Cost-Effectiveness Analysis of Dasatinib versus Imatinib in Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Patients in China

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Abstract

Background: Tyrosine kinase inhibitors (TKI) are recommended for pediatric Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), and the one commonly used in China is imatinib. However, it's worth noting that clinical needs could not be met gradually with the increasing resistance of imatinib. Dasatinib, the second-generation TKI, has been proved by Food and Drug Administration because of the better efficacy and comparative safety. This study aims to supplement economic evidence for multi-dimensional value by comparing the cost-effectiveness between imatinib and dasatinib in treating pediatric patients with in China, and to help clinical rational drug use and drug policy adjustment.

Methods: A decision tree model combined with a 10-year Markov model was established based on the published data and real-world cohort study. The main outcomes were incremental costs, which expressed in 2019 China yuan (CNY), and quality-adjusted life years (QALYs), both were discounted at 5%. Cost-effectiveness analysis was used to calculate the incremental cost-effectiveness ratio (ICER) between the two drugs in Chinese pediatric Ph+ ALL patients from the health system perspective. The Sensitivity analysis were conducted to assess the uncertainty and result robustness. The set willingness-to-pay (WTP) threshold was 1 times per capita GDP of China in 2019, recommended by the World Health Organization (WHO).

Results: The total costs were CNY 1,020,995.35 and CNY 1,035,788.50 in imatinib group and dasatinib group over the simulative course of a decade, and the total QALYs were 2.59 and 4.84. Compared with the imatinib treatment group, the ICER of dasatinib treatment was around CNY 6,575.78/ QALY, which was less than the set threshold. The sensitive analysis indicated the robustness of the results.

Conclusions: The cost-effectiveness analysis shows that dasatinib has potential cost-effective advantages compared with imatinib for pediatric Ph+ ALL patients under the set WTP threshold, which indicates that those patients could achieve more QALYs by paying acceptable fee.

Background

Acute lymphocytic leukemia (ALL), the rapidly progressing disease, accounts for more than 70% of childhood leukemia. As a rare disease, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) appears in 3–5% of childhood ALL [1], which contains an abnormal BCR-ABL1 fusion gene caused by the Philadelphia chromosome translocation. The poor prognosis, high probability of recurrence, and serious economic and psychological burdens make Ph + ALL an important high-risk factor for childhood leukemia [2]. As a result, it becomes quite significant to find the effective treatment and improve the clinical efficacy.

Tyrosine kinase inhibitor (TKI) is a class of compounds which can inhibit the activity of tyrosine kinases. By inhibiting the phosphorylation of protein tyrosine residues, it can block the conduction of downstream signal pathways to inhibit the growth and metastasis of tumor cells [3]. It was reported that the addition

of TKIs into the original chemotherapy in the Ph + ALL treatment could significantly improve the 5-year event-free survival (EFS) rate [4], about 20–30% [5, 6].

Imatinib and dasatinib are the two representative TKIs in China. Using imatinib or dasatinib is a dilemma for clinicians in China. Imatinib, the first-generation TKI, has been approved for treating pediatric Ph + ALL by China National Medical Products Administration (NMPA), and also been included in the medical insurance reimbursement catalog in China. However, there are still some shortcomings of imatinib, such as relapse of disease and drug resistance. As the second-generation TKI, dasatinib has a better mechanism, which could help achieve efficacy faster, reduce drug resistance and recurrence, and meet the needs of rapid clinical control of pediatric Ph + ALL patients [7]. Several researches have indicated a better clinical efficacy and comparable safety for the dasatinib compared with Imatinib [8, 9]. The using of dasatinib would improve the complete response (CR) in induction therapy and minimal residual disease (MRD) negative rate (< 0.01%) after induction therapy and before consolidation chemotherapy [9]. What's more, the 4-year EFS rate and 4-year overall survival (OS) rate could be improved significantly by 22.1% and 19.2%, meanwhile the 4-year cumulative recurrence rate could be significantly reduced by 14.6% [8]. Nowadays, although dasatinib is a recommended treatment according to the diagnosis and treatment standard of childhood acute lymphoblastic leukemia (2018 version) [10], it has not been approved for pediatric Ph + ALL by China NMPA, let alone been included in the medical insurance reimbursement catalog. The off-label clinical usage may result in some legal risks and huge economic burden.

More evidence about safety, efficacy and economy should be presented for facilitating indication approval and even for adjusting national drug policies. After the literature review, there has been a multi-center randomized controlled trial compared the two drugs in Ph + ALL children in China observing the PFS rate, OS rate, adverse events and other outcomes. But there were no relative studies about the economic evaluation of the disease, or the economic comparison between the two drugs in treating Ph + ALL. Therefore, this study conducted a cost-effectiveness analysis comparing dasatinib and imatinib for pediatric Ph + ALL patients to supplement economic evidence based on the reported data of the clinical trial and the real-world data of our hospital.

Method

Patient population

In order to better reflect the characteristics and disease progression of pediatric Ph + ALL patients in China, a real-world cohort survey was conducted in our hospital to collect baseline characteristics, diagnosis and treatment information, cost information and so on. A total of 32 pediatric Ph + ALL patients were included from the electronic medical record, 14 of whom were treated with imatinib, while the others were received dasatinib [8]. The median age was 7 years old. In the cohort study, the pediatric patients received approximately a 4-week induction therapy and a 44-week intensive chemotherapy.

Model Structure

It was assumed that the patients were separated into two groups receiving either imatinib (300mg/ day, per square meter of body surface area) or dasatinib (70mg/ day, per square meter of body surface area) during the treatment period. According to the diagnosis and treatment standard of childhood ALL, Ph + ALL patients should undergo induction therapy, intensive chemotherapy, and maintenance treatment. A combined decision tree and 10-year Markov model was developed to estimate the increase cost-effectiveness between imatinib and dasatinib from the health system perspective, seen Fig. 1. In the model, the disease progression was simplified to a few disease states, and all the patients would be in only one state in any cycle. The decision tree model was used to simulate the progression in the induction therapy and intensive chemotherapy. The total duration for these two periods was about one year. At the end of the two period of therapy, patients would be in one of three states: (1) CR, (2) non-CR, and (3) death, and then turned into the 10-years Markov simulation phase. In the Markov model, the state of each patient was decided by the end of intensive chemotherapy and the single cycle was one year. If non-CR patients or those who relapsed from CR state have passed doctor's assessment, they would receive hematopoietic stem cell transplantation (HSCT), otherwise they might stay at the relapse or non-CR state and receive the chemotherapy again to keep alive. If transplantation failed, they might choose other possible therapeutic schedules, like immunotherapy. In each state, the patients had the possibility to die.

Transition Probabilities

In this study, the transition probabilities were consisted of two parts. For the decision tree model, the parameters were collected from the real-world retrospective cohort study from our hospital. The rate of each transition was calculated. At the end of the 4-week induction chemotherapy, none of the patients treated with imatinib reached the CR state, while 3 of those treated with dasatinib (16.7%) became CR. At the end of the 44-week intensive chemotherapy, the CR rate for imatinib group and dasatinib group was 50% and 83.5% respectively [11]. For the Markov model, the parameters were from published articles and experts’ opinions. The rates from CR state to Relapse or Death state in maintenance therapy of the two group were from the published data of head-to-head clinical trial in China [8], and were estimated to the annual probabilities via transformation formula [12]. The parameters after transplantation were estimated from a relevant article [13]. And other parameters like the death rate of non-CR patients in maintenance therapy, the transplantation rate, the successful rate for transplantation were from experts’ opinions, seen Table 1.

Table 1
Base Case Parameter Values and Clinically Plausible Ranges for Model

Parameter	Base-case value (range)	Distribution	Reference
Transition Probabilities			
Imatinib			
non-CR after induction therapy	1	Beta	Cao 2021[11]
non-CR after intensive chemotherapy	0.5	Beta	Cao 2021[11]
Relapse in maintenance therapy	0.1000 (0.0415, 0.1729)	Beta	Shen 2020[8]
Death of CR patients in maintenance therapy	0.0879 (0.0364,0.1365)	Beta	Shen 2020[8]
Dasatinib			
non-CR after induction therapy	0.833	Beta	Cao 2021[11]
CR of CR patients in intensive chemotherapy	1	Beta	Cao 2021[11]
CR of non-CR patients in intensive chemotherapy	0.875	Beta	Cao 2021[11]
Relapse in maintenance therapy	0.0537 (0.0107, 0.1035)	Beta	Shen 2020[8]
Death of CR patients in maintenance therapy	0.0304 (0.0099, 0.0504)	Beta	Shen 2020[8]
Death of non-CR patients in maintenance therapy	0.6 (0.54, 0.66)	Beta	Experts' opinions
Transplantation			
Transplantation in non-CR patients	0.1 (0.09, 0.11)	Beta	Experts' opinions
Success in transplantation	0.4 (0.3, 0.5)	Beta	Experts' opinions
Relapse after transplantation	0.0582 (0.0354, 0.0806)	Beta	Lin 2019[13]
Death in CR patients after transplantation	0.23 (0.21, 0.25)	Beta	Lin 2019[13]

CR complete response, non-CR non-complete response, QALY quality-adjusted life year.

Parameter	Base-case value (range)	Distribution	Reference
Death in non-CR/ relapse patients after transplantation	0.57 (0.49, 0.64)	Beta	Lin 2019[13]
Costs, CNY, per year			
Imatinib			
Drug	104857.2 (83885.76, 125828.64)	Gamma	Expense list
Other costs in induction therapy	71019.18 (10168.61, 170406.88)	Gamma	Expense list
Other costs in intensive chemotherapy	266871.23 (120615.16, 398733.09)	Gamma	Expense list
Dasatinib			
Drug	51100 (40880, 61320)	Gamma	Expense list
Other costs in induction therapy	91338.95 (26639.48, 176128.92)	Gamma	Expense list
Other costs in intensive chemotherapy	208152.13 (141714.97, 274986.24)	Gamma	Expense list
Other costs for maintenance in CR state	57500 (46000, 69000)	Gamma	Expense list
Maintenance in non-CR state	375953.99 (244489.6, 531322.71)	Gamma	Expense list
Transplantation	250000 (200000, 300000)	Gamma	Experts' opinions
Maintenance in CR state after transplantation	399953.99 (268489.6, 555322.71)	Gamma	Expense list
non-CR/ relapse after transplantation	1000000 (800000, 1200000)	Gamma	Experts' opinions
Time horizon, year			
Imatinib			
Induction therapy	0.0795		Cao 2021[11]
Intensive chemotherapy	0.8164		Cao 2021[11]
Dasatinib			

CR complete response, non-CR non-complete response, QALY quality-adjusted life year.

Parameter	Base-case value (range)	Distribution	Reference
Induction therapy	0.0849		Cao 2021[11]
Intensive chemotherapy	0.6822		Cao 2021[11]
Utilities, QALYs			
CR	0.88 (0.82, 0.93)	Beta	Lin 2019[13]
non-CR/ relapse	0.76 (0.7, 0.82)	Beta	Lin 2019[13]
CR after transplantation (first 5 years)	0.8 (0.74, 0.86)	Beta	Lin 2019[13]
CR after transplantation (second 5 years)	0.86 (0.8, 0.91)	Beta	Lin 2019[13]
non-CR/ relapse after transplantation	0.73 (0.67, 0.79)	Beta	Lin 2019[13]
CR complete response, non-CR non-complete response, QALY quality-adjusted life year.			

Cost And Utility

From the health system perspective, direct health care costs were included, such as drug costs, other medical-related treatment costs like testing costs and hospitalization costs during induction therapy and intensive chemotherapy, the cost in CR or non-CR or relapse state during the maintenance period, and the cost of bone marrow transplantation and in the following states. The annual original drug costs were calculated according to the usage and dosage specified in the instructions. In the base case analysis, a 7-years-old child who weighed 20 kg with a 0.8m2 body surface area was set as a sample. Other cost parameters were collected from the expense list in the hospital, and the experts' opinions would be chosen if there was no relevant list, as shown in the Table 1. The costs were expressed in 2019 China yuan (CNY).

The outcome used in this study was quality-adjusted life years (QALYs). QALYs were calculated by multiplying the health utility of a specific health state by the number of years lived in that state. Utility score of the states in different periods were collected from published related literature, as presented in Table 1 [13]. It was assumed that non-CR and relapse states have the same utility. The discount rate for cost and utility was 5% as recommended [14].

Base Case Analysis

In base case analysis, total cost and total QALYs of the two group over a decade time horizon were calculated. ICER was defined as the differences in costs divided by the differences in health outcomes of dasatinib and imatinib. The willingness to pay (WTP) threshold value for QALY was set at one capita of the gross domestic product (GDP) according to the 2020 China Guidelines for Pharmacoeconomic Evaluations [14]. As reported in China statistical Bulletin of National Economic and Social Development 2019, the 1 time GDP per capita is CNY 70,892 [15], which was the set threshold in the incremental analysis through TreeAge Pro 2011 software.

Sensitivity Analysis

One-way sensitivity analysis was conducted to alter variations such as costs, the recurrence rate, the mortality rate, and utilities in model input to assess the influence on our conclusions. If there was not reported the variance or the range of the parameters in reference, the cost and utility parameters were fluctuated by ± 20% of the base value, and the transfer probability parameters were ± 10% according to experts' consultation. The annual discount rate fluctuated between 3% and 8%.

A probability sensitivity analysis was also conducted with Monte Carlo simulation to explored the association of input parameter uncertainty with model outcomes. It was assumed that the costs obeyed the Gamma distribution, the utility and transition probability value obeyed the Beta distribution, and the discount rate obeyed the Triangle distribution. The value of each model input was randomly drawn from the assigned parametric distributions in one thousand Monte-Carlo simulation.

Considering the using of cheaper generic drugs in China, which have already passed the consistency evaluation, a scenario analysis was conducted to calculate the ICER of generic drug usage with other conditions remain unchanged.

Results

Base case results

In this simulation of time horizon, the total QALY for patients under dasatinib or imatinib treatment were 4.84 and 2.59 respectively, implying the incremental 2.25 QALYs over the simulative course of a decade. Meanwhile, patient treated with dasatinib was associated with CNY 1,035,788.50 total cost, with an increasing of CNY 14,793.15 than those treated with imatinib, shown in Table 2. Compared with the imatinib treatment group, the ICER of using dasatinib in treating pediatric Ph + ALL patients were around CNY 6,575.78/QALY. The results indicated that dasatinib would be a cost-effective intervention compared with imatinib, considering the ICER was less than the WTP threshold of CNY 70,892/QALY.

Table 2
Base case cost-effectiveness analysis results

Strategy	Total		Incremental		ICER
	Cost (CNY)	QALYs	Cost (CNY)	QALYs	
Imatinib	1,020,995.35	2.59	-	-	-
Dasatinib	1,035,788.50	4.84	14,793.15	2.25	6,575.78

QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio.

Sensitivity Analysis Results

The results were robust across one-way sensitivity analysis. As presented in Fig. 2, the horizontal line represented the influence range of the parameter. The first five factors that greatly influenced the results including the other costs in induction therapy of dasatinib group (except dasatinib costs), the recurrence rate of dasatinib group in maintenance therapy period, the other costs in intensive chemotherapy of dasatinib group (except dasatinib costs), the cost for non-CR state in maintenance therapy period (except dasatinib costs), and the annual cost of dasatinib. As shown in Fig. 3, the probability sensitivity analysis showed a 75.7% probability of dasatinib being more cost-effectiveness than imatinib at a threshold of CNY 70,892 per QALY. With the increasing of the willingness to pay, the acceptability of dasatinib treatment was greatly improved, which was obviously shown in Fig. 4.

Under the scenario assumption, the annual cost for generic dasatinib and imatinib was CNY 28,207.2 and CNY 8,555.6 respectively. The incremental cost of dasatinib group was CNY 132,476.42, with an incremental 2.25 QALYs. The ICER was CNY 58,887.82/QALY, which is still less than the set threshold.

Discussion

To the best of our knowledge, our study is the first to establish a combined economic model based on real-world data, to evaluate the cost-effectiveness of using dasatinib compared with imatinib in pediatric Ph + ALL patients in China. Using dasatinib could improve 2.25 QALYs with an increasing cost of CNY 14,793.15. The ICER was acceptable comparing with the set threshold. The sensitivity analysis showed the robustness of the results under the variation of parameters. Considering the potential widely use of generic drugs in China, the drug price would be significantly reduced. In scenario analysis, ICER was improved from CNY 6,575.78/QALY to 58,887.82/QALY, close to the set WTP threshold.

Understanding the value of a new or alternative clinical intervention is crucial to guide rational clinical use of drugs. As the second generation TKI, dasatinib can help pediatric Ph + ALL patients control the disease progression more quickly and improve the survival rate. Considering the higher price, it is necessary to take the economic evidence into consideration in evaluating the value of dasatinib in treating Ph + ALL. During the literature research, there were no published economic evaluations between dasatinib and

imatinib in treating pediatric Ph + ALL, but there was several about chronic myeloid leukemia (CML). Wantanee Kulpeng did a cost-utility analysis from the societal perspective in thailand, which indicated the cost-effective advantage of dasatinib in CML patients, by yielding 2.13 QALYs at $49,106 reduction on cost [16]. Ola Ghatnekar proved the potential economic advantage of dasatinib by calculating the ICER, which was EUR 6,880 per QALY, lower than the willingness to pay threshold in Sweden [17]. Wu Bin also proved that dasatinib was cost-saving compared to high-dose imatinib [18]. Though the published researches mainly targeted CML rather than ALL, the result of using dasatinib was cost-effective. On the contrary, there were also several studies showing the low cost-effective of dasatinib, in which ICER per QALY may exceed the WTP threshold [19–21]. Therefore, it is necessary to conduct pharmacoeconomic evaluation for specific diseases in specific countries, which means this study help fills the research gap to some extent.

It should be pointed out that, in the study, the WTP threshold was 1 time GDP per capita according to the China Guidelines for Pharmacoeconomic Evaluations guideline, but there has no established standard for the value of QALY in China yet. Some experts consider that the current cost-effectiveness threshold used in China is much higher, the more appropriate threshold would be 63% of GDP per capita [22]. If taking this into consideration, it would be less economical when using generic dasatinb rather than generic imatinib unless the annual cost for dasatinib is less than CNY 21,928.36, which means the price should be reduced from CNY 69 per piece to CNY 53.64 per piece.

There are also still some limitations in this study. Firstly, we simplified the disease treatment pathway into three periods based on the experts' opinion, which may not totally reflect the real condition. Secondly, the patient-level parameters of the decision tree were derived from a real-world retrospective cohort study in our single hospital. The limited number of patients may not be applicable to the whole country. Multi-center real world data can be collected in the next step to enhance the reliability of evidence the biased result. Thirdly, the transition probabilities in Markov model were estimated from a 4-year OS rate and EFS rate, which may overestimate or underestimate the probability of metastasis of actual disease progression. Nevertheless, we incorporate significant sensitivity analysis to address these limitations and find our results to be robust. It is necessary to update the parameters from the deepen and further clinical trials or follow-up visiting in future to provide more support evidence for using dasatinib.

In conclusion, using dasatinib in treatment of pediatric Ph + ALL patients would be a better alternative considering the clinical requirements. The acceptable increasing cost would bring with more efficacy, which may help promote rational clinical use and improve the quality of life of patients.

Conclusion

This study is the first cost-effectiveness analysis comparing the advantages between dasatinib and imatinib for pediatric Ph + ALL patients in China. Our results suggest that using dasatinib as the added TKI might be a cost-effective choice under the health system perspective.

Abbreviations

CML
chronic myeloid leukemia
CR
complete response
EFS
event-free survival
GDP
gross domestic product
HSCT
hematopoietic stem cell transplantation
ICER
incremental cost-effectiveness ratio
MRD
minimal residual disease
NMPA
National Medical Products Administration
OS
overall survival
Ph + ALL
Philadelphia-positive acute lymphoblastic leukemia
QALYs
quality-adjusted life years
TKI
Tyrosine kinase inhibitors
WTP
willingness-to-pay
WHO
World Health Organization.

Declarations

Ethics approval and consent to participate

All the methods were carried out in accordance with relevant guidelines and regulations. Ethics approval and consent for the study was approved by the Ethics Committee of Beijing Children's Hospital (No.2018-62). The informed consent was obtained from all subjects and/or their legal guardian(s) and all the patients' identity is fully anonymized in this report.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated or analyzed during the current study are from the following published article: (1) Shen S, Chen X, Cai J, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Onco. 2020;6(3):358-366, doi: 10.1001/jamaoncol.2019.5868., and (2) Cao W, Yu Y-C, Liu L, et al. Comprehensive Clinical Evaluation of Dasatinib in the Treatment of Children with Philadelphia-positive Acute Lymphoblastic Leukemia. Chinese Journal of Drug Evaluation. 2021;38(03):183-190, doi:10.3969/j.issn.2095-3593.2021.03.002.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wang Cao is responsible for the study design, establishment of economic model, data analysis and interpretation, and drafting of this article. Yuncui Yu is responsible for the real-world data collection, analysis and interpretation, and review of the article. Yingpeng Qiu, Liwei Shi and Yue Xiao are responsible for the adaptation of Markov model and data interpretation. Lu Liu and Hao Zhang are responsible for the real-world data collection and proofreading. Ruidong Zhang is responsible for the real-world data proofreading, and presentation and interpretation of clinical perspectives. Lulu Jia and Xiaoling Wang are responsible for the study concept and design, and the review of draft and final article.

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Figures

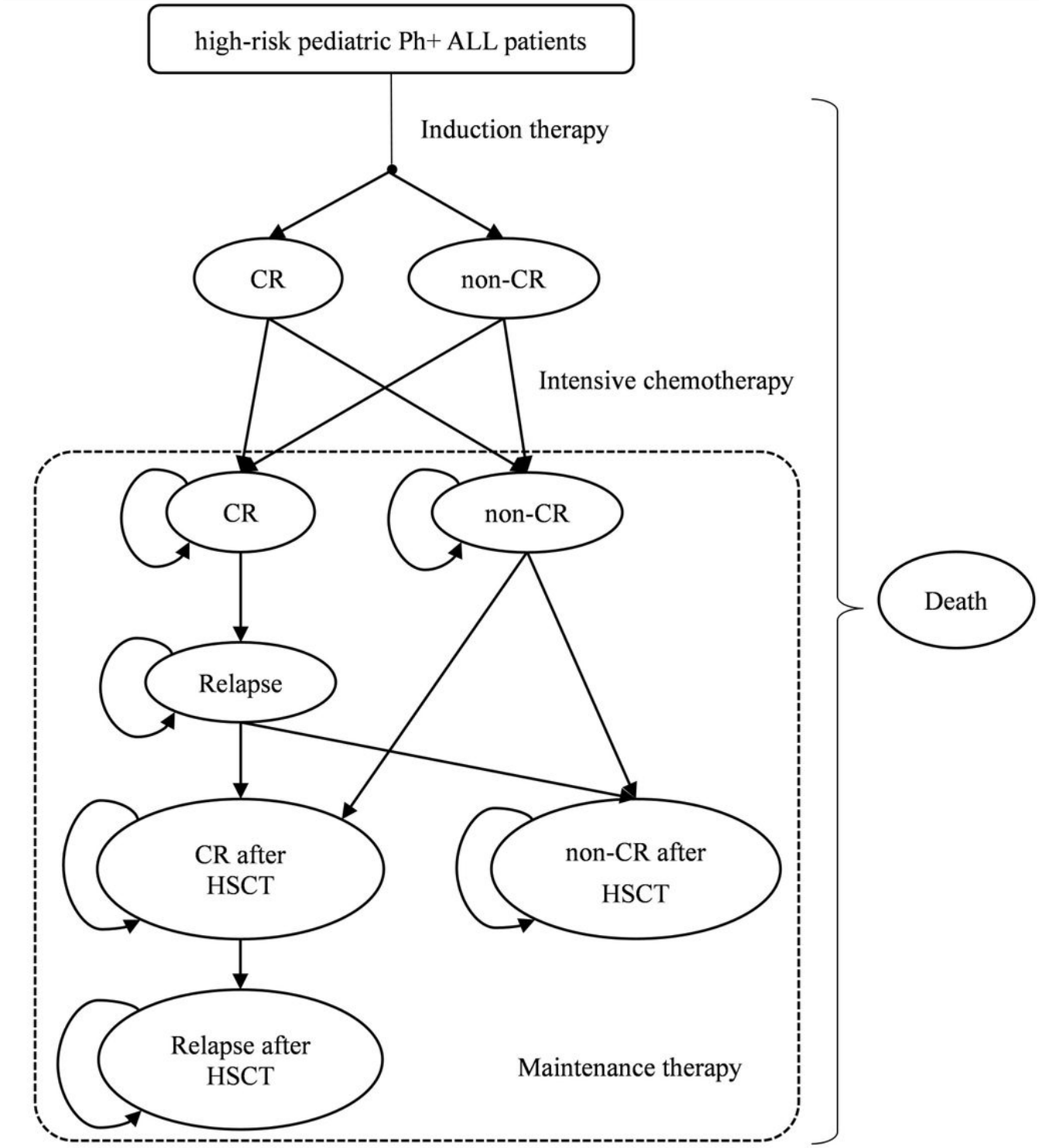

Figure 1

Simple Model Structure

CR complete response, non-CR non-complete response, HSCT hematopoietic stem cell transplantation.

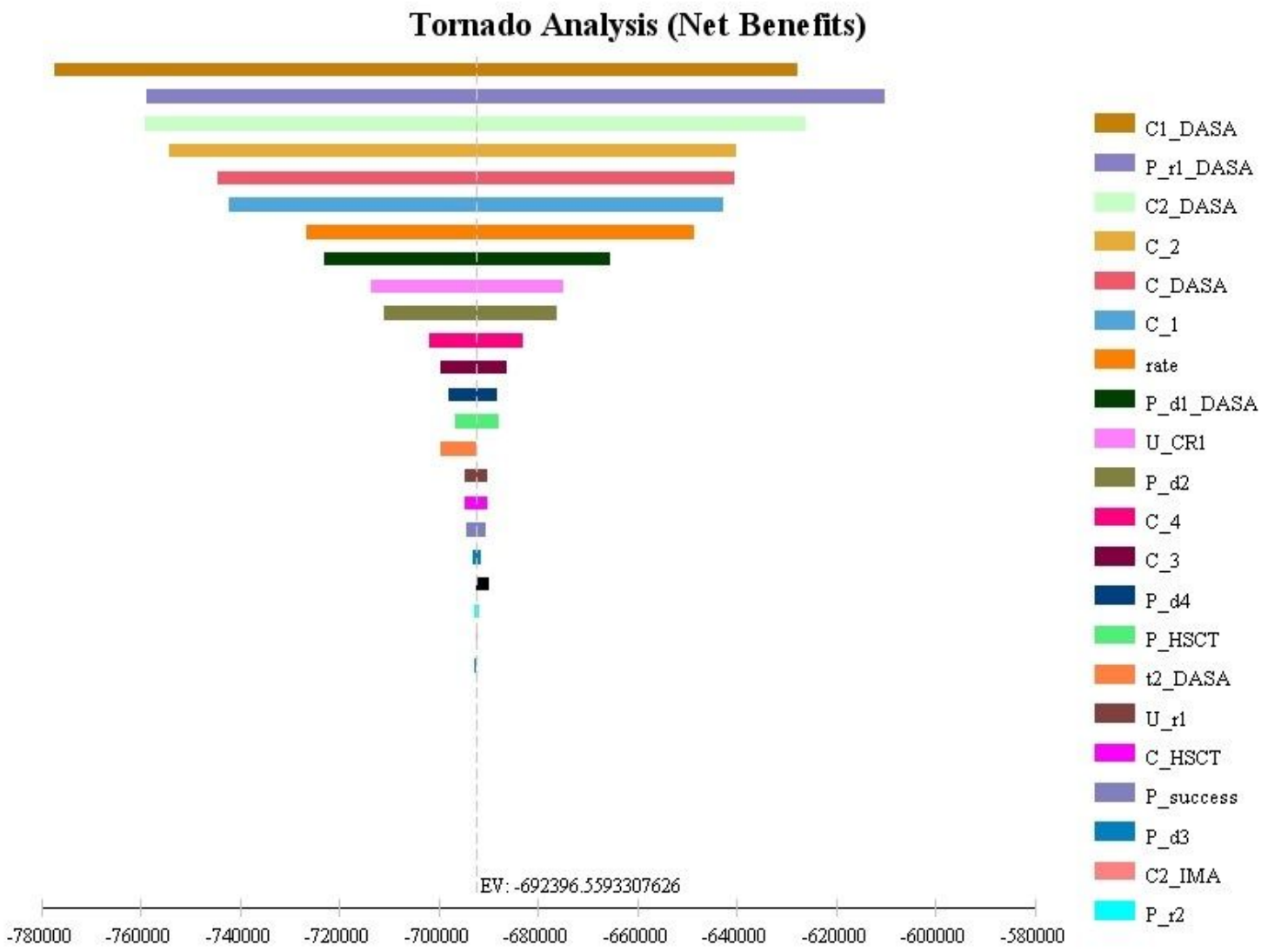

Figure 2

One-way sensitivity analysis (tornado diagrams)

C1_DASA indicates other costs in induction therapy of dasatinib group; P_r1_DASA, the recurrence rate of dasatinib group in maintenance therapy period; C2_DASA, the other costs in intensive chemotherapy of dasatinib group; C_2, the cost for non-CR state in maintenance therapy period; C_DASA, the annual cost of dasatinib other costs in induction therapy of dasatinib group; C_1, the annual other cost for CR state in maintenance therapy period; P_d1_DASA, the mortality rate of CR patients in maintenance therapy in dasatinib group; U_CR1, utility of CR; P_d2, the mortality rate of non-CR patients in maintenance therapy; C_4, annual cost of non-CR or relapse patients after transplantation ; C_3, annual cost of CR patients after transplantation; P_d4, the mortality rate in non-CR/ relapse patients after transplantation; P_HSCT, transition probabilities of transplantation in non-CR patients; t2-DASA, time for intensive chemotherapy of dasatinib group; U_r1, utility of non-CR/ relapse; C_HSCT, cost of transplantation; P_success, transition probabilities of success in transplantation; P_d3, the mortality rate in CR patients after transplantation;

C2_IMA, the other costs in intensive chemotherapy of imatinib group; P_r2, transition probabilities of relapse after transplantation.

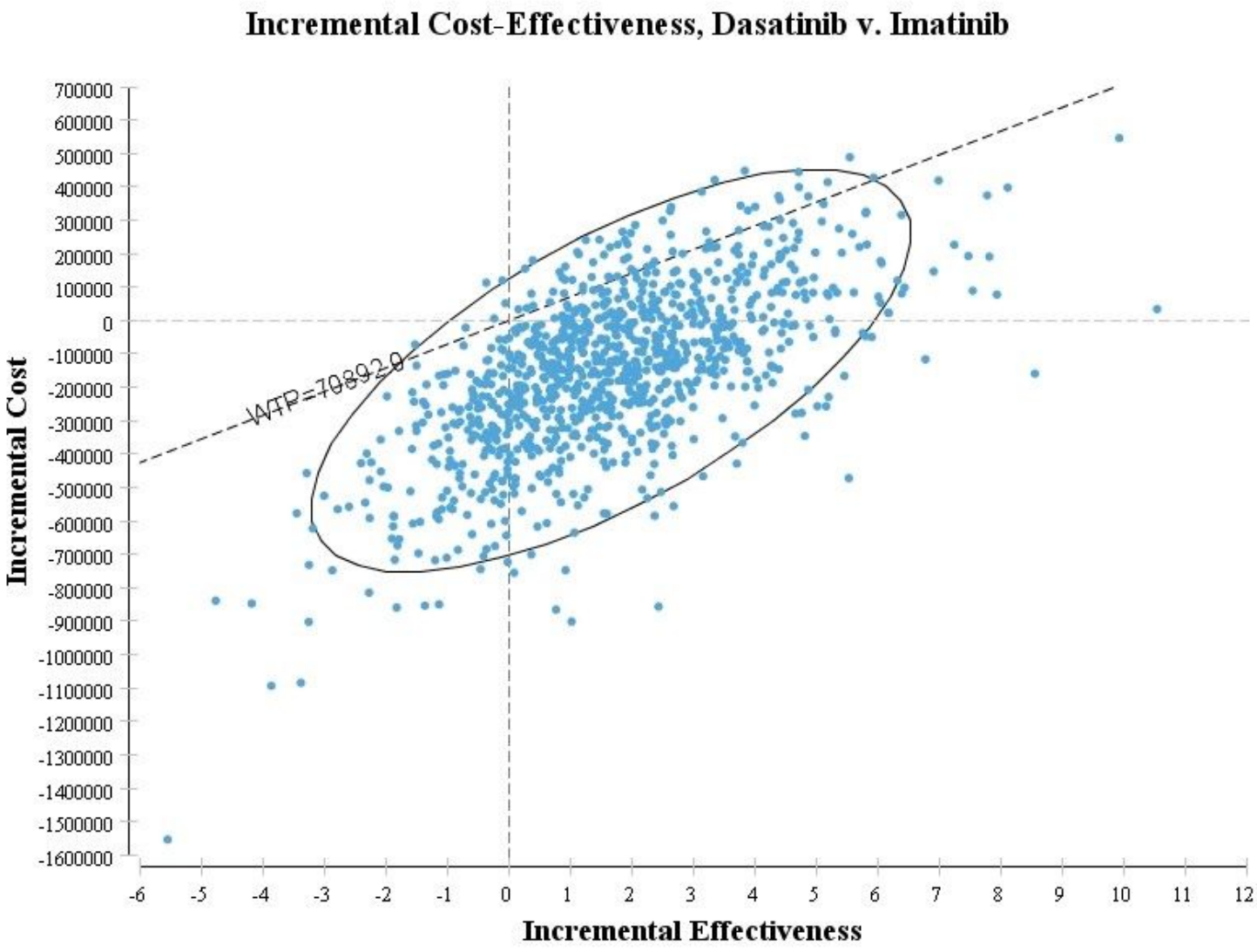

Figure 3

Scatter plot of dasatinib vs. imatinib

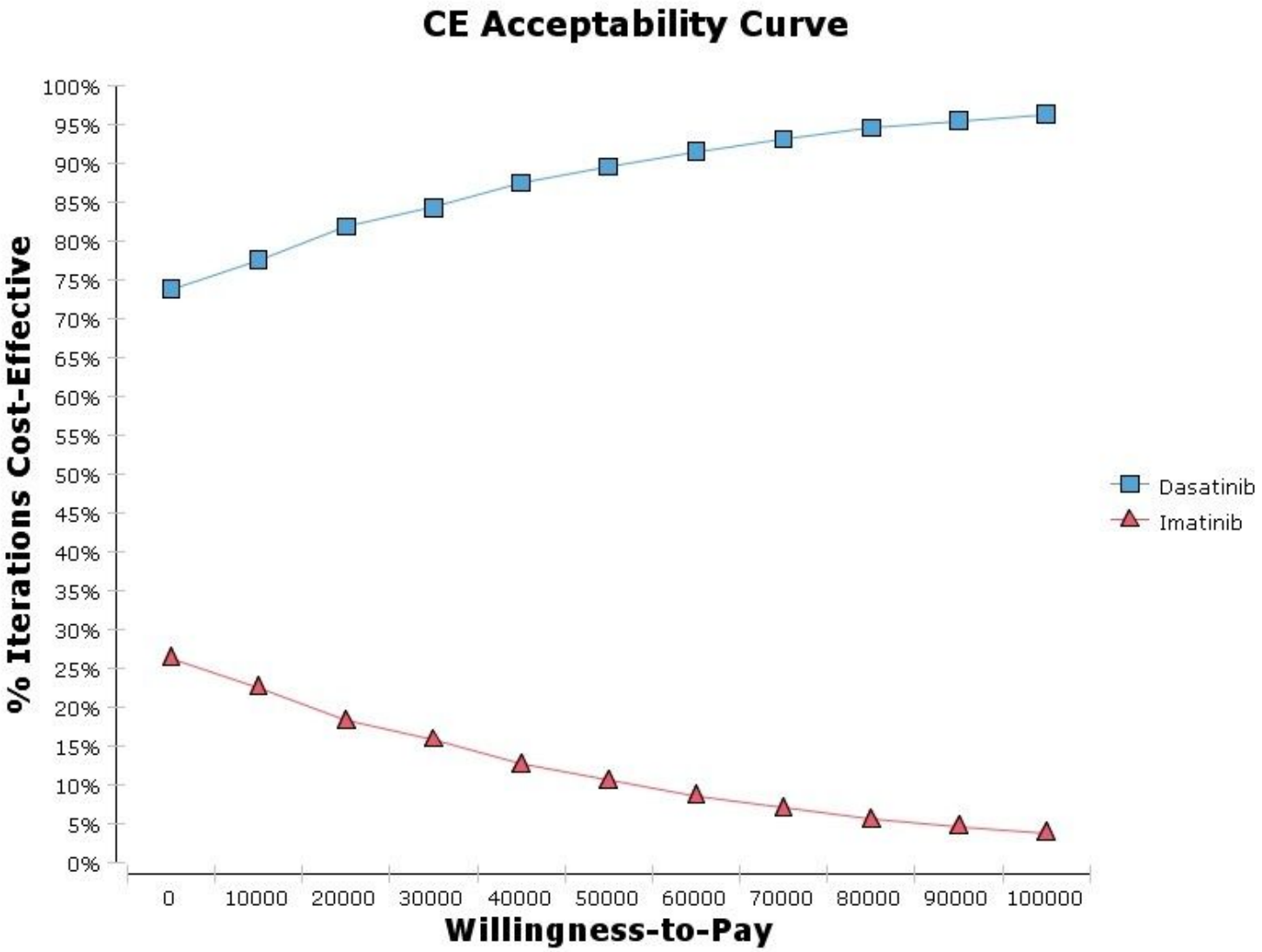

Figure 4

Cost-effectiveness acceptable curve