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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Abstract

Objectives: The purpose of this study was to evaluate the cost effectiveness of Trifluridine/tipiracil(FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) in the TAGS experiment(NCT02500043). A partition survival model was constructed to analyze the cost effectiveness analysis of FTD/TPI compared to the placebo in heavily pretreated metastatic gastric cancer, and only direct medical costs were included in the model. Then we did sensitivity analyses to assess the robustness of the model's findings.

Outcomes: The model results are mainly from Chinese medical and health system. The output result is the Quality-Adjusted Life Years (QALYs) and incremental cost-effective ratio (ICER).

Results: According to the results of the model, compared with placebo, FTD/TPI generated an additional cost of $25,922.48 and 0.8652 QALYs, and ICER value of the FTD/TPI and placebo is $29,963.45/QALY. Sensitivity analyses showed that the utility value of the PFS stage and FTD/TPI adverse events costs were the main influencing parameters, and the results were stable.

Conclusion: Compared with placebo, from the perspective of Chinese healthcare system, FTD/TPI is a cost-effective choice for patients with heavily pretreated metastatic gastric cancer.

Keywords: heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil;

partition survival model; cost-effectiveness analysis

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Strengths and limitations of this study:1.This study used partition survival model to analyze the cost-effectiveness analysis of Trifluridine/tipiracil(FTD/TPI)for the treatment of heavily pretreated metastatic gastric cancer in China.

2. we had to extrapolate utility value based on the published article due to the lack of the clinical trial data.

3.the cost of adverse event only takes into account the severe adverse events(AEs) of grade 3 and above, and all adverse events are not considered

4. based on the population distribution of TAGS participants, the majority of participants are Europeans, so there may be biases in real-world clinical efficacy in China.

1. Introduction

According to the latest statistics of the WTO in 2022, gastric cancer is the fourth cause of global cancer death [1]. According to Chinese gastric cancer statistics in 2020 [2], the incidence rate and mortality of gastric cancer rank third in all kinds of malignant tumors, about 1.2 million new cases of gastric cancer occur worldwide every year, with China accounting for approximately 40% of them. Many patients are in an advanced state of cancer cell metastasis when gastric cancer is discovered [3], the treatment is usually limited to palliated chemotherapy due to poor expected results.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) recommend many treatment options for metastatic gastric cancer, such as combinate chemotherapy and single-agent chemotherapy. Due to the generally poor physical condition of patients with advanced third-line gastric cancer, the proportion of patients who can receive combinate chemotherapy third-line chemotherapy is extremely low, and single-agent treatment is mainly used. Patients have received these chemotherapy treatments before received FTD/TPI treatment, but the effect is always not satisfactory, and the price is also not negligible. According to IQVIA[4], Global spending on oncology drugs will continue to increase at a double-digit rate, Therefore, it is a global question to find a well-effective and inexpensive gastric cancer treatment.

NCCN recommended treatment of metastatic gastric cancer, FTD/TPI was a dded to systematic second-line and back-line treatment plan for the first time. Acc ording to the TAGS trial [5], In 2021, Generic tablets of FTD/TPI, which was app roved for listing by National Medical Products Administration (NMPA) for the fir st time [6].This greatly reduces the cost of FTD/TPI in China. Due to the lack of in clusion of FTD/TPI in the CSCO guidelines for the treatment of metastatic gastric cancer, the effectiveness and economics of FTD/TPI in the treatment of metastati c gastric cancer can be demonstrated based on TAGS clinical data and the results

of this study. Therefore, this study is to evaluate the cost-effectiveness analysis of FTD/TPI in the treatment of patients with heavily pretreated metastatic gastric ca ncer from the perspective of Chinese healthcare system.

2. Methods

2.1 Patient Population

The data selected from the clinical trial of the TAGS. This is a phase III study with randomized, double-blind, placebo-controlled, and multinational. The study began in July 2015 and ended in September 2021, in 17 countries (including Japan, France, etc.), 110 academic hospitals. Evaluated the efficacy and safety of FTD/TPI plus Best Supporting Treatment (BSC) (FTD/TPI) and placebo plus BSC (Placebo) in metastatic gastric cancer. After screening and excluding, a total of 507 patients participated in this clinical trial. These patients had received at least two advanced gastric cancer treatment before. Eligible patients will be concentrated randomly (2: 1) to FTD/TPI (337) or Placebo (170). The main end of the experiment is overall survival(OS), and the secondary end point is Progression-free Survival(PFS. The purpose is to explore whether the patient's Quality of Life(QoL) can be improved to the maximum extent without antitumor factors.

2.1.1 Inclusion and exclusion criteria

Inclusion criteria:

1. Patient age ≥ 18 years.
2. Patient has histologically confirmed and unresectable metastatic gastric cancer, ECOG score status is 0 or 1, and at least two advanced gastric cancer treatment (at least one cycle for each treatment plan)
3. Previous treatment schemes include Platinum based chemotherapy drugs, Fluoropyridine and paclitaxel.
4. Patients progressed according to the image results after three months or the last time.

Exclusion criteria:

1. Patients with other severe diseases or infections.
2. Receive major surgery before random grouping, and have received any anti -cancer therapy within three weeks.
3. Patients who have received FTD/TPI treatment.
4. Pregnant women and breastfeeding patients.

2.2 medication scheme

Participants received 35 milligrams per meter square (mg/m^2) of FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks followed by 14 days rest in each 28-day cycle along with BSC until the patient meets the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to 4 non-hematological events, doctor's decision, participants are pregnant, or death)

2.3 Model parameter

A partition survival model was developed to simulate the disease process of heavily pretreated metastatic gastric cancer by Treeage Pro 2019. Including three disease status (Progression-free Survival (PFS), Progressed Disease (PD), death (D)).Patients enter this model in PFS state and after entering PD you cannot return to the previous level. According to the model, the Markov cycle is 28 days. Since 99.9% of patients enter the state of death (D)after 60 model cycles, and the overall 5-year survival rate of progressive gastric cancer is only 35.1% [7], The model is limited to 5 years. The discount rate is recommended according to the "Chinese Pharmaceutical Economics Evaluation Guide" (2020) [8], and the discount rate of cost and utility value is 5%.

2.4 Input parameters

2.4.1 Probability of transferring

The OS and PFS curves were derived from TAGS trail. GetData Graph Digitizer software was used to collect data points from OS and PFS curves. then cleaned up the data and converted into a data format suitable

for survival analysis. The data were analyzed by Kaplan-Meier through R4.2.0 software, and the data were refitted using weibull, gamma, lognormal, log-logistic, and exponential distributions (Table 1). According to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), the smaller the AIC and BIC values, The better the fit [9]. Therefore, the lognormal distribution was selected as the optimal distribution according to AIC and BIC combined with a visual inspection of FTD/TPI and Placebo. The μ value and θ value of each group of OS and PFS curve parameters can be obtained to calculate the transfer probability of transfer from PFS to PFS (PFTF). Assumed that the probability of transfer from PFS to D (PFTD) is a per capita mortality rate of 7.37‰ in 2022 [10]. From this, you can find PFTP =1-PFTF-PFTD. According to the OS curve parameter, it can be obtained from the transfer probability (PSTS) from the survival state to the survival state, which can calculate the PSTD =1-PSTS. According to Zhou T [11], the transfer probability (PPTP) from PD to PD shall be corrected. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in PFS and PD state in the previous cycle.

Table 1 PFS and OS data fit results

Group	Observation	Distribution	AIC	BIC
FTD/TPI	PFS	weibull	1,515.56	1,523.2
		gamma	1,480.323	1,487.963
		lognormal	1,424.173	1,431.813
		log-logistic	1,649.843	1,657.483
		exponential	1,590.963	1,594.783
	OS	weibull	2,015.341	2,022.981
		gamma	2,003.665	2,011.305
		lognormal	1,993.852	2,001.492
		log-logistic	2,156.712	2,164.352
		exponential	2,064.761	2,068.581
Placebo	PFS	weibull	911.2514	917.5924
		gamma	899.762	906.103
		lognormal	853.3578	859.6987
		log-logistic	1,025.024	1,031.365
		exponential	916.1268	919.2973
	OS	weibull	1,098.377	1,104.718
		gamma	1,091.463	1,097.804
		lognormal	1,081.386	1,087.727
		log-logistic	1,181.045	1,187.386
		exponential	1117.249	1120.419

2.4.2 Cost input

From the perspective of the Chinese healthcare system, this study determines and analyzes the following direct costs: drug costs, management costs (including hospitalization costs, nursing costs, etc.), adverse costs, image costs, and BSC costs. Among them, the cost of drugs comes from Yaozhi.com [12], taking the median bid price of the drugs in each province as the price of the cost of drug (Table 2). Because the dosage of the patient is based on the patient's body surface area (BSA) in the TAGS clinical trial, the body surface area is 1.60m^2 based on the Stevenson formula and the average height and weight of China. The cost of disease control, image cost, and BSC costs all come from the price catalog of the medical service project of the Anhui Provincial Medical Insurance Bureau[13]. According to TAGS trail[4], laboratory examination is performed every 1 cycle (including blood routine, urine routine, routine feces, and hematic biochemical examinations), and every 2 cycles are performed. The adverse treatment plan comes from the NCCN

hematopoietic factors [14]. The cost of adverse only takes into account the severe adverse events(AEs) of grade 3 and above(grade ≥3) (such as Neutropenia(34%), anemia (19%) and Leukopenia(9%) in the FTD/TPI, bellyache(9%), anemia (8%)in the placebo). The willingness-to-pay (WTP) in the cost-effectiveness analysis is 3 times $35,580.01 (¥257,094) of Chinese Gross Domestic Product (GDP) in 2022[15]. All costs are shown in US dollars (1 US dollar = CNY 7.23).

Table 2 cost and utility values parameters

Variable	Median	Range		Distribution	Source
cost		Lower limit	Higher limit		
FTD/TPI	$2,112.50	$1,690	$2,535	gamma	[10]
adverse（TAGS）	$3,485.00	$2,788	$4,182	gamma	Estimate
Neutropenia（34%）	$3,448.75	$2,759	$4,138.5	gamma	[12]
anaemia（19%）	$24.62	$19.70	$29.54	gamma	[12]
Leukopenia（9%）	$11.62	$9.30	$13.94	gamma	[12]
adverse（placebo）	$27.33	$21.86	$32.80	gamma	Estimate
bellyache（9%）	$2.71	$2.17	$3.25	gamma	Estimate
anaemia（8%）	$24.62	$19.70	$29.54	gamma	[12]
image	$348.50	$278.8	$418.2	gamma	[11]
disease control cost	$220.74	$176.59	$264.89	gamma	[11]
BSC	$553.57	$442.86	$664.28	gamma	[11]
untility					
PFS	0.74	0.592	0.888	beta	[16]
PD	0.58	0.464	0.696	beta	[16]
D	0	0	0	beta	[16]

2.4.3 Input of health utility values

Because the patient's Quality of Life (QoL) scoring data is not counted in TAGS, this study uses the utility value of Al-Batran Se [16]. According to the results of research, the utility value of the patient in the PFS state is 0.74, the utility value of the patient in the PD state is 0.58, and the utility value of the patient in the death state is 0.

2.5 sensitivity analysis

In order to test the uncertainty of the partition survival model, one-way sensitivity analysis and probabilistic sensitivity analysis(PSA) were used to explore the effects of different parameters on basic analysis results and the

range of data to ± 20%. Sensitivity analysis is performed through the TreeagePro 2019 software. One-way sensitivity analysis results are presented in the form of a tornado diagram, which can reflect the size of multiple uncertain factors on the result[17]. The gamma distribution was selected for the cost parameters, and the beta distribution was used for the transition probability and utility parameters. Probabilistic sensitivity analysis (PSA) was performed through 1000 Monte Carlo simulations, and the results were presented in the form of cost-acceptability curve.

3. Result

3.1 Basic analysis results

According to the lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 months and 3.6 months, and the median survival for PFS was 2 months and 1.8 months, the simulated PFS curve and OS curve were basically similar to the original data ,and the fit was acceptable and reasonable.

Based on the partition survival model, from the perspective of Chinese healthcare system, the total cost of the FTD/TPI was $29,340.17(¥212,006.2), and the total cost of the placebo was $3,416.92(¥24,690). Compared with the placebo, FTD/TPI provides more than 0.8652 QALYs value. At the same time, the ICER value corresponding to each QALY is $29,963.45(¥216,510.11)(Table 3), which is lower than the WTP threshold $35,580.01 (¥257,094). Therefore, compared with the placebo, FTD/TPI treats heavily pretreated metastatic gastric cancer is more economical.

Table 3 Basic Analysis Data

Treatment	cost	Increase cost	QALY	Increase QALY	ICER
FTD/TPI	$29,340.17	NA	3.0376	NA	NA
Placebo	$3,416.92	$25,922.48	2.1724	0.8652	$29,963.45

3.2 sensitivity analysis

3.2.1 One-way sensitivity analysis

According to the tornado diagram in Fig 1, the utility value of PFS

stage has the greatest effect on the ICER value, followed by the adverse events cost of the FTD/TPI. The specific impact is: 1.The utility value of PFS stage increase, ICER value decreases; its cost decreases, ICER value increases. 2. The cost of adverse enters in FTD/TPI increases, the ICER value increases; its cost decreases, and the ICER value decreases. 3. The cost of FTD/TPI increases, and the ICER value increases; its cost decreases, and the ICER value decreases. Individual parameter changes may slightly alter the overall value associated with treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

3.2.2 Probabilistic sensitivity analysis

According to the cost-acceptability curve (Fig 2), when WTP increases with the 1-3 times threshold($11,860-$35,580.01) (¥85,698-¥257,094) of the 1-3 times threshold of GDP, FTD/TPI has an increase in economic probability. When the WTP value is $29,650.01(¥214,245), FTD/TPI was more economical than placebo. FTD/TPI treatment of heavily pretreated metastatic gastric cancer is an acceptable choice.

4. Discussion

This study evaluates the cost effectiveness analysis of FTD/TPI for the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system. FTD/TPI can significantly improve the overall survival period of heavily pretreated metastatic gastric cancer compared to placebo. FTD/TPI is a novel oral cytotoxic chemotherapy ,which consisting of a thymidine-based nucleoside analogue, trifluridine, and a thymidine [18]. As the main active ingredient, Trifluridine inhibits cell proliferation by direct insertion into the DNA after phosphorylation, leading to DNA dysfunction and cell death [18,19]. Thereby playing an anti-tumor role when combined with trifluridine to form FTD/TPI, prevents the rapid degradation of the trifluridine, allowing for the maintenance of adequate plasma levels of the active drug [19,20].

The current first-line combination chemotherapy regimen recommended in CSCO and NCCN guidelines is trastuzumab plus fluorouracil and cisplatin. If firs t-line chemotherapy fails, monotherapy (e.g., docetaxel or irinotecan), single-age nt paclitaxel, or ramucirumab + paclitaxel may be used [21,22]. According to a Chin ese survey literature [23], about 44% of cancer survivors over the age of 65 borrow ed money or went into debt for cancer treatment, and more than 55% of young pa tients (P<0.01) report cancer-related debt. And more than 65% of the borrowers b orrowed more than 50,000 yuan, which seriously reduced the quality of life of pat ients. Therefore, clinicians should combine the patient's condition and family situ ation when choosing a treatment plan, and try to choose a treatment plan with a s uitable price and good treatment effect

According to the analysis results of TAGS clinical data, compared to placeb o, FTD/TPI can significantly improve the overall survival of patients with heavily pretreated metastatic gastric cancer[FTD/TPI: median survival:5.7months(9 5%CI:4.8-6.2),placebo: median survival :3.6months(95%CI:3.1-4.1)(H azard Ratio(HR):0.69(95%CI:0.56-0.85)); p=0.00029]. This study shows that under the condition of 3 times the GDP as a threshold, the total cost and utilit y of the FTD/TPI was $29,340.17 and 3.0376QALYs, and the total cost and utilit y of placebo was $3,416.92and 2.1724QALYs. This shows that the increase cost was $25,922.48, and the increase utility value was 0.8652QALYs, the ICER valu e was $29,963.45. The maximum value of the WTP that did not exceed the preset $35,580.01. Therefore, it can be considered that under the perspective of the Chin ese healthcare system, FTD/TPI treatment of heavily pretreated metastatic gastric cancer is a cost-effectiveness choice. One-way sensitivity analysis results show th at utility value of the PFS, FTD/TPI adverse events costs and FTD/TPI costs still have great impacts on the model. When the WTP value is $29,650.01(¥214,245), FTD/TPI was more economical than placebo.

At present, the only pharmacoeconomic studies on TAGS clinical trial data at abroad are the cost-effectiveness analysis of the comparison of FTD/TPI and nivolumab in Japan [24] and the cost-effectiveness analysis of TAGS data from the

US payer perspective[25].Takushima Y used partitioned survival model(PSM) to compare FTD/TPI with nivolumab, evaluate the economic benefits between them. The partitioned survival model includes three health states (PFS, PD, D). According to the results of the article, the ICER of nivolumab and FTD/TPI is 32,352,489 yen/QALYs, and the WTP threshold is 7,500,000 yen. Therefore, the analysis of FTD/TPI in Japanese public healthcare payment perspective is more economical than nivolumab. This is consistent with the results of our study. According to other article, Zhou K developed a Markov model, including three health status (PFS, PD, D) to judge the cost effectiveness of FTD/TPI through the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, far exceeding their WTP threshold ($50,000-150,000), so it can be obtained that FTD/TPI does not have cost benefits through the perspective of US payers. Their results are not consistent with our study, which may be related to the different prices of FTD/TPI in different countries. Chinese generic drugs are in a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility[26]. According to the data[27], in 2020, the proportion of generic drugs in the domestic drug market was 63%. Moreover, domestic generic drug manufacturers have implemented price Porter's generic strategies. Resulting in an average profit margin of only 5% -10% for generic drugs in China, which is far lower than the average profit margin of international generic drugs (30%-60%)[28]. Therefore, the cost of generic drugs in China is generally low compared to foreign drugs.

At the same time, this study also has some limitations. The first utility value is derived from published article and is not obtained from TAGS clinical data. Due to differences in regional race and other factors, sensitivity analysis is conducted to evaluate the impact of various parameters on the model. However, according to the sensitivity analysis results, utility value of the PFS, the cost of adverse reactions in the FTD/TPI group, and the cost of FTD/TPI have a significant impact on the results. Secondly, only considering the cost of adverse

reactions at level three or above, without considering all adverse reactions, may result in bias in the data. Thirdly, according to the population distribution of participants in the TAGS trial, the majority of participants are Europeans, so there may be biases in real-world clinical efficacy in China.

5. Conclusion

In summary, from the perspective of Chinese healthcare system, FTD/TPI is cost-effectiveness choice in systematic second-line and back-line medication for heavily pretreated metastatic gastric cancer. The results of this study can provide an economically significant solution for doctors to treat heavily pretreated metastatic gastric cancer.

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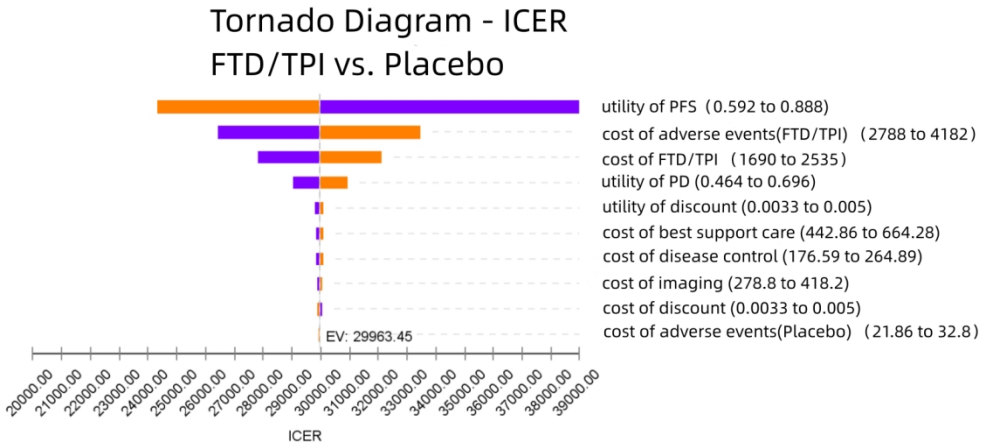

Fig 1 cost and utility range fluctuations ± 20%Plum order factors one-way tornado chart

1095x518mm (38 x 38 DPI)

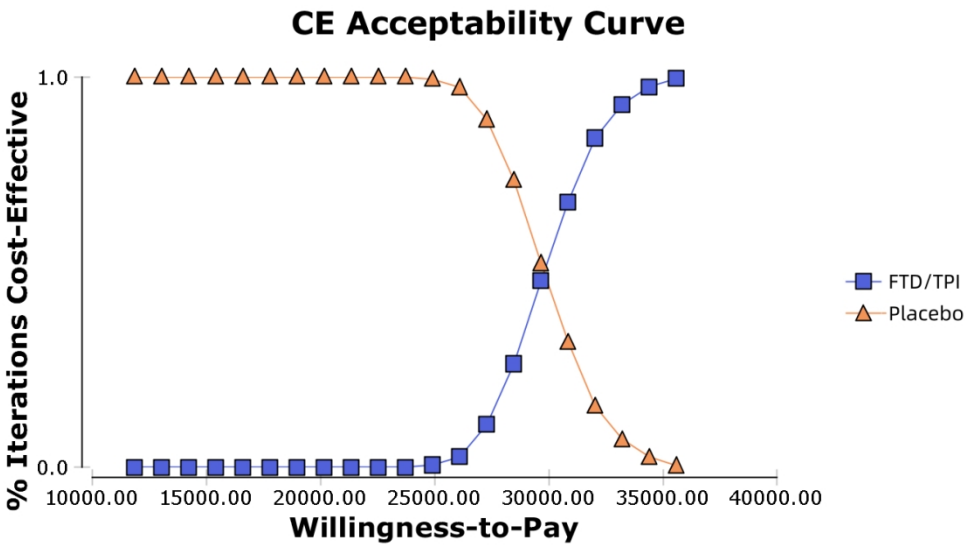

Fig 2 The cost of probability sensitivity analysis-effect acceptable curve

913x513mm (38 x 38 DPI)

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

Ting Ying[1,2#],Runan Xia[1,2#],Yuanyuan Zhang[2,3], Jiahui Dai[1,2], Yadong Wang[1,2], Xuefeng Xie[3,4*]

Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness of Trifluridine/tipiracil (FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) data from the TAGS trial (NCT02500043). A Markov model was constructed to analyze the cost-effectiveness of FTD/TPI compared to the placebo in heavily pretreated metastatic gastric cancer. The model only included direct medical costs. We then conducted sensitivity analyses to evaluate the robustness of the model's findings.

Outcomes: The model results are mainly from Chinese healthcare system. The output result is the Quality-Adjusted Life Years (QALYs) and incremental cost-effective ratio (ICER).

Results: According to the model results, FTD/TPI generated an additional cost of $26,345.84 and 0.88 QALYs compared to the placebo. ICER value of FTD/TPI compared to placebo is $39,915.79 per QALY. Sensitivity analyses revealed that the utility value of the PFS stage and FTD/TPI adverse events costs were the main influencing parameters, ensuring stable results.

Conclusion: From the perspective of Chinese healthcare system, FTD/TPI is a cost-effective option for patients with heavily pretreated metastatic gastric cancer compared to a placebo.

Keywords: heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil; Markov model; cost-effectiveness analysis

Word count:3382 words

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Strengths and limitations of this study: 1. This study used a Markov model to analyze the cost-effectiveness of Trifluridine/tipiracil (FTD/TPI) for the treatment of heavily pretreated metastatic gastric cancer in China.

2. The model uncertainty concerning short-term survival rates is small owing to the good fitness of the model. But the long-term benefits of FTD/TPI remain an open question.

3.The cost of adverse events only takes into account the severe adverse events (AEs) of grade 3 and above, and does not consider all adverse events.

4.Based on the population distribution of TAGS participants, the majority are Europeans. This may introduce biases in assessing real-world clinical efficacy in China.

1. Introduction

According to the latest statistics from the World Health Organization (WHO) in 2022, gastric cancer is the fourth leading cause of cancer-related deaths worldwide[1]. About 1.2 million new cases of gastric cancer occur worldwide every year, with China accounting for approximately 40% of them[2]. Many patients are in an advanced state of cancer cell metastasis when gastric cancer is discovered[1].a)[3], the treatment is usually limited to palliated chemotherapy due to poor expected results.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) recommend several treatment options for metastatic gastric cancer, including combination chemotherapy and single-agent chemotherapy. Due to the generally poor physical condition of patients with advanced third-line gastric cancer, the proportion of patients who can receive combination third-line chemotherapy is extremely low, and single-agent treatment is mainly used. Patients who have received these chemotherapy treatments before receiving FTD/TPI treatment, but the results unsatisfactory, and the cost is also significant. According to IQVIA[4], global spending on oncology drugs will continue to increase at a double-digit rate. Therefore, it is a global challenge to find a cost-effective and efficient treatment for gastric cancer.

In 2019, the European Commission (EC) and the Food and Drug Administration (FDA) approved FTD/TPI for the treatment of adult patients with metastatic gastric cancer who have received at least two prior systemic treatment regimens to manage advanced disease. FTD/TPI is a novel oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analogue, trifluridine, and thymidine[5]. As the main active ingredient, Trifluridine inhibits cell proliferation by direct insertion into the DNA after phosphorylation, leading to DNA dysfunction and cell death [5,6]. Thereby playing an anti-tumor role when combined with trifluridine to form FTD/TPI, it prevents the rapid degradation of trifluridine, allowing for the maintenance of adequate plasma levels of the active drug [6,7]. In China, Trifluridi

ne/tipiracil has been approved for metastatic colorectal cancer but not for gastric cancer. In 2021, generic tablets of FTD/TPI were approved for listing by the Nati onal Medical Products Administration (NMPA) for the first time [8]. This greatly reduces the cost of FTD/TPI in China. Although the current CSCO guideline does not include FTD/TPI as a treatment option for metastatic gastric cancer, the analy sis of TAGS clinical data and generic drugs launched in China suggests that FTD/ TPI may be cost-effective in the treatment of metastatic gastric cancer within the Chinese healthcare system, which provides the possibility of incorporating FTD/ TPI into the Chinese gastric cancer diagnostic and treatment guidelines. Therefor e, this study will evaluate the cost-effectiveness analysis of FTD/TPI in treating a significant number of heavily metastatic gastric cancer patients from the perspecti ve of the Chinese healthcare system. The results of this study can provide clinicia ns, payers, and budget holders with economically viable options.

2. Methods

2.1 Patient Population

The data were selected from the clinical trial of the TAGS (NCT02500043, Taiho Oncology, Inc.). This is a Phase III study with randomized, double-blind, placebo-controlled, and multinational. The study began in July 2015 and ended in September 2021, in 17 countries including Japan, France, among others, and involving 110 academic hospitals. The efficacy and safety of FTD/TPI plus Best Supportive Care (BSC) (FTD/TPI) and placebo plus BSC (Placebo) in metastatic gastric cancer. After screening and excluding, a total of 507 patients participated in this clinical trial. These patients had received at least two treatments for advanced gastric cancer before. Eligible patients will be randomly (2: 1) to either FTD/TPI (337) or Placebo (170). The main end of the experiment is overall survival (OS), and the secondary endpoint is progression-free survival (PFS). The purpose is to explore whether the patient's Quality of Life (QoL) can be improved to the maximum extent without anti-tumor factors. Patients or members of the public were not involved in the design of this study.

2.2 medication scheme

Participants received 35 milligrams per meter square (mg/m^2) of FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks followed by 14 days rest in each 28-day cycle along with BSC until the patient meets the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to 4 non-hematological events, doctor's decision, participants are pregnant, or death)

2.3 Model parameter

A Markov model was developed to simulate the disease progression of heavily pretreated metastatic gastric cancer by TreeagePro 2019. Including three disease statuses (Progression-free Survival (PFS), Progressed Disease (PD), death (D)). Patients enter this model in the PFS state, and after entering PD, they cannot return to the previous state. According to the model, the Markov cycle is 28 days. Since 99.9% of patients enter the state of death (D) after 60 model cycles, and the overall 5-year survival rate of progressive gastric cancer is only 35.1% [9], the model is limited to 5 years. The discount rate of 5% for cost and utility value is recommended according to the "Chinese Pharmaceutical Economics Evaluation Guide" (2020) [10].

2.4 Input parameters

2.4.1 Probability of transferring

The OS and PFS curves were derived from TAGS trail. GetData Graph Digitizer software was used to collect data points from OS and PFS curves. then cleaned up the data and converted into a data format suitable for survival analysis. The data were analyzed by Kaplan-Meier through R4.2.0 software, and the data were refitted using weibull, gamma, lognormal, log-logistic, and exponential distributions (Table 1). According to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), the smaller the AIC and BIC values, The better the fit[11]. Therefore, the lognormal distribution was selected as the optimal distribution according to AIC and BIC combined with a visual inspection

of FTD/TPI and Placebo. The μ value and θ value of each group of OS and PFS curve parameters can be obtained to calculate the transfer probability of transfer from PFS to PFS (PFTF). Assumed that the probability of transfer from PFS to D (PFTD) is a per capita mortality rate of 7.37‰ in 2022[12]. From this, you can find PFTP =1-PFTF-PFTD. According to the OS curve parameter, it can be obtained from the transfer probability (PSTS) from the survival state to the survival state, which can calculate the PSTD =1-PSTS. According to Zhou T[13], the transfer probability (PPTP) from PD to PD shall be corrected. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in PFS and PD state in the previous cycle.

Table 1 Progression-free survival and Overall survival data fit results

Group	Observation	Distribution	AIC	BIC
FTD/TPI	Progression-free survival	weibull	1,515.56	1,523.2
		gamma	1,480.323	1,487.963
		lognormal	1,424.173	1,431.813
		log-logistic	1,649.843	1,657.483
		exponential	1,590.963	1,594.783
	Overall survival	weibull	2,015.341	2,022.981
		gamma	2,003.665	2,011.305
		lognormal	1,993.852	2,001.492
		log-logistic	2,156.712	2,164.352
		exponential	2,064.761	2,068.581
Placebo	Progression-free survival	weibull	911.2514	917.5924
		gamma	899.762	906.103
		lognormal	853.3578	859.6987
		log-logistic	1,025.024	1,031.365
		exponential	916.1268	919.2973
	Overall survival	weibull	1,098.377	1,104.718
		gamma	1,091.463	1,097.804
		lognormal	1,081.386	1,087.727
		log-logistic	1,181.045	1,187.386
		exponential	1,117.249	1,120.419

2.4.2 Cost input

From the perspective of the Chinese healthcare system, this study determines and analyzes the following direct costs: drug costs, administration costs, adverse costs, imaging costs, and BSC costs. Among them, the cost of drugs is sourced from Yaozhi.com [14], with the median bid price of the drugs in each province considered as the cost of the drugs (Table 2). In the TAGS clinical trial, the patient's dosage is determined by their body surface area (BSA), which is calculated to be 1.60m^2 using the Stevenson formula and the average height and weight of individuals in China. Six provinces in China, including Hunan, Henan, Jiangsu, Anhui, Shaanxi, and Shandong, were selected to estimate the administrative cost, imaging cost, and BSC cost based on the prices listed in the price catalog of medical services of the Medical Insurance Bureau of each province. According to TAGS trail[15], laboratory examinations are conducted every cycle (including blood routine, urine routine, routine feces, and hematic biochemical examinations), while imaging tests such as CT, MRI, PET-CT, and radiography are conducted every two cycles. Since there is no standard treatment for a large number of pretreated metastatic gastric cancer patients, the Best Supportive Care (BSC) cost was estimated based on the possible monitoring components of palliative care outlined in the 2022 gastric cancer treatment guidelines[16]. This includes corresponding administration measures such as the presence of bleeding, obstruction, pain, and other factors. The estimation was made in conjunction with the median prices listed in the medical services of the healthcare bureaus of six provinces. It was assumed that patients would undergo BSC treatment after PD. The adverse treatment plan is derived from the NCCN hematopoietic factors [17]. The cost of adverse events only takes into account the severe adverse events (AEs) of grade 3 and above (grade ≥3), such as Neutropenia (34%), anemia (19%), and Leukopenia (9%) in the FTD/TPI group, and bellyache (9%) and anemia (8%) in the placebo. The willingness-to-pay (WTP) in the cost-effectiveness analysis is three times the Chinese Gross

Domestic Product (GDP) in 2022[18], amounting to $35,559.34. All costs are shown in US dollars (1 US dollar = CNY 7.23).

Table 2 cost and utility values parameters

Variable	Median	Range		Distribution	Source
cost		Lower limit	Higher limit		
FTD/TPI	$2,112.50	$1,690	$2,535	gamma	[14]
adverse（TAGS）	$3,485.00	$2,788	$4,182	gamma	Estimate
Neutropenia（34%）	$3,448.75	$2,759	$4,138.5	gamma	[17]
Anaemia（19%）	$24.62	$19.70	$29.54	gamma	[17]
Leukopenia（9%）	$11.62	$9.30	$13.94	gamma	[17]
adverse（placebo）	$27.33	$21.86	$32.80	gamma	Estimate
Bellyache（9%）	$2.71	$2.17	$3.25	gamma	Estimate
Anaemia（8%）	$24.62	$19.70	$29.54	gamma	[17]
Imaging	$304.55	$243.64	$365.46	gamma	Estimate
administration cost	$353.22	$282.58	$423.86	gamma	Estimate
Best Supportive Care (BSC)	$1,127.97	$902.38	$1,353.56	gamma	Estimate
utility					
progression-free survival	0.764	0.611	0.917	beta	[19]
Progressed Disease	0.652	0.522	0.782	beta	[19]
Death	0	0	0	beta	[19]

2.4.3 Input of health utility values

In 2021, the health-related quality of life (HRQoL) was assessed in TAGS using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Patients completed the EORTC QLQ-C30 questionnaire within 7 days prior to randomization, predose on Day 1 of at least 2 treatment cycles, and at the safety follow-up 30 days after the last dose (if not performed within the previous 4 weeks). Leanne Hamerton *et al*. [19] used a published algorithm by Kontodimopoulos *et al.* to map the scores from EORTC QLQ-C30. The resultant utility values applied within the model were 0.764 for PFD and 0.652 for PD.

2.5 Model based results

The model results were mainly from the Chinese healthcare system. The outputs included Quality-adjusted life years (QALYs) and Incremental Cost-Effectiveness Ratio (ICER). When the ICER value was less than the set WTP

threshold ($35,559.34), FTD/TPI was found to be more cost-effective than the placebo.

2.6 sensitivity analysis

In order to test the uncertainty of the Markov model, one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to explore the effects of different parameters on basic analysis results and the range of data to ± 20%. Sensitivity analysis is conducted using the TreeagePro 2019 software. One-way sensitivity analysis results are typically presented in the form of a tornado diagram, which can reflect the size of multiple uncertain factors on the outcome [20]. The gamma distribution was chosen for the cost parameters, while the beta distribution was used for the transition probability and utility parameters. Probabilistic sensitivity analysis (PSA) was performed using 1000 Monte Carlo simulations, and the results were presented in the form of a cost-acceptability curve.

3. Result

3.1 Basic analysis results

According to the lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 months and 3.6 months. The median survival for PFS was 2 months and 1.8 months, the simulated PFS curve and OS curve closely resembled the original data, indicating an acceptable and reasonable fit.

Based on the Markov model, from the perspective of Chinese healthcare system, the total cost of the FTD/TPI was $32,234.26, while the total cost of the placebo was $5,888.42. Compared with the placebo, FTD/TPI provides more than 0.88 QALYs in value. At the same time, the ICER value corresponding to each QALY is $29,915.79 (Table 3), which is lower than the WTP threshold of $35,559.34. Therefore, compared with the placebo, FTD/TPI is a cost-effective treatment option for heavily pretreated metastatic gastric cancer.

Table 3 Basic Analysis Data

Treatment	cost	Increase cost	QALY	Increase QALY	ICER
FTD/TPI	$32,234.26	NA	3.20	NA	NA
Placebo	$5,888.42	$26,345.84	2.32	0.88	$29,915.79

3.2 sensitivity analysis

3.2.1 One-way sensitivity analysis

According to the tornado diagram in Fig 1 Cost and utility value range fluctuation ±20% under the order factor sensitivity analysis tornado diagram, the utility value of PFS stage has the greatest effect on the ICER value, followed by the adverse events cost of the FTD/TPI. The specific impact is as follows: 1. The utility value of PFS stage increases, leading to a decrease in ICER value; as its cost decreases, the ICER value increases. 2. As the cost of adverse events in FTD/TPI increases, the ICER value also increases; conversely, as the cost decreases, the ICER value decreases. 3. As the cost of FTD/TPI increases, ICER value also increases; conversely, as the cost decreases, the ICER value decreases as well. Individual parameter changes may slightly alter the overall value associated with the treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

3.2.2 Probabilistic sensitivity analysis

According to the cost-acceptability curve (Fig 2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis), when WTP increases within the range of 1-3 times threshold($11,860-$35,559.34) of the GDP, the FTD/TPI shows an increase in economic feasibility. When the WTP value is $29,632.64, FTD/TPI was more cost-effective than the placebo. FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a viable option.

4. Discussion

In the present study, the TAGS trial shows that compared with placebo, FTD/TPI provides a significant survival benefit for patients with heavily pretreated gastric cancer (FTD/TPI: median survival: 5.7 months (95% CI: 4.8-6.2), placebo:

median survival: 3.6 months (95% CI: 3.1-4.1) (Hazard Ratio (HR): 0.69 (95% CI: 0.56-0.85); p = 0.00029). We intended to conduct a Markov model analysis of FTD/TPI compared to a placebo in patients with metastatic gastric cancer from the perspective of the Chinese healthcare system. According to our analysis, FTD/TPI costs $26,345.84 more than the placebo but provides an additional 0.88 QALYs, resulting in an ICER of $29,915.79 per QALY, which is below the defined WTP of $35,559.34 per QALY gained. Therefore, it can be considered that from the perspective of the Chinese healthcare system, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a cost-effective option. The cost-effective estimate remained stable in sensitivity analyses. The evidence from this study emphasizes the value of FTD/TPI in clinical and pharmacoeconomic settings. It supports FTD/TPI as a systematic second-line and back-line treatment option for patients with metastatic gastric cancer in China, and provides a reference for the dynamic adjustment of the catalog of medicines covered by the national medical insurance system.

Since the study population consists of patients with metastatic gastric cancer who have previously undergone two or more chemotherapy regimens for advanced or metastatic disease with poor outcomes. Considering the entire treatment process for diagnosed patients, a brief cost-effectiveness analysis of first-line and second-line therapeutic agents for gastric cancer will be conducted. According to CSCO guidelines, patients are initially treated with first-line and second-line therapies after being diagnosed with advanced metastatic gastric cancer. The first-line therapy includes doublet (fluorouracil plus platinum) or a triplet (fluorouracil plus paclitaxel/anthracycline plus platinum). Jingjing Xie *et al*[21]. analyzed the cost-effectiveness of the current first-line drug combination regimens for gastric cancer (oxaliplatin plus capecitabine (51 cases), cisplatin plus capecitabine (49 cases), and paclitaxel plus capecitabine (51 cases)) using real-world data. The study considered one cycle of 21 days and a total of 4 cycles. According to the results, the cisplatin plus capecitabine group was more cost-effective (cost-effectiveness ratio: ¥106.29), but the paclitaxel plus capecitabine group had a better treatment outcome.

Trastuzumab plus paclitaxel was preferred for second-line treatment. Chen Jia *et al*[22]. explored the cost-effectiveness of trastuzumab from the perspective of the Chinese healthcare system. They constructed a partitioned survival model using data from the ToGA trial (NCT01041404, Hoffmann-La Roche), with one cycle lasting 21 days and a total of 6 cycles. According to the results, the combination of trastuzumab and chemotherapy increased 0.19 QALY over chemotherapy alone, but required an additional cost of $65,352.42, which exceeded the willingness-to-pay threshold (WTP). Therefore, the use of trastuzumab in combination with chemotherapy for the treatment of HER-2 positive advanced gastric cancer is not a cost-effective option from the perspective of the Chinese healthcare system. And subsequent studies need to be further analyzed in conjunction with real-world data.

Several international publications currently use data from the TAGS trial to compare the Pharmacoeconomics of FTD/TPI with a placebo in patients with heavily pretreated metastatic gastric cancer. Takushima Y[23] used a partitioned survival model to estimate the cost-effectiveness of FTD/TPI versus nivolumab from the perspective of the Japanese public healthcare payer. According to the results of the article, the ICER of nivolumab and FTD/TPI is ¥32,352,489 yen/QALYs, and the WTP threshold is 7,500,000 yen. Therefore, the analysis of FTD/TPI from the Japanese public healthcare payment perspective shows that it is more cost-effective than nivolumab. We cannot compare the results of Takushima with this study due to the different comparator.

In a study by Leanne Hamerton *et al*[19]. in Britain, a partitioned survival model was used to compare FTD/TPI with BSC. They employed a lognormal distribution to fit OS and a generalized gamma model to fit PFS and time-to-treatment-discontinuation (TTD). According to the study results, FTD/TPI was associated with an ICER of £37,907 per QALY gained compared with BSC. Therefore, FTD/TPI is a cost-effective treatment for patients with pretreated metastatic gastric cancer from a UK perspective.

Overall, published literature supports the findings of the present analysis, except for the study by Zhou K *et al*[24]. They developed a Markov model to assess

the cost-effectiveness of FTD/TPI from the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, which is far beyond their WTP threshold($50,000-$150,000) concluded that FTD/TPI does not provide cost benefits from the perspective of US payers. Their results are not consistent with our study, which may be attributed to the varying prices of FTD/TPI in different countries. Chinese generic drugs hold a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility [25]. According to the data [26], in 2020, the proportion of generic drugs in the domestic drug market was 63%. Moreover, domestic generic drug manufacturers have implemented Porter's generic strategies to adjust prices. Resulting in an average profit margin of only 5% to 10% for generic drugs in China, which is significantly lower than the average profit margin of international generic drugs (30% to 60%) [27]. Therefore, the cost of generic drugs in China is generally lower compared to foreign drugs.

However, our study also has some limitations. First, the model uncertainty concerning the short-term survival rates is small owing to the excellent fit of the model. But the long-term benefits of FTD/TPI remain an open question. The model can be validated using long-term survival data once more mature data becomes available in the future. Secondly, only considering the cost of adverse reactions at level three or above, without taking into account all adverse reactions, may lead to bias in the data. Thirdly, based on the population distribution of participants in the TAGS trial, the majority are Europeans. This could introduce biases in real-world clinical efficacy in China, potentially impacting the trial's generalizability. Fortunately, there are already exploratory studies on FTD/TPI for advanced unresectable gastric cancer in the Chinese population registered in the Chinese Clinical Trial Registry (ChiCTR2400080940) and clinical trial (NCT05029102). As data is continually updated, this study will also be updated accordingly.

5. Conclusion

In summary, from the perspective of the Chinese healthcare system, is a cost-effective choice for systematic second-line and back-line medication for FTD/TPI heavily pretreated metastatic gastric cancer. The results of this study can offer an economically significant solution for clinicians, payers, and budget holders to treat heavily pretreated metastatic gastric cancer.

Ethics Approval：This study is an economic evaluation analysis and does not involve human subjects. Input data includes human material or human data derived from other published studies conducted with the approval of an appropriate ethics committee. Therefore, no ethics approval is required for conducting this cost-effectiveness analysis.

Figure 1: Cost and utility value range fluctuation ±20% under the order factor sensitivity analysis tornado diagram

Figure 2: Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

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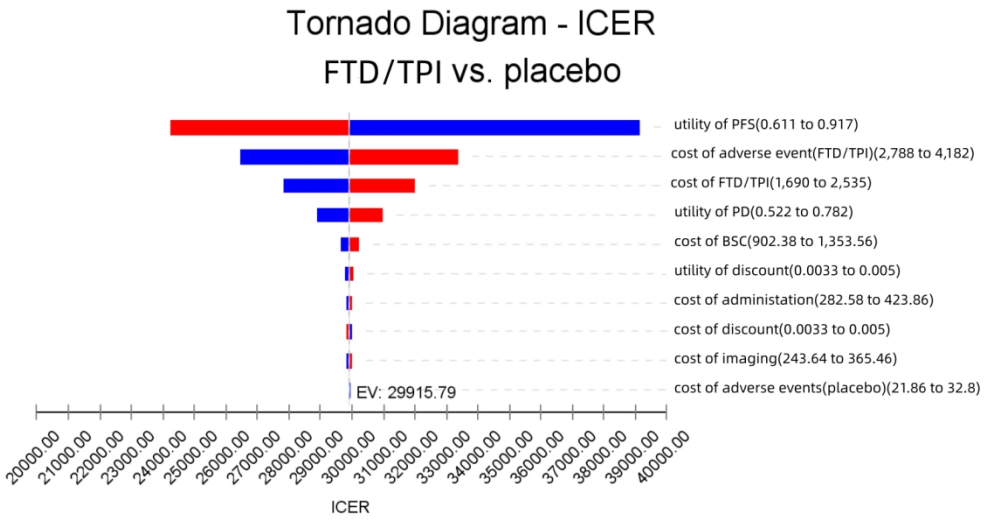
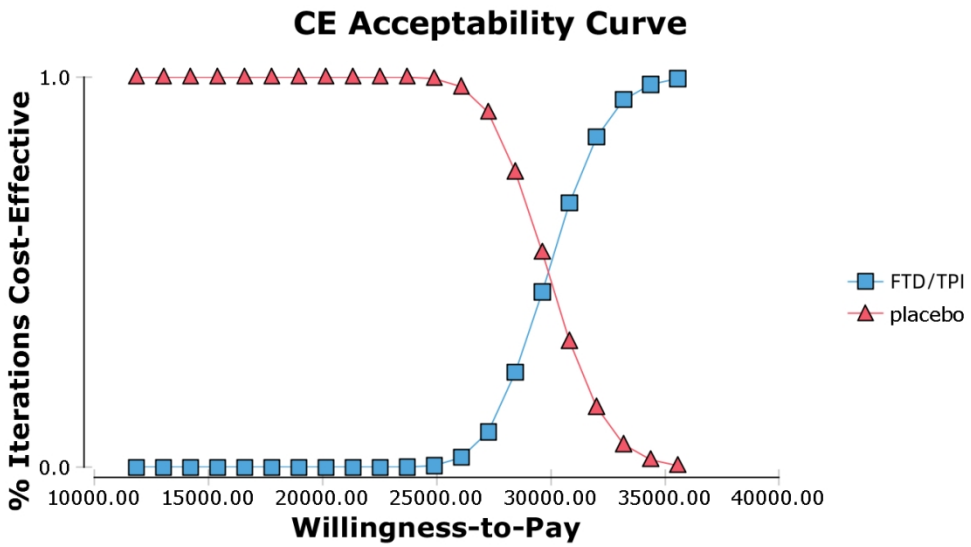


Cost and utility value range fluctuation ±20% under the order factor sensitivity analysis tornado diagram

1095x601mm (38 x 38 DPI)



Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

913x513mm (38 x 38 DPI)

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) data from the TAGS trial (NCT02500043), a three-state Markov model (PFS , progressed disease, and death) was constructed to analyze the cost-effectiveness of FTD/TPI compared with the placebo in heavily pretreated metastatic gastric cancer. Cost was from pricing records and the literature. The model was simulated for 5 years with monthly cycles. Costs and health outcomes were discounted by 5%. We then conducted sensitivity analyses to evaluate the robustness of the parameters.

Outcomes: The model results were mainly from the Chinese healthcare system. The output results were the quality-adjusted life years (QALYs) and incremental cost-effective ratio (ICER).

Results: According to the model results, FTD/TPI generated an additional cost of $26,855.66 and 0.88 QALYs compared with the placebo. ICER of FTD/TPI compared with the placebo was $30,494.89 per QALY. Sensitivity analyses revealed that the utility value of the PFS stage and FTD/TPI adverse event costs were the main influencing parameters, ensuring stable results.

Conclusion: From the perspective of the Chinese healthcare system, FTD/TPI is a more cost-effective option compared with the placebo for the treatment of heavily pretreated metastatic gastric cancer in patients who have received at least two prior

advanced treatment regimens.

Keywords: Heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil; Markov model; Cost-effectiveness analysis; Placebo; Economic evaluation

Word count: 3578 words

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Strengths and limitations of this study: 1. This study used a Markov model to analyze the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for the treatment of heavily pretreated metastatic gastric cancer in China.

2. The cost of adverse events (AEs) only considers the severe AEs of grade 3 and above and does not consider all AEs.

3. Based on the population distribution of TAGS participants, the majority are Europeans. This limitation may introduce biases in assessing real-world clinical efficacy in China.

4. The model uncertainty concerning short-term survival rates is small owing to the good fitness of the model. But the long-term benefits of FTD/TPI remain an open question.

1. Introduction

According to the latest statistics from the World Health Organization in 202 2, gastric cancer is the fourth leading cause of cancer-related deaths worldwide [1]. About 1.2 million new cases of gastric cancer occur worldwide every year, with China accounting for approximately 40% of them [2]. Many patients are in an ad vanced state of cancer cell metastasis when gastric cancer is discovered [3], and tr eatment is usually limited to palliative chemotherapy because of poor expected re sults.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSC O) and the National Comprehensive Cancer Network (NCCN) recommend severa l treatment options for metastatic gastric cancer, including combination chemothe rapy and single-agent chemotherapy. As a result of the generally poor physical co ndition of patients with advanced third-line gastric cancer, the proportion of patie nts who can receive combination third-line chemotherapy is extremely low, and si ngle-agent treatment is mainly used. Patients who have received these chemother apy treatments before receiving trifluridine/tipiracil (FTD/TPI) treatment have re ported unsatisfactory results, and the cost is also high. According to IQVIA [4], g lobal expenditure on oncology drugs will continue to increase at a double-digit rat e. Therefore, a cost-effective and efficient treatment for gastric cancer remains a global challenge.

In 2019, the European Commission and the Food and Drug Administration a pproved FTD/TPI for the treatment of adult patients with metastatic gastric cance r who have received at least two prior systemic treatment regimens to manage adv anced disease. FTD/TPI is a novel oral cytotoxic chemotherapy consisting of a th ymidine-based nucleoside analog, trifluridine, and thymidine [5]. As the main acti ve ingredient, trifluridine inhibits cell proliferation by direct insertion into DNA a fter phosphorylation, leading to DNA dysfunction and cell death [5,6]. In addition to its anti-tumor role when combined with trifluridine to form FTD/TPI, it preve nts the rapid degradation of trifluridine, allowing for the maintenance of adequate

plasma levels of the active drug [6,7]. In 2021, FTD/TPI generic tablets were first approved for marketing by the State Drug Administration [8]. This move greatly reduced the cost of using FTD/TPI in China. FTD/TPI has been approved for metastatic colorectal cancer in the current CSCO guidelines, but it has not been approved for gastric cancer. There is currently no cost-effectiveness analysis evaluating FTD/TPI for the treatment of a significant number of patients with severe metastatic gastric cancer from the perspective of the Chinese healthcare system. Therefore, this study conducted a cost-effectiveness analysis of FTD/TPI for treating a large number of patients with severe metastatic gastric cancer from the perspective of the Chinese healthcare system. The results of this study could offer clinicians and payers economic evidence to consider incorporating FTD/TPI into Chinese guidelines for the diagnosis and treatment of gastric cancer.

2. Methods

2.1 Patients

The data were selected from the clinical trial of TAGS (NCT02500043, Taiho Oncology, Inc.). This work is a phase III study with randomized, double-blind, placebo-controlled, and multinational cases. The study began in July 2015 and ended in September 2021, in 17 countries including Japan and France. It involved 110 academic hospitals. The efficacy and safety of FTD/TPI plus best supportive care (BSC; FTD/TPI) and placebo plus BSC (placebo) in metastatic gastric cancer were determined. After screening and excluding the cases, a total of 507 patients participated in this clinical trial. These patients had received at least two treatments for advanced gastric cancer before. Eligible patients were randomly classified (2: 1) into either the FTD/TPI group (337) or placebo group (170). The main end of the experiment was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). The purpose of this work was to explore whether the patient's quality of life (QoL) can be improved to the maximum extent without anti-tumor factors. Patients or members of the public were not involved in the design of this study.

2.2 Treatment

Participants received 35 mg/m^2 FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks, followed by 14 days of rest in each 28-day cycle along with BSC until the patient met the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to four non-hematological events, doctor's decision, participants are pregnant, or death).

2.3 Model structure

A Markov model was developed to simulate the disease progression of heavily pretreated metastatic gastric cancer by TreeagePro 2019. It included three disease statuses (PFS, progressed disease [PD], and death [D]). Patients entered this model in the PFS state, and they could not return to the previous state after entering PD. The time of entry into the model for patients in this study was set to the average age of patients in the TAGS trial (62.5 years). According to the model, the Markov cycle was 28 days. Given that 99.9% of patients entered the state of death (D) after 60 model cycles, and the overall 5-year survival rate of progressive gastric cancer was only 35.1% [9], the model was limited to 5 years. The discount rate of 5% for cost and utility value is recommended according to the Chinese Pharmaceutical Economics Evaluation Guide (2020) [10].

2.4 Clinical inputs

2.4.1 Transition probability

The OS and PFS curves were derived from the TAGS trial. GetData Graph Digitizer software was used to collect data points from OS and PFS curves. The data were then cleaned and converted into a format suitable for survival analysis. The data were analyzed by Kaplan–Meier analysis through R4.2.0 software, and the survival curve extrapolation was conducted using Standard Parametric Model (SPM) by using weibull, gamma, lognormal, log-logistic, and exponential distributions (Table 1). According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the smaller the AIC and BIC values, the better

the fit [11]. Therefore, the log-normal distribution was selected as the optimal distribution according to AIC and BIC combined with a visual inspection of FTD/TPI and placebo. We added both the original survival curves compared to the simulated survival curves (Table 2). The μ value and θ value of each group of OS and PFS curve parameters were obtained to calculate the transfer probability of transfer from PFS to PFS (PFTF). Assuming that the transition probability from PFS to D (PFTD) is a per capita mortality rate of 7.37‰ in 2022 [12], PFTP =1-PFTF-PFTD. The OS curve parameter can be used to determine the transition probability from the survival state to the survival state (PSTS) as follows: PSTD =1-PSTS. According to Zhou T. [13], the transition probability from PD to PD (PPTP) should be corrected. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in PFS and PD state in the previous cycle, respectively.

Table 1 Progression-free survival and Overall survival data fit results

Group	Observation	Distribution	AIC	BIC
FTD/TPI	Progression-free survival	weibull	1,515.56	1,523.2
		gamma	1,480.323	1,487.963
		lognormal	1,424.173	1,431.813
		log-logistic	1,649.843	1,657.483
		exponential	1,590.963	1,594.783
	Overall survival	weibull	2,015.341	2,022.981
		gamma	2,003.665	2,011.305
		lognormal	1,993.852	2,001.492
		log-logistic	2,156.712	2,164.352
		exponential	2,064.761	2,068.581
Placebo	Progression-free survival	weibull	911.2514	917.5924
		gamma	899.762	906.103
		lognormal	853.3578	859.6987
		log-logistic	1,025.024	1,031.365
		exponential	916.1268	919.2973
	Overall survival	weibull	1,098.377	1,104.718
		gamma	1,091.463	1,097.804
		lognormal	1,081.386	1,087.727

log-logistic	1,181.045	1,187.386
exponential	1,117.249	1,120.419

Table 2 Comparison of original survival curves with simulated survival curves

	simulated survival curves	original survival curves
OS follow-up Time	25.1 months	46 months
PFS follow-up Time	13.2 months	46 months
Statistical methods	Kaplan-Meier	Kaplan-Meier
P	<0.0001	<0.0001

2.4.2 Costs

From the perspective of the Chinese healthcare system, this study determined and analyzed the following direct costs (US dollar [US $]; 1 US dollar = CNY 7.23 [2023]): drug costs, administration costs, adverse costs, imaging costs, and BSC costs. Costs were discounted by 5%. We assumed that FTD/TPI was used continuously until death. Among them, the cost of drugs was sourced from Yaozhi.com [14], with the median bid price of the drugs in each province considered as the cost of the drugs (Table 2). In the TAGS clinical trial, the patient's dosage was determined by their body surface area (BSA), which was calculated to be 1.60 m^2 using the Stevenson formula and the average height and weight of individuals in China. Six provinces in China [15–20], namely, Hunan, Henan, Jiangsu, Anhui, Shaanxi, and Shandong, were selected to estimate the administration cost, imaging cost, and BSC cost based on the prices listed in the price catalog of medical services of the Medical Insurance Bureau of each province. Administration cost was estimated based on the province's medical service price item catalog in six provinces. It included the cost of accommodating patients during their hospital stay, standard nursing care, and routine tests (including blood, urine, and fecal examinations). Imaging tests such as CT, MRI, PET-CT, and radiography were conducted every two cycles. Given the absence of standard treatment for a large number of pretreated patients with metastatic gastric cancer, the

BSC cost was estimated based on the possible monitoring components of palliative care outlined in the 2022 gastric cancer treatment guidelines [21]. This included corresponding administration measures such as the presence of bleeding, obstruction, pain, and other factors. The estimation was made in conjunction with the median prices listed in the medical service price item catalog of the six provinces. We assumed that patients would undergo BSC treatment after PD. The adverse treatment plan was derived from the NCCN hematopoietic factors [22]. Of these, the cost of adverse treatment was estimated based on the medical service price item catalog in six provinces and Yaozhi.com. The cost of adverse events (AEs) only takes into account the severe AEs of grade 3 and above (grade ≥3), such as neutropenia (34%), anemia (19%), and leukopenia (9%) in the FTD/TPI group, as well as bellyache (9%) and anemia (8%) in the placebo. For a health intervention to be considered cost-effective, a willingness-to-pay (WTP) threshold of $35,559.34 per QALY was used in the current analysis. Published studies reported that a treatment should be considered cost-effective if the ICER is between one and three times the GDP per capita of that country, and a treatment is considered highly cost-effective at less than one times the GDP per capita [23–25].

Table 3 cost and utility values parameters

Variable	Median	Range		Distribution	Source
cost		Lower limit	Higher limit		
FTD/TPI（per cycle）	$2,112.50	$1901.25	$2323.75	gamma	[14]
adverse（TAGS）	$3,485.00	$3136.5	$3833.5	gamma	[15-20] [22]
Neutropenia（34%）（per cycle）	$3,448.75	$3103.88	$3793.63	gamma	[15-20] [22]
Anaemia（19%）（per cycle）	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Leukopenia（9%）（per cycle）	$11.62	$10.64	$12.78	gamma	[15-20] [22]
adverse（placebo）	$27.33	$24.6	$30.06	gamma	[15-20] [22]
Bellyache（9%）（per cycle）	$2.71	$2.44	$2.98	gamma	[15-20] [22]
Anaemia（8%）（per cycle）	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Imaging	$304.55	$274.1	$335.01	gamma	[15-20]

（per cycle）					
administration cost （per cycle）	$353.22	$317.9	$388.54	gamma	[15-20]
Best Supportive Care （per cycle）	$1,127.97	$1015.17	$1240.77	gamma	[15-20][21]
utility					
progression-free survival	0.764	0.688	0.841	beta	[19]
Progressed Disease	0.652	0.587	0.717	beta	[19]
Death	0	0	0	beta	[19]

2.4.3 Utilities

In 2021, the health-related quality of life was assessed in TAGS using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Patients completed the EORTC QLQ-C30 questionnaire within 7 days prior to randomization, predose on Day 1 of at least two treatment cycles, and at the safety follow-up 30 days after the last dose (if not performed within the previous 4 weeks). Leanne Hamerton *et al*. [26] used a published algorithm by Kontodimopoulos *et al.* to map the scores from EORTC QLQ-C30. The resulting utility values applied within the model were 0.764 for PFD and 0.652 for PD.

2.5 Model based results

The model results were mainly from the Chinese healthcare system. The outputs included Quality-adjusted life years (QALYs) and Incremental Cost-Effectiveness Ratio (ICER). When the ICER value was less than the set WTP threshold ($35,559.34), FTD/TPI was found to be more cost-effective than the placebo.

2.6 sensitivity analysis

To test the uncertainty of the Markov model, we performed one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) to explore the effects of different parameters on the basic analysis results and determine the range of data with an accuracy of ±10%. Sensitivity analysis was conducted using TreeagePro 2019 software. One-way sensitivity analysis results are typically presented in the form of a tornado diagram, which can reflect the size

of multiple uncertain factors on the outcome [27]. The gamma distribution was chosen for the cost parameters, whereas the beta distribution was used for the transition probability and utility parameters. PSA was performed using 1000 Monte Carlo simulations, and the results were presented in the form of a cost-effectiveness acceptability curve.

3. Result

3.1 Base-case analysis

According to lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 and 3.6 months, respectively. The median survival for PFS for FTD/TPI and placebo was 2 and 1.8 months, respectively. The simulated PFS curve and OS curve closely resembled the original data (the median survival of OS for FTD/TPI and the placebo was 5.7 and 3.6 months, respectively. whereas the median survival for PFS for FTD/TPI and the placebo was 2 and 1.8 months, respectively), indicating an acceptable and reasonable fit.

Based on the Markov model, from the perspective of Chinese healthcare system, the total cost of the FTD/TPI was $32,234.26, while the total cost of the placebo was $5,378.6. Compared with the placebo, FTD/TPI provides more than 0.88 QALYs in value. At the same time, the ICER value corresponding to each QALY is $30,494.89 (Table 3), which is lower than the WTP threshold of $35,559.34. Therefore, compared with the placebo, FTD/TPI is a cost-effective treatment option for heavily pretreated metastatic gastric cancer.

Table 4 Basic Analysis Data

Treatment	cost	Increase cost	QALY	Increase QALY	ICER
FTD/TPI	$32,234.26	NA	3.20	NA	NA
Placebo	$5,378.6	$26,855.66	2.32	0.88	$30,494.89

3.2 sensitivity analysis

3.2.1 One-way sensitivity analysis

The tornado diagram in Fig. 1 shows that the cost and utility value

range fluctuated by ±10% in the order factor sensitivity analysis. The utility value of the PFS stage had the greatest effect on the ICER value, followed by the AE cost of FTD/TPI. The specific impact is as follows: 1. The utility value of the PFS stage increases, leading to a decrease in ICER value; as its cost decreases, the ICER value increases. 2. As the cost of AEs in FTD/TPI increases, the ICER value also increases; conversely, as the cost decreases, the ICER value decreases. 3. As the cost of FTD/TPI increases, ICER value also increases; conversely, as the cost decreases, the ICER value decreases as well. FTD/TPI remained a cost-effective treatment given that the ICER per QALY gained remained below the threshold of $35559.34 per QALY gained. Individual parameter changes may slightly alter the overall value associated with the treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

3.2.2 PSA

According to the cost-effectiveness acceptability curve (Fig. 2 Cost-effectiveness Acceptability Curve for Probabilistic Sensitivity Analysis), when WTP increased within the range of 1–3 times threshold ($11,860–$35,559.34) of the GDP, the FTD/TPI showed an increase in economic feasibility. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo, at a WTP threshold of $35559.34. When the WTP value was $30,494.89, FTD/TPI was more cost-effective than the placebo. Thus, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a viable option. At a threshold of 2.5 times per capita GDP, FTD/TPI's cost-effectiveness probability dropped to 34.1%, whereas that of the placebo increased to 65.9%.

4. Discussion

The study population consisted of patients with metastatic gastric cancer who have previously undergone two or more chemotherapy regimens for advanced or metastatic disease with poor outcomes. Recent studies have demonstrated that

FTD/TPI has a relatively clear efficacy in the treatment of second- and back-line metastatic gastric cancer. Although it has not yet been included in the CSCO guidelines, the decrease in the price of the drugs used makes studying their effectiveness in the treatment of metastatic gastric cancer valuable. This is important from an economic standpoint, for the patients' physiological and psychological health, and in terms of the social significance of the disease.

In this study, the TAGS trial showed that FTD/TPI provided a significant survival benefit for patients with heavily pretreated gastric cancer compared with the placebo. We aimed to conduct a Markov model analysis of FTD/TPI compared with the placebo in patients with metastatic gastric cancer from the perspective of the Chinese healthcare system. According to our analysis, FTD/TPI cost $26,855.66 more than the placebo but provided an additional 0.88 QALYs, resulting in an ICER of $30,494.89 per QALY, which was below the defined WTP of $35,559.34 per QALY gained. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo at a WTP threshold of $35559.34. Therefore, from the perspective of the Chinese healthcare system, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a cost-effective option. The cost-effective estimate remained stable in sensitivity analyses. The evidence from this study emphasized the value of FTD/TPI in clinical and pharmacoeconomic settings. This work supports FTD/TPI as a systematic second-line and back-line treatment option for patients with metastatic gastric cancer in China, and it provides a reference for the dynamic adjustment of the catalog of medicines covered by the national medical insurance system.

Several international publications currently use data from the TAGS trial to compare the pharmacoeconomics of FTD/TPI in patients with heavily pretreated metastatic gastric cancer. Takushima Y. [28] used a partitioned survival model to estimate the cost-effectiveness of FTD/TPI versus nivolumab from the perspective of the Japanese public healthcare payer. According to their results, the ICER of nivolumab and FTD/TPI is ¥32,352,489 yen/QALYs, and the WTP threshold is

7,500,000 yen. Therefore, the analysis of FTD/TPI from the Japanese public healthcare payment perspective shows that it is more cost-effective than nivolumab. However, as a result of differences in the controlled drugs, we could not compare the results of Takushima with this study due to the different factors involved. In Britain, a partitioned survival model was used to compare FTD/TPI with BSC in the UK. A lognormal distribution to fit OS and a generalized gamma model to fit PFS and time-to-treatment-discontinuation were employed. According to the study results, FTD/TPI was associated with an ICER of £37,907 per QALY gained compared with BSC. Therefore, FTD/TPI is a cost-effective treatment for patients with pretreated metastatic gastric cancer from a UK perspective. In Greece, George Gourzoulidis *et al*. analyzed the TAGS data through a partitioned survival model from the perspective of the Greek public payer. They reported an ICER of €47,144 per QALY gained and €28,112 per LY gained compared with BSC. Therefore, FTD/TPI was estimated to be a cost-effective treatment option for eligible third-line treatment of patients with metastatic gastric cancer in Greece. The results of both are consistent with the results of our study.

Overall, the published literature supported the findings of the present analysis, except for the study by Zhou K *et al.* [29]. They developed a Markov model to assess the cost-effectiveness of FTD/TPI from the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, which is far beyond their WTP threshold ($50,000– $150,000). They found that FTD/TPI does not provide cost benefits from the perspective of US payers. Their results were not consistent with our study, which may be attributed to the varying prices of FTD/TPI in different countries. Chinese generic drugs hold a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility [30]. Domestic generic drug manufacturers have implemented Porter's generic strategies to adjust prices, resulting in an average profit margin of only 5% to 10% for generic drugs in China, which is significantly lower than the average profit margin of international generic drugs

(30% to 60%) [31]. Therefore, the cost of generic drugs in China is generally lower compared with the cost of foreign drugs.

However, our study also had some limitations. First, the model uncertainty concerning the short-term survival rates was small due to the excellent fit of the model. The long-term benefits of FTD/TPI remain an open question. The model could be validated using long-term survival data once more mature data become available in the future. Second, only considering the cost of AEs at level three or above, without taking into account all AEs, may lead to bias in the data. Third, based on the population distribution of participants in the TAGS trial, the majority were Europeans. This could introduce biases in real-world clinical efficacy in China, potentially impacting the trial's generalizability. Fortunately, exploratory studies on FTD/TPI for advanced unresectable gastric cancer in the Chinese population registered in the Chinese Clinical Trial Registry (ChiCTR2400080940) and clinical trial (NCT05029102) are currently underway. As data are continually updated, this study will also be updated.

5. Conclusion

In summary, from the perspective of the Chinese healthcare system, FTD/TPI is a cost-effective choice for systematic second-line and back-line medication for heavily pretreated metastatic gastric cancer. The results of this study offer an economically significant solution for clinicians, payers, and budget holders to treat heavily pretreated metastatic gastric cancer.

Ethics Approval：This study is an economic evaluation analysis and does not involve human subjects. Input data includes human material or human data derived from other published studies conducted with the approval of an appropriate ethics committee. Therefore, no ethics approval is required for conducting this cost-effectiveness analysis.

Figure 1: Cost and utility value range fluctuation ±10% under the order factor

sensitivity analysis tornado diagram

Figure 2: Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

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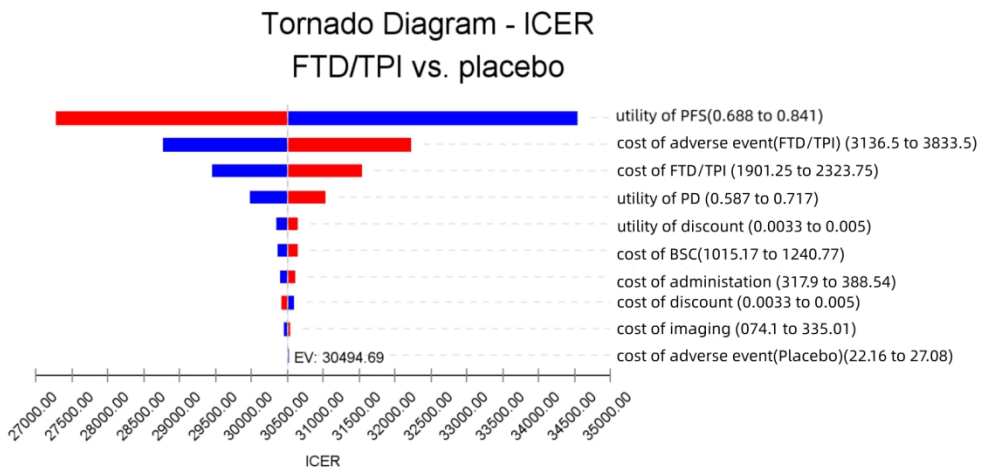

Fig1 Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

1203x764mm (38 x 38 DPI)

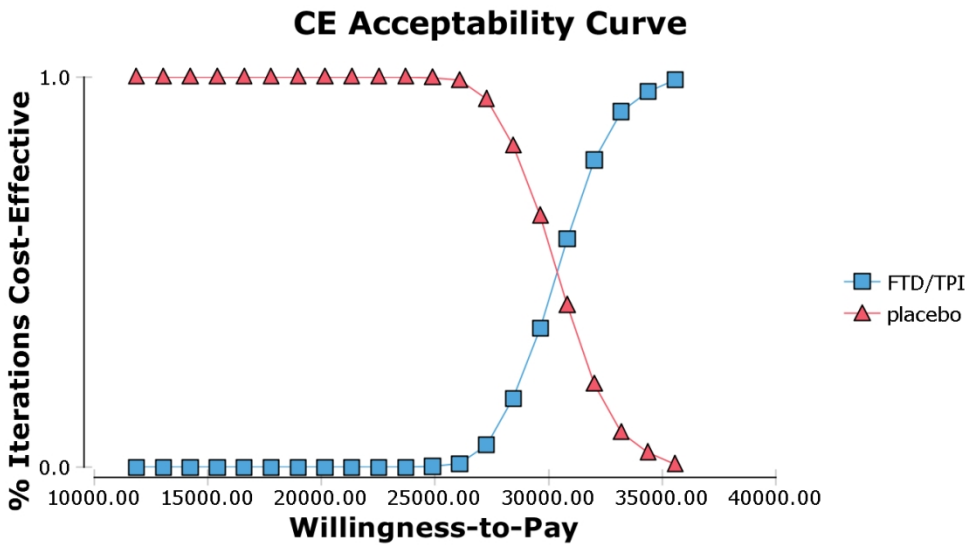

Fig2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

481x270mm (72 x 72 DPI)

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

Ting Ying[1,2#],Runan Xia[1,2#],Yuanyuan Zhang[2,3], Jiahui Dai[1,2], Yadong Wang[1,2], Xuefeng Xie[3,4*]

Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) data from the TAGS trial (NCT02500043), a three-state Markov model (PFS , progressed disease, and death) was constructed to analyze the cost-effectiveness of FTD/TPI compared with the placebo in heavily pretreated metastatic gastric cancer. Cost and Utility were from pricing records and the literature. The model was simulated for 5 years with monthly cycles. Costs and health outcomes were discounted by 5%. We then conducted sensitivity analyses to evaluate the robustness of the parameters. The model results were from the Chinese healthcare system. The output results were the quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER).

Results: According to the model results, FTD/TPI generated an additional cost of $26,855.66 and 0.88 QALYs compared with the placebo. ICER of FTD/TPI compared with the placebo was $30,494.89 per QALY. Sensitivity analyses revealed that the utility value of the PFS stage and FTD/TPI adverse event costs were the main influencing parameters, ensuring stable results. At a threshold of three times per capita GDP of China ($35,559.34 in 2022), the probability of FTD/TPI being cost-effective compared to placebo was 99.2%.

Conclusion: From the perspective of the Chinese healthcare system, FTD/TPI is a more cost-effective option compared with the placebo for the treatment of heavily

pretreated metastatic gastric cancer in patients who have received at least two prior advanced treatment regimens.

Keywords: Heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil; Markov model; Cost-effectiveness analysis; Placebo; Economic evaluation

Word count: 3608 words

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Strengths and limitations of this study: 1. This study used a Markov model to analyze the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for the treatment of heavily pretreated metastatic gastric cancer in China.

2. The cost of adverse events (AEs) only considers the severe AEs of grade 3 and above and does not consider all AEs.

3. Based on the population distribution of TAGS participants, the majority are Europeans. This limitation may introduce biases in assessing real-world clinical efficacy in China.

4. The model uncertainty concerning short-term survival rates is small owing to the good fitness of the model. But the long-term benefits of FTD/TPI remain an open question.

1. Introduction

According to the latest statistics from the World Health Organization in 202 2, gastric cancer is the fourth leading cause of cancer-related deaths worldwide16 [1].a)[1] . About 1.2 million new cases of gastric cancer occur worldwide every y ear, with China accounting for approximately 40% of them[1].a)[2][2]. Many pati ents are in an advanced state of cancer cell metastasis when gastric cancer is disc overed[3], and treatment is usually limited to palliative chemotherapy because of poor expected results.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSC O) and the National Comprehensive Cancer Network (NCCN) recommend severa l treatment options for metastatic gastric cancer, including combination chemothe rapy and single-agent chemotherapy. As a result of the generally poor physical co ndition of patients with advanced third-line gastric cancer, the proportion of patie nts who can receive combination third-line chemotherapy is extremely low, and si ngle-agent treatment is mainly used. Patients who have received these chemother apy treatments before receiving trifluridine/tipiracil (FTD/TPI) treatment have re ported unsatisfactory results, and the cost is also high. According to IQVIA [4], g lobal expenditure on oncology drugs will continue to increase at a double-digit rat e. Therefore, a cost-effective and efficient treatment for gastric cancer remains a global challenge.

In 2019, the European Commission and the Food and Drug Administration (FDA) approved FTD/TPI for the treatment of adult patients with metastatic gastri c cancer who have received at least two prior systemic treatment regimens to man age advanced disease. FTD/TPI is a novel oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analog, trifluridine, and thymidine[5]. As the m ain active ingredient, trifluridine inhibits cell proliferation by direct insertion into DNA after phosphorylation, leading to DNA dysfunction and cell death[6]. In add ition to its anti-tumor role when combined with trifluridine to form FTD/TPI, it pr events the rapid degradation of trifluridine, allowing for the maintenance of adeq

uate plasma levels of the active drug [7].

In 2015, FTD/TPI was first approved by FDA and expanded globally including European Union and China for the treatment of patients with metastatic colorectal cancer[8]. In 2021, FTD/TPI generic tablets were first approved for marketing by National Medical Products Administration[9]. This move greatly reduced the cost of using FTD/TPI in China. FTD/TPI has been approved for metastatic colorectal cancer in the current CSCO guidelines, but it has not been approved for gastric cancer. There is currently no cost-effectiveness analysis evaluating FTD/TPI for the treatment of a significant number of patients with severe metastatic gastric cancer from the perspective of the Chinese healthcare system. Therefore, this study conducted a cost-effectiveness analysis of FTD/TPI for treating a large number of patients with severe metastatic gastric cancer from the perspective of the Chinese healthcare system. The results of this study could offer clinicians and payers economic evidence to consider incorporating FTD/TPI into Chinese guidelines for the diagnosis and treatment of gastric cancer and guide the pricing of the originator for metastatic colorectal cancer and other indications.

2. Methods

2.1 Patients

The data were selected from the clinical trial of TAGS[10](NCT02500043, Taiho Oncology, Inc.). This work is a phase III study with randomized, double-blind, placebo-controlled, and multinational cases. The study began in July 2015 and ended in September 2021, in 17 countries including Japan and Israel. It involved 110 academic hospitals. The efficacy and safety of FTD/TPI plus best supportive care (BSC; FTD/TPI) and placebo plus BSC (placebo) in metastatic gastric cancer were determined. After screening and excluding the cases, a total of 507 patients participated in this clinical trial. These patients had received at least two treatments for advanced gastric cancer before. Eligible patients were randomly classified (2: 1) into either the FTD/TPI group (337) or placebo group (170). The main end of the experiment was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). The purpose of this

work was to explore whether the patient's quality of life (QoL) can be improved to the maximum extent without anti-tumor factors. Patients or members of the public were not involved in the design of this study.

2.2 Treatment

Participants received 35 mg/m^2 FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks, followed by 14 days of rest in each 28-day cycle along with BSC until the patient met the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to four non-hematological events, doctor's decision, participants are pregnant, or death).

2.3 Model structure

A Markov model was developed to simulate the disease progression of heavily pretreated metastatic gastric cancer by TreeagePro 2019. It included three disease statuses (PFS, progressed disease [PD], and death [D]). Patients entered this model in the PFS state, and they could not return to the previous state after entering PD. The time of entry into the model for patients in this study was set to the average age of patients in the TAGS trial (62.5 years). According to the model, the Markov cycle was 28 days. Given that 99.9% of patients entered the state of death (D) after 60 model cycles, and the overall 5-year survival rate of progressive gastric cancer was only 35.1% [11], the model was limited to 5 years. The discount rate of 5% for cost and utility value is recommended according to the Chinese Pharmaceutical Economics Evaluation Guide (2020)[12].

2.4 Transition probability

The OS and PFS curves were derived from the TAGS trial. GetData Graph Digitizer software was used to collect data points from OS and PFS curves. The data were then cleaned and converted into a format suitable for survival analysis. The data were analyzed by Kaplan–Meier analysis through R4.2.0 software, and the survival curve extrapolation was conducted using Standard Parametric Model (SPM) by using weibull,

gamma, lognormal, log-logistic, and exponential distributions (Table 1). According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the smaller the AIC and BIC values, the better the fit [13]. Therefore, the log-normal distribution was selected as the optimal distribution according to AIC and BIC combined with a visual inspection of FTD/TPI and placebo. We added both the original survival curves compared to the simulated survival curves (Table 2). The μ value and θ value of each group of OS and PFS curve parameters were obtained to calculate the transfer probability of transfer from PFS to PFS (PFTF). Assuming that the transition probability from PFS to D (PFTD) is a per capita mortality rate of 7.37‰ in 2022 [14], PFTP =1-PFTF-PFTD. The OS curve parameter can be used to determine the transition probability from the survival state to the survival state (PSTS) as follows: PSTD =1-PSTS. According to Zhou T. [15], the transition probability from PD to PD (PPTP) should be adjusted. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in PFS and PD state in the previous cycle, respectively.

Table 1 Progression-free survival and Overall survival data fit results

Group	Observation	Distribution	AIC	BIC
FTD/TPI	Progression-free survival	weibull	1,515.56	1,523.2
		gamma	1,480.323	1,487.963
		lognormal	1,424.173	1,431.813
		log-logistic	1,649.843	1,657.483
		exponential	1,590.963	1,594.783
	Overall survival	weibull	2,015.341	2,022.981
		gamma	2,003.665	2,011.305
		lognormal	1,993.852	2,001.492
		log-logistic	2,156.712	2,164.352
		exponential	2,064.761	2,068.581
Placebo	Progression-free survival	weibull	911.2514	917.5924
		gamma	899.762	906.103
		lognormal	853.3578	859.6987
		log-logistic	1,025.024	1,031.365
		exponential	916.1268	919.2973
	Overall survival	weibull	1,098.377	1,104.718
		gamma	1,091.463	1,097.804

	Overall survival	lognormal	1,081.386	1,087.727
		log-logistic	1,181.045	1,187.386
		exponential	1,117.249	1,120.419

Table 2 Comparison of original survival curves with simulated survival curves

	simulated survival curves	original survival curves
OS follow-up Time	60 months	46 months
PFS follow-up Time	60 months	46 months
Statistical methods	Kaplan-Meier	Kaplan-Meier
P	<0.0001	<0.0001

2.5 Costs

From the perspective of the Chinese healthcare system, this study determined and analyzed the following direct costs (US dollar [US $]; 1 US dollar = CNY 7.23 [2023]): drug costs, administration costs, adverse costs, imaging costs, and BSC costs. Costs were discounted by 5%. We assumed that FTD/TPI was used continuously until the patient met the drug suspension standard. Among them, the cost of drugs was sourced from Yaozhi.com [16], with the median bid price of the drugs in each province considered as the cost of the drugs (Table 2). In the TAGS clinical trial, the patient's dosage was determined by their body surface area (BSA), which was calculated to be 1.60 m^2 using the Stevenson formula and the average height and weight of individuals in China. Six provinces in China [17], namely, Hunan, Henan, Jiangsu, Anhui, Shaanxi, and Shandong, were selected to estimate the administration cost, imaging cost, and BSC cost based on the prices listed in the price catalog of medical services of the Medical Insurance Bureau of each province. Administration cost was estimated based on the province's medical service price item catalog in six provinces. It included the cost of accommodating patients during their hospital stay, standard nursing care, and routine tests (including blood, urine, and fecal examinations). Imaging tests such as CT, MRI, PET-CT, and radiography were conducted every two cycles. Given

the absence of standard treatment for a large number of pretreated patients with metastatic gastric cancer, the BSC cost was estimated based on the possible monitoring components of palliative care outlined in the 2022 gastric cancer treatment guidelines [23]. This included corresponding administration measures such as the presence of bleeding, obstruction, pain, and other factors. The estimation was made in conjunction with the median prices listed in the medical service price item catalog of the six provinces. We assumed that patients would undergo BSC treatment after PD. The adverse treatment plan was derived from the NCCN hematopoietic factors [24]. Of these, the cost of adverse treatment was estimated based on the medical service price item catalog in six provinces and Yaozhi.com. The cost of adverse events (AEs) only takes into account the severe AEs of grade 3 and above (grade ≥3), such as neutropenia (34%), anemia (19%), and leukopenia (9%) in the FTD/TPI group, as well as bellyache (9%) and anemia (8%) in the placebo.

Table 3 cost and utility values parameters

Variable	Median	Range		Distribution	Source
cost		Lower limit	Higher limit		
FTD/TPI（per cycle）	$2,112.50	$1901.25	$2323.75	gamma	[14]
adverse（TAGS）	$3,485.00	$3136.5	$3833.5	gamma	[15-20] [22]
Neutropenia（34%）（per cycle）	$3,448.75	$3103.88	$3793.63	gamma	[15-20] [22]
Anaemia（19%）（per cycle）	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Leukopenia（9%）（per cycle）	$11.62	$10.64	$12.78	gamma	[15-20] [22]
adverse（placebo）	$27.33	$24.6	$30.06	gamma	[15-20] [22]
Bellyache（9%）（per cycle）	$2.71	$2.44	$2.98	gamma	[15-20] [22]
Anaemia（8%）（per cycle）	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Imaging（per cycle）	$304.55	$274.1	$335.01	gamma	[15-20]
administration cost（per cycle）	$353.22	$317.9	$388.54	gamma	[15-20]
Best Supportive Care（per cycle）	$1,127.97	$1015.17	$1240.77	gamma	[15-20][21]
utility					

progression-free survival	0.764	0.688	0.841	beta	[19]
Progressed Disease	0.652	0.587	0.717	beta	[19]
Death	0	0	0	beta	[19]

2.6 Utilities

In 2021, the health-related quality of life was assessed in TAGS using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Patients completed the EORTC QLQ-C30 questionnaire within 7 days prior to randomization, predose on Day 1 of at least two treatment cycles, and at the safety follow-up 30 days after the last dose (if not performed within the previous 4 weeks). Leanne Hamerton *et al*. [25] used a published algorithm by Kontodimopoulos *et al.* to map the scores from EORTC QLQ-C30. The resulting utility values applied within the model were 0.764 for PFD and 0.652 for PD.

2.7 Model based results

The model results were from the Chinese healthcare system. The outputs included Quality-adjusted life years (QALYs) and Incremental Cost-Effectiveness Ratio (ICER). When the ICER value was less than the set WTP threshold ($35,559.34), FTD/TPI was found to be more cost-effective than the placebo. For a health intervention to be considered cost-effective, a willingness-to-pay (WTP) threshold of $35,559.34 per QALY was used in the current analysis. Published studies reported that a treatment should be considered cost-effective if the ICER is between one and three times the GDP per capita of that country, and a treatment is considered highly cost-effective at less than one times the GDP per capita [26].

2.8 sensitivity analysis

To test the uncertainty of the Markov model, we performed one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) to explore the effects of different parameters on the basic analysis results and determine the range of data with an accuracy of ±10%. Sensitivity analysis was conducted using TreeagePro 2019 software. One-way sensitivity analysis results are

typically presented in the form of a tornado diagram, which can reflect the size of multiple uncertain factors on the outcome [25]. The gamma distribution was chosen for the cost parameters, whereas the beta distribution was used for the transition probability and utility parameters. PSA was performed using 1000 Monte Carlo simulations, and the results were presented in the form of a cost-effectiveness acceptability curve.

3. Result

3.1 Base-case analysis

According to lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 and 3.6 months, respectively. The median survival for PFS for FTD/TPI and placebo was 2 and 1.8 months, respectively. The simulated PFS curve and OS curve closely resembled the original data (the median survival of OS for FTD/TPI and the placebo was 5.7 and 3.6 months, respectively. whereas the median survival for PFS for FTD/TPI and the placebo was 2 and 1.8 months, respectively), indicating an acceptable and reasonable fit.

Based on the Markov model, from the perspective of Chinese healthcare system, the total cost of the FTD/TPI was $32,234.26, while the total cost of the placebo was $5,378.6. Compared with the placebo, FTD/TPI provides more than 0.88 QALYs in value. At the same time, the ICER value corresponding to each QALY is $30,494.89 (Table 3), which is lower than the WTP threshold of $35,559.34. Therefore, compared with the placebo, FTD/TPI is a cost-effective treatment option for heavily pretreated metastatic gastric cancer.

Table 4 Basic Analysis Data

Treatment	cost	Increase cost	QALY	Increase QALY	ICER
FTD/TPI	$32,234.26	NA	3.20	NA	NA
Placebo	$5,378.6	$26,855.66	2.32	0.88	$30,494.89

3.2 sensitivity analysis

3.2.1 One-way sensitivity analysis

The tornado diagram in Fig. 1 shows that the cost and utility value range fluctuated by ±10% in the order factor sensitivity analysis. The utility value of the PFS stage had the greatest effect on the ICER value, followed by the AE cost of FTD/TPI. The specific impact is as follows: 1. The utility value of the PFS stage increases, leading to a decrease in ICER value; as its cost decreases, the ICER value increases. 2. As the cost of AEs in FTD/TPI increases, the ICER value also increases; conversely, as the cost decreases, the ICER value decreases. 3. As the cost of FTD/TPI increases, ICER value also increases; conversely, as the cost decreases, the ICER value decreases as well. FTD/TPI remained a cost-effective treatment given that the ICER per QALY gained remained below the threshold of $35,559.34 per QALY gained. Individual parameter changes may slightly alter the overall value associated with the treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

3.2.2 PSA

According to the cost-effectiveness acceptability curve (Fig. 2 Cost-effectiveness Acceptability Curve for Probabilistic Sensitivity Analysis), when WTP increased within the range of 1–3 times threshold ($11,860–$35,559.34) of the GDP, the FTD/TPI showed an increase in economic feasibility. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo, at a WTP threshold of $35,559.34. Thus, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a viable option. At a threshold of 2.5 times per capita for GDP, FTD/TPI's cost-effectiveness probability dropped to 34.1%, whereas that of the placebo increased to 65.9%.

4. Discussion

The study population consisted of patients with metastatic gastric cancer who have previously undergone two or more chemotherapy regimens for advanced or metastatic disease with poor outcomes. Recent studies have demonstrated that

FTD/TPI has a relatively clear efficacy in the treatment of second- and back-line metastatic gastric cancer. Although it has not yet been included in the CSCO guidelines, the decrease in the price of the drugs used makes studying their effectiveness in the treatment of metastatic gastric cancer valuable. This is important from an economic standpoint, for the patients' physiological and psychological health, and in terms of the social significance of the disease.

In this study, the TAGS trial showed that FTD/TPI provided a significant survival benefit for patients with heavily pretreated gastric cancer compared with the placebo. We aimed to conduct a Markov model analysis of FTD/TPI compared with the placebo in patients with metastatic gastric cancer from the perspective of the Chinese healthcare system. According to our analysis, FTD/TPI cost $26,855.66 more than the placebo but provided an additional 0.88 QALYs, resulting in an ICER of $30,494.89 per QALY, which was below the defined WTP of $35,559.34 per QALY gained. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo at a WTP threshold of $35,559.34. Therefore, from the perspective of the Chinese healthcare system, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a cost-effective option. The cost-effective estimate remained stable in sensitivity analyses. The evidence from this study emphasized the value of FTD/TPI in clinical and pharmacoeconomic settings. This work supports FTD/TPI as a systematic second-line and back-line treatment option for patients with metastatic gastric cancer in China, and it provides a reference for the dynamic adjustment of the catalog of medicines covered by the national medical insurance system.

Several international publications currently use data from the TAGS trial to compare the pharmacoeconomics of FTD/TPI in patients with heavily pretreated metastatic gastric cancer. Takushima Y. [29]used a partitioned survival model to estimate the cost-effectiveness of FTD/TPI versus nivolumab from the perspective of the Japanese public healthcare payer. According to their results, the ICER of nivolumab and FTD/TPI is ¥32,352,489 yen/QALYs, and the WTP threshold is

7,500,000 yen. Therefore, the analysis of FTD/TPI from the Japanese public healthcare payment perspective shows that it is more cost-effective than nivolumab. However, as a result of differences in the controlled drugs, we could not compare the results of Takushima with this study due to the different factors involved. In Britain, Hamerton used a partitioned survival model to compare FTD/TPI with BSC in the UK[25]. A lognormal distribution to fit OS and a generalized gamma model to fit PFS and time-to-treatment-discontinuation were employed. According to the study results, FTD/TPI was associated with an ICER of £37,907 per QALY gained compared with BSC. Therefore, FTD/TPI is a cost-effective treatment for patients with pretreated metastatic gastric cancer from a UK perspective. In Greece, Tzanetakos *et al*. [30]analyzed the TAGS data through a partitioned survival model from the perspective of the Greek public payer. They reported an ICER of €47,144 per QALY gained and €28,112 per LY gained compared with BSC. Therefore, FTD/TPI was estimated to be a cost-effective treatment option for eligible third-line treatment of patients with metastatic gastric cancer in Greece. The results of both are consistent with the results of our study.

Overall, the published literature supported the findings of the present analysis, except for the study by Zhou K *et al.* [31]. They developed a Markov model to assess the cost-effectiveness of FTD/TPI from the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, which is far beyond their WTP threshold ($50,000– $150,000). They found that FTD/TPI does not provide cost benefits from the perspective of US payers. Their results were not consistent with our study, which may be attributed to the varying prices of FTD/TPI in different countries. Chinese generic drugs hold a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility [32]. Domestic generic drug manufacturers have implemented Porter's generic strategies to adjust prices, resulting in an average profit margin of only 5% to 10% for generic drugs in China, which is significantly lower than the average profit margin of international generic drugs

(30% to 60%) [33]. Therefore, the cost of generic drugs in China is generally lower compared with the cost of foreign drugs.

However, our study also had some limitations. First, the model uncertainty concerning the short-term survival rates was small due to the excellent fit of the model. The long-term benefits of FTD/TPI remain an open question. The model could be validated using long-term survival data once more mature data become available in the future. Second, only considering the cost of AEs at level three or above, without taking into account all AEs, may lead to bias in the data. Third, based on the population distribution of participants in the TAGS trial, the majority were Europeans. This could introduce biases in real-world clinical efficacy in China, potentially impacting the trial's generalizability. Fortunately, exploratory studies on FTD/TPI for advanced unresectable gastric cancer in the Chinese population registered in the Chinese Clinical Trial Registry (ChiCTR2400080940) and clinical trial (NCT05029102) are currently underway. As data are continually updated, this study will also be updated.

5. Conclusion

In summary, from the perspective of the Chinese healthcare system, FTD/TPI is a cost-effective choice for systematic second-line and back-line medication for heavily pretreated metastatic gastric cancer. The results of this study offer an economically significant solution for clinicians and payers to treat heavily pretreated metastatic gastric cancer.

Ethics Approval：This study is an economic evaluation analysis and does not involve human subjects. Input data includes human material or human data derived from other published studies conducted with the approval of an appropriate ethics committee. Therefore, no ethics approval is required for conducting this cost-effectiveness analysis.

Figure 1: Cost and utility value range fluctuation ±10% under the order factor

sensitivity analysis tornado diagram

Figure 2: Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

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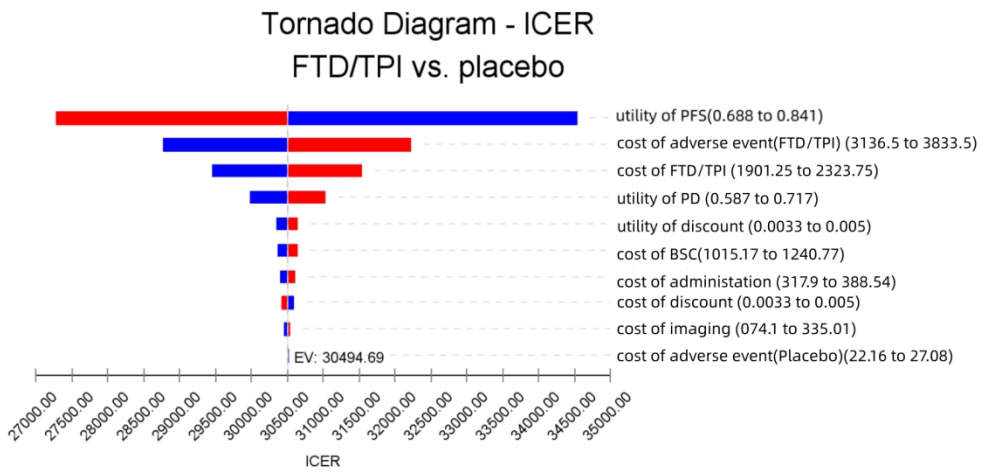

Fig1 Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

1203x764mm (38 x 38 DPI)

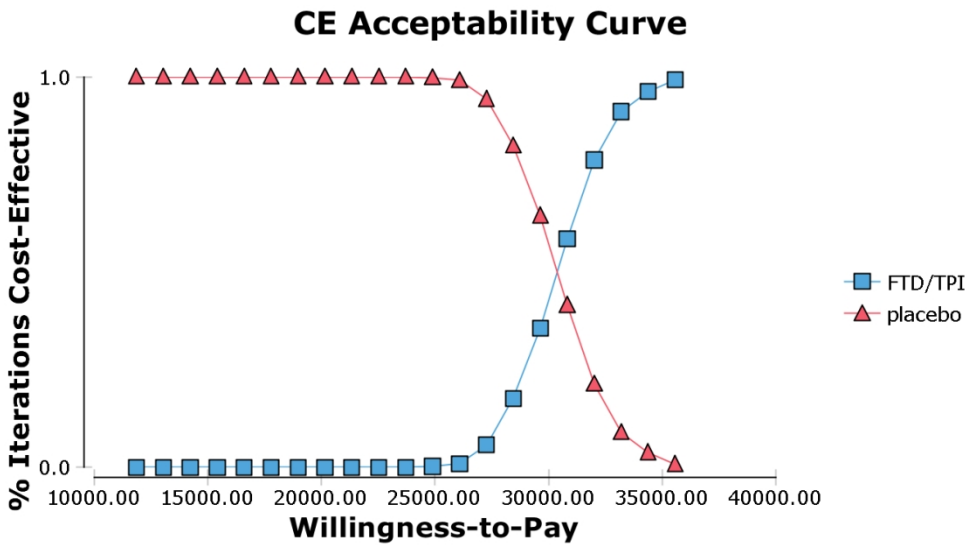

Fig2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Keywords:	HEALTH ECONOMICS, Gastrointestinal tumours < ONCOLOGY, China

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) data from the TAGS trial (NCT02500043), a three-state Markov model (PFS, progressed disease, and death) was constructed to analyze the cost-effectiveness of FTD/TPI compared with the placebo in heavily pretreated metastatic gastric cancer. Cost and utility were from pricing records and the literature. The model was simulated for 5 years with monthly cycles. Costs and health outcomes were discounted by 5%. We then conducted sensitivity analyses to evaluate the robustness of the parameters. The model results were from the Chinese healthcare system. The output results were the quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER).

Results: According to the model results, FTD/TPI generated an additional cost of $26,855.66 and 0.88 QALYs compared with the placebo. ICER of FTD/TPI compared with the placebo was $30,494.89 per QALY. Sensitivity analyses revealed that the utility value of the PFS stage and FTD/TPI adverse event costs were the main influencing parameters, ensuring stable results. At a threshold of three times per capita GDP of China ($35,559.34 in 2022), the probability of FTD/TPI being cost-effective compared to placebo was 99.2%.

Conclusion: From the perspective of the Chinese healthcare system, FTD/TPI is a more cost-effective option compared with the placebo for the treatment of heavily

pretreated metastatic gastric cancer in patients who have received at least two prior advanced treatment regimens.

Keywords: Heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil; Markov model; Cost-effectiveness analysis; Placebo; Economic evaluation

Word count: 3540 words

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Strengths and limitations of this study: 1. This study used a Markov model to analyze the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for the treatment of heavily pretreated metastatic gastric cancer in China.

2. The cost of adverse events (AEs) only considers the severe AEs of grade 3 and above and does not consider all AEs.

3. Based on the population distribution of TAGS participants, the majority are Europeans. This limitation may introduce biases in assessing real-world clinical efficacy in China.

4. The model uncertainty concerning short-term survival rates is small owing to the good fitness of the model. But the long-term benefits of FTD/TPI require further analysis.

1. Introduction

According to the latest statistics from the World Health Organization in 2022, gastric cancer is the fourth leading cause of cancer-related deaths worldwide160 . About 1.2 million new cases of gastric cancer occur worldwide every year, with China accounting for approximately 40% of them00. Many patients are in an advanced state of cancer cell metastasis when gastric cancer is discovered0, and treatment is usually limited to palliative chemotherapy because of poor expected results.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) recommend several treatment options for metastatic gastric cancer, including combination chemotherapy and single-agent chemotherapy. As a result of the generally poor physical condition of patients with advanced third-line gastric cancer, the proportion of patients who can receive combination third-line chemotherapy is extremely low, and single-agent treatment is mainly used. Patients who have received these chemotherapy treatments before receiving trifluridine/tipiracil (FTD/TPI) treatment have reported unsatisfactory results, and the cost is also high. According to IQVIA 0, global expenditure on oncology drugs will continue to increase at a double-digit rate. Therefore, a cost-effective and efficient treatment for gastric cancer remains a global challenge.

In 2019, the European Commission and the Food and Drug Administration (FDA) approved FTD/TPI for the treatment of adult patients with metastatic gastric cancer who have received at least two prior systemic treatment regimens to manage advanced disease. FTD/TPI is a novel oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analog, trifluridine, and thymidine0. As the main active ingredient, trifluridine inhibits cell proliferation by direct insertion into DNA after phosphorylation, leading to DNA dysfunction and cell death0. In addition to its anti-tumor role when combined with trifluridine to form FTD/TPI, it prevents the rapid degradation of trifluridine, allowing for the

maintenance of adequate plasma levels of the active drug 0.

In 2015, FTD/TPI was first approved by FDA and expanded globally including European Union and China for the treatment of patients with heavily pretreated metastatic colorectal cancer0. In 2021, FTD/TPI generic tablets were first approved for marketing by National Medical Products Administration (NMPA)0. This move greatly reduced the cost of using FTD/TPI in China. FTD/TPI has been approved for metastatic colorectal cancer in the current CSCO guidelines, but it has not been approved for metastatic gastric cancer. There is currently no cost-effectiveness analysis evaluating FTD/TPI for the treatment of a significant number of patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. Therefore, this study conducted a cost-effectiveness analysis of FTD/TPI for treating a large number of patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. The results of this study could provide clinicians and payers with economic evidence to consider incorporating FTD/TPI into Chinese guidelines for the diagnosis and treatment of heavily pretreated metastatic gastric cancer and guide the pricing of the originator for metastatic colorectal cancer and other indications.

2. Methods

2.1 Patients

The data were selected from the TAGS trial.0(NCT02500043, Taiho Oncology, Inc.). This work is a phase III study with randomized, double-blind, placebo-controlled, and multinational cases. The study began in July 2015 and concluded in September 2021, including 17 countries and involving 110 academic hospitals, evaluating the efficacy and safety of FTD/TPI plus BSC versus placebo plus BSC in participants with heavily pretreated metastatic gastric cancer. After screening and excluding certain cases, a total of 507 patients participated in this clinical trial. These patients had received at least two treatments for advanced gastric cancer before. Eligible patients were randomly assigned in a 2:1 ratio to either the FTD/TPI group (337 patients) or the placebo

group (170 patients). The primary endpoint of the study was overall survival (OS), while the secondary endpoint was progression-free survival (PFS). The objective of this research was to investigate whether the quality of life (QoL) of patients could be maximized without the influence of anti-tumor factors. Patients or members of the public were not involved in the design of this study.

2.2 Treatment

Participants received 35 mg/m^2 FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks, followed by 14 days of rest in each 28-day cycle along with BSC until the patient met the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to four non-hematological events, doctor's decision, participants are pregnant, or death).

2.3 Model structure

A three-state Markov model was constructed to simulate the cost-effectiveness differences between FTD/TPI plus BSC and placebo plus BSC for treating heavily pretreated metastatic gastric cancer using TreeagePro 2019. Including progression-free survival(PFS), progressed disease(PD), and death(D) states. Patients entered this model in the PFS state, and could not return to the previous state after entering PD. The entry point into the model for patients in this study was established at the average age of participants in the TAGS trial (62.5 years). According to the model, the Markov cycle was 28 days. Given that 99.9% of patients entered the death (D) state after 60 model cycles, and the overall 5-year survival rate for progressive gastric cancer is only 35.1% [11], the model was limited to a duration of 5 years. A discount rate of 5% for both cost and utility values are recommended according to the Chinese Pharmaceutical Economics Evaluation Guide (2020) [12].

2.4 Transition probability

The OS and PFS curves were derived from the TAGS trial. GetData Graph Digitizer software was used to collect data points from OS and

PFS survival curves. The data were then cleaned and converted into a format suitable for survival analysis. The data were analyzed by Kaplan–Meier analysis through R4.2.0 software, and survival curve extrapolation was conducted using the Standard Parametric Model (SPM) with Weibull, Gamma, Lognormal, Log-logistic, and Exponential distributions (Table 1). According to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), the smaller the AIC and BIC values, the better the fit 0. Therefore, the log-normal distribution was selected as the optimal distribution based on AIC and BIC, along with a visual inspection of the FTD/TPI and placebo data. We included both the original survival curves and the simulated survival curves (Table 2). The parameters μ and θ for each group of OS and PFS curve parameters were obtained to calculate the transition probability from PFS to PFS (PFTF). Assuming that the transition probability from PFS to D (PFTD) corresponds to a per capita mortality rate of 7.37‰ in 2022 [14], PFTP =1-PFTF-PFTD. The OS curve parameters can be used to determine the transition probability from the survival state to the survival state (PSTS) as follows: PSTD =1-PSTS. According to Zhou T. [15], the transition probability from PD to PD (PPTP) should be adjusted. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in the PFS and PD states in the previous cycle, respectively.

Table 1 Progression-free survival and Overall survival data fit results

Group	Observation	Distribution	AIC	BIC
FTD/TPI	Progression-free survival	Weibull	1,515.56	1,523.20
		Gamma	1,480.32	1,487.96
		Lognormal	1,424.17	1,431.81
		Log-logistic	1,649.84	1,657.48
		Exponential	1,590.96	1,594.78
		Weibull	2,015.34	2,022.98
		Gamma	2,003.67	2,011.31

	Overall survival	Lognormal	1,993.85	2,001.49
		Log-logistic	2,156.71	2,164.35
		Exponential	2,064.76	2,068.58
		Weibull	911.25	917.59
		Gamma	899.76	906.10
	Progression-free survival	Lognormal	853.36	859.70
		Log-logistic	1,025.02	1,031.36
Placebo		Exponential	916.12	919.30
		Weibull	1,098.38	1,104.72
		Gamma	1,091.46	1,097.80
	Overall survival	Lognormal	1,081.39	1,087.73
		Log-logistic	1,181.05	1,187.39
		Exponential	1,117.25	1,120.42

Table 2 Comparison of simulated survival curves with original survival curves

	Simulated survival curves	Original survival curves
OS follow-up Time	60 months	46 months
PFS follow-up Time	60 months	46 months
Statistical methods	Kaplan-Meier	Kaplan-Meier
P	<0.0001	<0.0001

2.4 Costs

From the perspective of the Chinese healthcare system, this study determined and analyzed the following direct costs (US dollar [US $]; 1 US dollar = CNY 7.23 [2022]): drug costs, administration costs, adverse event costs, imaging costs, and BSC costs. All costs were discounted by 5%. We assumed that FTD/TPI was used continuously until the patients met the drug suspension standard. The cost of the drugs was sourced from Yaozhi.com [16], with the median bid price of the drugs in each province considered as the cost of the drugs (Table 3). In the TAGS trial, the patient's dosage was determined based on their body surface area (BSA) , which was calculated to be 1.60 m^2 using the Stevenson formula and the average height and weight of individuals in China. Six provinces in China 0, including Hunan, Henan, Jiangsu, Anhui, Shaanxi and Shandong, were selected to estimate the administration cost, imaging cost and BSC cost based on the prices listed in the price catalog of medical services of the

Medical Insurance Bureau of each province. Administration costs include the expenses associated with patient accommodation during hospitalization, nursing fees, and routine examinations, such as blood routine, urine routine and stool routine. Imaging tests such as CT, MRI, PET-CT, and radiography were conducted every two cycles. Given the absence of standard treatment for a large number of pretreated patients with heavily pretreated metastatic gastric cancer, the cost of BSC was estimated based on the potential monitoring components of palliative care outlined in the 2022 gastric cancer treatment guidelines [23]. This included corresponding administrative measures such as the presence of hemorrhage, obstruction, pain, and other relevant factors. The estimation was conducted in conjunction with the median prices listed in the medical service price item catalog of the six provinces. We assumed that patients would receive BSC treatment after PD. The adverse events treatment was derived from the NCCN guidelines for hematopoietic factors [24]. The cost of adverse events treatment was estimated based on the medical service price item catalog of the six provinces and Yaozhi.com. The cost of adverse events (AEs) only considers severe AEs of grade 3 and above (grade ≥3), including neutropenia (34%), anemia (19%), and leukopenia (9%) in the FTD/TPI group, as well as bellyache (9%) and anemia (8%) in the placebo group.

Table 3 Costs and utilities values parameters

Variable	Median	Range		Distribution	Source
Costs		Lower limit	Higher limit		
FTD/TPI(per cycle)	$2,112.50	$1,901.25	$2,323.75	gamma	[14]
Adverse events(TAGS)	$3,485.00	$3,136.50	$3,833.5	gamma	[15-20] [22]
Neutropenia(34%) (per cycle)	$3,448.75	$3,103.88	$3,793.63	gamma	[15-20] [22]
Anaemia(19%) (per cycle)	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Leukopenia(9%) (per cycle)	$11.62	$10.64	$12.78	gamma	[15-20] [22]
Adverse events(placebo)	$27.33	$24.60	$30.06	gamma	[15-20] [22]

Bellyache(9%) (per cycle)	$2.71	$2.44	$2.98	gamma	[15-20] [22]
Anaemia(8%) (per cycle)	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Imaging (per cycle)	$304.55	$274.1	$335.01	gamma	[15-20]
Administration cost (per cycle)	$353.22	$317.9	$388.54	gamma	[15-20] [22]
Best supportive care (per cycle)	$1,127.97	$1,015.17	$1,240.77	gamma	[15-20][21]
Utilities					
Progression-free survival	0.764	0.688	0.841	beta	[19]
Progressed disease	0.652	0.587	0.717	beta	[19]
Death	0	0	0	beta	[19]

2.5 Utilities

In 2021, the health-related quality of life in the TAGS study was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Patients completed the EORTC QLQ-C30 questionnaire within 7 days prior to randomization, before dosing on Day 1 of at least two treatment cycles, and during the safety follow-up 30 days after the last dose (if not conducted within the previous 4 weeks). Leanne Hamerton *et al*. [25] used a published algorithm by Kontodimopoulos *et al*. to map the scores from the EORTC QLQ-C30. The resulting utility values applied within the model were 0.764 for PFS and 0.652 for PD.

2.7 Model based results

The output results were the quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER). When the ICER value was less than the set willingness-to-pay (WTP) threshold ($35,559.34), FTD/TPI was found to be more cost-effective than the placebo. For a health intervention to be considered cost-effective, a WTP threshold of $35,559.34 per QALY was used in the current analysis. Published studies reported that a treatment should be considered cost-effective if the ICER is between one and three times the GDP per capita of that country, and a treatment is considered highly cost-effective at less than one times the GDP per capita 0.

2.8 sensitivity analysis

To evaluate the robustness of the Markov model, we performed one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) to assess the impact of different parameters on the basic analysis results. The range of each variable was floated by 10% based on the base value. Sensitivity analysis was performed using TreeagePro 2019 software. One-way sensitivity analysis results are typically presented in the form of a tornado diagram, which can reflect the size of multiple uncertain factors on the outcome [25]. In the PSA, we set the cost parameter as the gamma distribution and the utility value as the beta distribution, extracting values from the corresponding distribution for 1,000 Monte Carlo simulations, and the results were presented as a cost-effectiveness acceptability curve.

3. Result

3.1 Base-case analysis

According to lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 and 3.6 months, and the median survival for PFS for FTD/TPI and placebo was 2 and 1.8 months, respectively. The simulated PFS curve and OS curve closely resembled the original data (the median survival of OS for FTD/TPI and the placebo was 5.7 and 3.6 months, whereas the median survival for PFS for FTD/TPI and the placebo was 2 and 1.8 months), indicating an acceptable and reasonable fit.

Based on the Markov model, from the perspective of Chinese healthcare system, the total treatment for FTD/TPI was $32,234.26, while that for placebo was $5,378.6. Compared with the placebo, FTD/TPI provides more than 0.88 QALYs in value. At the same time, the ICER value corresponding to each QALY is $30,494.89 (Table 4), which is lower than the WTP threshold of $35,559.34. Therefore, compared with the placebo, FTD/TPI is a cost-effective treatment option for heavily pretreated metastatic gastric cancer.

Table 4 Results of the base-case analysis

Treatment	cost	Increase cost	QALY	Increase QALY	ICER
FTD/TPI	$32,234.26	NA	3.20	NA	NA
Placebo	$5,378.6	$26,855.66	2.32	0.88	$30,494.89

3.2 sensitivity analysis

3.2.1 One-way sensitivity analysis

The tornado diagram in Fig. 1 shows that the cost and utility value range fluctuated by ±10% in the order factor sensitivity analysis. The utility value of the PFS stage had the greatest effect on the ICER value, followed by the AE cost of FTD/TPI. The specific impact is as follows: 1. The utility value of the PFS stage increases, leading to a decrease in ICER value; as its cost decreases, the ICER value increases. 2. As the cost of AEs in FTD/TPI increases, the ICER value also increases; conversely, as the cost decreases, the ICER value decreases. 3. As the cost of FTD/TPI increases, ICER value also increases; conversely, as the cost decreases, the ICER value decreases as well. FTD/TPI remained a cost-effective treatment given that the ICER per QALY gained remained below the threshold of $35,559.34 per QALY gained. Individual parameter changes may slightly alter the overall value associated with the treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

Fig 1: Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

3.2.2 PSA

According to the cost-effectiveness acceptability curve (Fig. 2), when WTP increased within the range of 1–3 times threshold ($11,860–$35,559.34) of the GDP, the FTD/TPI showed an increase in economic feasibility. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo, at a WTP threshold of $35,559.34. Thus, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a viable option. At a threshold of 2.5 times per capita for

GDP, FTD/TPI's cost-effectiveness probability dropped to 34.1%, whereas that of the placebo increased to 65.9%.

Fig 2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

4. Discussion

Recent research has shown that FTD/TPI has a relatively clear efficacy in the treatment of heavily pretreated metastatic gastric cancer. Although it has not yet been included in the CSCO guidelines, the decrease in the price of the drugs used makes studying their effectiveness in the treatment of metastatic gastric cancer valuable. This is important from an economic standpoint, for the patients' physiological and psychological health, and in terms of the social significance of the disease.

In this study, the TAGS trial showed that FTD/TPI provided a significant survival benefit for patients with heavily pretreated gastric cancer compared with the placebo. We aimed to conduct a Markov model analysis of FTD/TPI compared with the placebo in patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. According to our analysis, FTD/TPI cost $26,855.66 more than the placebo and provided an additional 0.88 QALYs, resulting in an ICER of $30,494.89 per QALY, which was below the defined WTP of $35,559.34 per QALY gained. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo at a WTP threshold of $35,559.34. Therefore, from the perspective of the Chinese healthcare system, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is cost-effective compared to placebo.

Several international publications currently use data from the TAGS trial to compare the pharmacoeconomics of FTD/TPI in patients with heavily pretreated metastatic gastric cancer. Takushima Y.0 used a partitioned survival model(PSM) to estimate the cost-effectiveness of FTD/TPI versus nivolumab from the perspective of the Japanese public healthcare payer. According to their results, the ICER of nivolumab and FTD/TPI is ¥32,352,489 yen/QALYs, and the WTP

threshold is 7,500,000yen. Therefore, the analysis of FTD/TPI from the Japanese public healthcare payment perspective shows that it is more cost-effective than nivolumab. However, as a result of differences in the controlled drugs, we could not compare the results of Takushima with this study due to the different factors involved. In Britain, Hamerton used a partitioned survival model to compare FTD/TPI with BSC in the UK0. A lognormal distribution to fit OS and a generalized gamma model to fit PFS and time-to-treatment-discontinuation were employed. According to the study results, FTD/TPI was associated with an ICER of £37,907 per QALY gained compared with BSC. Therefore, FTD/TPI is a cost-effective treatment for patients with heavily pretreated metastatic gastric cancer from a UK perspective. In Greece, Tzanetakos *et al*. 0analyzed the TAGS data through a partitioned survival model from the perspective of the Greek public payer. They reported an ICER of €47,144 per QALY gained and €28,112 per LY gained compared with BSC. Therefore, FTD/TPI was estimated to be a cost-effective treatment option for eligible third-line treatment of patients with metastatic gastric cancer in Greece. The results of both are consistent with the results of our study.

Overall, the published literature supported the findings of the present analysis, except for the study by Zhou K *et al.* 0. They developed a Markov model to assess the cost-effectiveness of FTD/TPI from the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, which is far beyond their WTP threshold ($50,000– $150,000). They found that FTD/TPI does not provide cost benefits from the perspective of US payers. Their results were not consistent with our study, which may be attributed to the varying prices of FTD/TPI in different countries. Chinese generic drugs hold a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility 0. Domestic generic drug manufacturers have implemented Porter's generic strategies to adjust prices, resulting in an average profit margin of only 5% to 10% for generic drugs in China, which is

significantly lower than the average profit margin of international generic drugs (30% to 60%) 0. Therefore, the cost of generic drugs in China is generally lower compared with the cost of foreign drugs.

However, our study also had some limitations. First, the model uncertainty concerning the original survival rates was small due to the excellent fit of the model. The long-term benefits of FTD/TPI require more analysis. Second, only considering the cost of AEs at level three or above, without taking into account all AEs, may lead to bias in the data. Third, based on the population distribution of participants in the TAGS trial, the majority were Europeans. This could introduce biases in real-world clinical efficacy in China, potentially impacting the trial's generalizability. Fortunately, exploratory studies on FTD/TPI for heavily pretreated metastatic gastric cancer in the Chinese population registered in the Chinese Clinical Trial Registry (ChiCTR2400080940) and clinical trial (NCT05029102) are currently underway. As data are continually updated, this study will also be updated.

5. Conclusion

In summary, from the perspective of the Chinese healthcare system, FTD/TPI is a cost-effective choice for heavily pretreated metastatic gastric cancer. The results of this study could provide clinicians and payers with economic evidence to consider incorporating FTD/TPI into CSCO guidelines for the diagnosis and treatment of heavily pretreated metastatic gastric cancer and guide the pricing of the originator for metastatic colorectal cancer and other indications.

Figure 1: Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

Figure 2: Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

Ethics Approval：This study is an economic evaluation analysis and does not involve human subjects. Input data includes human material or human data derived

from other published studies conducted with the approval of an appropriate ethics committee. Therefore, no ethics approval is required for conducting this cost-effectiveness analysis.

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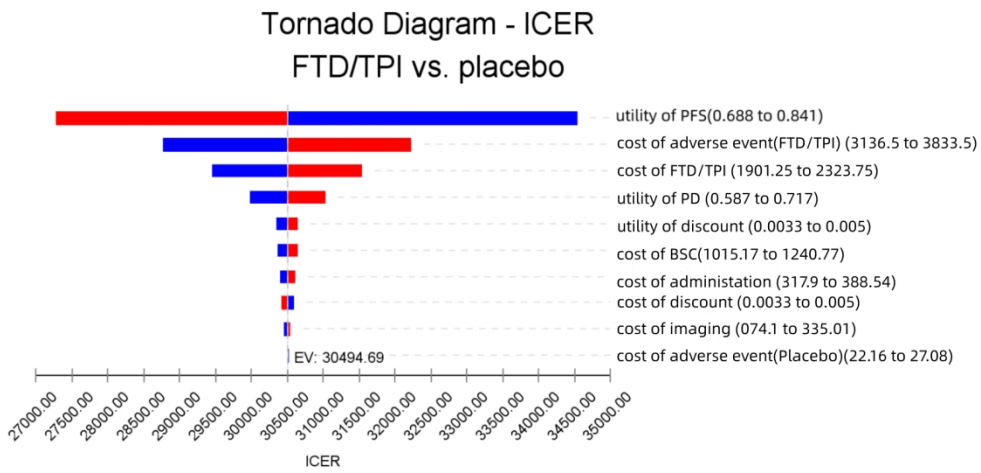

Fig1 Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

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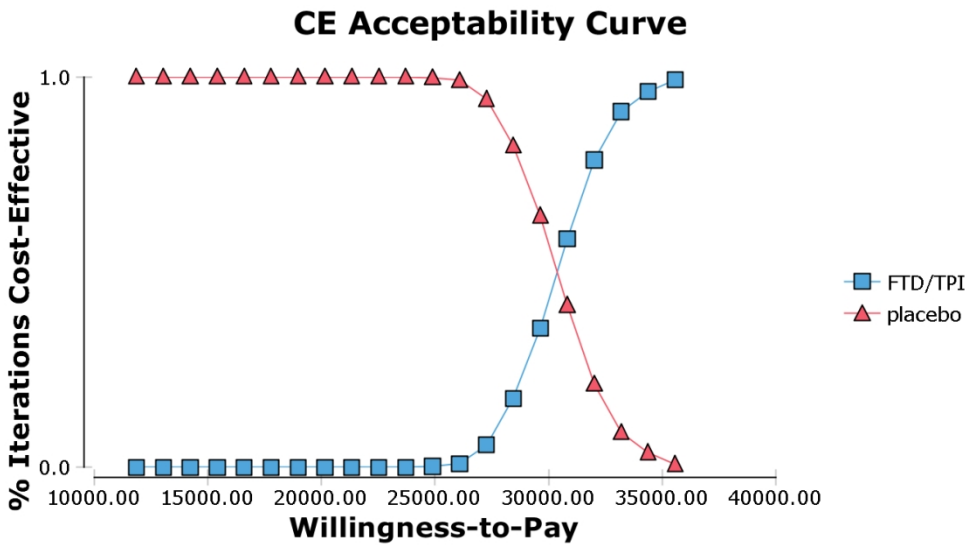

Fig2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

481x270mm (72 x 72 DPI)

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

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Cost-effectiveness analysis of Trifluridine/tipiracil in the treatment of heavily pretreated metastatic gastric cancer from the perspective of Chinese healthcare system

Ting Ying[1,2#],Runan Xia[1,2#],Yuanyuan Zhang[2,3], Jiahui Dai[1,2], Yadong Wang[1,2], Xuefeng Xie[3,4*]

Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system.

Designs: Based on the overall survival (OS) and progression-free survival (PFS) data from the TAGS trial (NCT02500043), a three-state Markov model (PFS, progressed disease, and death) was constructed to analyze the cost-effectiveness of FTD/TPI compared with the placebo in heavily pretreated metastatic gastric cancer. Cost and utility were from pricing records and the literature. The model was simulated for 5 years with monthly cycles. Costs and health outcomes were discounted by 5%. We then conducted sensitivity analyses to evaluate the robustness of the parameters. The model results were from the Chinese healthcare system.

Outcome measures: The output results were the quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER).

Results: According to the model results, FTD/TPI generated an additional cost of $26,855.66 and 0.88 QALYs compared with the placebo. ICER of FTD/TPI compared with the placebo was $30,494.89 per QALY. Sensitivity analyses revealed that the utility value of the PFS stage and FTD/TPI adverse event costs were the main influencing parameters, and the results were stable. At a threshold of three times per capita GDP of China ($35,559.34 in 2022), the probability of FTD/TPI being cost-effective compared to placebo was 99.2%.

Conclusion: From the perspective of the Chinese healthcare system, FTD/TPI is a

more cost-effective option compared with the placebo for the treatment of heavily pretreated metastatic gastric cancer in patients who have received at least two prior advanced treatment regimens.

Keywords: Heavily pretreated metastatic gastric cancer; Trifluridine/tipiracil; Markov model; Cost-effectiveness analysis; Placebo; Economic evaluation

Word count: 3396 words

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Strengths and limitations of this study: 1. This study used a Markov model to analyze the cost-effectiveness of trifluridine/tipiracil (FTD/TPI) for the treatment of heavily pretreated metastatic gastric cancer in China.

2. The cost of adverse events (AEs) only considers the severe AEs of grade 3 and above and does not consider all AEs.

3. Based on the population distribution of TAGS participants, the majority are Europeans. This limitation may introduce biases in assessing real-world clinical efficacy in China.

4. The model uncertainty concerning short-term survival rates is small owing to the good fitness of the model. But the long-term benefits of FTD/TPI require further analysis.

1. Introduction

According to the latest statistics from the World Health Organization in 2022, gastric cancer is the fourth leading cause of cancer-related deaths worldwide16[1]. About 1.2 million new cases of gastric cancer occur worldwide every year, with China accounting for approximately 40% of them0[2]. Many patients are in an advanced state of cancer cell metastasis when gastric cancer is discovered[3], and treatment is usually limited to palliative chemotherapy because of poor expected results.

At present, the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) recommend several treatment options for metastatic gastric cancer, including combination chemotherapy and single-agent chemotherapy. As a result of the generally poor physical condition of patients with advanced third-line gastric cancer, the proportion of patients who can receive combination third-line chemotherapy is extremely low, and single-agent treatment is mainly used. Patients who have received these chemotherapy treatments before receiving trifluridine/tipiracil (FTD/TPI) treatment have reported unsatisfactory results, and the cost is also high. According to IQVIA[4], global expenditure on oncology drugs will continue to increase at a double-digit rate. Therefore, a cost-effective and efficient treatment for gastric cancer remains a global challenge.

In 2019, the European Commission and the Food and Drug Administration (FDA) approved FTD/TPI for the treatment of adult patients with metastatic gastric cancer who have received at least two prior systemic treatment regimens to manage advanced disease. FTD/TPI is a novel oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analog, trifluridine, and thymidine[5]. As the main active ingredient, trifluridine inhibits cell proliferation by direct insertion into DNA after phosphorylation, leading to DNA dysfunction and cell death[5,6]. In addition to its anti-tumor role when combined with trifluridine to form FTD/TPI, it prevents the rapid degradation of trifluridine, allowing for the

maintenance of adequate plasma levels of the active drug[6,7].

In 2015, FTD/TPI was first approved by FDA and expanded globally including European Union and China for the treatment of patients with heavily pretreated metastatic colorectal cancer[8]. In 2021, FTD/TPI generic tablets were first approved for marketing by National Medical Products Administration (NMPA)[9]. This move greatly reduced the cost of using FTD/TPI in China. FTD/TPI has been approved for metastatic colorectal cancer in the current CSCO guidelines, but it has not been approved for metastatic gastric cancer. There is currently no cost-effectiveness analysis evaluating FTD/TPI for the treatment of a significant number of patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. Therefore, this study conducted a cost-effectiveness analysis of FTD/TPI for treating a large number of patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. The results of this study could provide clinicians and payers with economic evidence to consider incorporating FTD/TPI into Chinese guidelines for the diagnosis and treatment of heavily pretreated metastatic gastric cancer and guide the pricing of the originator for metastatic colorectal cancer and other indications.

2. Methods

2.1 Patients

The data were selected from the TAGS trial.[10] (NCT02500043, Taiho Oncology, Inc.). This work is a phase III study with randomized, double-blind, placebo-controlled, and multinational cases. The study began in July 2015 and concluded in September 2021, including 17 countries and involving 110 academic hospitals, evaluating the efficacy and safety of FTD/TPI plus best support care (BSC) versus placebo plus BSC in participants with heavily pretreated metastatic gastric cancer. After screening and excluding certain cases, a total of 507 patients participated in this clinical trial. These patients had received at least two treatments for advanced gastric cancer before. Eligible patients were randomly assigned in a 2:1 ratio to either the FTD/TPI group (337

patients) or the placebo group (170 patients). The primary endpoint of the study was overall survival (OS), while the secondary endpoint was progression-free survival (PFS). The objective of TAGS trial was to investigate whether the quality of life (QoL) of patients could be maximized without the influence of anti-tumor factors. Patients or members of the public were not involved in the design of this study.

2.2 Treatment

Participants received 35 mg/m^2 FTD/TPI tablets orally twice daily (BID) for 5 days per week (from Days 1 to 5 and Days 8 to 12) for 2 weeks, followed by 14 days of rest in each 28-day cycle along with BSC until the patient met the drug suspension standard (including participant withdrawal, disease progress, irreversible treatment related to four non-hematological events, doctor's decision, participants are pregnant, or death).

2.3 Model structure

A three-state Markov model was constructed to simulate the cost-effectiveness differences between FTD/TPI plus BSC and placebo plus BSC for treating heavily pretreated metastatic gastric cancer using TreeagePro 2019. Including progression-free survival(PFS), progressed disease(PD), and death(D) states. Patients entered this model in the PFS state, and could not return to the previous state after entering PD. The entry point into the model for patients in this study was established at the average age of participants in the TAGS trial (62.5 years). According to the model, the Markov cycle was 28 days. Given that 99.9% of patients entered the death (D) state after 60 model cycles, and the overall 5-year survival rate for progressive gastric cancer is only 35.1%[11], the model was limited to a duration of 5 years. A discount rate of 5% for both cost and utility values are recommended according to the Chinese Pharmaceutical Economics Evaluation Guide (2020) [12].

2.4 Transition probability

The OS and PFS curves were derived from the TAGS trial. GetData

Graph Digitizer software was used to collect data points from OS and PFS survival curves. The data were then cleaned and converted into a format suitable for survival analysis. The data were analyzed by Kaplan–Meier analysis through R4.2.0 software, and survival curve extrapolation was conducted using the Standard Parametric Model (SPM) with Weibull, Gamma, Lognormal, Log-logistic, and Exponential distributions (Table 1). According to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), the smaller the AIC and BIC values, the better the fit[13]. Therefore, the log-normal distribution was selected as the optimal distribution based on AIC and BIC, along with a visual inspection of the FTD/TPI and placebo data. We included both the original survival curves and the simulated survival curves (Table 2). The parameters μ and θ for each group of OS and PFS curve parameters were obtained to calculate the transition probability from PFS to PFS (PFTF). Assuming that the transition probability from PFS to D (PFTD) corresponds to a per capita mortality rate of 7.37‰ in 2022[14], PFS to PD (PFTP) =1-PFTF-PFTD. The OS curve parameters can be used to determine the transition probability from the survival state to the survival state (PSTS) . and the survival state to D (PSTD)=1-PSTS. According to Zhou T.[15], the transition probability from PD to PD (PPTP) should be adjusted. Therefore, PPTP = ([nPFS+nPD]×PSTS-nPFS× PFTF- NPFS× PFTD]/nPD, PPTD=1-PPTP. Among them, nPFS and nPD are the number of patients in the PFS and PD states in the previous cycle, respectively.

Table 1 Progression-free survival and Overall survival data fit results

Group	Observation	Distribution	AIC	BIC
	Progression-free survival	Weibull	1,515.56	1,523.20
		Gamma	1,480.32	1,487.96
		Lognormal	1,424.17	1,431.81
		Log-logistic	1,649.84	1,657.48
		Exponential	1,590.96	1,594.78

FTD/TPI		Weibull	2,015.34	2,022.98
		Gamma	2,003.67	2,011.31
	Overall survival	Lognormal	1,993.85	2,001.49
		Log-logistic	2,156.71	2,164.35
		Exponential	2,064.76	2,068.58
		Weibull	911.25	917.59
		Gamma	899.76	906.10
	Progression-free survival	Lognormal	853.36	859.70
		Log-logistic	1,025.02	1,031.36
Placebo		Exponential	916.12	919.30
		Weibull	1,098.38	1,104.72
		Gamma	1,091.46	1,097.80
	Overall survival	Lognormal	1,081.39	1,087.73
		Log-logistic	1,181.05	1,187.39
		Exponential	1,117.25	1,120.42

Table 2 Comparison of simulated survival curves with original survival curves

	Simulated survival curves	Original survival curves
OS follow-up Time	60 months	46 months
PFS follow-up Time	60 months	46 months
Statistical methods	Kaplan-Meier	Kaplan-Meier
P	<0.0001	<0.0001

2.4 Costs

From the perspective of the Chinese healthcare system, this study determined and analyzed the following direct costs (US dollar [US $]; 1 US dollar = CNY 7.23 [2023]): drug costs, administration costs, adverse event costs, imaging costs, and BSC costs. All costs were discounted by 5%. We assumed that FTD/TPI was used continuously until the patients met the drug suspension standard. The cost of the drugs was sourced from Yaozhi.com [16], with the median bid price of the drugs in each province considered as the cost of the drugs (Table 3). In the TAGS trial, the patient's dosage was determined based on their body surface area (BSA) , which was calculated to be 1.60 m^2 using the Stevenson formula and the average height and weight of individuals in China. Six provinces in China[17-22], including Hunan, Henan, Jiangsu, Anhui, Shaanxi and Shandong, were selected to estimate the administration cost, imaging cost

and BSC cost based on the prices listed in the price catalog of medical services of the Medical Insurance Bureau of each province. Administration costs include the expenses associated with patient accommodation during hospitalization, nursing fees, and routine examinations, such as blood routine, urine routine and stool routine. Imaging tests such as CT, MRI, PET-CT, and radiography were conducted every two cycles. The cost of BSC was estimated based on the potential monitoring components of palliative care outlined in the 2022 gastric cancer treatment guidelines[23]. The estimation was conducted in conjunction with the median prices listed in the medical service price item catalog of the six provinces.

We assumed that patients would receive BSC treatment after PD. Treatment options for adverse events were derived from the NCCN guidelines [24]. The cost of adverse events treatment was estimated based on the medical service price item catalog of the six provinces and Yaozhi.com. The cost of adverse events (AEs) only considers severe AEs of grade 3 and above (grade ≥3), including neutropenia (34%), anemia (19%), and leukopenia (9%) in the FTD/TPI group, as well as bellyache (9%) and anemia (8%) in the placebo group.

Table 3 Costs and utilities values parameters

Variable	Median	Range		Distribution	Source
Costs		Lower limit	Higher limit		
FTD/TPI(per cycle)	$2,112.50	$1,901.25	$2,323.75	gamma	[14]
Adverse events cost (TAGS)	$3,485.00	$3,136.50	$3,833.5	gamma	[15-20] [22]
Neutropenia(34%) (per cycle)	$3,448.75	$3,103.88	$3,793.63	gamma	[15-20] [22]
Anaemia(19%) (per cycle)	$24.62	$22.16	$27.08	gamma	[15-20] [22]
Leukopenia(9%) (per cycle)	$11.62	$10.64	$12.78	gamma	[15-20] [22]
Adverse events cost (placebo)	$27.33	$24.60	$30.06	gamma	[15-20] [22]
Bellyache(9%) (per cycle)	$2.71	$2.44	$2.98	gamma	[15-20] [22]
Anaemia(8%) (per cycle)	$24.62	$22.16	$27.08	gamma	[15-20] [22]

Imaging cost (per cycle)	$304.55	$274.1	$335.01	gamma	[15-20]
Administration cost (per cycle)	$353.22	$317.9	$388.54	gamma	[15-20] [22]
Best supportive care cost (per cycle)	$1,127.97	$1,015.17	$1,240.77	gamma	[15-20][21]
Utilities					
Progression-free survival	0.764	0.688	0.841	beta	[19]
Progressed disease	0.652	0.587	0.717	beta	[19]
Death	0	0	0	beta	[19]

2.5 Utility

In 2021, the health-related quality of life in the TAGS study was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Patients completed the EORTC QLQ-C30 questionnaire within 7 days prior to randomization, before dosing on Day 1 of at least two treatment cycles, and during the safety follow-up 30 days after the last dose (if not conducted within the previous 4 weeks). To obtain EQ-5D utility weights to populate the model. Leanne Hamerton *et al*. [25] used a published algorithm by Kontodimopoulos *et al*. to map the scores from the EORTC QLQ-C30. The resulting utility values applied within the model were 0.764 for PFS and 0.652 for PD.

2.7 Model based results

The output results were the quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER). Willing-to-pay (WTP) is suggested as three times per capita GDP in China. When the ICER value was less than Willing-to-pay (WTP) ($35,559.34). FTD/TPI was found to be more cost-effective than the placebo. For a health intervention to be considered cost-effective, a WTP threshold of $35,559.34 per QALY was used in the current analysis. Published studies reported that a treatment should be considered cost-effective if the ICER is between one and three times the GDP per capita of that country, and a treatment is considered highly cost-effective at less than one times the GDP per capita[26-28].

2.8 Sensitivity analysis

To evaluate the robustness of the Markov model, we performed one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) to assess the impact of different parameters on the basic analysis results. The range of each variable was floated by 10% based on the base value. Sensitivity analysis was performed using TreeagePro 2019 software. One-way sensitivity analysis results are typically presented in the form of a tornado diagram, which can reflect the size of multiple uncertain factors on the outcome [25]. In the PSA, we set the cost parameter as the gamma distribution and the utility value as the beta distribution, extracting values from the corresponding distribution for 1,000 Monte Carlo simulations, and the results were presented as a cost-effectiveness acceptability curve.

3. Result

3.1 Base-case analysis

According to lognormal fitting, the median survival of OS for FTD/TPI and placebo was 6 and 3.6 months, and the median survival for PFS for FTD/TPI and placebo was 2 and 1.8 months, respectively. The simulated PFS curve and OS curve closely resembled the original data (the median survival of OS for FTD/TPI and the placebo was 5.7 and 3.6 months, the median survival for PFS for FTD/TPI and the placebo was 2 and 1.8 months), indicating an acceptable and reasonable fit.

Based on the Markov model, from the perspective of Chinese healthcare system (Table 4), the total treatment cost for FTD/TPI was $32,234.26, while that for placebo was $5,378.6. Compared with the placebo, the ICER value for FTD/TPI was $30,494.89 per QALY gained, with an incremental cost of $26,855.66 and an incremental QALY of 0.88, which was lower than WTP. Therefore, compared with the placebo, FTD/TPI is a cost-effective treatment option for heavily pretreated metastatic gastric cancer.

Table 4 Results of the base-case analysis

Treatment	cost	Incremental cost	QALY	Incremental QALY	ICER
FTD/TPI	$32,234.26	NA	3.20	NA	NA
Placebo	$5,378.6	$26,855.66	2.32	0.88	$30,494.89

3.2 Sensitivity analysis

3.2.1 One-way sensitivity analysis

The tornado diagram in Fig. 1 shows the rank order of the impact degree of each variable on the results. The utility value of the PFS stage had the greatest effect on the ICER value, followed by the AE cost of FTD/TPI. FTD/TPI remained a cost-effective treatment given that the ICER per QALY gained remained below the threshold of $35,559.34 per QALY gained. Individual parameter changes may slightly alter the overall value associated with the treatment, but they do not change the ICER-based conclusion of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer.

Fig 1: Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

3.2.2 PSA

According to the cost-effectiveness acceptability curve (Fig. 2), when WTP increased within the range of 1–3 times threshold ($11,860–$35,559.34) of the GDP, the FTD/TPI showed an increase in economic feasibility. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo, at a WTP threshold of $35,559.34. Thus, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is a cost-effective option. At a threshold of 2.5 times per capita for GDP, FTD/TPI's cost-effectiveness probability dropped to 34.1%, whereas that of the placebo increased to 65.9%.

Fig 2 Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

4. Discussion

Recent research has shown that FTD/TPI has an obvious effect on heavily pretreated metastatic gastric cancer. Although it has not yet been included in the CSCO guidelines, with the discovery of the value of FTD/TPI in the treatment of heavily pretreated metastatic gastric cancer, the use of FTD/TPI can be considered for the treatment of patients in the clinic. This has significant implications for the physiological and psychological well-being of patients, and has significant social implications.

In this study, the TAGS trial showed that FTD/TPI provided a significant survival benefit for patients with heavily pretreated gastric cancer compared with the placebo. We aimed to conduct a Markov model analysis of FTD/TPI compared with the placebo in patients with heavily pretreated metastatic gastric cancer from the perspective of the Chinese healthcare system. According to our analysis, FTD/TPI cost $26,855.66 more than the placebo and provided an additional 0.88 QALYs, resulting in an ICER of $30,494.89 per QALY, which was below the defined WTP of $35,559.34 per QALY gained. The analysis showed that FTD/TPI had a probability of 99.2% of being a cost-effective option compared with the placebo at a WTP threshold of $35,559.34. Therefore, from the perspective of the Chinese healthcare system, FTD/TPI treatment for heavily pretreated metastatic gastric cancer is cost-effective compared to placebo.

Several international publications currently use data from the TAGS trial to compare the cost-effectiveness of FTD/TPI in patients with heavily pretreated metastatic gastric cancer. Takushima Y.[29] used a partitioned survival model(PSM) to estimate the cost-effectiveness of FTD/TPI versus nivolumab from the perspective of the Japanese public healthcare payer. According to their results, the ICER of nivolumab and FTD/TPI is ¥32,352,489 yen/QALYs, and the WTP threshold is 7,500,000yen. Therefore, the analysis of FTD/TPI from the Japanese public healthcare payment perspective shows that it is more cost-effective than nivolumab. However, as a result of differences between nivolumab and placebo, we could not compare the results of Takushima with this study due to the different factors involved. In Britain, Hamerton used a partitioned survival model to

compare FTD/TPI with BSC in the UK[25]. A lognormal distribution to fit OS and a generalized gamma model to fit PFS and time-to-treatment-discontinuation were employed. According to the study results, FTD/TPI was associated with an ICER of £37,907 per QALY gained compared with BSC. Therefore, FTD/TPI is a cost-effective treatment for patients with heavily pretreated metastatic gastric cancer from a UK perspective. In Greece, Tzanetakos *et al*. [30]analyzed the TAGS data through a partitioned survival model from the perspective of the Greek public payer. They reported an ICER of €47,144 per QALY gained and €28,112 per LY gained compared with BSC. Therefore, FTD/TPI was estimated to be a cost-effective treatment option for eligible third-line treatment of patients with metastatic gastric cancer in Greece. The results of both are consistent with the results of our study.

Overall, the published literature supported the findings of the present analysis, except for the study by Zhou K *et al.*[31]. They developed a Markov model to assess the cost-effectiveness of FTD/TPI from the perspective of the US payer. According to the results, compared with the placebo, the increase in FTD/TPI is 0.06 QALYs, and the ICER value is $986,333, which is far beyond their WTP threshold ($50,000– $150,000). They found that FTD/TPI does not provide cost benefits from the perspective of US payers. Their results were not consistent with our study, which may be attributed to the varying prices of FTD/TPI in different countries. Chinese generic drugs hold a dominant position in the domestic drug market. The emergence of generic drugs can reduce drug prices and increase drug accessibility[32]. Domestic generic drug manufacturers have implemented Porter's generic strategies to adjust prices, resulting in an average profit margin of only 5% to 10% for generic drugs in China, which is significantly lower than the average profit margin of international generic drugs (30% to 60%)[33]. Therefore, the cost of generic drugs in China is generally lower compared with the cost of foreign drugs.

However, our study also had some limitations. First, the model uncertainty concerning the original survival rates was small due to the excellent fit of the

model. The long-term benefits of FTD/TPI require more analysis. Second, only considering the cost of AEs at level three or above, without taking into account all AEs, may lead to bias in the data. Third, based on the population distribution of participants in the TAGS trial, the majority were Europeans. This could introduce biases in real-world clinical efficacy in China, potentially impacting the trial's generalizability. Fortunately, exploratory studies on FTD/TPI for heavily pretreated metastatic gastric cancer in the Chinese population registered in the Chinese Clinical Trial Registry (ChiCTR2400080940) and clinical trial (NCT05029102) are currently underway. As data are continually updated, this study will also be updated.

5. Conclusion

In summary, from the perspective of the Chinese healthcare system, FTD/TPI is a cost-effective choice for heavily pretreated metastatic gastric cancer. The results of this study could provide clinicians and payers with economic evidence to consider incorporating FTD/TPI into CSCO guidelines for the diagnosis and treatment of heavily pretreated metastatic gastric cancer and guide the pricing of the originator for metastatic colorectal cancer and other indications.

Figure 1: Cost and utility value range fluctuation ±10% under the order factor sensitivity analysis tornado diagram

Figure 2: Cost-Acceptability Curve for Probabilistic Sensitivity Analysis

Ethics Approval： This study is an economic evaluation analysis and does not involve human subjects. Input data includes human material or human data derived from other published studies conducted with the approval of an appropriate ethics committee. Therefore, no ethics approval is required for conducting this cost-effectiveness analysis.

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