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An economic analysis of high-dose imatinib, dasatinib, and nilotinib for imatinib-resistant chronic phase chronic myeloid leukemia in China

A CHEERS-compliant article

Bin Wu, PhD[a], Maobai Liu, PhD[b], Te Li, PharmD[c], Houwen Lin, PhD[d], Hua Zhong, PhD, MD[e,*]

Abstract

Background: The aim of the study was to test the cost-effectiveness of dasatinib compared to high-dose imatinib and nilotinib in Chinese patients who were diagnosed with imatinib-resistant chronic myeloid leukemia in the chronic phase (CML-CP).

Methods: A Markov model combined with clinical effectiveness, utility, and cost data was used. The sensitivity analyses were conducted to determine the robustness of the model outcomes. The impact of patient assistance programs (PAPs) was assessed.

Results: Treatment with dasatinib is expected to produce 3.65, 0.59, and 0.15 more quality-adjusted life years (QALYs) in comparison with high-dose imatinib (600 and 800 mg) and nilotinib, respectively. When a PAP was available, dasatinib yielded an incremental cost of $16,417 per QALY compared to imatinib (600 mg) and was cost-saving compared to imatinib (800 mg) and nilotinib.

Conclusion: When PAP is available in the Chinese setting, dasatinib is likely to be a cost-effective strategy for patients with CML-CP standard-dose imatinib resistance. The results should be carefully explained due to the assumptions and limitations used in the study.

Abbreviations: AEs = adverse events, AP = accelerated phase, BC = blast crisis, CCyR = complete cytogenetic response, CHR = complete hematological response, CML = chronic myeloid leukemia, CP = chronic phase, GDP = gross domestic product, ICER = incremental cost-effectiveness ratio, LY = life years, NR = no response to treatment, OS = overall survival, PAP = patient assistance programme, PCyR = partial cytogenetic response, PFS = progression-free survival, PFT = post-failure treatments, QALY = quality-adjusted life-year, TKI = tyrosine kinase inhibitor.

Keywords: chronic myeloid leukemia, cost-effectiveness, dasatinib, Markov model

1. Introduction

Chronic myeloid leukemia (CML) is the third most common type of leukemia worldwide. Worldwide, the average annual incidence of CML is 0.6 to 2 new cases per 100,000 people (median age: 53 years).[1] In China, 5000 to 8000 new cases are diagnosed annually, and the median age is much younger (40 years).[2] The natural course of CML consists of the following 3 gradually progressive phases: (1) chronic phase (CP), (2) accelerated phase (AP), and (3) blast crisis (BC). The CP is the benign phase of CML that is characterized by mild symptoms, including fatigue and weight loss. The advanced phases (AP and BC) are associated with disease progression and a much poorer prognosis. Most people (approximately 90%) are diagnosed during the CP.[1]

Imatinib was the first TKI utilized for the treatment of CML and is widely prescribed. According to the International Randomized Study of Interferon and STI571 (IRIS) study, patients randomized to receive imatinib demonstrated an 85% overall survival (OS) rate (8 year data) and 0.9%, 0.5%, 0%, 0%, and 0.4% annual rates of progression to AP or BC in years 4 to 8, respectively, after imatinib therapy onset.[3] Imatinib is the first-line treatment recommendation for newly diagnosed CML patients.[4] However, nearly 40% of patients discontinue imatinib after 5 years due to the absence of efficacy (primary resistance), loss of previously obtained responses (acquired resistance), and/or intolerance to therapy.[1] High-dose imatinib (600 or 800 mg per day) and second-generation TKIs, including dasatinib and nilotinib, have been used to treat imatinib-resistant CML.[5] According to economic analyses, dasatinib and nilotinib offer good value-for-money for CML patients who experience imatinib failure in Sweden, the United Kingdom, and Thailand.[6–8] However, these results might not be applicable

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[a] Medical Decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, [b] Department of Pharmacy, Fujian Union Hospital, Affiliated with Fujian Medical University, Fujian, [c] Department of Pharmacy, Yuxi People's Hospital, Affiliated with the Kunming Medical College, Yuxi, [d] Department of Pharmacy, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, [e] Department of Hematology, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China.

[*] Correspondence: Hua Zhong, Department of Hematology, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China, (e-mail: zhrenji@126.com).

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for decision making in China because of dealing with economic data transferability[9] is still in challenge due to different epidemiological variables, clinical practice, health resource consumption associated with CML, prices of TKIs, and their preferential policies in different regions. As a BRIC (Brazil, Russia, India, and China) country with a huge population and medium incomes, Chinese decision makers face the question of whether second-generation TKIs should be covered by insurance. The results of the current analysis also might be a reference for other East Asian regions and BRIC countries.

In this study, we examined whether dasatinib (100 mg) and nilotinib (800 mg) are cost-effective treatments for CML-CP patients who are resistant to normal-dose imatinib in China.

2. Patients and methods

2.1. Model structure

A Markov cost-effectiveness model was developed to model the lifetime disease progression in patients with CML-CP and failure of normal-dose imatinib (Fig. 1). In the Markov model, the modeling diseases are structured around a set of mutually exclusive and collectively exhaustive health states, and a hypothetical individual must be in only 1 state in any cycle. The average number of cycles that individuals reside in each state can be used in conjunction with state values (e.g., life-years, health-related quality-of-life, and cost) to estimate life expectancy, quality-adjusted life expectancy, and expected costs.[10] The model consists of the following 3 health states: (1) stable disease, (2) progressed disease, and (3) death; the model uses monthly cycles with probabilities for the likelihood of a health state transition. All the patients were assumed to start with one of the following treatments for CML-CP: (1) nilotinib 800 mg daily (nilotinib strategy), (2) dasatinib 100 mg daily (dasatinib strategy), (3) imatinib 600 mg daily (imatinib 600 mg strategy), or (4) imatinib 800 mg daily (imatinib 800 mg strategy). The following 4 responses to medical treatment after an initial 3-month treatment period were used to predict disease progression: (1) no response to treatment (NR); (2) achieved a complete hematologic response (CHR); (3) achieved a partial cytogenetic response (PCyR); or (4) achieved a complete cytogenetic response (CCyR). It was assumed that when patients failed the therapy (i.e., the patients were categorized as "no response") or the disease progressed and they discontinued treatment that all patients received similar postfailure treatments (PFT) according to an expert's opinion. The patients included in the model at baseline reflected the normal clinical characteristics (such as age) of the Chinese patients.[2] The model was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA).

Life expectancy (life years, LYs), quality-adjusted life years (QALYs), and the associated direct medical costs were the primary outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated and expressed as cost per additional QALY gained. Future costs and QALYs were annually discounted at 3%. This economic study was based on a literature review and model techniques, and did not require approval by the institutional Research Ethics Board.

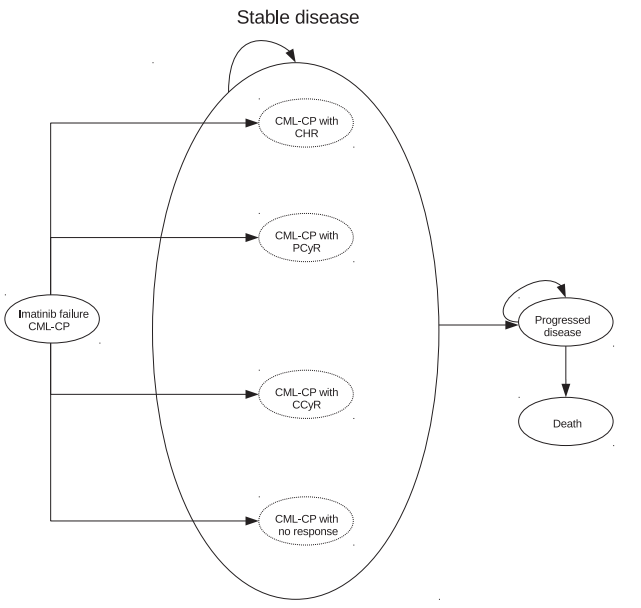

Figure 1. General process for second-line treatments in patients with imatinib-resistant or intolerant CML. The risk of disease progression depends on the underlying treatment strategy and treatment response. CCyR = complete cytogenetic response, CML = chronic myeloid leukemia, CHR = complete hematologic response, PCyR = partial cytogenetic response.

2.2. Clinical data

Based on the 2 small confirmatory clinical trials, the similar efficacy of TKIs was found between Chinese and other populations,[11,12] which enrolled 119 patients receiving dasatinib 100 mg daily and 23 patients receiving nilotinib 800 mg daily treatment, respectively. Thus, the current analysis would assume the clinical data from abroad pivotal clinical trials [13–16] would be same with the Chinese setting. The efficacy data for imatinib (600 mg), imatinib (800 mg), nilotinib, and dasatinib used in the model achieved initial response rates within 24 months (Table 1), including CCyR, PCyR, and CHR, the known surrogates for progression-free survival (PFS). Although these efficacy data were obtained from different trials, we assumed they were comparable as previous reports had done[6–8] because of their similar inclusion and exclusion criteria and the recommendation of clinical guidelines used them as the evidence source.[17,18] We would check this assumption in the sensitivity analysis. The PFS data were obtained from the CA180-034 study, where 670 patients with CML-CP and imatinib failure received dasatinib at doses of 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily; the estimated 6-year protocol-defined PFS rates for the different doses of dasatinib were 49%, 51%, 40%, and 47%, respectively.[13] The Kaplan–Meier survival data for PFS in patients with CCyR, PCyR, and CHR was fitted to

Table 1

Initial response to treatment and Weibull parameters according to the responses.

Parameter	NR	CHR	PCyR	CCyR	Source
Response of treatment					
600 mg-imatinib	56.4%	15.4%	28.2%	0.0%	[15]
800 mg-imatinib	32.1%	13.3%	14.1%	40.5%	[16]
Nilotinib 800 mg	6.0%	35.0%	18.0%	41.0%	[15]
Dasatinib 400 mg	8.1%	33.1%	15.3%	43.5%	[14]
Weibull survival model of PFS based on the response					
Lambda	0.149	0.0029	0.0028	0.0004	[13]
Gamma	0.5856	1.5947	1.3009	1.4295	[13]

CCyR = complete cytogenetic response, CHR = complete hematologic response, NR = no response, PCyR = partial cytogenetic response, PFS = progression-free survival.

the Weibull distribution, where the lambda gamma parameters were measured. The risk for transitioning from CP to advanced phases was estimated from the Weibull survival model.[19] It was assumed that the prognosis was dependent on the treatment response regardless of the specific TKI prescribed.[20–22]

After the disease progressed to the advanced phase, the median OS was 12 months.[23] The survival time spent in the AP and BC phases was assumed to be independent of treatment. The unspecified mortality in the CP was modeled as a function of age and sex from the current Chinese life-table.[24]

The data related to adverse events (AEs) were extracted from trials.[13–16] We analyzed the frequency of AEs over time. Because nearly 95% of AEs occurred during the first year (not more than a 5% increase during the second year),[25] we decided to quantify AEs only during the first year of TKI therapy in our model. Furthermore, we identified only grade 3/4 AEs occurring in 10% or more of the patients for model input based on a Chinese hematologist's opinion.[7]

2.3. Cost and utility

Chinese clinical practices related to CML were validated from interviews with 2 Chinese clinical hematologists at the same facility. "Cost" is from the perspective of the Chinese health care system. Direct medical costs (Table 2), such as pharmaceuticals and laboratory tests, as well as inpatient costs were obtained from official Chinese sources.[26] All the costs were converted into 2015 US dollars (CYN 6.20 = US $1.00).

Costs for dasatinib, nilotinib, and imatinib were added for each month that a patient remained in the CP. The drug dosages were based on trials from which we sourced the initial responses (Table 1). Because TKIs are administered orally, no administration costs would be incurred. The monthly costs associated with follow-up visits and SAE management in CML-CP patients were estimated from Chinese clinical experts. After disease progression, the monthly cost of PFT was obtained via medical chart reviews from local hospitals.

Utility scores published in the literature were included in the current analysis (Table 2). The impact of the SAEs on health utility was also captured in the model, where the utility estimates for SAEs were assumed to be a 5% decrement because no reference was identified.

2.4. Sensitivity analyses

Because it can be challenging for patients to afford TKIs in health resource-limited settings, a patient assistance program (PAP) would possibly be introduced to make TKIs available to eligible patients. Currently, CML patients in a PAP would pay for 3 months of TKIs and receive 9 months of donations every year. Therefore, the scenario analyses assessed the impact of dasatinib PAP for targeted therapy.

Sensitivity analyses included univariate and probabilistic sensitivity analyses. A wide range of univariate sensitivity analyses were conducted to test the robustness of the model outcomes by varying effectiveness, utility, and cost parameters. Probabilistic sensitivity analyses were conducted using a Monte Carlo simulation. One thousand simulations of the model were run in the probabilistic sensitivity analysis, which adopted probabilities, proportions, and utilities following beta distributions, nondrug costs following gamma distributions, and dose intensities (normal distributions).

We used 3× the per capita gross domestic product (GDP) of China in 2014 as the cost-effective threshold according to WHO recommendations.[27–29]

3. Results

3.1. Base-case analyses

The model-derived PFS probabilities were calculated according to the initial responses during the time from the first month to the 48th month, and the simulated PFS curves satisfactorily matched those from the clinical trial (Fig. 2). The goodness-of-fit test showed that the adjusted R^2 values for CHR, PCyR, and CCyR were 0.97, 0.94, and 0.77, respectively.

Dasatinib treatment provided more health benefits compared to high-dose imatinib and nilotinib. Additional PFS times for dasatinib (400 mg) versus imatinib (600 mg), imatinib (800 mg), and nilotinib (800 mg) were 5.96, 0.72, and 0.22 years, respectively, and the LYs increased by 5.89, 0.71, and 0.22 years,

Table 2

Costs and utilities.

Parameters	Unit cost	Range	Source
Resource use per month, US $			
Imatinib 600 mg	1542	771–1542*	Local charge
Imatinib 800 mg	2056	1028–2056*	Local charge
Nilotinib 800 mg	1579	789–1579*	Local charge
Dasatinib 100 mg	1276	638–1276*	Local charge
Follow-up visiting for responders	141	59–225	Expert opinion
Follow-up visiting for nonresponders	320	199–609	Expert opinion
Postfailure treatment†	950	443–885	Expert opinion
Management of SAEs in imatinib 600 mg arm‡	297	298–595	Expert opinion
Management of SAEs in imatinib 800 mg arm‡	297	298–595	Expert opinion
Management of SAEs in nilotinib 800 mg arm‡	497	497–995	Expert opinion
Management of SAEs in dasatinib 100 mg arm‡	372	372–744	Expert opinion
Utility score			
CML-CP with response	0.84	0.82–0.86	[27]
CML-CP with no response	0.66	0.63–0.68	[27]
Progressed disease	0.21	0.19–0.24	[27]

* The range was assumed for a 1-way sensitivity analysis.

† The cost was estimated based on expert opinion; 50% of patients received chemotherapy; 30% received bone marrow transplantation; and the remaining patients received palliative care.

‡ The costs related to the management of SAEs were derived from hematologists who determined the costs by multiplying the unit cost of treating SAEs and the probabilities of SAEs from trials.[13–16]

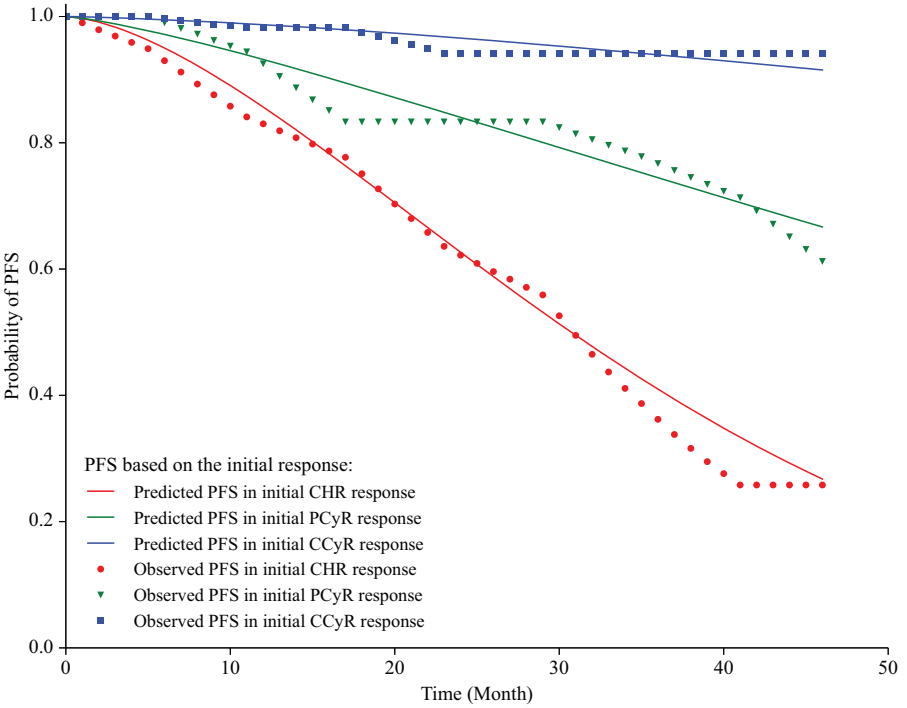

Figure 2. Calibration curves for PFS based on the achieved initial response. CCyR = complete cytogenetic response, CHR = complete hematologic response, PCyR = partial cytogenetic response, PFS = progression-free survival.

respectively. The additional QALYs gained of dasatinib were ranged from 0.15 against nilotinib to 3.65 against imatinib (600 mg) (Table 3). The increased cost of dasatinib over imatinib (600 mg) without or with the PAP was $215,084 and $59,859, which yielded ICERs of $58,989 and $16,417/QALY, respectively. Compared to imatinib (800 mg) and nilotinib, dasatinib treatment saved money and was effective (Fig. 3).

3.2. Sensitivity analyses

Because dasatinib and nilotinib have been recommended for the management of patients with imatinib failure and PAP was available in the Chinese setting, a 1-way sensitivity analysis for dasatinib versus nilotinib with PAP was performed. Dasatinib was more effective than nilotinib according to most of the sensitivity analyses (Table 4). The initial treatment response has a substantial impact. If the CCyR of dasatinib decreased to 39.5% or the CCyR of nilotinib increased to 44%, the dasatinib strategy would become less effective.

Based on the probabilistic sensitivity analyses, the cost-effectiveness acceptability curves showed that dasatinib without and with PAP had a 0 and 0.90 probability, respectively, of being cost-effective at a willingness-to-pay threshold of $22,455/QALY (Fig. 4).

4. Discussion

We evaluated the cost-effectiveness of 4different treatments in Chinese CML patients who were resistant to standard-dose imatinib. Our findings identified dasatinib as the dominant strategy in terms of incremental costs per additional QALY gained. This finding may be due to both the considerable survival and quality of life advantages offered by dasatinib.[13–16] The ICERs of dasatinib versus the imatinib (600 mg) strategy ranged from $61,429/QALY without PAP to $18,021/QALY with PAP in the base-case analysis, which indicates that dasatinib with PAP was more cost-effective compared to thresholds applied in China ($22,455/QALY).

Table 3

Base-case results.

Strategy	Imatinib 600 mg	Imatinib 800 mg	Nilotinib 800 mg	Dasatinib 100 mg
PFS year	3.49	8.73	9.23	9.45
LY	4.96	10.14	10.63	10.85
QALY	2.70	5.75	6.19	6.34
Cost, $				
without PAP	176,630	392,151	407,211	391,715
with PAP	74,007	137,199	141,184	133,866
ICER, $/QALY				
without PAP	–	70,601	66,005	58,989
with PAP	–	20,701	19,230	16,417

ICER = incremental cost-effectiveness ratio, LY = life years, PAP = patient assistance program, PFS = progression-free survival, QALY = quality-adjusted life years.

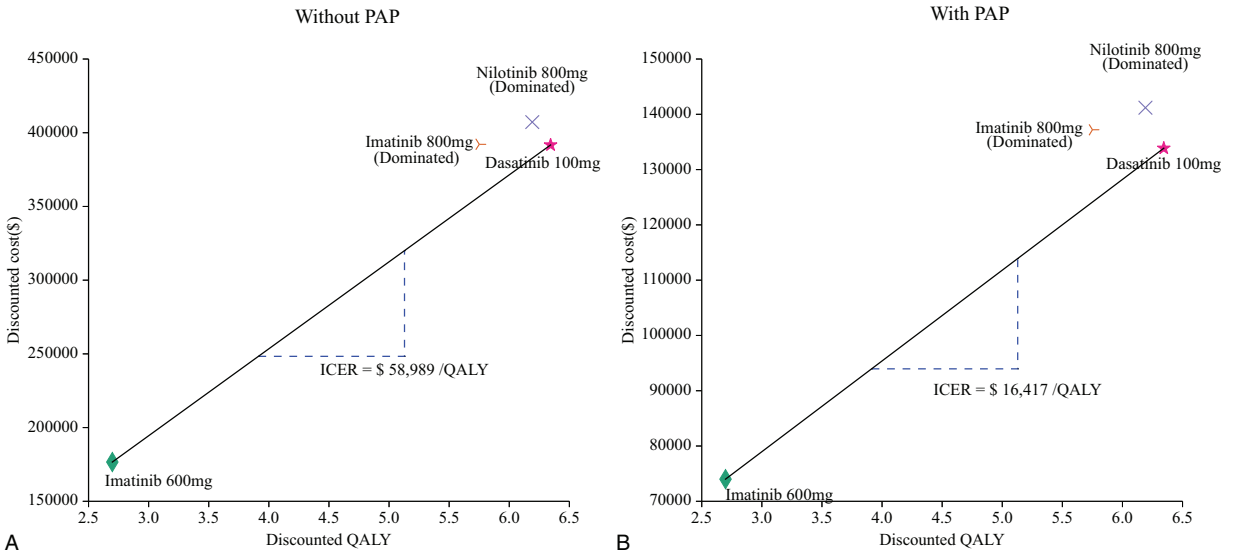

Figure 3. Cost-effective frontier analysis (A) without PAP or (B) with PAP. PAP = patient assistance program, QALY = quality-adjusted life years.

Several previous studies have attempted to estimate the cost-effectiveness of second-generation TKIs in CML patients who are resistant to standard-dose imatinib.[6–8] Ghatnekar et al[6] (2010) conducted an economic analysis of dasatinib versus imatinib (800 mg); dasatinib was a cost-effective treatment because it offered an additional 0.62 QALY with an additional US $4,521 cost during a lifetime period, which resulted in US $7,318 per QALY gained in the Swedish healthcare system. This study used different initial responses and PFS benefits beyond the duration of the trial.[30,31] In Thailand, Kulpeng et al[7] (2014) reported that treatment with dasatinib gained more QALYs (2.13) at a lower cost (US $46,166) and an ICER of THB US $2,358 per QALY for nilotinib compared to imatinib (800 mg) strategy. In our study, dasatinib with PAP was a cost-effective strategy (consistent with the previous 2 studies), although many factors differed in our analysis, including the discount rates, background mortality rates, unit prices, and resource use. Hoyle et al (2011) conducted an economic analysis of dasatinib and nilotinib compared to imatinib (800 mg) from the perspective of the UK National Health Service. The authors found that nilotinib was better than high-dose imatinib with an additional 0.32 QALYs at a slightly lower cost (US $13,862). The authors also concluded that dasatinib provided slightly more (0.53) QALYs at a substantially greater cost (US $61,071), which yielded a very high incremental cost-effectiveness ratio of US $114,274/QALY versus high-dose imatinib.[8] One potential reason for this finding might be the different costs of TKIs. The cost of imatinib (800 mg) per day in the UK was nearly 23% higher than nilotinib and 28% higher than dasatinib. In our study, the cost of imatinib (800 mg) per day was nearly 30% higher than nilotinib and 60% higher than dasatinib.

Due to the intolerance of most Chinese CML patients to imatinib (800 mg), the imatinib (600 mg) strategy has always been administered for CML patients who are resistant to standard-dose imatinib in Chinese clinical practices.[32,33] Thus, one of the strengths of this study was the use of imatinib (600 mg) as a baseline strategy in contrast to previous studies that utilized the imatinib (800 mg) strategy. Imatinib dose escalation would notably increase the cost of drug acquisition but limit efficacy.[32] This study identified the most beneficial baseline strategy for assessing the cost-effectiveness of second-generation TKIs in a Chinese context. However, the observational times for these dasatinib and nilotinib trials were short, and patients with CML-CP typically survive for many years. Thus, accurately extrapolating the survival times beyond the current follow-up times would be necessary. The prognosis data used in this model was

Table 4

One-way sensitivity analysis (dasatinib vs nilotinib) with PAP.

Parameters	Base value	Low value		High value	
		Value	ICER	Value	ICER
Median survival time after progression	12 months	6 months	Dominates	24 months	Dominates
Cost of dasatinib, reduction	75%	80%	Dominates	70%	Dominates
Cost of nilotinib, reduction	75%	80%	Dominates	70%	Dominates
Cost of postfailure treatment	$950	$403	Dominates	$1290	Dominates
Cost of blood transfusion	$39	$19	Dominates	$81	Dominates
Utility of chronic phase with response	0.84	0.82	Dominates	0.86	Dominates
Utility of chronic phase without response	0.66	0.63	Dominates	0.68	Dominates
Age	43 years	35 years	Dominates	60 years	Dominates
Discounting	3%	0%	Dominates	8%	Dominates

CCyR = complete cytogenetic response, ICER = incremental cost-effectiveness ratio, PAP = patient assistance program.

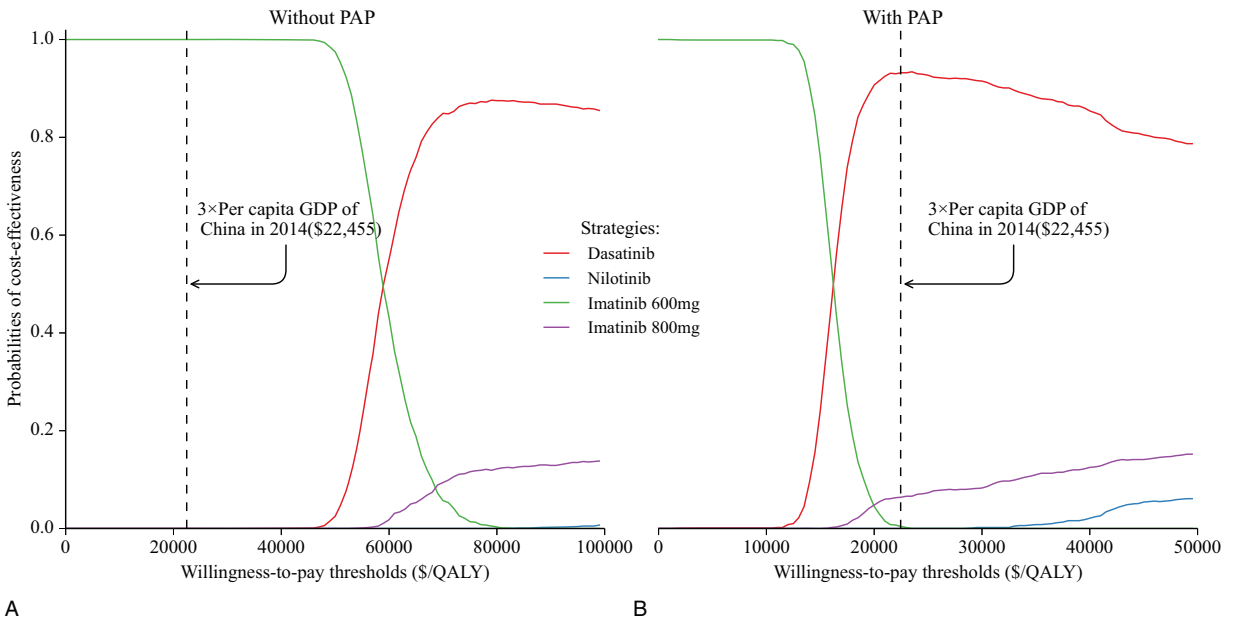

Figure 4. Cost-effectiveness acceptability curves showing the probability that each option is cost-effective at different values of the willingness-to-pay for a QALY without PAP (A) or with PAP (B). PAP = patient assistance program, QALY = quality-adjusted life years.

derived from a study with a longer follow-up time, which was parametrized using the Weibull model.[13]

Nonetheless, the results from this analysis must be interpreted carefully within the limitations of the data and study design. First and foremost, owing to the absence of head-to-head trials for all 4 competing strategies for the second-line therapy of CML resistant to standard-dose imatinib, the clinical efficacy data used in this study were obtained from 3 different clinical trials, and an indirect comparison was conducted. Second, new therapies are rapidly being developed for managing imatinib-resistant CML, including bosutinib.[34] This approach has improved the long-term efficacy and tolerance results for patients with imatinib-resistant or imatinib-intolerant CML.[35] However, these new agents tend to be more expensive than current therapies. The current analysis did not trace all the medical resources associated with the potential new agents. Third, a relationship is assumed between PFS and initial treatment response for predicting the lifetime health outcome. However, the lifetime results in this study were derived from a relatively short-term study.[13] We also assumed that this relationship was the same for all strategies.[8] This is a common dilemma when modeling economic analyses. When more information becomes available, the analysis should be updated. Fourth, the long-term use of nilotinib would increase the risk of cardiovascular toxicity,[36,37] and the current analysis did not evaluate the impact of these toxicities. Fifth, with the approval and sales of generics, the costs of these TKIs would be decreased. However, only brand-name drugs were evaluated in the present study because the quality of Chinese generics of dasatinib and imatinib are always to be suspected and need to be further examined in Chinese clinical practice. Finally, the utility scores in current analysis were categorized based on the treatment responses, and it was assumed that utility scores for high-dose imatinib were equal to dasatinib and nilotinib. However, the incidence of adverse events in patients receiving high-dose imatinib was higher compared to dasatinib and nilotinib,[38] which affects quality of life.[39] Nonetheless, the results of the present modeling study can be used to inform health policy decisions in a Chinese context.

5. Conclusions

The high cost-effectiveness ratio of dasatinib for CML patients resistant to standard-dose imatinib is based on plausible structural assumptions when PAP is available in a Chinese setting. The most critical weakness is that our model was synthesized from a heterogeneous collection of clinical outcome data derived from studies with varying designs. The results should be explained carefully. When higher quality data become available, the results will need to be updated.

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