S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer: a cost-effectiveness analysis

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Research article

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Abstract

Background: A multicenter, open-label, randomized, phase 3 trial (SOLAR) conducted in 62 centers across Japan and South Korea showed that S-1 plus leucovorin and oxaliplatin showed improved overall response rate, progression-free survival (PFS), and overall survival (OS) compared with S-1 plus cisplatin. This study aimed to investigate whether S-1 plus leucovorin and oxaliplatin is cost-effective compared with S-1 plus cisplatin as the first-line therapy of advanced gastric cancer from the perspective of Chinese society.

Materials and methods: The clinical data for this model was derived from the SOLAR trial. Costs and utility were either derived from the standard fee database or extracted from previously published literature. A Markov model was developed to simulate the disease process of patients with advanced gastric cancer. One-way sensitivity analyses were conducted to investigate the impact of variables on the analysis model. A second-order probabilistic sensitivity analysis was performed based on 1,000 Monte-Carlo simulations.

Results: S-1 plus leucovorin and oxaliplatin cohort provided an incremental 0.02 QALYs with an incremental cost of $1,527.31, compared with the S-1 plus cisplatin cohort, resulting in the incremental cost-effectiveness ratio (ICER) of $61,331.63/QALY, which beyond the willingness to pay threshold. Costs of drugs in the PFS state in both cohorts and utility of PFS state were the most influential factors in this study.

Conclusion: S-1 plus leucovorin and oxaliplatin is not cost-effective compared with S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer from the Chinese society perspective.

Introduction

Gastric cancer is still the fifth most common malignancy (the second in China) and the third leading cause of cancer-related mortality (the third in China) worldwide, although due to early detection and endoscopic or surgical resection, the global age-adjusted mortality rate of gastric cancer has been decreasing recently [1–2]. For unresectable advanced, recurrent gastric cancer, chemotherapy had shown the prolongation of overall survival compared with Best Supportive Care (BSC) [2]. At present, doublet chemotherapy with fluoropyrimidine and platinum has been recommended as first-line therapy, while there are many options for doublet chemotherapy, such as fluorouracil, S-1, or capecitabine for fluoropyrimidine, and cisplatin or oxaliplatin for platinum [3–6].

In eastern Asia, S-1 plus cisplatin has been widely used as first-line therapy for advanced gastric cancer based on several clinical trials [5–7] and was recommended in clinical guidelines (Evidence level 1A) by the Chinese Society of Clinical Oncology (CSCO) [8]. Recently, a multicenter, open-label, randomized, phase 3 trial (SOLAR) [9] showed that S-1 plus leucovorin and oxaliplatin showed improved overall response rate, progression-free survival (PFS), and overall survival (OS) compared with S-1 plus cisplatin, with manageable toxicities in most patients.

What remains ambiguous is the cost-effectiveness of these two doublet chemotherapy regimens, and an economic model based on the disease pattern of advanced gastric cancer will help to answer this question. Thus, we conducted this study to investigate whether S-1 plus leucovorin and oxaliplatin is cost-effective compared with S-1 plus cisplatin as the first-line therapy of advanced gastric cancer from the perspective of Chinese society.

Materials And Methods

Patients and interventions

The clinical data for this model was derived from the SOLAR trial [9]. The inclusion criteria were histologically confirmed metastatic or recurrent adenocarcinoma of the stomach or gastro-esophageal junction with no previous treatment (e.g. radiotherapy, chemotherapy, or hormonal therapy). The eligible patients were enrolled by physicians and automatically randomized (1:1) to S-1 plus leucovorin and oxaliplatin or S-1 plus cisplatin to receive cycles of S-1 orally twice daily for 7 days, and oxaliplatin (85 mg/m^2) intravenously on day 1, every 2 weeks or cycles of S-1 orally twice daily for 21 days, and cisplatin (60 mg/m^2) intravenously on day 8 in Japan or on day 1 in South Korea, every 5 weeks. A radiographic imaging examination using CT or MRI was repeated every 6 weeks. A survival follow-up was required every 12 weeks. The median PFS was 7.1 months in the oxaliplatin cohort, and 6.4 months in the cisplatin cohort. The median OS of the oxaliplatin cohort and the cisplatin cohort was 16.0 and 15.1 months, respectively [9]. Other clinical efficacy and the proportion of patients with grade 3–4 adverse events (AEs) are shown in Table 1.

Table 1
Clinical efficacy and proportion of patients with grade 3–4 adverse events

	S-1 plus leucovorin and oxaliplatin	S-1 plus cisplatin
Clinical efficacy-months (95% CI)		
Median OS	16.0(13.8–18.3)	15.1(13.6–16.4)
Median PFS	7.1(6.8–8.3)	6.4(5.6–6.9)
Proportion of patients with grade 3–4 AEs		
Neutropenia	0.15	0.25
Anemia	0.16	0.18
Decreased appetite	0.15	0.13
Diarrhea	0.09	0.04
Peripheral sensory neuropathy	0.09	< 0.01
Leukopenia	0.02	0.10
Weight decrease	0.05	0.03
Hypoalbuminemia	0.04	0.03
OS, overall survival; PFS, progression-free survival; AE, adverse event.		

Model construction

A Markov model was developed with TreeAge Pro 2011 (TreeAge Software, Inc., Williamstown, MA, USA) to simulate the disease process of patients with advanced gastric cancer. The decision model structure comprised three mutually exclusive health states: PFS, progressive disease (PD), and death. The cycle length was 1 month. During each cycle, patients either stayed in the initial health status or progressed to another health status, as shown in Fig. 1. Monthly transition probabilities of health states were calculated by the following formula: P (1 month) = 1− (0.5) $^{(1/\text{median time to event})}$, which was derived from the equations: P = 1 − e^{-R} and R = − ln [0.5]/(time to event/number of treatment cycles).

Costs

Costs in this study were either derived from the 2020 standard fee database of West China Hospital, Sichuan University, or extracted from previously published literature. Direct medical costs included anticancer drugs, tests, hospitalization, and management of AEs. The median relative dose intensity (RDI) was 79.6% for S-1 and leucovorin and 68.3% for oxaliplatin in S-1 plus leucovorin and oxaliplatin group, and 86.7% for S-1 and 91.6% for cisplatin in S-1 plus cisplatin group [9]. Societal costs included absenteeism and travel costs. Absenteeism costs were calculated based on the average salary in China in

2019 at $35.6 per day. Travel costs were estimated at $10.2 per patient each trip to the hospital [10]. Most of the patients in both groups received at least one subsequent therapy (83.8%), including chemotherapy and other anticancer procedures. Chemotherapy drugs that were most frequently used were paclitaxel (75.0%), ramucirumab (54.9%), and irinotecan (51.0%). Based on the mean Asian body surface area of 1.72 m^2 and a mean weight of 65 Kg, the costs for each month were calculated. Costs were converted to US dollars at the exchange rate of $1 = ¥6.97 (July 2020). Costs and benefits were discounted to present values at 3% for 1 year.

Health outcome

Quality-adjusted life years (QALYs) were estimated for the different treatments. QALYs were calculated as the duration in a health state multiplied by the utility weight of the corresponding health state [11]. The Euro-Qol five-dimensional questionnaire (EQ-5D) encompasses a descriptive system of health-related quality of life expressed as utility indexes, ranging from perfect health (1) to death (0) [12]. Unfortunately, the phase 3 trial (SOLAR) did not collect direct information about the quality of life. According to a previous cost-effectiveness model of advanced gastric cancer, the utility for PFS was 0.797, for PD was 0.577, and for death was 0 [13].

Sensitivity analysis

One-way sensitivity analyses were conducted to investigate the impact of variables on the analysis model by varying variables with a range of ± 30%, the results of which were shown as a tornado diagram. To explore the impact of parameter uncertainty, a second-order probabilistic sensitivity analysis was performed based on 1,000 Monte-Carlo simulations. Cost-effectiveness acceptability curves were developed to reflect the probability that treatment to be cost-effective by varying ceiling ratios [14]. A willingness to pay (WTP) threshold of $30,505 was applied to the analysis according to WHO guidelines, three times the Gross Domestic Product per Capita (GDP) in China in 2019 [15].

Results

Costs outcomes

The estimated monthly costs of both treatments are briefly presented in Table 2. As for the costs for the PFS state, the greatest cost was drugs ($410.97 for oxaliplatin cohort and $344.80 for cisplatin cohort), and the costs of drugs were adjusted based on the RDI ($311.02 for oxaliplatin cohort and $302.89 for cisplatin cohort). The hospitalization fees and test costs were the same in these 2 groups. Moreover, the costs related to grade 3–4 AEs were $175.32 for the oxaliplatin cohort and $235.94 for the cisplatin cohort. As for the costs for PD state, the total cost was $22,622.3 for both treatment groups. After running the Markov model, the cumulative costs were $130,677.30 for the oxaliplatin cohort, which was higher than that of $129,149.99 for the cisplatin cohort (Table 3).

Table 2
Input parameters and ranges

	S-1 plus leucovorin and oxaliplatin	S-1 plus cisplatin	References
Costs ($)			
Costs for PFS per month			
Costs of drug	410.97(287.68-534.26)	344.80(241.36-448.25)	a
RDI-adjusted drug costs	311.02(217.71-404.33)	302.89(212.02-393.76)	[9]
Hospitalization	32.07(22.45–41.69)	32.07(22.45–41.69)	[22]
Test	202.49(141.74-263.24)	202.49(141.74-263.24)	[22]
AE	175.32(122.72-227.92)	235.94(165.16-306.72)	[23]
Societal costs	254.18(177.93-330.43)	101.67(71.17-132.18)	[10], b
Total costs	975.08(682.56-1267.61)	875.06(612.55-1137.58)	
Costs for PD per month			
Costs of drug	22283.78(15598.65-28968.91)	22283.78(15598.65-28968.91)	[24]
Hospitalization	32.07(22.45–41.69)	32.07(22.45–41.69)	[22]
Test	202.49(141.74-263.24)	202.49(141.74-263.24)	[22]
Societal costs	103.96(72.77-135.15)	103.96(72.77-135.15)	[10]
Total	22622.3(15835.61-29408.99)	22622.3(15835.61-29408.99)	
Transition probabilities			
PPFS-PFS	0.865(0.606-1.000)	0.855(0.599-1.000)	-
PPFS-PD	0.093(0.065–0.121)	0.100(0.070–0.130)	-
PPFS-death	0.042(0.029–0.055)	0.045(0.032–0.059)	-
PPD-PD	0.925(0.648-1.000)	0.923(0.646-1.000)	-
PPD-death	0.075(0.053–0.098)	0.077(0.054-0.100)	-
Utilities			
PFS state	0.797(0.558-1.000)	0.797(0.558-1.000)	[13]
PD state	0.577(0.404–0.750)	0.577(0.404–0.750)	[13]
Death state	0.000	0.000	[13]

	S-1 plus leucovorin and oxaliplatin	S-1 plus cisplatin	References
AE, adverse event; P: transition probability; PFS, progression-free survival; PD, progressive disease; RDI, relative dose intensity; a: Standard fee database of West China Hospital; b: Calculated based on average salary in China in 2019 at $35.6 per day.			

Table 3
Results of the cost-effectiveness analysis.

	S-1 plus leucovorin and oxaliplatin	S-1 plus cisplatin
Costs ($)		
Costs for PFS state	5,599.32	4,712.82
Costs for PD state	125,077.98	124,437.17
Total costs	130,677.30	129,149.99
Incremental costs	1,527.31	
Effectiveness (QALYs)		
Effectiveness for PFS state	0.38	0.36
Effectiveness for PD state	0.26	0.26
Total effectiveness	0.64	0.62
Incremental effectiveness	0.02	
ICER ($ per QALY)	61,331.63	
AE, adverse event; PFS, progression-free survival; PD, progressive disease; QALY, quality-adjusted life year; ICER: incremental cost-effectiveness ratio.		

Cost-effectiveness

As shown in Table 3, the oxaliplatin cohort provided an incremental 0.02 QALYs with incremental costs of $1,527.31, compared with cisplatin cohort, resulting in the incremental cost-effectiveness ratio (ICER) of $61,331.63/QALY.

Sensitivity analysis

The one-way sensitivity analyses are displayed in the tornado diagram in Fig. 2, in which we varied variables across a range of ± 30%. RDI-adjusted costs of drugs in PFS state in both cohorts and utility of PFS state were the most influential factors in this study. Nevertheless, societal costs in the oxaliplatin cohort, and costs of grade 3–4 AEs in both cohorts had important impacts on the outcomes. The result of

the Monte Carlo simulation of 1,000 patients showed that the mean cost and effectiveness gained were: $130,212.06 ± 23,815.32 and 0.64 ± 0.09 QALY for oxaliplatin cohort, while $128,960.14 ± 24,886.97 and 0.62 ± 0.09 QALY for cisplatin cohort. The probabilistic sensitivity analysis indicated S-1 plus leucovorin and oxaliplatin was less possible to be accepted by patients compared with S-1 plus cisplatin until WTP thresholds reached approximately $60,000 per QALY (Fig. 3).

Discussion

China is the most affected country by gastric cancer as it accounts for 42.6% of the global gastric cancer incidence and 45% of all gastric cancer-related deaths [8]. Gastric cancer has a heavy societal burden for China, so an economic assessment of therapy regimens is vital to keep the balance between clinical benefits and health care costs. Therefore, we established a cost-effective analysis from the Chinese societal perspective to investigate the cost-effectiveness of S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer. In this study, oxaliplatin cohort costs more ($130,677.30 vs $129,149.99) and yields more health outcomes (0.64 QALYs vs 0.62 QALYs) than cisplatin cohort, resulting in the ICER of $61,331.63/QALY, which beyond the prespecified WTP threshold ($30,505/QALY), suggesting that S-1 plus leucovorin and oxaliplatin is not a cost-effective choice compared with S-1 plus cisplatin. Probabilistic sensitivity analysis suggested that this result was robust.

In terms of cost-effectiveness acceptability, as shown in Fig. 3, the acceptance rate varied as the WTP threshold changed. Oxaliplatin regimen was less likely to be accepted by patients until the WTP threshold was over $60,000/QALY. According to the WTP threshold we set before at $30,505/QALY, the oxaliplatin regimen is not cost-effective.

The most influential factors driving our model were RDI-adjusted costs of drug in PFS state in both cohorts and utility of PFS state, followed by societal costs in oxaliplatin cohort and costs of grade 3–4 AEs in both cohorts. The main differences of PFS state costs between the two cohorts were the price of oxaliplatin and cisplatin ($0.49 per mg vs $0.22 per mg), so decreasing the price of oxaliplatin could be a way to reduce ICER. Besides, the usage of S-1 was quite different (S-1 orally twice daily for 7 days every 2 weeks in oxaliplatin cohort vs S-1 orally twice daily for 21 days every 5 weeks in cisplatin cohort). Moreover, before and after treatment of the cisplatin group, hydration shall be performed to maintain sufficient urinary volume, and 5-HT_3 receptor antagonist and steroid are recommended to be administered as pretreatment for nausea and vomiting. All the above were the reasons for the different costs in the PFS state between two cohorts.

Oxaliplatin cohort and cisplatin cohort both maintain a manageable toxicity profile. In terms of the grade 3–4 AEs, decreased appetite, diarrhea, peripheral sensory neuropathy, weight decrease, and hypoalbuminemia occurred more frequently in the oxaliplatin cohort, whereas neutropenia, anemia, and leukopenia were greater in the cisplatin cohort. Since the toxicity-related dose reduction may affect the results, we adjusted the drug costs according to RDI given by SOLAR. In the S-1 plus leucovorin and

oxaliplatin group, 50% patients required S-1 and leucovorin dose reduction and oxaliplatin dose reduction was required in 48% patients. In the S-1 plus cisplatin group, 34% patients required S-1 dose reduction and cisplatin dose reduction was required in 28% patients. The AEs related costs were $175.32 and $235.94 per month in the oxaliplatin cohort and cisplatin cohort, respectively. The sensitivity analysis revealed that AEs related costs in both cohorts had an important impact on the ICER.

Many cost-effectiveness analyses have previously investigated chemotherapy regimens for gastric cancer. Some literature [16–17] has been published to compare S-1 and XELOX (capecitabine plus oxaliplatin) and concluded that XELOX was more cost-effective as adjuvant treatment, while capecitabine monotherapy was proved to be cost-effective compared with XELOX for elderly patients [18]. ECX (epirubicin, cisplatin, and capecitabine) followed by FOLFIRI (fluorouracil, leucovorin, and irinotecan) has been demonstrated to be a preferred strategy [19]. Another analysis [20] has been conducted to compare second-line treatment options for patients with advanced gastric cancer and revealed that irinotecan alone was the most cost-effective regimen. Moreover, recent evidence [21] suggested that compared with FOLFIRI, FOLFOX7 (oxaliplatin, 5-fluorouracil, and leucovorin) was a more cost-effective alternative as the first-line treatment. To our best knowledge, this study is the first economic evaluation to investigate the cost-effectiveness of S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer.

There exist several limitations in this cost-effectiveness study. First and foremost, due to the SOLAR trial hadn’t collected quality of life-related information, the utility of disease pattern was extracted from a previously published advanced gastric cancer economic model, which may not accurately reflect the patients’ quality of life in the SOLAR trial. An updated health quality survey might improve accuracy and robustness. Moreover, detailed information about subsequent therapy was not given in the SOLAR trial, therefore, differences in the usage, dosage, and duration of paclitaxel, ramucirumab, and irinotecan in subsequent therapy could lead to calculation bias. Last but not least, costs could vary between different medical centers or different countries, and this may affect the generalizability of our research. In our sensitivity analysis, the costs of drugs in both cohorts had the most significant impact on the ICER. A future prospective cost-effectiveness study of S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in advanced gastric cancer is expected to further verify our results.

In conclusion, this study indicates that S-1 plus leucovorin and oxaliplatin is not a cost-effective choice compared with S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer from a Chinese society perspective, which could be considered in the decision-making process to make recommendations regarding the therapy for advanced gastric cancer patients.

Declarations

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Ethics approval: This is an observational study. This article does not contain any studies with human or animal subjects performed by any of the authors. The Sichuan University Research Ethics Committee has confirmed that no ethical approval is required.

Availability of data and material: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Conflict of interest: The authors declare that they have no conflict of interest.

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Figures

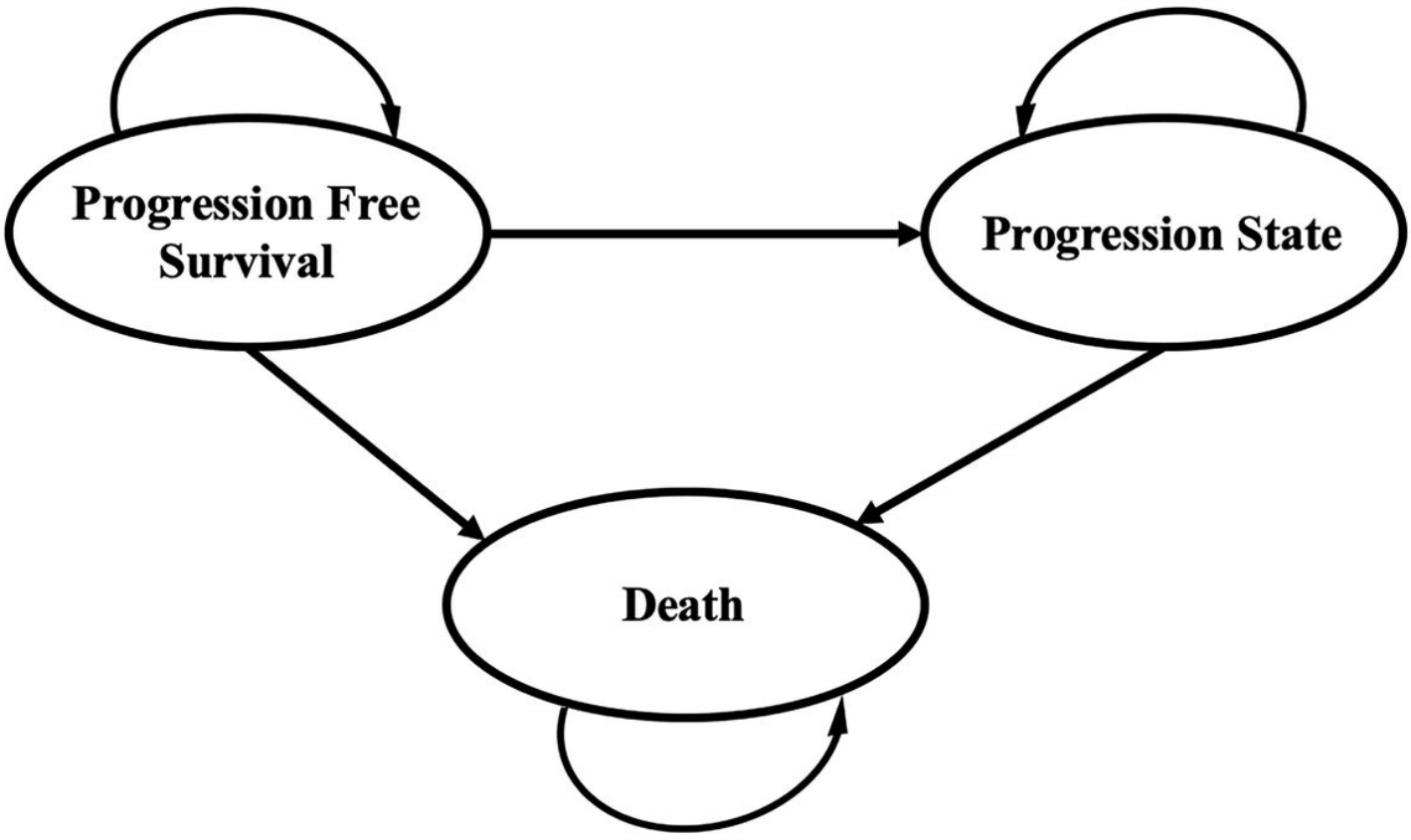

Figure 1

Markov model for advanced gastric cancer. A Markov model comprising three health states was built.

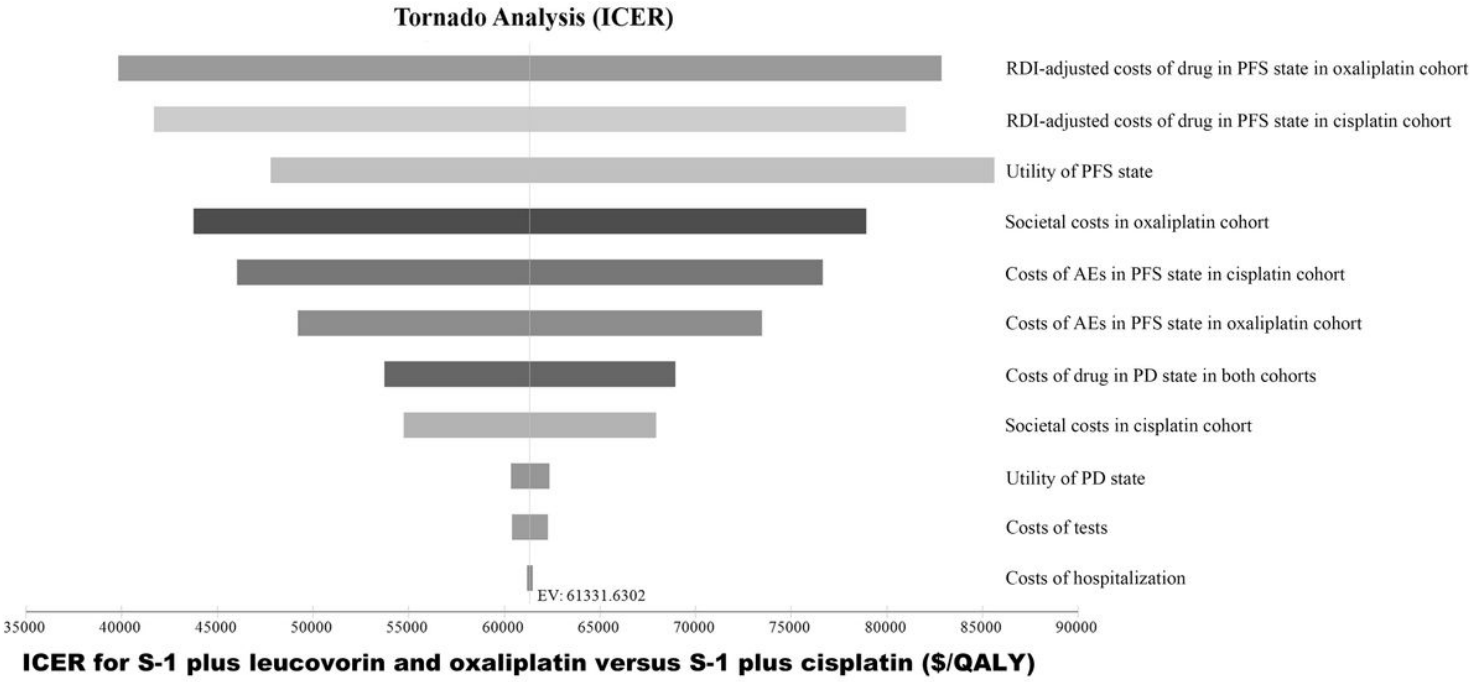

Figure 2

Tornado diagram. The tornado diagram shows the one-way sensitivity analyses within the appropriate range for each variable. Abbreviations: ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; AE, adverse effect; PFS, progression-free survival; PD, progressive disease; QALY, quality-adjusted life year; EV, expected value.

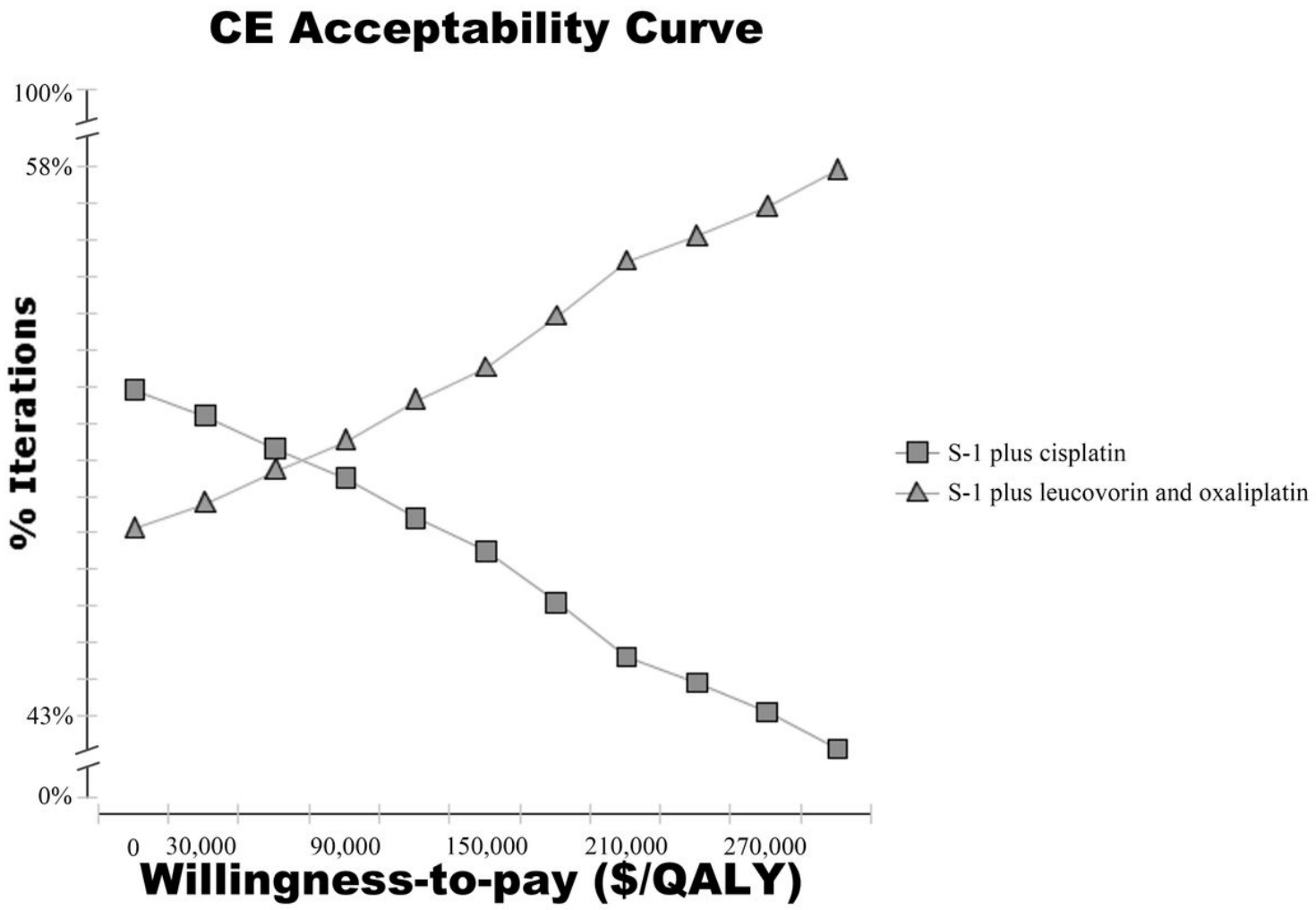

Figure 3

Probabilistic sensitivity analysis. The cost-effectiveness acceptability curve indicates the probability (y-axis) of S-1 plus leucovorin and oxaliplatin being cost effective compared with S-1 plus cisplatin given the threshold value (x-axis). Abbreviations: CE, cost-effectiveness; QALY, quality-adjusted life year.

Supplementary Files

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

- CHEERSchecklist.pdf