ABSTRACT

Objectives It is unclear whether the use of antineoplastic drugs for patients with lung cancer in China has changed after the implementation of the national drug price negotiation in 2016 and continual update of clinical guidelines. This study aims to evaluate the trends in antineoplastic drug use, cost and prescribing patterns among patients with lung cancer in major cities of China.

Design We conducted a retrospective observational study using data from January 2016 to December 2020.

Setting This study used prescription records based on inpatient and outpatient hospital data from 97 hospitals in 9 major cities of China.

Participants A total of 218,325 antineoplastic drug prescriptions in patients with lung cancer were retrospectively collected from the Hospital Prescription Analysis Cooperative Project during the study period.

Outcome measures Trends in antineoplastic drug use, cost and prescribing patterns among patients with lung cancer.

Results The yearly antineoplastic prescriptions increased by 85.6% from 28,594 in 2016 to 53,063 in 2020 (Z = 1.71, p = 0.086). Significant increases were seen in the prescriptions for protein kinase inhibitors (PKIs) and monoclonal antibodies (mAbs), whereas significant decreases were observed in antimetabolites, plant alkaloids and platinum compounds. The yearly cost increased progressively by 145.0% from ¥113.6 million in 2016 to ¥278.3 million in 2020 (Z = 2.20, p = 0.027). The top three anticancer drug classes in terms of total cost were PKIs, antimetabolites and mAbs. In prescribing patterns of antineoplastic agents for lung cancer, monotherapy, and triple or more drug combinations gradually increased, while dual combinations decreased significantly from 30.8% to 19.6%.

Conclusions Prescription practices among patients with lung cancer in China underwent major changes during the study period. The observed trends can aid in understanding the present medication use status of patients with lung cancer in China and provide information for future drug management.

INTRODUCTION

Primary bronchial lung cancer, referred to as lung cancer, is one of the malignant tumours with significant morbidity and fatality rate.1 According to the GLOBOCAN 2020 database,2 China is one of the countries with a heavy burden of lung cancer in the world, accounting for 23.7% of the total number of lung cancer diagnoses and 30.0% of deaths.3 The incidence of lung cancer has maintained an upward trend in both men and women in China during the past few years, posing a serious threat to public health.4
Simultaneously, lung cancer treatment expenditures appear to be catastrophic for patients in China. Past treatment regimens have established the role of chemotherapy and radiation therapy to help address the local and systemic nature of lung cancer. The chemotherapy regimens for lung cancer recommended by the guidelines mainly include etoposide plus cisplatin, vinorelbine plus cisplatin, pemetrexed plus cisplatin or carboplatin, paclitaxel plus cisplatin or carboplatin. However, these regimens have limitations in their tolerability due to toxicity. Additionally, cytotoxic chemotherapy has limited efficacy in preventing systemic spread of lung cancer. Newer systemic agents such as molecularly targeted therapeutics and immune checkpoint inhibitors have shown improved survival and have the advantage of more limited toxicity profiles compared with cytotoxic chemotherapy.

In China, six epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, icotinib, afatinib, dacomitinib and osimertinib) were approved for first-line treatment in EGFR-mutated patients, and the programmed cell death protein 1 (PD-1) inhibitor (pembrolizumab) single agent as first-line therapy in patients with programmed cell death ligand 1 (PD-L1) more than 50%, and pembrolizumab or camrelizumab combined with chemotherapy as first-line therapy regardless of PD-L1 expression were recommended by clinical guidelines up to December 2020.

The launch of novel targeted therapy and immune checkpoint inhibitors brings hope for patients with lung cancer, but at the same time, their high prices and expanding expenditure pose challenges for patients. To reduce the price of novel medicines with high clinical value and relieve the patients’ financial burden, the Chinese government designed a national drug price negotiation policy in 2016. The price of medicines was reduced prior to their being included in the National Reimbursement Drug List (NRDL). Patients can obtain reimbursement for negotiated medicines, many of which are anticancer drugs. In 2016, the government initiated the first round of the national drug price negotiation and successfully negotiated two targeted anticancer medicines, gefitinib and icotinib, which were used for lung cancer treatment. Immediately following the 2016 negotiation, the government conducted the second round of the national drug price negotiation in 2017. Thirty-six innovative medicines were successfully negotiated; among them, erlotinib and bevacizumab were innovative anticancer medicines for lung cancer treatment. The third round of the national drug price negotiation was held in 2018. Seventeen anticancer medicines were successfully included in the NRDL; among them, afatinib, osimertinib, anlotinib, crizotinib and ceritinib were used for lung cancer treatment. Since 2018, the Chinese government has implemented two rounds of the national drug price negotiation to introduce 17 and 70 innovative and unaffordable medicines into the NRDL until December 2020; among them, alemtuzumab, monoclonal antibodies (mAbs) and camrelizumab were anti-lung cancer medicines. The prices of these newly covered innovative medications were reduced by approximately 40%. However, other targeted and immunotherapy anticancer drugs were not included in the National Medical Insurance Catalogue.

The rising prevalence of lung cancer in China and the dearth of innovative medication status highlight the need for a greater understanding of how lung cancer is treated within the framework of the current healthcare system. To our knowledge, there is no previous research on the nationwide prescribing trends and costs of antineoplastic drugs for patients with lung cancer after the implementation of the national drug price negotiation in China. Thus, we use a large clinical prescription database to assess and track prescribing trends in drug use, cost and prescribing patterns for antineoplastic drug therapies among patients with lung cancer in major cities of China from 2016 to 2020.

**METHODS**

**Study design and data source**

This study was designed as a retrospective observational study based on prescriptions. The prescriptions were retrospectively extracted from the database of the Hospital Prescription Analysis Cooperative Project. The programme randomly selected 10-day prescription data from each hospital each quarter. The patient’s several hospital admissions or visits were documented as independent of information. In China, this database was frequently used for pharmacoepidemiological investigations.

In this study, prescription data were collected from 97 hospitals in 9 major cities of China.

**Prescription inclusion and information collection**

Prescriptions containing at least one antineoplastic agent for patients who had the diagnosis of lung cancer were included. Inclusion criteria were unrestricted to diagnostic criteria and staging of lung cancer. The research was conducted between January 2016 and December 2020. The hospital information (location, time, hospital level, hospital code, source), hospital status (inpatient or outpatient) and prescription information (prescription code, gender, age, reimbursement, diagnosis, prescription code, drug code, generic name, trade name, drug specification and price) were extracted from the database. Prescriptions with incomplete information were removed. Prescription codes were used to deidentify patients’ information to protect patient identity.

**Drug classes**

According to the WHO anatomical therapeutic chemical (ATC) classification system (https://www.whocc.no/atc_ddd_index/), antineoplastic drugs in our data were divided into seven classes (L01A—alkylating agents, L01B—antimetabolites, L01C—plant alkaloids, L01D—cytotoxic antibiotics, L01E—protein kinase inhibitors (PKIs), L01F—monoclonal antibodies (mAbs) and...
L01X—other antineoplastic agents). The specific drug classification was shown in online supplemental table 1.

In the analysis process, the first step was to analyse the prescriptions for each class of antineoplastic agents according to the ATC classification. In the second step, we further analysed the subclasses and specific drugs contained in L01E—PKIs (L01EB—EGFR-TKIs, L01ED—anaplastic lymphoma kinase (ALK) inhibitors and L01EX—other PKIs) and L01F—mAbs (L01FE—EGFR inhibitors, L01FF—PD-1/PD-L1 inhibitors and L01FG—vascular endothelial growth factor (VEGF)/VEGFR receptor (VEGFR) inhibitors), with significant rising trend in the first step.

Statistical analyses
Treatment prescriptions, cost of antineoplastic agents and prescribing patterns for patients with lung cancer were analysed. A visit was defined as one prescription containing antineoplastic agents, regardless of inpatient or outpatient status. The per cent of visits (PV) was the proportion of specific class, subclass or drug prescriptions in the total number of antineoplastic drug prescriptions. The drug cost was the sum of all the antineoplastic drugs. The average cost per visit was calculated by the cost of total antineoplastic agents divided by the total number of visits of patients. Overall trends in each class and the use of some specific antineoplastic agents were evaluated over the 5-year observation period. Monotherapy and combination therapy were analysed as prescribing patterns.

Since the antineoplastic drug treatment of patients with lung cancer is less affected by seasonal factors, and China’s drug policy is usually adjusted annually, trends were analysed at the annual level. The Mann-Kendall test was used to estimate the statistical significance of overall trends for the number and cost of total prescriptions. A positive value of Z indicated an upward trend, and a negative value indicated a downward trend. Comparisons of the groups of sex, age and patient identity were carried out using one-way analysis of variance or independent-samples t-test. Statistical significance was identified as p<0.05. The statistical analyses were conducted using R software (V.4.2.0).

RESULTS
Descriptive statistics for total prescriptions
A total of 218,325 prescriptions for patients with lung cancer were identified and extracted from 97 hospitals in 9 major cities of China (Beijing, Chengdu, Guangzhou, Harbin, Hangzhou, Shanghai, Shenyang, Tianjin and Zhengzhou) from 2016 to 2020. The data cleaning process is shown in figure 1. These nine cities were spread throughout the northeastern, northern, eastern, central, southwestern and southern areas of China. There were 88 tertiary hospitals and 9 secondary hospitals. The regional distribution characteristics of the included prescriptions are shown in table 1. The average cost per visit was relatively higher in Beijing, Guangzhou and Shanghai than in other cities.

Table 1 Regional distribution characteristics of included prescriptions in China from 2016 to 2020

<table>
<thead>
<tr>
<th>Region</th>
<th>City</th>
<th>Hospital level (n)</th>
<th>Prescriptions (n)</th>
<th>Average cost per visit (¥)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast China</td>
<td>Shenyang</td>
<td>0</td>
<td>11</td>
<td>5882</td>
</tr>
<tr>
<td></td>
<td>Harbin</td>
<td>0</td>
<td>11</td>
<td>1979</td>
</tr>
<tr>
<td>Northern China</td>
<td>Beijing</td>
<td>1</td>
<td>6</td>
<td>691</td>
</tr>
<tr>
<td></td>
<td>Tianjin</td>
<td>1</td>
<td>5</td>
<td>127</td>
</tr>
<tr>
<td>Eastern China</td>
<td>Hangzhou</td>
<td>0</td>
<td>12</td>
<td>5253</td>
</tr>
<tr>
<td></td>
<td>Shanghai</td>
<td>5</td>
<td>15</td>
<td>6293</td>
</tr>
<tr>
<td>Central China</td>
<td>Zhengzhou</td>
<td>1</td>
<td>9</td>
<td>2994</td>
</tr>
<tr>
<td>Southwest China</td>
<td>Chengdu</td>
<td>1</td>
<td>8</td>
<td>1753</td>
</tr>
<tr>
<td>Southern China</td>
<td>Guangzhou</td>
<td>0</td>
<td>11</td>
<td>3622</td>
</tr>
</tbody>
</table>
As depicted in figure 2, the yearly prescriptions for antineoplastic drugs (including clinic and ward prescriptions) continuously increased by 103.5%, from 28,594 in 2016 to 58,181 in 2019, and then decreased by 8.8% (53,063) in 2020 (Z=1.71, p=0.086). The annual cost of antineoplastic drugs increased progressively by 145.0%, from ¥113.6 million in 2016 to ¥278.3 million in 2020 (Z=2.20, p=0.027), and the average cost of antineoplastic drugs per visit for patients with lung cancer rose by 32.0%, from ¥3,974 to ¥5,244 (Z=1.22, p=0.22).

Trends stratified by age and sex
The demographic characteristics of participants who were given prescriptions are shown in table 2. The PV containing antineoplastic drugs for each age group differed greatly. Prescriptions for patients with lung cancer aged between 40 and 79 years old accounted for 94.1% of the sample over 5 years. The patients with lung cancer aged below 40 and over 79 years were fewer, with a total of approximately 5.0% each year. The prescriptions for each age group hardly changed over the course of the study (p>0.05). There were more prescriptions for male patients with lung cancer than female patients (p=0.002), accounting for 61.4% of the sample from 2016 to 2020. The proportion of prescriptions for male patients fell annually (from 68.7% in 2016 to 56.4% in 2020), while the proportion of prescriptions for female patients increased (Z=2.20, p=0.027). The most common way patients chose to pay for their prescriptions each year was through Urban Basic Medical Insurance (UBMI), followed by out of pocket (OOP).

Trends stratified by drug type
Trends by drug class
According to the WHO ATC classification, an analysis of drug classes for antineoplastic prescriptions was conducted. Figure 3A,B shows the prescription and cost trends in each class of antineoplastic drugs during the study period, respectively. The first drug class category by total prescriptions was L01E—PKIs, with PV of 15.6% in 2016, then gradually increased by 54.3% in 2020 (Z=2.20, p=0.027). The cost of L01E—PKIs also ranked first in all antineoplastic drugs and continued to increase (Z=2.20, p=0.027). The PV for L01X—other antineoplastic agents containing most platinum compounds (Z=−2.20, p=0.027), L01C—plant alkaloids (Z=−2.20, p=0.027) and L01B—antimetabolites (Z=−2.20, p=0.027) showed downward trends, ranking second, third and fourth,
Table 2  Demographic characteristics of participants who were given prescriptions from 2016 to 2020*

<table>
<thead>
<tr>
<th>Year</th>
<th>Sex</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>19634 (68.66)</td>
<td>22324 (65.90)</td>
<td>27486 (61.60)</td>
<td>33899 (58.26)</td>
<td>29918 (56.38)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8960 (31.33)</td>
<td>11549 (34.09)</td>
<td>17128 (38.39)</td>
<td>24282 (41.73)</td>
<td>23145 (43.61)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>&lt;39</td>
<td>602 (2.10)</td>
<td>772 (2.27)</td>
<td>994 (2.22)</td>
<td>1296 (2.22)</td>
<td>1290 (2.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40–79</td>
<td>27265 (95.35)</td>
<td>32250 (95.20)</td>
<td>42025 (94.19)</td>
<td>54465 (93.61)</td>
<td>49406 (93.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥80</td>
<td>727 (2.54)</td>
<td>851 (2.51)</td>
<td>1595 (3.57)</td>
<td>2420 (4.15)</td>
<td>2367 (4.46)</td>
</tr>
<tr>
<td></td>
<td>Medical payment types</td>
<td>UBMI</td>
<td>18424 (64.43)</td>
<td>22222 (65.60)</td>
<td>31469 (70.53)</td>
<td>41517 (71.35)</td>
<td>37515 (70.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRCMS</td>
<td>2636 (9.21)</td>
<td>2459 (7.25)</td>
<td>3008 (6.74)</td>
<td>2951 (5.07)</td>
<td>1045 (1.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMI</td>
<td>285 (0.99)</td>
<td>183 (0.54)</td>
<td>161 (0.36)</td>
<td>252 (0.43)</td>
<td>363 (0.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OOP</td>
<td>8358 (29.22)</td>
<td>10206 (30.13)</td>
<td>11631 (26.07)</td>
<td>15158 (26.05)</td>
<td>15039 (28.34)</td>
</tr>
</tbody>
</table>

*Data were represented as prescriptions (%).
NRCMS, New Rural Cooperative Medical Insurance Scheme; OOP, out of pocket; PMI, Private Medical Insurance; UBMI, Urban Basic Medical Insurance.

Figure 3  Prescription (A) and cost (B) trends of classes for anti-lung cancer drugs from 2016 to 2020. aTrends at p<0.05 in the line graph were represented by solid lines. bTrends at p<0.05 in the bar chart were represented by patterned bars. mAbs, monoclonal antibodies; PKIs, protein kinase inhibitors.
respectively. The cost of L01B—antimetabolites ranked second, which decreased by 32.4% during the 5 years (Z=−0.75, p=0.46). PV of L01F—mAbs ranked fifth and increased from 1.3% in 2016 to 8.2% in 2020 (Z=2.20, p=0.027). It was worth noting that the cost of mAbs ranked third in all drug classes, increasing from ¥8.7 million in 2016 to ¥33.4 million in 2020 (Z=2.20, p=0.027). L01A—alkylating agent and L01D—cytotoxic antibiotics and related substances were used in a few prescriptions, with annual PV not exceeding 1%.

Trends by drug subclass

Further analysis of L01E—PKIs and L01F—mAbs prescriptions was conducted, which revealed significant rising trends, as shown in figures 4 and 5.

As demonstrated in figure 4, among the L01E—PKIs subclasses used for the treatment of lung cancer, the highest proportion of prescriptions was for EGFR-TKIs, and the upward trend was significant year by year (Z=2.20, p=0.027). EGFR-TKI gefitinib was the most prescribed drug in the L01E—PKIs class and increased yearly (Z=1.71, p=0.086), whereas the cost trend decreased gradually (Z=−0.24, p=0.81). ALK inhibitors and other PKIs were less commonly used; the PV of ALK inhibitors increased from 0.1% in 2016 to 4.8% in 2020 (Z=1.71, p=0.086), and the PV of other PKIs increased by 6.7% over 5 years (Z=1.71, p=0.086). As with the general trend in prescriptions of L01E—PKIs, osimertinib (Z=2.20, p=0.027), anlotinib (Z=2.02, p=0.043) and afatinib (Z=2.02, p=0.043) significantly increased over 5 years, and their cost trends also raised accordingly (osimertinib (Z=2.20, p=0.027), anlotinib (Z=2.02, p=0.043), afatinib (Z=2.02, p=0.043)). The increased trends in prescriptions of icotinib (Z=0.24, p=0.81), erlotinib (Z=−0.73, p=0.46), crizotinib (Z=1.71, p=0.086) and alecinib (Z=1.66, p=0.096) were not significant. The PV of almonertinib, ceritinib, sunitinib and sorafenib only accounted for about 0.01% during the last 5 years.

VEGF/VEGFR was the commonly used subclass of L01F—mAbs, with PV increasing from 1.3% in 2016 to 6.4% in 2020 (Z=2.20, p=0.027), as illustrated in figure 5. PV of the PD-1/PD-L1 mAbs also increased relatively fast from 0.0% to 1.7% in a span of 5 years, although these are still less widely used. There were fewer than 0.1% of the mAbs used to target EGFR. Bevacizumab was the most prescribed drug in the L01F—mAbs class, and the PV (Z=2.20, p=0.027) and cost (Z=2.20, p=0.027) showed significant upward trends in the past 5 years. Among the other mAbs drugs, the most frequently prescribed was sintilimab, which increased by 0.9% (Z=1.66, p=0.096), and the most costly was pembrolizumab, which increased from 0.6 million in 2018 to 4.7 million in 2020 (Z=2.02, p=0.043).

Trends in prescribing patterns

Trends in prescribing patterns for monotherapy, dual combination, triple or more antineoplastic drug combinations in patients with lung cancer are shown in figure 6.

The percentage of monotherapy, with mainly L01E—PKIs, increased from 68.4% in 2016 to 77.8% in 2020 (Z=2.20, p=0.027). The percentage of dual combinations, mainly the chemotherapy combination of antimitabolites or plant alkaloids and platinum compounds, decreased from 30.8% in 2016 to 19.6% in 2020 (Z=−2.20, p=0.027). The percentage of three or more drug regimens was 0.8% in 2016 and increased slightly to 2.5% in 2020 (Z=1.71, p=0.086), which was mostly a combination of chemotherapy and mAbs.

**DISCUSSION**

This study demonstrated actual trends in the prescription status of antineoplastic drugs among patients with lung cancer in China from 2016 to 2020. The findings were typical of the whole country since prescriptions from 97 hospitals were included. It was found that both the prescription and cost of antineoplastic drugs increased progressively during 5 years. The use of innovative anticancer medications increased noticeably, whereas there was a discernible fall in the usage of conventional chemotherapy medications.

Prescriptions for antineoplastic drugs increased from January 2016 to December 2019, which could be attributed to the growing number of patients with lung cancer as well as the increasing number of hospital admissions and clinical visits per patient, before declining in 2020. This may result from the shortage of resources, health system closures, and delays in diagnosis and treatment prompted by individuals’ anxieties about the COVID-19 pandemic. The top three cities in terms of average cost per visit were Beijing, Guangzhou and Shanghai, as the proportion of prescriptions for PKIs and mAbs in these cities was relatively higher than in other cities. Several other influential factors might contribute to the discrepancy including the difference in physicians’ treatment level, incidence of diseases, average socioeconomic level of patients and the accessibility of the innovative anticancer medicines in different cities. Further research at an individual level is warranted to investigate the utilisation pattern of anticancer medicines. Similar to the finding in previous studies, the percentage of prescriptions for female patients with lung cancer increased year by year. This may be attributable to several factors including recent changes in smoking behaviours in both sexes and other sex-related factors such as genetic susceptibility, exposure to sex hormones and molecular characteristics.

PKIs and platinum compounds were more frequently used throughout the 5-year course, according to our analysis. The favoured antineoplastic drugs were cisplatin, gefitinib, etoposide, pemetrexed and icotinib. Significant increases were seen in the prescriptions of PKIs and mAbs, whereas significant decreases were observed in antimitabolites, plant alkaloids and platinum compounds. The cost of antineoplastic drugs for patients with lung cancer increased during the 5-year period, which was similar to those of previous studies. This might be caused by the
A considerable increase in the prescriptions of innovative anticancer drugs in China compared with traditional chemotherapy. The majority of prescribing patterns were monotherapy, with mainly L01E—PKIs. This was attributable to the emergence of the various PKI monotherapy schemes recommended by clinical guidelines and the expansion of patients’ access to innovative anticancer drugs because of the implementation of the national drug price negotiation since 2016. The treatment cost of patients with lung cancer was mainly covered by UBMI, followed by OOP, New Rural Cooperative Medical Insurance Scheme and Private Medical Insurance. This demonstrated that China’s medical security has yet to reach comprehensive coverage and confronts numerous obstacles.

New therapeutic drugs are gradually emerging, and the current treatment regimens of antineoplastic drugs are continually changed from traditional cytotoxic drugs to a

Figure 4  Prescription and cost trends of subclasses and specific drugs for PKIs (L01E). (A) Prescription trend of subclasses; (B) prescription trend of specific drugs; (C) cost trend of specific drugs. Each column shows the distribution rate of prescriptions for specific drugs, and the width of the column represents the relative number of hospitals. *Trends at p<0.05 in the line graph were represented by solid lines. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PKIs, protein kinase inhibitors; TKIs, tyrosine kinase inhibitors.
variety of innovative anticancer drugs. PKIs were the most commonly used antitumour drugs in patients with lung cancer during the study period, and their usage increased noticeably. This was possibly due to the implementation of the national drug price negotiation. Then, the price of PKI drugs, originally expensive, has significantly decreased, which reduced the economic cost and burden of drug use for patients and improved the survival rate of patients with lung cancer. In Asian populations, EGFR mutation is the most common type of mutation in non-small cell lung cancer (NSCLC), accounting for about 51.4%, while ALK rearrangement is less likely to occur in NSCLC. Thus, the clinical application rate of EGFR-TKIs is higher than ALK inhibitors in China. During the study period, the first-generation EGFR-TKIs, gefitinib and icotinib, the top two prescribed PKIs, were successfully negotiated for the first time in 2016 and directly included in the routine medical insurance list in 2017. Erlotinib, also the first-generation EGFR-TKI, has been compared with chemotherapy in several clinical trials in patients with EGFR-mutated lung cancer, all of which demonstrated that erlotinib had a benefit in progression-free
survival, but not in overall survival. It was indicated in our study that erlotinib was relatively less used. Afatinib, a second-generation drug, is an irreversible EGFR-TKI, which has been shown to have clinical activity in multiple clinical trials. However, there is no solid evidence that afatinib had greater efficacy, especially in terms of overall survival benefit, than the first-generation EGFR-TKIs in the first-line treatment of EGFR-mutated NSCLC. Meanwhile, the overall incidence of grade 3/4 adverse events of afatinib was comparable with that of erlotinib but higher than that of gefitinib. As a result, the use of afatinib was also relatively less in our analysis. Osimertinib, the third-generation agent, was initially marketed in China in 2017 and approved in 2019 as a first-line treatment for advanced NSCLC with EGFR mutation. Although first-generation (gefitinib, erlotinib and icotinib) and second-generation (afatinib) TKIs have been standard of care for initial management of EGFR, newer data suggest improved outcomes with front-line treatment with osimertinib. Given these data, osimertinib has become the preferred EGFR-TKI, although earlier-generation EGFR-TKIs remain acceptable alternatives. The mAbs were also the fastest growing agent in the global biopharmaceutical field. During the study period, the top three mAbs drugs used were bevacizumab, sintilimab and pembrolizumab. However, the number of prescriptions for other mAbs was modest due to the short introduction and supply time in China. Bevacizumab, ranked 14th in all antineoplastic drug prescriptions, was available for lung cancer treatment and added to the medical insurance list in China in 2017. Pembrolizumab showed good efficacy and safety for patients with advanced NSCLC; however, it was rarely used and not a cost-effective option in China due to its high price. Although the cost of sintilimab was much lower than pembrolizumab, the prescriptions were also less as it was not included in clinical guidelines for lung cancer during the study period. Several limitations of this study need to be acknowledged. First, given that the sample hospitals were often located in major metropolitan areas and the prescriptions were selected at random, the prescriptions in different regions might vary from 1 year to the next. It was possible that the sampling method has some inherent bias. Second, our sample hospitals were in major cities across several Chinese provinces, so they might not be representative of the total number of Chinese patients with lung cancer, especially in rural and economically underdeveloped areas. Third, there was a paucity of comprehensive prescription information, such as the lung cancer disease stage, surgical background and pathological findings. Therefore, this meant that neither the effectiveness of the anticancer therapy nor the appropriateness of the antineoplastic medication treatment could be assessed. Last, the p value of the trend obtained by the Mann-Kendall test might be biased since this study investigated yearly changes, a small sample size, over 5 years.

Conclusions

Prescription practices for Chinese patients with lung cancer underwent major changes during the study period. The usage of innovative antineoplastic drugs grew dramatically after the implementation of the national drug price negotiation in 2016 and continual update of clinical guidelines. Therefore, the Chinese government needs to expand benefits packages and strengthen the public medical assistance system for providing adequate and equitable cancer treatment. Our investigation will aid in understanding the present medication use status of patients with lung cancer in China, provide information...
for future drug management and act as a benchmark for other countries with situations similar to China’s.

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4other countries with situations similar to China’s.

Contributors
The contributions were made by all authors. JS and L2 screened and completed data extractions. JS and YL contributed to the first draft of the manuscript. LH, FY, YL and CZ revised the initial manuscript. XZ, RF, LZ and YF edited the manuscript. YL was responsible for the overall content as guarantor. All authors read the article and approved the final version.

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None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not required.

Ethics approval
Prescription codes were used to de-identify patients’ information to protect patient identity. Prescription extraction was approved by the ethics committee at each hospital. Human subjects research review was not required according to Peking University People’s Hospital Institutional Review Board regulations.

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No data are available.

Supplemental material
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