purchasing Spending (USD) per month					
Study group	6761.6***	-143.0*	6614.9***	154.6	8470.1***
Control group	2093.9***	20.5	-766.2	48.9	-179.7
*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$;					
†Study group: 6 targeted anticancer medications newly listed in provincial reimbursement scheme in Zhejiang;					
‡Control group: 4 targeted anticancer medications unlisted in provincial reimbursement scheme;					
§Absolute change: changes at 12 months after the policy implementation					

The changes in the average daily cost of listed and unlisted TAMs

The average daily cost of the 6 listed TAMs in the study group declined after the policy implementation (Fig. 2). Before February 2015, the daily costs of TAMs from both groups were stable. After enlistment in the provincial reimbursement scheme in Zhejiang, the daily cost of the 6 listed TAMs in the study group experienced an abrupt decrease while no significant change was observed about those in the control group.

The changes in the HPV per month, HPS per month and daily cost of listed TAMs

Each of the listed TAMs in the study group experienced significant increases in the HPV per month and the HPS per month after enlistment on the PRDL except for nimotuzumab and imatinib (Fig. 3; Table 3). The HPV per month of trastuzumab increased by 172.8 DDDs ($p < 0.001$) by the end of observation. Other listed TAMs like gefitinib (80.0 DDDs, $p < 0.05$), rituximab (11.7 DDDs, $p < 0.05$) and cetuximab (6.3 DDDs, $p < 0.05$) also increased significantly in HPV per month. Similarly, there were significant increases in the HPS per month for these 4 listed TAMs with trastuzumab exhibiting the most increase in spending (\$23187.6, $p < 0.001$). As for nimotuzumab and imatinib, there was no statistically significant change in HPV or HPS even 12 months after enlistment in the provincial reimbursement scheme.

Table 3
Estimates from ITS models of changes in the HPV and HPS of the listed TAMs

	Hospital Purchasing Volume (DDD) per month			Hospital Purchasing Spending (USD) per month		
	Level change	Trend change	Absolute change	Level change	Trend change	Absolute change†
Gefitinib	31.8	4	80.0*	2302.6	265.7	5491.4*
Rituximab	8.0*	0.3	11.7*	7703.2*	207.6	10194.3*
Nimotuzumab	35.3	-2.4	6.4	4316	-466	-1275.7
Trastuzumab	115.6***	4.8	172.8***	17588.1***	466.6	23187.6***
Cetuximab	6.6	-0.03	6.3*	4859.5	-48.3	4279.8*
Imatinib	5.4	0.2	7.7	923.4	17.2	1129.5
*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$;						
†Absolute changes: changes at 12 months after the policy implementation						

The daily cost of each of the 6 listed TAMs in the study group all declined following the PRDL policy implementation (Fig. 3). The daily cost of each of the 6 listed TAMs was stable before February 2015 and remained so until an abrupt decrease observed after March 2015. Out of the 6 listed TAMs, the cut in the daily cost of nimotuzumab was the greatest (from about \$160 to \$120).

Discussion

Our study showed that, after enlistment on the PRDL, the average HPV per month and the average HPS per month of the anticancer medications selected in this study increased significantly in Zhejiang province. Furthermore, the average daily cost of these newly listed anticancer medications declined shortly after the enlistment and remained stabilized

overtime. These findings suggested that the PRDL policy was successful at encouraging the use of anticancer medications, promoting the access and improving patients' affordability.

The time of the PRDL policy implementation in this study was set as February 2015 when 6 TAMs were newly enlisted on the PRDL in Zhejiang province. The average of the HPV per month for the 6 listed TAMs increased significantly after the enlistment and throughout the study period. This shows that the provincial reimbursement scheme was an effective way to promote the use of anticancer medications, which is consistent with previous studies. (15, 25, 26) This is especially evident when comparing gefitinib (listed TAM) and erlotinib (unlisted TAM) as shown in this study. Both of these medications were first-line TAMs for non-small-cell lung cancer patients with somatic EGFR mutations in China. (27) Erlotinib was also a second-line TAM after failure of at least one prior chemotherapy regimen. However, we found that the HPV per month and the HPS per month of gefitinib increased significantly after enlistment of the PRDL while there was no change for erlotinib. Such differences suggest that the tertiary hospitals had a higher tendency to purchase medications listed in the provincial reimbursement scheme emphasizing the positive role that the PRDL policy may play in encouraging the use of anticancer medications.

TAMs have been the focus of cancer drug development over the past two decades, (28, 29) which meanwhile have raised major concerns over their affordability due to skyrocketing prices. (30) In this study, we found that the daily cost of the 6 expensive TAMs successfully decreased after enlistment, which reflected the improvement in patients' affordability. According to the reimbursement policy, when patients were prescribed with listed medications, after a deductible of CNY 20000 (USD 3077), the provincial reimbursement scheme would help pay a pre-defined portion of the total amount of patient's payment (e.g. 70% in Hangzhou, the capital city of Zhejiang province (31)), and the patients would have to bear the remaining cost (e.g. 30% in Hangzhou). Listing of the medications on the reimbursement list can decrease patients' out-of-pocket spending. The policy relieved the economic burden of patients and improved access to expensive anticancer medications in Zhejiang province.

We have also identified 2 important factors when evaluating the implementation of the PDRL policy in this study: the availability of generic medicines and the time lag between policy issuance and implementation. At the individual level, not every anticancer medication showed significant increase in the HPV per month and the HPS per month following reimbursement inclusion. Imatinib (listed medication) included in our study was the branded originator which showed no significant change in terms of the HPV per month nor the HPS per month. Since patent protection of imatinib was expired before February 2015, generic of imatinib was already available locally marketed at a lower price compared to its originator. The availability of the generic medications would impact the use and cost of anticancer medications in China. (18, 32) Patients taking generic imatinib might not turn to branded imatinib even when the originator became listed on the PDRL.

Our study also found that, while the average HPV per month and the average HPS per month of the newly listed TAMs increased immediately after enlistment in February 2015, the average daily cost of these TAMs only declined after 2 months in April 2015. Each province had a medicine tender bidding center to select medicine manufacturers and to determine medicine prices for government-run healthcare institutions. (33) In Zhejiang, the HRSS department issued the enlistment announcement on February 4, but the prices of listed medications on medicine tender bidding center were only updated in April 2015 showing a 2-month lag period. (34) Although such delay due to policy coordination among departments may be inevitable, improved coordination and cooperation between related sectors were vital to achieve "health in all policies" in the most timely manner. (35) More effective mechanisms are needed to improve intersectoral coordination and shorten implementation delay between departments.

There were several limitations in this study. First, only patients from 22 of more than 130 tertiary hospitals (4) of Zhejiang province were included in our study, the findings of which were not able to fully reflect the monthly medication

consumption and spending of all hospitals in the province; Second, there were related Patient Assistance Programs (PAPs) existing in China, like Iressa Means–Tested Drug Donation(36) for gefitinib. Low income patients who could not afford continuous treatment could receive free Iressa after paying for the first several courses of treatment. The influence of programs alike was not taken into account in our analysis. However, the number of patients who participate in PAPs was limited and almost 70% of medication sales in China occurred in hospitals. (37) Third, the data we used was from hospital procurement records, which did not directly reflect the access to medications at patient level. Further study is needed to evaluate patients’ access to TAMs using claim data or prescription data. Patients in secondary hospitals should also be enrolled.

Conclusion

The PDRL policy has shown positive impact on promoting the use of anticancer medications and improving patients’ affordability in Zhejiang province, China. After enlisting on the PDRL, the HPV per month and the HPS per month of expensive anticancer medication increased significantly at hospital level and thus the out-of-pocket expenses were reduced at patient level. However, further study with claim data or prescription data is needed to provide more evidence on how patients’ access to different anticancer medication changes with provincial reimbursement inclusion policy. Our government should conduct further price negotiations and include more anticancer medications with clinical benefit into reimbursement schemes to relief patients’ financial burden and promote access.

Abbreviations

TAM	Targeted Anticancer Medication
PRDL	Provincial Reimbursement Drug List
HPV	Hospital Purchasing Volume
HPS	Hospital Purchasing Spending
USD	United States dollar
BMI	Basic Medical Insurance
MOHRSS	Ministry of Human Resources and Social Security
HRSS	Human Resources and Social Security
NRDL	National Reimbursement Drug List
ITS	Interrupted Time Series
CMEI	China Medicine Economic Information
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
NMPA	National Medical Products Administration
CPI	Consumer Price Index
CNY	Chinese yuan
PAP	Patient Assistance Program

Declarations

Ethics approval and consent to participate

Not applicable. The study was considered non-human subjects research by the Harvard Pilgrim Health Care Institutional Review Board. Ethical approval was not required according to the relevant requirements for conducting this type of survey in China.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xiaodong Guan, Cong Huang, Ziyue Xu and Yichen Zhang. The first draft of the manuscript was written by Cong Huang, Carolina Oi Lam Ung and Haishaerjiang Wushouer, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the staff of Chinese Pharmaceutical Association for their support and cooperation in data access and analysis.

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Figures

Figure 1

Changes in the average purchasing volume and spending for two groups. Changes in the average Hospital Purchasing Volume per month (A) and the average Hospital Purchasing Spending per month (B) for the study group (n=6) and the control group (n=4), 2014-2016.

Figure 2

Changes in the average daily cost for two group. Changes in the average daily cost between the study group (n=6) and the control group (n=4), 2014-2016.

Figure 3

Changes in the purchasing volume and spending for listed TAMs. Changes in the Hospital Purchasing Volume per month (A), the Hospital Purchasing Spending per month (B) and the daily cost (C) of the 6 listed targeted anticancer medications, 2014-2016

Supplementary Files

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