Cost-Effectiveness of Zanubrutinib versus Bendamustine and Rituximab in Patients with Untreated Chronic Lymphocytic Leukaemia

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Abstract

Background Zanubrutinib is a powerful specific and irreversible bruton tyrosine kinase (BTK) inhibitor. Whether used alone or in combination with other drugs, it is proved to be effective in untreated chronic lymphocytic leukemia (CLL). Here, we compared the cost-effectiveness of zanubrutinib and bendamustine-rituximab (R-bendamustine) to determine its effectiveness as first-line treatment for Chinese patients with untreated CLL.

Methods The cost-effectiveness of zanubrutinib and R-bendamustine treatment for CLL was evaluated by a partitioned survival model. It was constructed using TreeAge Pro 2011 software mainly based on the clinical data derived from SEQUOIA. Transition probabilities were estimated from the reported survival probabilities in trials using parametric survival modeling. In this analysis, the quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER) and lifetime cost were calculated from the Chinese healthcare system perspective. An entire life span horizon and annual 5% discounting were used. One-way analysis and probabilistic sensitivity analysis (PSA) were carried to explore the uncertainty of the modeling results. Additionally, several scenarios analysis, including different zanubrutinib price calculation and 20-year time horizon were evaluated.

Results The cost of zanubrutinib and R-bendamustine were $98711.7 and $53095.17. Zanubrutinib had an ICER of $58258.18 per additional QALYs gained compared with R-bendamustine. Research indicated that zanubrutinib achieved at least an 3.70% probability of cost-effectiveness at the threshold of $38223.34/QALY. One-way sensitivity analysis revealed that the results were sensitive to utility of PD. Scenario analysis showed that zanubrutinib was cost-effectiveness when its price reduced more than 20%.

Conclusions At current price, zanubrutinib was less cost-effectiveness for patients with CLL compared with R-bendamustine in China.

1 Introduction

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL; hereafter together referred to as CLL) are different manifestations of the same disease, characterized by progressive accumulation of monoclonal B lymphocytes. The incidence rate of CLL in China is less common compared with that in western countries[1, 2]. Nevertheless, with the aging of the population and the popularization of routine health examinations, the incidence rate of CLL is on the rise[3]. Currently, CLL is incurable, but the condition of patients will usually be effectively controlled after active surveillance and chemoimmunotherapy standard regimen[4]. The application of Bruton tyrosine kinase (BTK) inhibitors have brought a new breakthrough in the treatment of CLL. Currently, ibrutinib (Catalent), orelabrutinib (InnoCare) and zanubrutinib (BeiGene) have been approved by the National Medical Products Administration (NMPA) to treat CLL.
Zanubrutinib, as a second-generation selective covalent inhibitor of BTK inhibitor[5], was independently developed by Chinese pharmaceutical enterprises. Several large-scale clinical trials were carried out in a variety of lymphoma treatments, proving that it can inhibit the proliferation of malignant B cells. Whether used alone or in combination with other drugs, it is proved to be effective in CLL. Zanubrutinib is characterized by fewer off-target effects compared with ibrutinib. In an open-label, multicenter, phase III trial (SEQUOIA), estimated progression-free survival (PFS) of zanubrutinib versus bendamustine-rituximab (R-bendamustine) is 85.5% (95% CI 80.1 to 89.6) versus 69.5% (62.4 to 75.5) at 24 months[6]. Thus, zanubrutinib seems to be attractive options for the treatment of untreated CLL.

R-bendamustine was considered a standard of care in patients with untreated CLL, and it costs less due to its limited time on treatment. Nevertheless, zanubrutinib needs to be administered continuously until the disease progression or unacceptable toxicity. Generally, patients with CLL survive over 10 years from time of diagnosis[4]. In light of this, zanubrutinib is with high treatment cost. Although several relevant studies have evaluated the cost-effectiveness of different BTK inhibitor in the treatment of CLL, this is the first study to access the economic evaluation of zanubrutinib in patient with untreated CLL. This study aimed to investigate the cost-effectiveness of zanubrutinib versus R-bendamustine for untreated CLL from the Chinese healthcare system, in order to provide reference for clinical decision and national medical insurance policy.

2 Methods

2.1 Model Structure

We constructed a three health states Markov model, including PFS, progressed disease (PD), and death to estimate the cost and treatment efficacy of therapy with zanubrutinib versus R-bendamustine, shown in Fig.1. The hypothetical target population for this analysis was patients with untreated CLL and SLL, based on the patient characteristics of the SEQUOIA trial [6]. The characteristics is aged 65 years or older, or 18 years or older and had comorbidities, and an eastern cooperative oncology group ECOG performance status at a baseline of 0-2, and less and adequate hepatic, renal, and hematological function. It was assumed that all patients were start in PFS state, and at the end of each cycle, the patient may stay in this state or move to a poorer health state. The treatment regimen was consistent with the SEQUOIA trial in this study. The patients were randomly assigned to receive zanubrutinib (160 mg twice daily) or six cycles of intravenous bendamustine (90 mg/m² twice each cycle) plus rituximab (375 mg/m² of cycle 1, and 500 mg/m² of cycles 2 to 6)[6].

The data points were gathered from the PFS curves and OS curves using GetData Graph Digitizer (version 2.20), then reconstructed by the following parametric survival function: weibull, log-logistic, exponential, log-normal, gompertz and gengamma. The most appropriate survival function was chosen based on Akaike information criterion (AIC) and Bayesian information criterion (BIC), and the smaller value represents better goodness. It was determined that the best distribution is weibull for PFS of zanubrutinib and gompertz is suitable for PFS of R-bendamustine. Besides, the exponential model was the most
reasonable functions for extrapolating OS of both groups (see the Supplementary Appendix). Consequently, in our analysis, weibull, gompertz and exponential distribution was applied to calculate transition probability. Parametric survival curve was delineated by RStudio 2022.02.0 software and TreeAge Pro 2011 was used to construct the Markov model. In this study, the transition probability of PFS to death apply general population mortality, derived from mortality tables of resident population in 2021 published by National Bureau of Statistics[7].

In 2022, the average life expectancy of China is 78.3 years. In the light of the median age is 70.0 years for patients in the SEQUOIA study, the time duration was set to 10 years, a period expected to cover the patient’s entire life span. And each cycle in the model is consistent with the 28-day treatment period of clinical trial. The primary output of the model includes quality-adjusted life years (QALYs) of the treatment scheme, and incremental cost-effectiveness ratios (ICERs). On the basis of China guidelines for pharmacoeconomic evaluations (2020)[8], 5% discount rate and 1 ~ 3 times of Chinese per capita GDP was adopted. Here, 1 ~ 3 times of Chinese per capita GDP in 2022 was used as the willingness-to-pay (WTP) threshold (12741.11-38223.34 $/QALY)[9].

### 2.2 Costs and Utility Values

The evaluation is conducted from the Chinese healthcare system perspective. Hence, only direct medical expenses were taken into account, including the cost of drugs, follow-up test, best supportive care (BSC), terminal care cost (TCC) and management of serious adverse effects (SAEs). The unit price of zanubrutinib, R-bendamustine in China was obtained from Shandong drug centralized procurement platforms, and other cost data was derived from literatures. All the costs were adjusted for inflation to reflect 2021 US dollars according to Chinese Consumer Price Index (CPI) and based on the 2022 exchange rate (6.7261 RMB/US dollar). A base-case body surface area (BSA) of 1.72 m$^2$ was assumed to calculate the drug cost of chemotherapy[10, 11].

In our research, only SAEs (≥3 grade according to NCI-CTCAE V5.0 criteria) with an incidence of more than 10% was considered and we assumed that adverse events occurred independently, which helps to simplify the model. In addition, it was assumed that the probability of those events remained constant over the 10-year time horizon, and there was no incidence of discontinuation due to severe adverse reaction. For our base case, all adverse events of grade 3 and above were modeled to occur within the first 4 weeks of treatment initiation. All patients in the model were assumed to have regular laboratory testing with complete blood count (CBC), serum biochemical index and computed tomography (CT) every 3 months, regardless of receipt which therapy strategy[6]. The cost of BSC was the only cost included in this analysis after disease progression, and terminal care costs (TCC) were included in the final state. The utilities for patients with CLL were captured from the study by Kishan K. Patel and Michael Adena[4, 12], with the base values 0.81 and 0.62 for PFS and PD states, respectively. All information is listed in Table 1.

**Table 1 Model parameters: baseline values, ranges, and distributions for sensitivity analysis**
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expected Value</th>
<th>Range</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug costs ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanubrutinib/cycle</td>
<td>1415.38</td>
<td>1132.30~1698.45</td>
<td>gamma</td>
<td>[13]</td>
</tr>
<tr>
<td>Bendamustine/cycle</td>
<td>770.42</td>
<td>616.34~924.50</td>
<td>gamma</td>
<td>[13]</td>
</tr>
<tr>
<td>Rituximab (cycle 1)</td>
<td>1356.74</td>
<td>1085.39~1628.08</td>
<td>gamma</td>
<td>[13]</td>
</tr>
<tr>
<td>Rituximab (cycle 2-6)</td>
<td>1772.43</td>
<td>1417.95~2126.92</td>
<td>gamma</td>
<td>[13]</td>
</tr>
<tr>
<td>AEs costs ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3608.31</td>
<td>2886.64~4329.97</td>
<td>gamma</td>
<td>[14]</td>
</tr>
<tr>
<td>Infections</td>
<td>372.37</td>
<td>297.90~446.85</td>
<td>gamma</td>
<td>[15]</td>
</tr>
<tr>
<td>Follow up monitoring cost ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>29.74</td>
<td>23.79~35.69</td>
<td>gamma</td>
<td>local charge</td>
</tr>
<tr>
<td>Serum biochemical index</td>
<td>30.20</td>
<td>24.16~36.24</td>
<td>gamma</td>
<td>local charge</td>
</tr>
<tr>
<td>Count Blood Cell</td>
<td>6.54</td>
<td>5.24~7.85</td>
<td>gamma</td>
<td>local charge</td>
</tr>
<tr>
<td>Terminal care cost</td>
<td>85359.77</td>
<td>68287.82-102431.72</td>
<td>gamma</td>
<td>[16]</td>
</tr>
<tr>
<td>Utility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.81</td>
<td>0.78~0.91</td>
<td>gamma</td>
<td>[12]</td>
</tr>
<tr>
<td>PD</td>
<td>0.62</td>
<td>0.49~0.74</td>
<td>gamma</td>
<td>[12] [4]</td>
</tr>
<tr>
<td>Probabilities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanubrutinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11.00</td>
<td>8.80~13.20</td>
<td>beta</td>
<td>[6]</td>
</tr>
<tr>
<td>Infections</td>
<td>16.00</td>
<td>12.80~19.20</td>
<td>beta</td>
<td>[6]</td>
</tr>
<tr>
<td>R-Bendamustine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51.00</td>
<td>50.80~61.20</td>
<td>beta</td>
<td>[6]</td>
</tr>
<tr>
<td>Infections</td>
<td>19.00</td>
<td>15.20~22.80</td>
<td>beta</td>
<td>[6]</td>
</tr>
<tr>
<td>Discount (%)</td>
<td>5.00</td>
<td>0.00~8.00</td>
<td>beta</td>
<td>[8]</td>
</tr>
</tbody>
</table>

AE, Adverse Event; CT, computed tomography; BSC, best supportive care; PFS, progression-free survival; PD, progressed disease; R-Bendamustine, Bendamustine and rituximab.
2.3 Sensitivity Analysis

Sensitivity analysis was conducted using TreeAge Pro 2011 software to validate the model’s robustness when the results vary across a reasonable range, including one-way and probabilistic sensitivity analysis (PSA). In one-way sensitivity analysis, the influence of parameter change on ICER value was calculated one by one according to the lower and upper limits obtained from 95% confidence intervals (95% CIs) or a range of ±20% of the base case value[17]. PSA was carried out via 1000 Monte Carlo simulations according to the assumed statistical distribution form of parameters. The gamma distribution was applied for cost data, and beta distribution is used in utility and incidence data. The ranges and distributions of the parameters used in the sensitivity analysis is given in Tables 1.

2.4 Scenario Analysis

We conducted several scenarios analysis to assess the robustness of our model conclusions. In the first, the prices of zanubrutinib might be decreased following relevant drug policies in China. A hypothesis is that the price of drugs drops by 10%, 20% or 30%. In the second scenario analysis, the patient with CLL is typically incurable but with good prognosis. The median survival time is relatively long; therefore, the time duration was set to 20 years. All analysis was performed in TreeAge Pro 2011.

3 Results

3.1 Base-case Analysis

The costs for a 28-day medication were $1415.38, $770.42, $1356.74 and $1772.43 for zanubrutinib, bendamustine, rituximab (cycle 1) and rituximab (cycle 2-6), respectively. The cost of zanubrutinib, R-bendamustine were $98711.78 and $53095.17, shown in Table 2. ICERs was used to measure the cost-effectiveness of two treatment strategies, and the result showed higher than WTP threshold, with ICER of $58258.18.

Table 2. Base results of zanubrutinib versus R-bendamustine

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Total Costs ($)</th>
<th>Total QALYs</th>
<th>Incremental costs ($)</th>
<th>Incremental QALYs</th>
<th>ICER ($) versus baseline (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-bendamustine</td>
<td>53095.17</td>
<td>4.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanubrutinib</td>
<td>98711.78</td>
<td>5.01</td>
<td>45616.61</td>
<td>0.78</td>
<td>58258.18</td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; R-Bendamustine, Bendamustine and rituximab.

3.2 Sensitivity Analysis
The tornado diagram showed that the ICERs of zanubrutinib versus R-bendamustine was most sensitive to the utility of PD, followed by the cost of zanubrutinib, utility of PFS (Fig.2). The ICER was changed from $45616.61 to $97660.72, $39930.21 to $76593.89, $65776.27 to $42195.15, per QALY when the utility of PD (0.49~0.74), zanubrutinib (1132.30~1698.45), utility of PFS (0.78~0.91) increased to the higher threshold. Whereas, none reverses the model results. In each group, other variables (such as cost of R-bendamustine, discount rate, follow-up monitoring cost and adverse reaction treatment cost) had moderate or mild effects on ICER.

The results of probabilistic sensitivity analysis suggested that the probability of zanubrutinib being cost-effectiveness compared with R-bendamustine is 3.70% at a WTP threshold of $38223.34 per QALY, respectively (Fig.3). The results showed that R-bendamustine was more cost-effective for patients currently.

### Scenario Analysis

The results of scenario analysis are shown in Table 3. When the zanubrutinib price drops to 30%, its ICER ($30762.26) versus R-bendamustine would be within the WTP of three times GDP per capita and could be cost-effective. Expanding the time horizon to 20 years, caused little impact on the ICER ($51113.9).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>the cost of zanubrutinib drops by 10%</td>
<td>49092.84</td>
</tr>
<tr>
<td>the cost of zanubrutinib drops by 20%</td>
<td>39927.55</td>
</tr>
<tr>
<td>the cost of zanubrutinib drops by 30%</td>
<td>30762.26</td>
</tr>
<tr>
<td>time horizon of 20 years</td>
<td>51113.9</td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

### 4 Discussion

Although CLL remains an incurable disease, not all patients with CLL need treatment, unless the patients with symptomatic or advanced-stage disease[18]. The median survival of patients with CLL generally reaches 10 years, and the patients with del (17p) and/or TP53 gene mutations have the worst prognosis. In the guidelines, BTK inhibitors are first-line treatment for various CLL patients. Zanubrutinib-based regimens significantly improved PFS compared with R-bendamustine with an acceptable safety profile (HR 0.42 [95% CI 0.28 to 0.63]; two-sided p < 0.0001), according to a recent randomized phase III trial[6]. Wei Xu et al demonstrated that zanubrutinib in Chinese patients with relapsed/refractory CLL/SLL generally presented well tolerated and resulted in a high overall response rate[19]. But unlike R-
bendamustine with 6 cycles therapy, zanubrutinib requires continuous therapy. Consequently, economic burden become an important driver for its clinical application. The price of zanubrutinib have greatly reduced in China since it was approved, more than 50%, which extremely promoting its application to cover more patients with CLL. Therefore, we constructed a partitioned survival model to evaluate the cost-effectiveness of zanubrutinib.

Based on our model, zanubrutinib costs $58258.18 per additional QALY gained compared with R-bendamustine, which is way above WTP threshold. Findings of PSA indicated a high probability up to 94.50% that zanubrutinib would be cost-effective when WTP threshold was increased to $101928.88 per QALY (8 times GDP). Results of the one-way sensitivity analysis demonstrated that utility of PD was the most sensitive parameter in contrast to R-bendamustine, which indicated that patients gained less benefits with high utility of PD. The cost of zanubrutinib was also to be main influencing factor of economic results. When the price of zanubrutinib decreased by 20%, the ICER decreased to an acceptable level in those people. In general, rare of the variables in the model affect the ultimate result.

BTK inhibitors represent a milestone in treatment for CLL. Ibrutinib, as the first generation BTK inhibitor, has significant curative effect. There are several researches to evaluate the cost-effectiveness of ibrutinib. Kishan K. Pate et al. and James I. Barneshave et al demonstrated the ICER of ibrutinib as the first-line therapy to treat patient with CLL are $2,350,041 and $262,000 per QALY in the US. The high drug price leads to the ICER value far exceeding the threshold. Only substantial price reduction, ibrutinib could be a cost-effective regimen\[4, 20\]. Compared to ibrutinib, zanubrutinib has favorable safety characteristics, lower treatment discontinuation rate, fewer cardiac disease events, including fewer cardiac events leading to death\[21\]. To our knowledge, there is only one other published article regarding the cost-effectiveness of zanubrutinib in patients with Waldenström macroglobulinemia from a US payer perspective\[22\]. There is no research to evaluate the cost-effectiveness of zanubrutinib versus R-bendamustine for patients with relapsed CLL/SLL from the Chinese healthcare system perspective.

It is noteworthy that there are some limitations in this study. An important point is that data on zanubrutinib efficacy are available only up to approximately 3.5 years of treatment\[6\], but the time duration of our model simulation is far beyond this time period. There is a certain bias in survival curve data extrapolation. Another important limitation is that the transition probability is mainly based on SEQUOIA with only 2% Asian or Pacific Islander. But zanubrutinib also demonstrated a high overall response rate in Chinese population\[19\]. Bias exists to some extent, but our results are still desirable. In addition, we established a simple model to evaluate the pharmacoeconomics of zanubrutinib and R-bendamustine, subgroups analysis and first-line or greater-line stratification are not conducted in this study. Thereby, it’s difficult to accurately describe the disease progress. Despite these limitations, it affects little about the final outcome.

**5 Conclusion**
Despite the significantly improvement in PFS for patients with untreated CLL, our study suggests zanubrutinib is unlikely to be cost-effective for most adults compared with R-bendamustine at a WTP threshold of $12741.11-38223.34 /QALY from China healthcare system perspective. Nevertheless, our study provides evidence to guide the rational positioning of drug prices and promote the rational selection of drugs.

Declarations

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable

Availability of Data and Materials The datasets generated and/or analysed during the current study available from the corresponding author on reasonable request.

Competing Interests Jing Nie, Huina Wu, Huiyue Zhang, Lihui Liu, Wu Qian, Ke Tang, and Jiyong Wu declare that they have no conflict of interest.

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Authors’ Contributions All authors contributed to the study conception and design. Jiyong Wu and Jing Nie conceived the study idea, devised the study methodology and drafted of the manuscript. Huina Wu, Huiyue Zhang, Lihui Liu, Qian Wu and Ke Tang participated in data collection, and data interpretation. Jing Nie, Huina Wu and Huiyue Zhang did the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

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Statements All the database is publicly availability, URL as follows: https://pubmed.ncbi.nlm.nih.gov/35810754/.

We declare that human participants are not directly involved in the study.

References


**Figures**

![Figure 1](image_url)

**Figure 1**

Model structure for untreated CLL and SLL. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic lymphoma; PFS, progression-free survival; PD, progressed disease.
Figure 2

Tornado diagram of the one-way deterministic sensitivity analysis (Zanubrutinib versus R-Bendamustine). CBC, Count Blood Cell; CT, computed tomography; PD, progressed disease; PFS, progression-free survival; TCC, terminal care costs
Figure 3

1000 monte carlo simulation diagram of the probabilistic sensitivity analysis (Zanubrutinib versus R-Bendamustine)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx