

Cost-effectiveness analysis of Tumor Treating Fields in patient with newly diagnosed glioblastoma in China: results based on real-world data

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Background

- Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults^[1,2]. Despite advances in treatment options, GBM remains incurable, with a median survival of 15 months after diagnosis^[3,4]. According to the "Diagnostic and Treatment Guidelines for Gliomas (2018 edition)" in China, the annual incidence of gliomas ranges from 5 to 8 per 100,000 people^[5]. A retrospective study conducted in China, which included 1,285 patients with GBM, showed that the 5-year survival rate for 254 patients with GBM was only 9%^[6].
- Tumor Treating Fields (TTFields) is a novel, non-invasive treatment modality for GBM, which utilizes low-intensity alternating electric to selectively kill cancer cells by multiple mechanisms.. Several clinical studies have demonstrated the efficacy of TTFields as a monotherapy and concomitantly with chemotherapy in patients with recurrent or newly diagnosed GBM.
- Although TTFields has been approved by the US Food and Drug Administration, the European Medicines Agency and National Medical Products Administration (NMPA) for the treatment of GBM, the value of its application in China is uncertain due to the lack of clinical data and cost-effectiveness analysis. It is important to evaluate the clinical and economic impact of TTFields in the Chinese healthcare setting.

Objective

- The study aims to investigate the cost-effectiveness of TTFields therapy for the treatment of newly diagnosed GBM and provide economic evidence for clinical treatment, health insurance decisions, and policy making related to GBM

Methods

Population: Chinese patients with newly diagnosed GBM.

- Model Structure:** We figure out 2 treatment strategy for evaluation. A three states partitioned survival model (PSM), including progression-free survival (PFS), disease progression (PD), and death, is developed to estimate the incremental cost- effectiveness ratio (ICER). The study period was set at 4 weeks, with a total of 195 cycles, to simulate the long-term cost-effectiveness of patients with newly diagnosed GBM 15 years later.
- Therapy:** *TTFields+TMZ*. TTFields daily use (two patches per week) + temozolomide (TMZ) capsules (150mg/m², orally), with each cycle lasting 28 days, taking TMZ for 5 days and then stopping for 23 days; *TMZ capsules* (150mg/m², orally), with each cycle lasting 28 days, taking TMZ for 5 days and then stopping for 23 days.
- All patients undergo blood tests and MRI scans every three months when there is no progression, while every two months after progression.

Model assumptions: In order to fully evaluate the two therapy strategies, we constructed a PSM with the following assumptions.

- All patients used drugs or devices according to the set protocol, and there were no compliance issues.
- After disease progression, the intervention group and the control group received the same treatment for the progression stage.

Model Parameters

Transition probability

- The clinical efficacy data was gathered from one real-world study conducted in China^[7].
- Long-term overall survival rate was gathered from Porter et al.'s research^[8]. The study used GetData software to extract data from KM curves of real-world studies in China, and used SAS software to fit and reconstruct survival data. After obtaining the survival data, the study used Stata software to perform non-linear model fitting^[9], and selected the curve by comparing the fitted information criteria (AIC, BIC)^[10]. **Figure 1**

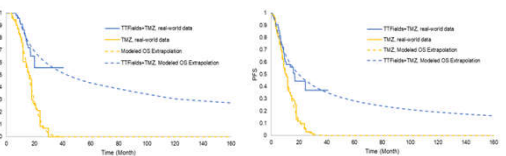


Figure 1: Modeled survival curves

Cost

- Cost measurement from a healthcare perspective only includes direct medical costs.
- The recommended dosage from drug package inserts was used for drug usage, the ratio of domestically produced generic TMZ to imported drugs was obtained from expert consultations as 0.69 to 0.31.
- The price was selected from the median price in the drug bidding database on Yaosh.com^[11].
- The price of TTFields was calculated after commercial health insurance and patient assistance program^[12]. (reimbursement ratio of commercial insurance was 30%).
- The cost of examination fees, bed fees, end-of-life expenses, and adverse events management fees were all derived from literature and government publicly available service price lists.
- All data were adjusted to 2021 price levels based on the Chinese Consumer Price Index, and a half-cycle correction was applied when inputting the model^[12], as shown in **Table 1**.

Table 1: Base case and plausible ranges of model cost (CNY) and utility

Parameter/Variable	Base Value	Minimum Value	Maximum Value	Distribution	Reference
Cost					
Treatment Cost					
TMZ-Drug Cost	¥2,753	¥2,478	¥3,028	Gamma	[11]
TTFields+TMZ- Treatment Cost	¥125,953	¥113,358	¥136,548	Gamma	Company provided, [11]
Drug Management Cost					
PFS-Drug Management Cost	¥12	¥11	¥13	Gamma	Shanghai Medical Service Price Standard
PFS- Disease Management Cost	¥369	¥332	¥406	Gamma	Shanghai Medical Service Price Standard
PD Treatment Cost					
TMZ- PD Treatment Cost	¥11,613	¥10,452	¥12,774	Gamma	Expert consultation, [11]
TTFields+TMZ- PD Treatment Cost	¥11,613	¥10,452	¥12,774	Gamma	Expert consultation, [11]
PD Surgery/Radiation Cost	¥11,221	¥10,099	¥12,343	Gamma	Shanghai Medical Service Price Standard
End-of-Life Care Cost	¥17,902	¥16,112	¥19,692	Gamma	[12]
AE Cost					
AE Cost- Leukopenia and Neutropenia	¥3,295	¥2,865	¥3,624	Gamma	[13]
AE Cost- Pulmonary Embolism	¥8,039	¥7,235	¥8,843	Gamma	[14]
AE Cost- Seizures	¥855	¥770	¥941	Gamma	[15]
AE Cost- Thrombocytopenia	¥28,798	¥26,816	¥30,775	Gamma	[16]
Utility					
PFS Utility					
TMZ_PFS_Utility	0.85	0.77	0.94	Beta	[19, 20]
TMZ+TTFields_PFS_Utility	0.85	0.77	0.94	Beta	[19, 20]
PD Utility					
TMZ_PD_Utility	0.73	0.66	0.80	Beta	[19, 20]
TMZ+TTFields_PD_Utility	0.73	0.66	0.80	Beta	[19, 20]

Utility

- The key health outcome measure in this study is utility, with quality-adjusted life years (QALYs) as the main utility measure.
- The utility values in this study were obtained from previous literature, as shown in **Table 1**.
- A half-cycle correction was applied when inputting the model.

Analysis&Threshold

- This study conducted a cost-effectiveness analysis of the intervention group and the control group, demonstrating the incremental costs, incremental benefits, and ICER of the two groups.
- The willingness-to-pay (WTP) method was used to evaluate the ICER.
- In this study, three times per capita GDP of China in 2021 is used as the WTP threshold.
- The threshold value set in this study is ¥242,928 per QALY gained^[12].

Discount Rate

- The Guidelines for Economic Evaluation of Pharmaceuticals in China suggest that cost and effect should be discounted, and the range of discount rates should be at least 0%-8%^[21].
- Discount rate of 5% is used in the study, with a sensitivity analysis range of 0%-8%.

Sensitivity analyses

- One-way sensitivity analyses were conducted in the models to test alternative modeling assumptions and alternative values for key model parameters.
- The utility values in this study were obtained from previous literature, as shown in **Table 1**.
- A half-cycle correction was applied when inputting the model.
- The overall impact of uncertainty in the model is assessed with probabilistic sensitivity analyses by defining distributions for key parameters in the model. The key parameters included in the PSA are clinical outcome, unit cost, and utility variables. The PSA is run for 1000 iterations (simulations), and the results are plotted on the cost-effectiveness plane as scatterplots and cost-effectiveness acceptability curves to evaluate the pharmacoeconomic value of the two treatments.

Base case result

- TMZ+TTFields group had higher cost, but also higher QALY gained compared to TMZ.
- Compared to TMZ, the ICER for TMZ+TTFields therapy is ¥ 228,086 per QALY. **Table 2**.
- TMZ+TTFields was cost-effectiveness.

Table 2: Cost-effectiveness results for TMZ and TMZ+TTFields

Group	Cost (CNY)	Effectiveness (QALY)	Incr Cost (CNY)	Incr Effectiveness (QALY)	ICER (CNY/QALY)
TMZ	103,341	1.069	-	-	-
TMZ + TTFields	785,546	4.060	682,206	2.991	228,086

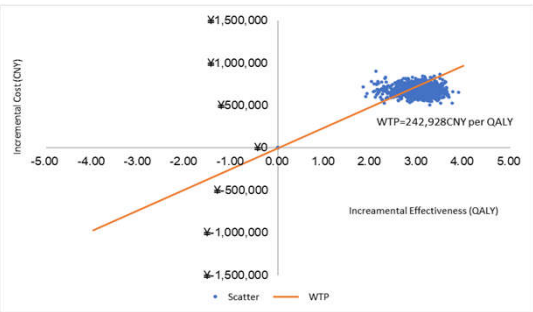


Figure 3: The probabilistic sensitivity analysis result of TMZ+TTFields VS. TMZ

Probabilistic sensitivity analyses

- The probability sensitivity analysis of ICER is carried out, and Monte Carlo simulation is conducted 1000 times to reflect the influence of each parameter on the model. **Figure 2, Figure 3 and Table 3**.
- With WTP threshold, the probability of cost-effectiveness of TMZ+TTFields versus TMZ is 71.0%.

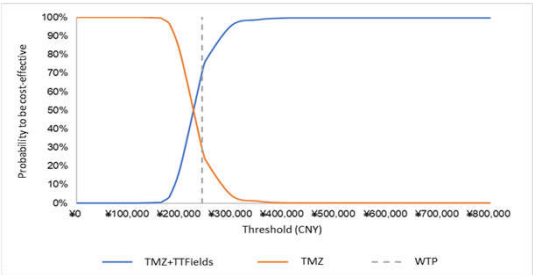


Figure 4: The Acceptability Curve of TMZ and TMZ+TTFields

Table 3: The Acceptability rate of TMZ and TMZ+TTFields in the threshold

WTP (CNY)	Strategy	Acceptability
242,928	TMZ+TTFields	71.0%
242,928	TMZ	29.0%

Results

One-way sensitivity analyses

- Net Monetary Benefit (NMB) was used as an indicator for sensitivity analysis.
- A tornado diagram was created as shown in **Figure 2**.
- The top five factors that have a significant impact on NMB are the QALY discount rate, PFS utility value, PD utility value, cost discount rate, treatment cost for TMZ+TTFields.

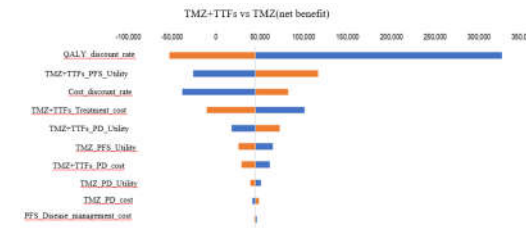


Figure 2: The one-way analysis result of TMZ+TTFields VS TMZ

Limitation

- We didn't consider the utility reduction caused by adverse events due to data limitations. This could under-estimate the impact of AEs in the model as TTFields therapy has a more favorable safety profile.
- The utility of patients of GBM in China was not reported and this information was sourced from published literature which conducted in western population.

Conclusion

- Compared to TMZ alone treating newly diagnosed GBM patients, "TTFields+TMZ" can bring significant utility improvements as Chinese patients have a high adherence rate and long electric field duration. Under the current threshold in China, "TTFields+TMZ" is a cost-effective treatment method.

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Funding

- This study was funded by Zai Lab (Shanghai) Co., Ltd.