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Cost-effectiveness analysis of gemcitabine plus cisplatin versus fluorouracil plus cisplatin for first-line treatment of recurrent or metastatic nasopharyngeal carcinoma

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ABSTRACT

Purpose: Compared with conventional fluorouracil plus cisplatin (FP) regimen, gemcitabine plus cisplatin (GP) can prolong survival in patients with recurrent or metastatic nasopharyngeal carcinoma, but the economic impact of this practice remains unknown. It's significant to evaluate its values by taking both efficacy and cost into consideration.

Methods: We developed a Markov model with 10 years horizon to compare the cost-effectiveness of GP and FP regimen. Clinical data came from a multicentre, randomised, open-label, phase 3 trial. Direct costs related to the treatment were estimated from the perspective of the Chinese healthcare system. Utility values were gathered from published study. Sensitivity analysis was conducted to confirm the robustness of the model.

Results: The total cost of FP regimen was $12,587 and yielded 0.964 QALYs, while the total cost of GP regimen was $17,920 and yielded 1.685 QALYs. The ICER of GP regimen versus FP regimen was $7,386 which was far less than the willingness-to-pay threshold ($26,508) in China.

Conclusion: From the perspective of Chinese healthcare system, GP regimen with superior efficacy was proved to be more cost-effective than the traditional FP regimen. It is likely that GP regimen may be recommended as the primarily first-line treatment option for recurrent or metastatic nasopharyngeal carcinoma.

Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer arising from the nasopharynx epithelium, with documented incidence rates of 10 to 150 cases per 100,000 populations per year in south China, southeastern Asia, and its surrounding regions [1–3]. The 5-year relative survival rate of NPC in China is 43.8%, which is lower than that in developed countries such as Europe and America, reflecting the burden of disease and economic [4,5]. About 90% of NPC are undifferentiated or poorly differentiated squamous cell carcinomas with the characteristics of easy recurrence and distant metastasis [6]. Majority of patients already have advanced disease when diagnosed due to its silent deep-seated location [7]. Varieties of chemotherapy regimens for NPC remain empirical and under debate [8,9]. The National

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Comprehensive Cancer Network guidelines recommend cisplatin-containing regimens for patients with recurrent or metastatic NPC [10]. At present, traditional fluorouracil plus cisplatin (FP) is routinely adopted as the standard regimen for decade which has been supported mainly by randomized controlled trials [11–13]. However, the serious adverse events of mucosal inflammation and the requirement of deep vein catheterisation restrict the application of this regimen [14].

Gemcitabine with extensive antitumor activity is used in combination chemotherapy for many cancers at present, including NPC [15]. Although it is off-label use for NPC, the gemcitabine plus cisplatin (GP) regimen show outstanding efficacy and predictable tolerability in a multicentre, randomised, open-label, phase 3 trial by Li Zhang et al, indicating that GP regimen may be the current standard first-line treatment option for recurrent or metastatic NPC patients [14].

Besides efficacy, evidence concerning the cost-effectiveness is also crucial for clinical decision-making because of the sharply rising health expenditure, especially in cancer treatments. However, no relative economic analysis about treatments of NPC had been published before. Within this study, we aim to investigate the costs and outcomes of GP versus FP regimens for recurrent or metastatic NPC patients from the perspective of the Chinese healthcare system through a ten-year horizon Markov model.

Methods

Clinical data

Our treatment schemes were obtained from a multicentre, randomised, open-label, phase 3 trial of patients with recurrent or metastatic nasopharyngeal carcinoma [14]. In this trial, eligible patients who had Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and measurable lesions were randomly assigned to received gemcitabine (1 g/m^2 on days 1and 8) plus cisplatin (80 mg/m^2 on day 1) versus fluorouracil (4 g/m^2 on day 1) plus cisplatin (80 mg/m^2 on day 1) for a maximum of six cycles every three weeks. The median progression-free survival (PFS) by blinded independent assessment was 7.0 versus 5.6 months (gemcitabine vs. fluorouracil, hazard ratio [HR] = 0.55; 95%CI = 0.44–0.68; $p < 0.0001$). The overall survival (OS) was 29.1 versus 20.9 months (HR = 0.62; 95%CI = 0.45–0.84; $p = 0.0025$).

Model overview

We established a Markov model to measure the clinical and economic outcomes of GP regimen versus FP regimen in patients with recurrent or metastatic NPC based on the clinical trial (Fig 1A). The cycle length was three weeks, as treatment cycle lasted three weeks in the clinical trial, with a ten years horizon. We supposed that all patients enrolled were 47 years old, the median age of the trial. There were three health states included in our model: Progression-free disease (PFD), Progressive disease (PD) and Death as shown in Fig 1B. As time passed, patients transferred gradually from PFD to PD, and from PD to Death. During each Markov cycle, the model redistributes the patients among three different health states according to the transition probability.

Model outcomes included costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs). All costs were discounted by 3% annually and converted into US dollars as the exchange rate of 2017 shown in the National Bureau of Statistics of China (1 US dollar = 6.7518 Chinese yuan renminbi) [16]. We used the per capita gross domestic product (GDP) in the People's Republic of China in 2017 ($8,836) as the extremely cost-effective threshold and three times of per capita GDP ($26,508) as cost-effective threshold according to the World Health Organization (WHO) recommendation [16–18]. Markov model was programmed by TreeAge Pro 2017 (TreeAge Software, Williamstown, MA) and R software (version 3.5.2, https://www.r-project.org) was used to perform statistical analyses.

Transition probability and survival estimates

Transition probability between health states was derived from trial data. R Software (digitize package) was used to extract data points from the PFS and OS Kaplan-Meier curves. We retrieved the individual patient time-to-event data and published at-risk data as the method developed by Martin Hoyle and William Henley [19]. Then the data points were applied to fit parametric survival models. Survival distributions among Weibull, Log-logistic, Log-normal, and Logistic were tested for goodness-of-fit for each curve. Finally, Weibull [$s(t) = \exp(-\lambda t^{\gamma})$] and Log-logistic [$s(t) = 1/(1 + (\exp(\theta)t^{\kappa})$] distributions were chosen to fit the PFS and OS survival model respectively according to Bayesian's information criterion and Akaike's information criterion (supplementary Tables S1 and S2). We also considered adjusted R^2 statistic, reflecting the fitness of predicted and observed survival curves [20–22]. Transition probability from PFD to PD and PD to Death in each cycle was estimated based on the formulation: $1 - \exp\{\lambda(t-1)^{\gamma} - \lambda t^{\gamma}\}$ for Weibull model and $1 - \{[1 + \exp(\theta)(t-1)^{\kappa}]/[1 + \exp(\theta)t^{\kappa}]\}$ for Log-logistic model, where t stands for the current cycle number in the Markov model [22,23]. Estimated model parameters and curves fitted to PFS and OS for GP and FP regimens were demonstrated in Table 1 and supplementary Fig S1.

Patients may die of other cause in PFD during the trial follow-up, so Chinese age-dependent mortality for all-cause described by Basu and Sanjay et al. [24] was used to estimate the mortality from PFD to Death in the model.

Costs

We calculated the costs at the perspective of Chinese healthcare system. All direct medical costs considered were as follows: drug costs, management of adverse events (AEs), administration costs, laboratory tests, imaging examination, hospitalization costs and subsequent chemotherapy (Table 2).

Drug costs including chemotherapy drug, antiemetic drug and drug for hydration as shown in supplementary Table S3. The sales price of each drug were estimated from the local bid-winning price [25]. The treatment regimen for first-line chemotherapy drug was based on the trial and the median relative dose intensity (RDI) of the fluorouracil and gemcitabine were 89% and 90%, respectively, which were multiplied by the drug dosage when calculating drug costs. Complete description of regimen for antiemetic and hydration could not be found in the trial proposal, therefore we selected the drug and followed the dosage and direction in dispensatory based on the opinions of Chinese clinical experts. For dosage calculating, we use a typically Chinese body surface area (BSA) of 1.72 m^2 [26].

In addition, the cost of management AEs ($\geq$3 grade) was calculated by multiplying the incidence rate reported in the clinical trial by per unit costs derived from the published literature [27,28]. Supplementary Table S4 presents a summary of the incidence rate and unit cost of each adverse event. Other medical costs such as administration costs, laboratory tests, imaging examination, and hospitalization costs were estimated based on the average medical service price from Guangzhou Development and Reform Commission of China [29].

The proportion of progressed patients received subsequent chemotherapy in our model was based on the trial, in which almost half of the patients (41% patients in the GP regimen and 48% patients in the FP regimen) received subsequent chemotherapy until died.

Utility values

Because no data on quality of life were collected, utility values of patients for different health states were adopted from the previous study that assessed recurrent nasopharyngeal carcinoma by Ruoh-Fang Yen et al. [30] In this study, the average utility values from ten NPC patients, using the method of visual analog scale (VAS), and opinions

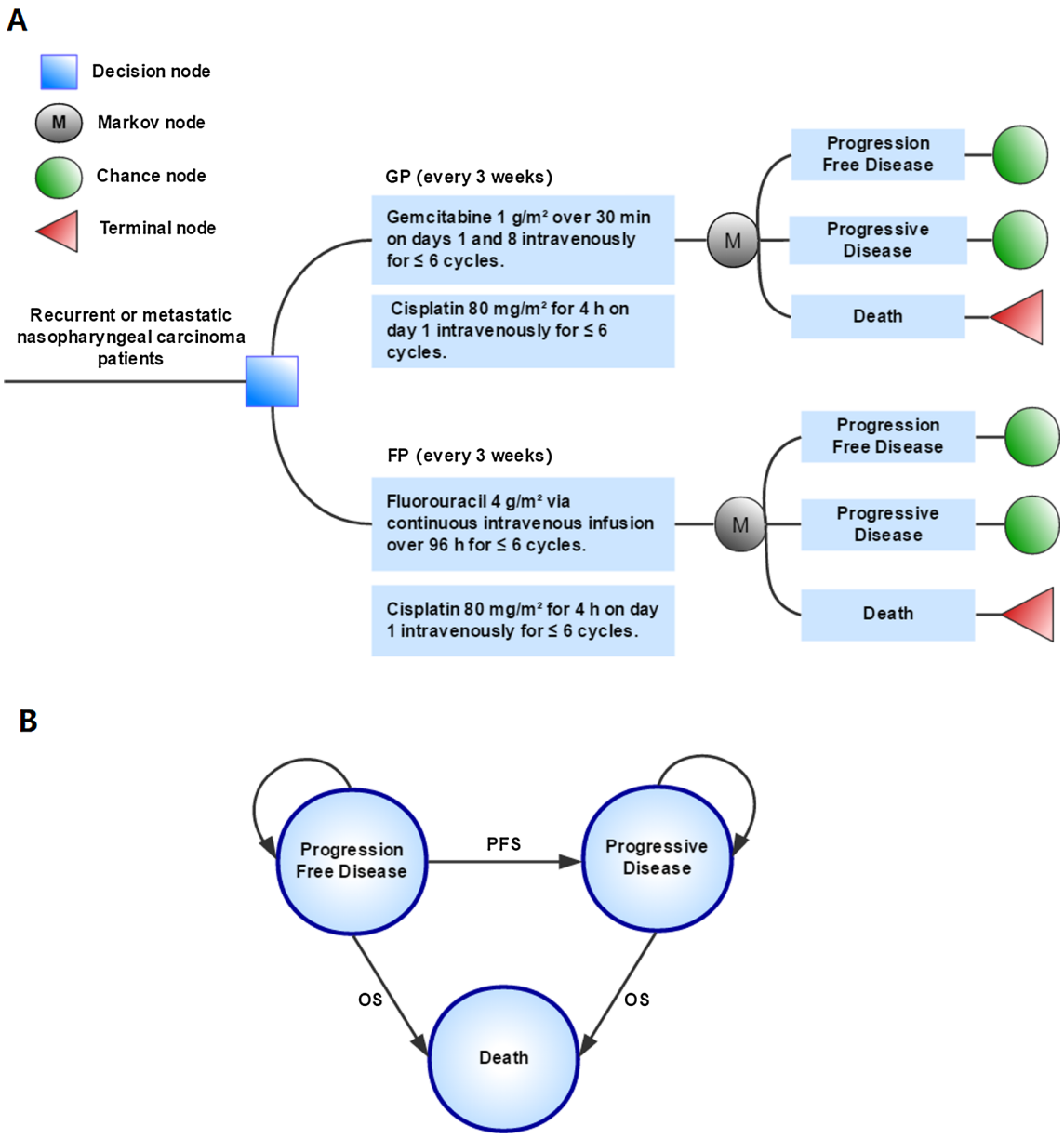

Fig. 1. (A) Markov model used to compare two different regimens for recurrent or metastatic nasopharyngeal carcinoma patients. (B) Three transitional health states linked by Markov node. PFS, progression-free survival; OS, overall survival.

Table 1
Model parameters for progression-free survival and overall survival.

	Parameter (Standard Error)		Adjusted R^2
Weibull survival model			
PFS of FP regimen	λ = 0.02504 (0.00324)	γ = 1.74453 (0.05946)	0.9945
Log-logistic survival model			
PFS of GP regimen	θ = -4.71823 (0.14331)	κ = 2.12154 (0.05627)	0.9918
OS of FP regimen	θ = -7.04065 (0.10517)	κ = 2.15312 (0.03071)	0.9962
OS of GP regimen	θ = -5.67791 (0.15423)	κ = 1.54131 (0.04241)	0.9891

Abbreviation: GP, gemcitabine plus cisplatin; FP, fluorouracil plus cisplatin; PFS, progression-free survival; OS, overall survival.

from oncologists were applied into the Markov model for there was no other study on quality of life about recurrent or metastatic NPC patients. Utility values of each health states are illustrated in Table 2.

Sensitivity analysis

To evaluate robustness of the model and address uncertainty of estimated parameters, we performed one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) with 1,000 replications. For one-way sensitivity analysis, the lower and upper values according to the practical situation, when available, were put into the model to evaluate the impact of the values on the incremental net health benefit. If the data were absent, ± 20% of the base-case values, in accordance with established approaches, were used to perform the one-way sensitivity analysis.

For probabilistic sensitivity analysis, we performed 1,000 Monte

Table 2
Base-case parameters, range, and type of distribution used in sensitivity analysis.

Parameter	GP regimen (Range)	FP regimen (Range)	Distribution	Reference
PFD cost ($)/cycle				
First-line chemotherapy				
Gemcitabine	788.70 (346.82–887.26)		γ	[25]
Fluorouracil		253.93 (137.85–453.45)	γ	[25]
Cisplatin	30.77 (9.17–32.99)	30.77 (9.17–32.99)	γ	[25]
Antiemetic drugs	35.02 (33.38–39.53)	32.17 (31.35–34.96)	γ	[25]
Administration	7.43 (6.71–8.14)	58.25 (47.14–69.35)	γ	[29], Expert opinion
Management of AEs	113.37 (63.48–176.85)*	28.21 (15.80–44.01)*	Cost:γ Rate:β	[27,28]
Hospitalization	24.99 (17.60–57.98)	41.66 (29.33–96.64)	γ	[29]
Hydration	5.19 (2.70–6.74)		γ	[25]
Laboratory tests	82.59 (58.46–99.23)		γ	[29]
Imaging examination	176.49 (156.88–196.10)		γ	[29]
TIVAP/one time		1,184.87 (647.9–1421.84)*	γ	Expert opinion
PD cost ($)/cycle				
Subsequent chemotherapy	218.96 (153.27–284.64)*	271.95 (190.37–353.54)*	γ	[25]
Utility				
Utility of PFD	0.76 (0.61–0.91)*		β	[30]
Utility of PD	0.35 (0.28–0.42)*		β	[30]
Other				
Start age	47 years old		Fix in PSA	[14]
Discount rate/year	3%		Fix in PSA	
Body surface area	1.72 m^2		Fix in PSA	[26]

Abbreviation: GP, gemcitabine plus cisplatin; FP, fluorouracil plus cisplatin; AEs, adverse events; TIVP, totally implantable venous access ports; PFD, progression-free disease; PD, progressive disease; PSA, probabilistic sensitivity analysis.
* The range was assumed to vary by ± 20%.

Carlo simulations, during which different values were sampling from their statistical distributions (Beta distribution for incidence rate and utility; Gamma distribution for cost) [31]. The outcome was used to plot cost-effectiveness acceptability curves, suggesting the probability of cost-effectiveness over the range of willingness to pay (WTP) threshold. Table 2 represents the values range and type of distribution used in sensitivity analysis.

Results

Base-case analysis

The results of base-case analysis with a 10 year-time horizon are displayed in Table 3. The total cost of FP regimen was $12,587 and yielded 0.964 QALYs, while the total cost of GP regimen was $17,920 and yielded 1.685 QALYs. In comparison with FP regimen, first-line GP regimen was associated with incremental costs and effectiveness of $5,333 and 0.722 QALYs, respectively. Therefore, the ICER of GP regimen versus FP regimen was $7,386 per QALY, which was far less than the WTP threshold suggesting that the GP regimen was extremely cost-effective.

Sensitivity analysis

The tornado diagram (Fig 2) depicts the result of one-way sensitivity analysis revealing that some model parameters had a significant impact on the ICER. Cost of subsequent chemotherapy, gemcitabine, and fluorouracil are the main ICER drivers in this study. As we varied the proportion of patients receiving subsequent chemotherapy by either direction in both GP and FP regimen, the ICER ranged from $4,784 to $14,573 and $2,826 to $9,840, respectively. Other parameters such as utility of PFD and PD also influenced the ICER. However, no matter the parameter changed in our model based on practical situation, ICER remained < $17,672 per QALY (2 × per capita GDP of China in 2017).

Scatter plot (Fig 3A) presents the result of PSA with three lines indicating the different WTP (threshold) of one, two and three times of per capita GDP of China in 2017, respectively. 68.4% of the scatter points were located below the line when WTP was $8,836 (1 × per capita GDP of China), suggesting the probability that GP regimen was extremely cost-effective. When WTP changed to $17,673 (2 × per capita GDP of China), GP regimen is likely to be cost-effective in nearly 99.8% using cases. The acceptability curves (Fig 3B) described the cost-effective regimen accounting for the change of WTP.

Table 3
Results of base-case analysis.

Treatment	Total cost ($)	QALY	Incremental cost ($)	Incremental QALY	ICER ($/QALY)
FP regimen	12,587	0.964	5,333	0.722	7,386
GP regimen	17,920	1.685			

Abbreviation: FP, fluorouracil plus cisplatin; GP, gemcitabine plus cisplatin; QALY, quality-adjusted life year; ICER, Incremental cost-effectiveness ratio.

Discussion

Although the use of fluorouracil is not specified in the FDA-approved label, FP regimen has remained the widely accepted standard first-line treatment for recurrent or metastatic NPC [11–13]. Off-label drug use (use of therapies for indications not approved) is common practice [32], particular in metastatic cancers (26% in head and neck cancer) [33]. Despite a series of negative influences have been found for lack of strong scientific evidence, off-label drug use is needed because the information including in dispensatory usually not up-to-date to guide clinical care of a variety of tumors types [33]. Especially for notably rare tumors, such as NPC with typically geographical characteristics, there may hardly be enough patients to provide supportive evidence through appropriate trial [34]. At present, the treatment options for recurrent or metastatic NPC are limited. FP regimen evolved in heavily mucosal inflammation. What's more, the risk of catheter-associated infection and thromboembolism due to the requirement of deep vein catheterization for fluorouracil infusion also restricts the application of FP regimen. Consequently, it's necessary to explore newly evidence-based treatment options. Fortunately, recent years more and

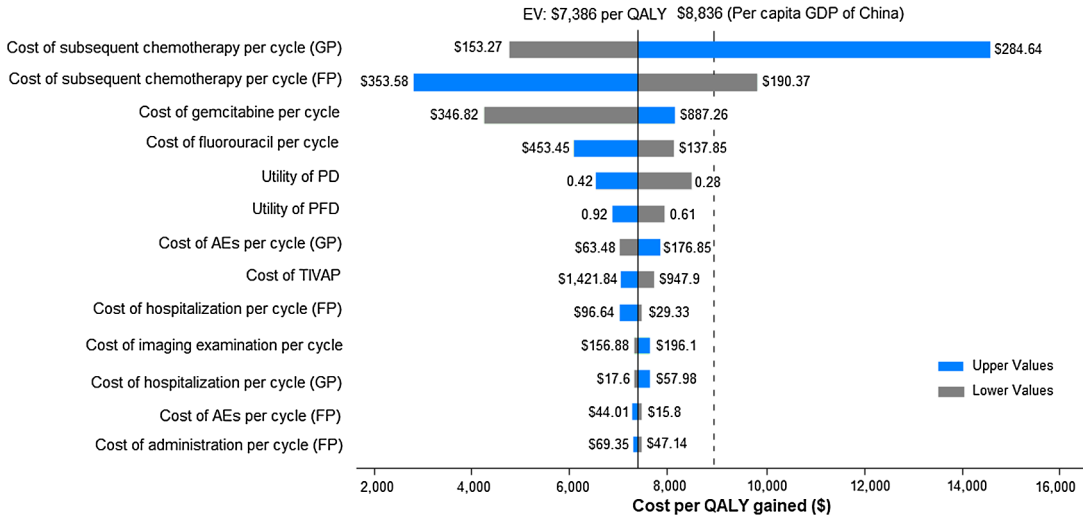

Fig. 2. Tornado diagram summarized the result of one-way sensitivity analysis. QALY, quality-adjusted life year; GDP, gross domestic product; GC, gemcitabine plus cisplatin; FC, fluorouracil plus cisplatin; AEs, adverse events; TIVP, totally implantable venous access ports; PFD, progression-free disease; PD, progressive disease.

more trials supplied plenty of evidence for the off-label use of GP regimen [35–37], particularly the first randomized, phase 3, head-to-head trial conducted by Li Zhang et al. In this trial, GP regimen showed remarkable health benefit and tolerable toxicity [14]. Because the risk-benefit ratio is usually unpredictable when off-label drug use occurs, comprehensive assessment becomes of great importance. Besides efficacy and safety, cost-effectiveness and affordability should be included in the evaluation frame for off-label drug application in clinical practice. Our analysis was the first time to compare the health outcomes and cost of different cisplatin-containing chemotherapy regimens for recurrent or metastatic NPC and demonstrated an example for economic evaluation for off-label drug use.

The result of our analysis proposed that GP regimen would be highly cost-effective for patient with recurrent or metastatic NPC with an ICER of 7,386 per QALY (< 1 × per capita GDP of China) from the perspective of Chinese healthcare system. The sensitivity analysis illustrated a high probability that GP regimen would be considered cost-effective at a willingness-to-pay threshold ranged from $8,836 to $26,508 per QALY. Moreover, although patients should receive gemcitabine twice a cycle, relatively simple administration way, shorter length of stay and lower hospitalization costs may, to some extent, improve the quality of life for the patients. Based on the previous trial and our study above, we can draw a preliminary conclusion that GP regimen with significant efficacy outcome and relatively tolerable AEs is estimated to be economical versus FP regimen. With the result of our study, it can provide more effective decision guidance for the use of GP regimen for recurrent or metastatic NPC patient taking consideration of the risk-benefit trade-off of off-label drug use.

As with any studies, several limitations should be mentioned in current analysis. First, we didn't consider the disutility values due to the lack of available data and may result in overestimation of the utility values of PFD and PD. Second, since there is no relative economic evaluation about NPC before, the cost of management AEs came from previous studies for other cancers. However, we performed a series of sensitivity analysis in which our conclusion remained substantially robust. Besides, our study was based on the only available random trial. As it was conducted on Chinese population, the generalization of the conclusion to other population should be taken with caution.

Conclusion

In conclusion, from the perspective of Chinese healthcare system, GP regimen with superior efficacy was proved more cost-effective than the traditional FP regimen. GP regimen may be recommended as first-line treatment option for recurrent or metastatic NPC even it is off-label practice under the circumstances that few on-label treatments were approved for NPC.

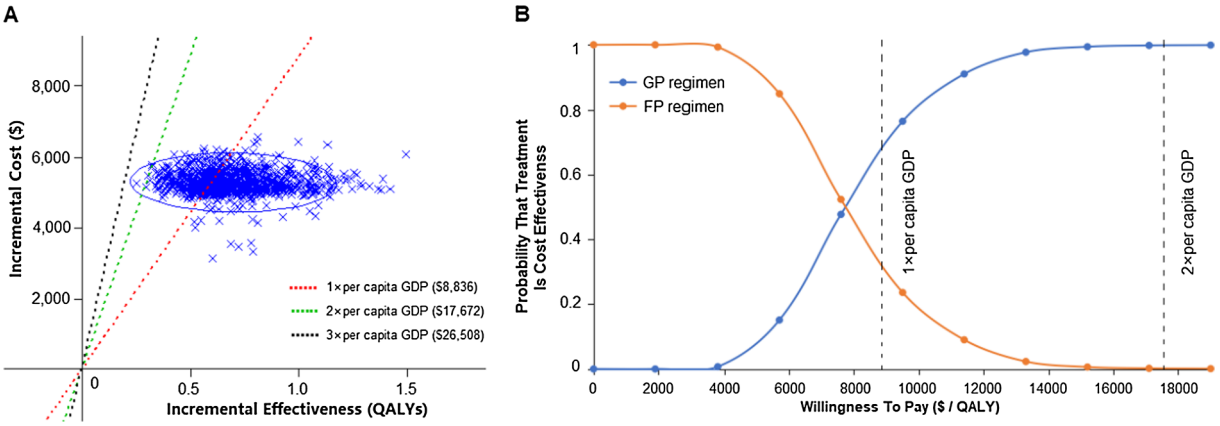

Fig. 3. Probabilistic sensitivity analysis. (A) Scatter plot with three lines stand for the threshold of willingness to pay varying from one to three times per capita GDP of China respectively. (B) Cost-effectiveness acceptability curves of two regimens at different willingness to pay thresholds. QALY, quality-adjusted life year; GDP, gross domestic product.

Role of the funding source

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Conflict of interest statement

No potential conflict of interest was reported by the authors.

Acknowledgments

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.04.022.

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