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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Imatinib, Dasatinib, and Nilotinib as First-Line Treatment for Chronic-Phase Chronic Myeloid Leukemia in China

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Abstract

Background and Objective Tyrosine kinase inhibitors (TKIs) have obvious effects on chronic myeloid leukemia (CML), but they are expensive in China. Moreover, the overall cost of treatment of CML is high and the medical economic burden of patients with CML on the government is heavy. This study tested the cost effectiveness of imatinib, nilotinib, and dasatinib as first-line treatment in Chinese patients who were first diagnosed with chronic myeloid leukemia in the chronic phase (CML-CP).

Methods A state-transition Markov model combining clinical effectiveness, utility, and cost data was used. Sensitivity analyses were conducted to determine the robustness of the model outcomes.

Results The imatinib-first, dasatinib-first, and nilotinib-first strategy offered patients 9.76, 9.87, and 9.72 quality-adjusted life years (QALYs) at a cost of US$303,502.42, US$381,681.03, and US$305,509.92 over 20 years, respectively. The nilotinib-first strategy exhibited the lowest utility and highest price and was thus eliminated. An incremental cost-effectiveness analysis of the imatinib-first strategy and the dasatinib-first strategy showed that the dasatinib-first strategy yielded an incremental cost–utility ratio (ICER) of 710,714.64 $/QALY compared with the imatinib-first strategy, which exceeded the threshold; hence, the dasatinib-first strategy was not cost effective and was eliminated. The results were robust for multiple sensitivity analyses.

Conclusion From the perspective of the Chinese medical system, imatinib is likely to be more cost effective than dasatinib and nilotinib for patients who were first diagnosed with CML-CP.

Key Points

This study tested the cost effectiveness of imatinib, nilotinib, and dasatinib as first-line treatment in Chinese patients who were first diagnosed with CML-CP.

The cost-effectiveness analysis suggested that imatinib is likely to be more cost effective than dasatinib and nilotinib as first-line treatment for patients who were first diagnosed with CML-CP from the perspective of the Chinese medical system.

1 Introduction

Chronic myeloid leukemia (CML) is a type of blood cancer that is most common among middle-aged adults and accounts for 15% of adult leukemia cases worldwide [1], and its annual incidence is 0.39–0.55/100,000 [2]. The clinical progression of the disease can be divided into three

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phases: (first) chronic phase (CP), (second) accelerated phase (AP), and (third) blast crisis phase (BC) [3]. Approximately 90% of patients are diagnosed during the CP and may survive between 3 and 8 in CP [4]. Blood cells retain their capacity to differentiate themselves normally. In blood circulation, immature cells (blasts) begin to be detected during AP and at + 30% during BC. During these phases, a patient's survival period decreases to months and even weeks.

Six drugs have been approved by the FDA for CML: imatinib, nilotinib, dasatinib, bosutinib, ponatinib, and omacetaxine; however, at present, only imatinib, dasatinib, and nilotinib are listed in China. The US FDA has approved the first line of treatment for patients of CML in the chronic phase (CML-CP), including imatinib, dasatinib, and nilotinib, but dasatinib and nilotinib are second-line treatments in most cases in China. Hence, this study selected imatinib, dasatinib, and nilotinib for comparison. Currently, TKIs are expensive in China, and the overall cost of treatment of CML is high; moreover, the medical economic burden of patients with CML and the government is heavy. According to economic analyses, dasatinib and nilotinib offer good value for money to patients with CML who experience imatinib failure in Thailand and Sweden [5, 6], but poor value for money in the United Kingdom [6, 7]. In the USA, studies have shown that when imatinib loses patent protection and its price declines, its use will be the cost-effective initial treatment strategy for CML-CP [8]. However, these results may not apply in China due to different epidemiological variables, clinical practices, health resource consumption associated with CML, prices of TKIs, and preferential policies in different regions.

As a developing country with a huge population and a shortage of health resources, policy makers in China are faced with the problem of choosing the TKI that is more cost effective for the initial treatment of CML-CP, and should be included in health insurance coverage.

In this study, we estimated the cost effectiveness of three TKIs (imatinib, nilotinib, and dasatinib) as first-line therapy for CML-CP based on the data of the Chinese population from the medical system perspective. Results of the current analysis might be a reference for the medical insurance department and clinicians.

2 Methods

2.1 Model Design

A cost-effectiveness analysis was performed from the medical system perspective using a Markov model (Fig. 1) with yearly cycles. The time frame is 20 years. Our model evaluated three different initial treatment strategies. The Markov model structure was designed based on the clinical setting in China and the China Clinical Practice Guidelines. Current guidelines in China recommend TKI as the first-line treatment of CML-CP, another TKI is given as replacement when first-line TKI resistance or intolerance occurs, and stem-cell transplantation (SCT) is considered when the second generation of TKI fails. We simplified the model and made some hypotheses. We suggested that treatment with any one of the three approved TKIs (imatinib, dasatinib, or nilotinib) should be initiated in CML-CP patients, and if the initial selection lacks efficacy or is not tolerated, the patients can either remain in the same health state or move to another TKI treatment in CP; when the second-line TKI does not work or is not tolerated, chemotherapy or SCT could be chosen. As the disease progresses, patients can move to AP and BC. Although patients can die in each health state from other causes, dying from CML is only possible in BC.

The primary health outcomes are QALYs, costs, and incremental cost–utility ratio (ICER) in US$/QALY gained. Cost and QALYs are discounted at an annual rate of 5%, in line with the Chinese guidelines for pharmacoeconomic evaluations [9]. ICER was calculated using the following formula:

$$\text{ICER} = \frac{(\text{cost [strategy A]} - \text{cost [strategy B]})}{(\text{effectiveness [strategy A]} - \text{effectiveness [strategy B]})}$$

We used 3 × the per capita gross domestic product (GDP) of China in 2016 (US$26,040) as the cost-effectiveness threshold according to the WHO recommendations [10–12].

The model was programed and analyzed in TreeAge 2015 (TreeAge Software, Inc., Williamstown, MA, USA).

2.2 Transition Probabilities

Due to the absence of head-to-head trials for all three competing strategies for the first-line therapy of CML, the transition probabilities of the models in this study were extracted from meta-analysis results based on the clinical studies in Chinese populations. Inclusion criteria for this meta-analysis were as follows: (1) randomized comparison clinical trial, (2) articles that evaluated the therapeutic effects of patients with CML using TKI, (3) the use of complete cytogenetic response at 12 months as the final indicator, and (4) studies written in Chinese or English.

Studies were identified by searching multiple literature databases, including PubMed, EMbase, the Cochrane Library, the China National Knowledge Infrastructure, VIP (Chinese Scientific and Technical Periodicals Database), and Wanfang Data (E-Resources for China Studies). The

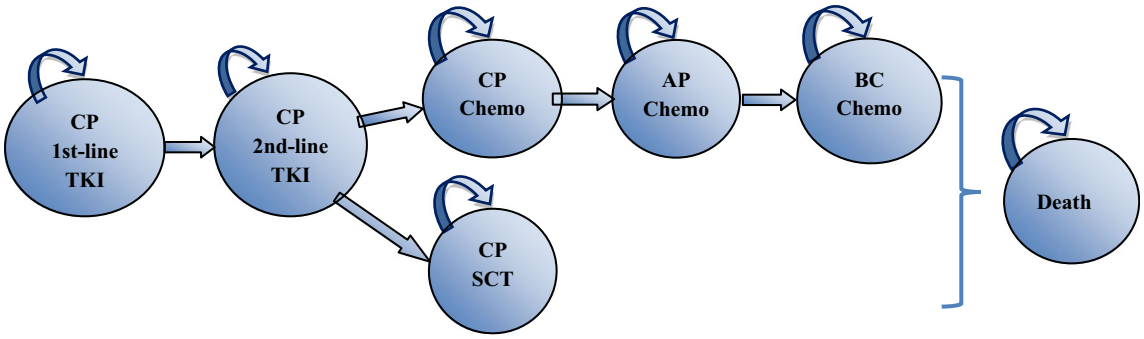

Fig. 1 State-transition diagram of the Markov state-transition model. *AP* accelerated phase, *BC* blast crisis phase, *CP* chronic phase, *SCT* stem cell transplantation, *TKI* tyrosine kinase inhibitor, *Chemo* chemotherapy

keywords "(imatinib OR nilotinib OR dasatinib) and (China OR Chinese) and (Clinical Trial)" were used. Queries were limited to those involving human subjects. Hand searches of reference lists of relevant literature reviews were used to complement the computer searches. Two reviewers independently assessed the quality of each study with the Cochrane Handbook Version 5.1.0 and extracted data independently.

Excluding the duplicates, we initially identified a total of 54 articles from all databases and search methods and then screened the literature by reading the abstract and full text for further evaluation. Eventually, nine studies of randomized controlled trials (RCTs) were chosen, of which four were in English and five were in Chinese [13–21]. The current meta-analysis is based on data extracted from international multicenter clinical trials on the Chinese population (ENESTchina) and international multicenter clinical trials on the East Asian population (DASISION) combined with the data of the clinical trials conducted in China.

The data extracted from RCT studies were incidence; thus, the formula $Pt = 1 - e^{(-rate \times t)}$ was used to convert the incidence to transition probabilities. When the study period in the literature was inconsistent with the cycle period of the model, the transformation formula $P1 = 1 - (1 - Pt)^{1/t}$ was used to convert [22] (Pt, transition probabilities in t cycles; P1, transition probabilities in the first cycles; rate, the incidence of events in the study; t, the study period) (Table 1).

2.3 Cost and Utilities

This analysis considered the setting of the Chinese medical system. Only direct medical costs were considered, including TKI costs, pharmaceuticals, treatment fee, and inpatient and outpatient costs (Table 2). The inpatient and outpatient costs, including the cost of diagnosis, health materials, inspection, laboratory tests, CT, MRI, color Doppler ultrasound, bed, care, other medical treatments, and blood transfusion, were obtained via medical chart reviews from local hospitals in 2015–2016. We obtained these data from the medical insurance institutions of Fujian province, China. The price of TKIs was inquired from the median price of the national drug-winning bid (Table 3). We searched the price in Yaozh (https://yaozh.com/), which is a Big Data service platform for China's health industry and provides information on the pharmaceutical industry, including the bidding information of medicines in all the provinces of China. The costs were converted into 2016 US dollars (CYN 6.2 = US $1).

Costs for dasatinib, nilotinib, and imatinib were added for each year that a patient remained in the CP. Drug dosages were based on the guidelines for diagnosis and treatment of CML in China (2016 edition) [2].

Preference-based health outcomes were considered in the current analysis. Life year (LY) was adjusted for health-related quality of life using utilities. Utility values can range from 1 (perfect health) to 0 (death) [25]. LYs were multiplied by utilities to derive QALYs. Utility values included in the current analysis were elicited from the published literature (Table 4) [25, 26].

2.4 Sensitivity Analyses

Sensitivity analyses included univariate and probabilistic analyses. Univariate sensitivity analyses were conducted to test the robustness of the model outcomes by varying effectiveness, cost, and utility parameters in a wide range. We varied the utility of each state, the cost of TKIs, chemotherapy, and SCT in the 10% range and varied the possible transition probability of each health state between the 95% confidence intervals. Probabilistic sensitivity analysis was performed using 1000 Monte Carlo simulations; gamma distributions were applied to costs and beta distributions for probabilities and utilities [8].

Table 1 Model input parameters for clinical effectiveness

Input parameter	Value	Source (references)
Probability of staying on first-line imatinib	0.53233	[13–17]
Probability of staying on first-line dasatinib	0.59343	[15, 16]
Probability of staying on first-line nilotinib	0.53976	[17]
Probability of staying on second-line dasatinib	0.33635	[18, 19]
Probability of staying on second-line nilotinib	0.46741	[20, 21]
Probability of staying in CP on chemotherapy after TKI failure	0.01	[21]
Probability of staying in AP on chemotherapy	0.11	[24]
Probability of dying from CML in BC on chemotherapy	0.09	[23]

CP chronic phase, *AP* accelerated phase, *BC* blast crisis phase, *TKI* tyrosine kinase inhibitor, *CML* chronic myeloid leukemia

Table 2 Cost data

	Cost (US$) per year	Source
Dasatinib first-line in CP	76,183.22	Medical insurance institution
Imatinib first-line in CP	43,845.35	Medical insurance institution
Nilotinib first-line in CP	57,328.51	Medical insurance institution
Nilotinib second-line in CP	85,679.38	Medical insurance institution
Dasatinib second-line in CP	76,183.22	Medical insurance institution
Chemo in CP	676.06	Medical insurance institution
SCT in CP	12,126.46	Medical insurance institution
Chemo in BC	5217.33	Medical insurance institution
Chemo in AP	1835.35	Medical insurance institution

CP chronic phase, *AP* accelerated phase, *BC* blast crisis phase, *SCT* stem cell transplantation

Table 3 Tyrosine kinase inhibitor drug price

Drug name	Manufacturer	Specification	Reference price (US$)	Source
Imatinib (Glivec)	Novartis	0.1 g × 60	1808.03	Yaozh
Dasatinib (Sprycel)	Bristol-Myers Squibb	20 mg × 60	2518.55	Yaozh
Nilotinib (Tasigna)	Novartis	0.15 g × 120	4725.15	Yaozh

Table 4 Utility values used in the model

Utilities	Value	Source (references)
Chronic phase	0.92	[26]
Accelerated phase	0.79	[26]
Blast phase	0.57	[26]

3 Results

3.1 Base-Case Analyses

Rollback analysis was conducted at a time frame of 20 years. Table 5 gives an overview of remaining QALYs, total cost of each strategy, and achieved ICER of the strategies. The nilotinib-first strategy had a low utility but was expensive; therefore, this strategy was eliminated. An incremental cost-effectiveness analysis of the imatinib-first strategy and the dasatinib-first strategy was proposed. The dasatinib-first strategy yielded an ICER of 710714.64 US$/QALY. Compared with the imatinib-first strategy, the ICER of the dasatinib-first strategy exceeded the threshold; thus, the strategy was not cost effective and was eliminated.

3.2 Queue Analysis

Queue analysis was conducted and the cycle was assumed to be 5, 10, and 20 years. Results showed that the imatinib-first strategy was still economically advantageous (Table 6).

3.3 Sensitivity Analyses

The robustness of the model and the results were tested using univariate and probabilistic sensitivity analyses. Figure 2 shows that the results were robust to the changes.

Table 5 Base-case results

Strategy	Costs (US$)	ΔCosts (US$)	QALYs	ΔQALYs	ICER (US$/QALY)
Imatinib first	303,502.42	0.00	9.76	0.00	
Nilotinib first	305,509.92	2,007.50	9.72	− 0.04	Eliminated
Dasatinib first	381,681.03	78,178.61	9.87	0.11	710,714.64

QALYs quality-adjusted life years, *ICER* incremental cost-effectiveness ratio

Table 6 Queue analysis results

Cycle (year)	Strategy	Costs (US$)	△Costs (US$)	QALYs	△QALYs	C/U	ICER (US$/QALY)
5	Imatinib first	230,590.96		4.75		48,545.47	
	Dasatinib first	302,405.40	71,814.44	4.78	0.03	63,264.73	2,393,814.67
10	Imatinib first	271,104.67		7.17		37,810.97	
	Dasatinib first	348,481.18	77,376.51	7.26	0.09	48,000.16	859,739.00
20	Imatinib first	306,055.51		9.96		30,728.46	
	Dasatinib first	384,251.35	78,195.84	10.08	0.12	38,120.17	651,631.97

QALYs quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *C/U* cost/utiity

The most sensitive parameters in the model were the utility in chronic phase (u_CP).

The probabilistic sensitivity analyses suggested that the imatinib-first therapy was overwhelmingly cost effective compared with the dasatinib-first therapy in 100% of 10,000 Monte Carlo simulations. The scatter plot shows that the circular line indicating the 95% confidence interval of ICERs among the simulations, and the dotted diagonal line indicates the willingness-to-pay threshold, which has a slope of US$26,040.0/QALY. Simulations appearing below this line favored the imatinib-first strategy as cost effective (Fig. 3). Cost-effectiveness acceptability curves (CEACs) of the three competing strategies were generated to present the probabilities of cost effectiveness. The CEACs are shown in Fig. 4. The imatinib-first strategy showed cost effectiveness in approximately 75% of the simulations, considering a cost-effectiveness threshold of US$26,040 (3 × the Chinese per capita GDP in 2016).

4 Discussion

We evaluated the cost effectiveness of three different treatments in Chinese patients with CML who were in CP at first diagnosis. Our findings identified imatinib as the dominant strategy in terms of incremental costs per additional QALY gained. Analysis results showed that the nilotinib-first strategy was eliminated because it cost more and gained fewer QALYs than the imatinib-first strategy. Moreover, the dasatinib-first strategy cost more and gained more QALYs than the imatinib-first strategy. Incremental analysis showed that the ICERs of the dasatinib-first strategy versus the imatinib-first strategy was 710714.64, which far exceeded the threshold in China (US$26,040/QALY).

Several previous studies have attempted to estimate the cost effectiveness of TKIs as first-line treatment for patients with CML-CP. Rochau et al. [26] identified the optimal sequential treatment strategy in terms of effectiveness and cost effectiveness for patients with CML within the US healthcare context. Imatinib → nilotinib → chemotherapy/SCT yielded an ICER of US$253,500/QALY compared with imatinib → chemotherapy/SCT. Nilotinib → dasatinib → chemotherapy/SCT yielded an ICER of US$445,100/QALY compared with imatinib → nilotinib → chemotherapy/SCT. Imatinib → nilotinib → chemotherapy/SCT and nilotinib → dasatinib → chemotherapy/SCT can be considered cost effective for patients with CML, depending on their willingness to pay [26]. Moreover, Rochau et al. [27] evaluated the long-term cost effectiveness of seven sequential therapy regimens for CML in Austria. The sequential application of TKIs was standard of care; thus, the analysis pointed toward imatinib followed by nilotinib as the most cost-effective strategy [27]. Romero et al. [28] conducted a cost-effectiveness analysis by using a Markov model to evaluate a hypothetical cohort of 100 55-year-old patients with newly diagnosed CML-CP. The authors found that in Colombia, using progression-free (PF)-LYs as the efficacy outcome, nilotinib was highly cost effective when compared with imatinib and was dominant versus dasatinib in first-line therapy for CML-CP [28]. Padula et al. [8] constructed Markov models to compare the 5-year cost effectiveness of imatinib-first versus physician's choice from a US

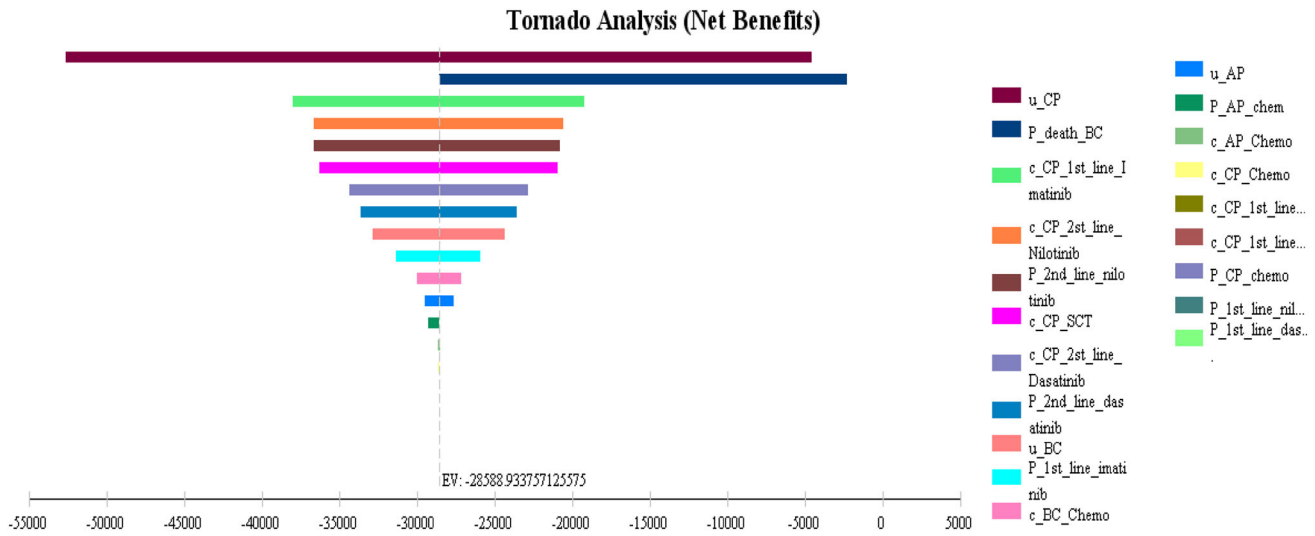

Fig. 2 One-way sensitivity analysis. *P_1st_line_ imatinib* probability of staying on first-line imatinib, *P_1st_line_dasatinib* probability of staying on first-line dasatinib, *P_1st-line_nilotinib* probability of staying on first-line nilotinib, *P_2nd_line_dasatinib* probability of staying on second-line dasatinib, *P_2nd_line_nilotinib* probability of staying on second-line nilotinib, *P_CP_chemo* probability of staying in CP on chemotherapy, *P_AP_chemo* probability of staying in AP on chemotherapy, *P_death_BC* probability of dying from CML in BC on chemotherapy, *c_CP_1st_line_dasatinib* the cost of the dasatinib strategy as first-line treatment in CML-CP, *c_CP_1st_line_imatinib* the cost of the imatinib strategy as first-line treatment in CML-CP, *c_CP_1st_line_nilotinib* the cost of the nilotinib strategy as first-line treatment in CML-CP, *c_CP_2nd_line_nilotinib* the cost of switching to nilotinib when first-line treatment of TKI has no effectiveness, *c_CP_2nd_line_dasatinib* the cost of switching to dasatinib when first-line treatment of TKI has no effectiveness, *c_CP_Chemo* the cost of chemotherapy in CML-CP, *c_CP_SCT* the cost of SCT in CML-CP, *c_AP_Chemo* the cost of chemotherapy in CML-AP, *c_BC_Chemo* the cost of chemotherapy in CML-BC, *u_CP* the utility in CML-CP, *u_AP* the utility in CML-AP, *u_BC* the utility in CML-BC. *c_CP_1st_line_dasatinib* the cost of the dasatinib strategy as first-line treatment in chronic-phase of CML, *c_CP_1st_line_imatinib* the cost of the imatinib strategy as first-line treatment in chronic-phase of CML, *c_CP_1st_line_nilotinib* the cost of the nilotinib strategy as first-line treatment in chronic-phase of CML, *c_CP_2nd_line_nilotinib* the cost of switching to nilotinib when first-line treatment of TKI have no effectiveness, *c_CP_2nd_line_dasatinib* the cost of switching to dasatinib when first-line treatment of TKI have no effectiveness, *c_CP_Chemo* the cost of chemotherapy in chronic-phase of CML, *c_CP_SCT* the cost of stem cell transplantation in chronic-phase of CML, *c_BC_Chemo* the cost of chemotherapy in blast-crisis phase of CML, *c_AP_Chemo* the cost of chemotherapy in accelerated phase of CML

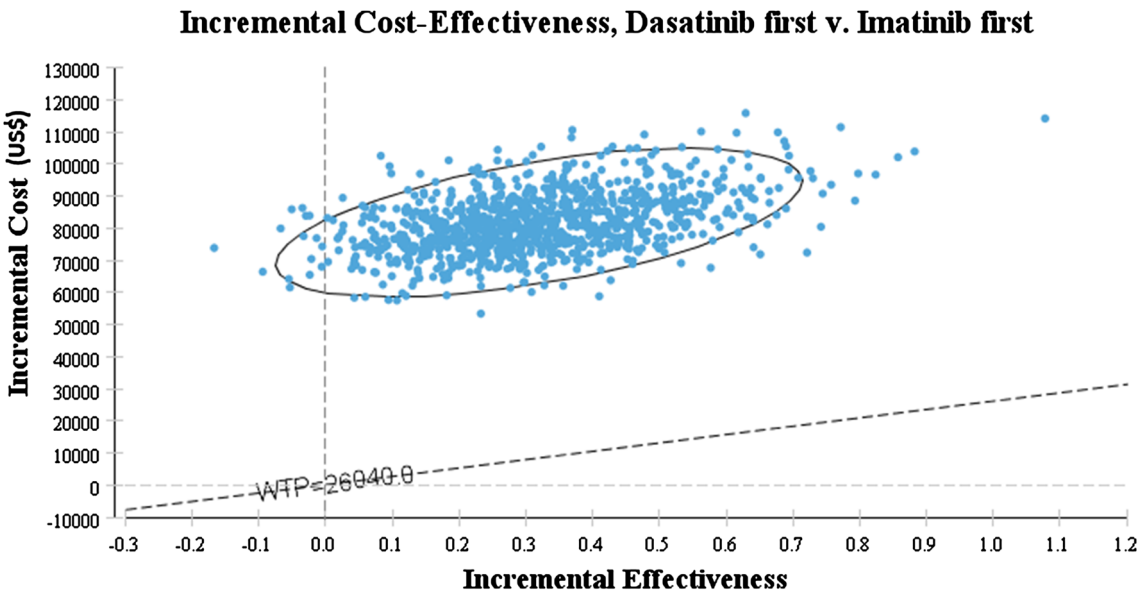

Fig. 3 Probabilistic sensitivity analyses for imatinib first versus dasatinib first. *WTP* willingness-to-pay in US$

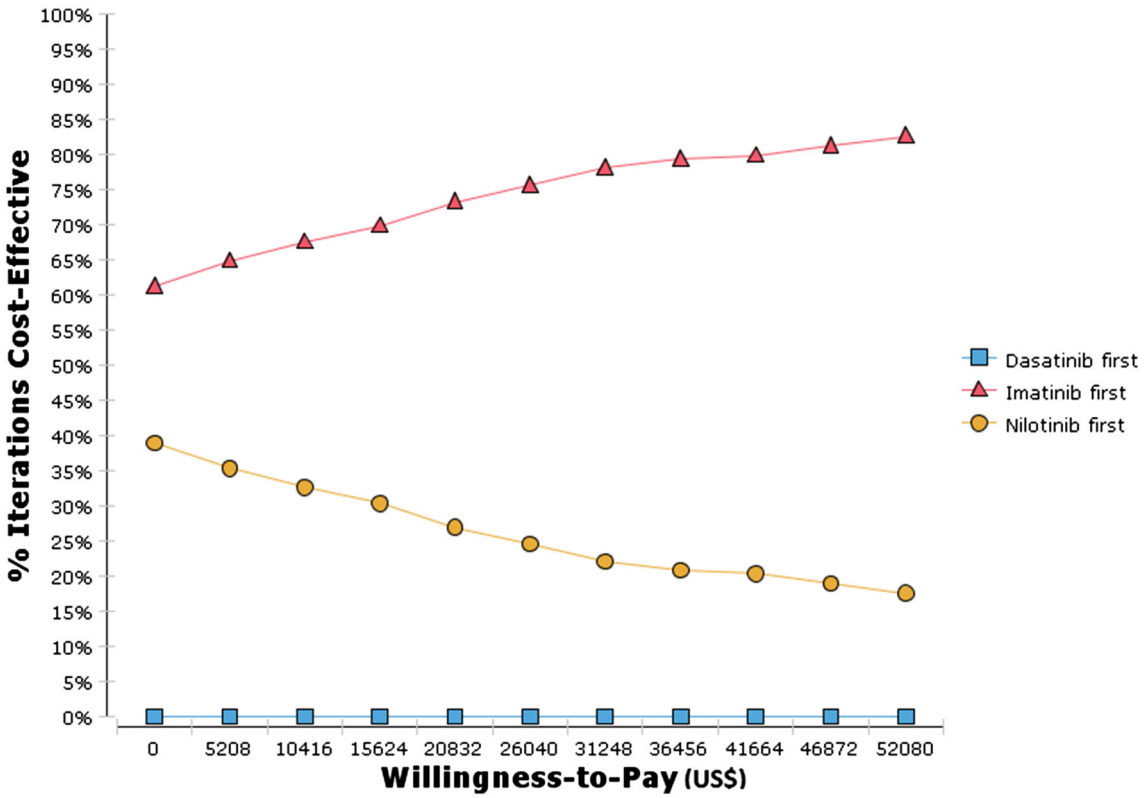

Fig. 4 Acceptability curves comparing the cost effectiveness of three competing strategies

commercial payer perspective. Imatinib-first (US$277,401, 3.87 QALYs) offered patients a 0.10 decrement in QALYs at a savings of US$88,343 over 5 years to payers compared with physician's choice (US$365,744, 3.97 QALYs). The imatinib-first ICER was approximately US$883,730/QALY [8]. The conclusion from each study was different, but the purpose of all these studies was to investigate how to choose TKI drugs as first-line treatment for CML-CP and which TKI is the most economic. The sequential treatment strategies we considered were consistent with the results of these studies, but because of the difference of the model design, parameters, and threshold, our results drew slightly different conclusions.

The data and study design had a number of limitations. First, our decision-analytic model was a simplification of reality. The treatments and practice patterns were derived from Chinese guidelines and Chinese CML experts, which were consistent with the NCCN Guidelines. Individual treatment decisions were not represented by our model. All cost parameters were derived specifically for the Chinese context, which may be different from other countries. The inpatient and outpatient costs were obtained from the medical insurance institutions of Fujian province, China. As the center province of China's health reform, Fujian province's medical models are spread across the country; hence, its treatment and practice patterns and costs are representative. Second, no utilities were available specifically for the Chinese setting and specific to each treatment line, which is a major limitation when comparing QALYs and can only be solved by conducting utility studies. Finally, the cost of the adverse events (AEs) of the three TKI drugs in this study was included in the cost of treatment, which was not calculated separately. The AEs of TKIs varied with different individuals and nearly 95% of AEs occurred during the first year (not more than a 5% increase during the second year) [28]. The most common grade 3/4 AEs included hematologic toxicities, such as thrombocytopenia and neutropenia, and nonhematologic toxicities, such as gastrointestinal disorders, edema, rash, and musculoskeletal discomfort. However, none of these led to cessation of treatment. The ratio of the cost of AEs to the overall cost was small and did not affect the conclusion. The sensitivity analysis was carried out to verify the stability of the scheme and the reliability of the model calculation.

5 Conclusion

Imatinib is a cost-effective strategy as first-line treatment for CML-CP in China. The decision on the cost effectiveness has to be made in the context of an individual or society's willingness to pay. These results may be used to support CML treatment decision making by clinicians and patients. Our model was synthesized from a heterogeneous collection of clinical outcome data derived from studies with varying designs. When high-quality data become available or drug prices change as generic drugs go on sale and national negotiations take place, the results will need to be updated.

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Compliance with Ethical Standards

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Conflict of interest The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflicts of interest to disclose.

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