

Patient Preferences For Chemotherapy In The Treatment Of Non-Small Cell Lung Cancer: A Multicenter Discrete Choice Experiment (DCE) Study In China

This article was published in the following Dove Press journal:
Patient Preference and Adherence

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Objective: The study aims to quantify patients' risk-benefit preferences for chemotherapy in the treatment of non-small cell lung cancer (NSCLC), and to elicit their willingness to pay (WTP) for treatment outcomes.

Methods: A face-to-face discrete choice experiment (DCE) was conducted on NSCLC patients in four tertiary hospitals each from Beijing, Shanghai, Guangzhou and Chengdu in China. Patients were invited to complete choice questions that constructed by seven attributes: progression-free survival (PFS), disease control rate (DCR), rash, nausea and vomiting, tiredness, mode of administration and out-of-pocket costs. A mixed logit model was used to evaluate the choice model. Estimates of relative preferences and marginal willingness to pay for each attribute were then explored.

Results: A total of 361 patients completed the survey. Improvements in PFS (10, 95% CI: 8.4–11.6) were the most important attribute for patients, followed by increase in DCR (4.6, 95% CI: 3.4–5.8). Tiredness (3.9, 95% CI: 2.9–5.1) was judged to be the most important risk. While remaining attributes were ranked in decreasing order of importance: nausea and vomiting (1.9, 95% CI: 0.9–3.0), mode of administration (0.8, 95% CI: 0.2–1.4) and rash (0.5, 95% CI: –0.6–1.5). There was little variation in preferences among patients with different sociodemographic characteristics. Patients were monthly willing to pay \$2304 (95% CI, \$1916–\$2754) that guaranteed 11 months of PFS, followed by \$1465 (95% CI, \$1163–\$1767) per month to improve their disease control rate by 90%.

Conclusion: The results suggested that efficacy was the most important attribute for patients. Side effects, mode of administration and treatment cost significantly influenced patient preferences. Patient engagement in prioritizing their treatment preferences should be emphasized during the clinical decision-making process and regimen implementation.

Keywords: non-small cell lung cancer, chemotherapy, patient preferences, discrete choice experiment

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide and the most common cause of cancer-related mortality, its health and economic burden on society are significant.¹ According to the annual Chinese cancer registry report in 2011, the mortality of lung cancer in China was 39.27/100,000.² In 2014, the mortality of lung cancer increased further to 45.80/100,000.³ The total treatment cost (including chemotherapy, biologic agents, targeted and radiation therapy) for

lung cancer in China reached 24.31 billion yuan in 2015.⁴ Non-small cell lung cancer (NSCLC) accounted for approximately 85% of all primary lung cancers, including squamous cell carcinoma (25–30%), adenocarcinoma (40%) and large cell carcinoma (10–15%).⁵

Implementation of NSCLC therapy aims to prolong the survival time, control tumor-related symptoms as well as improve patients' quality of life.^{5,6} Currently, surgery is the standard of care for resectable, early-stage and functionally operable NSCLC.⁷ Chemotherapy will be recommended for patients with stage IV NSCLC and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression.⁵ Recommended agents include platinum agents, taxanes, vinorelbine, etoposide, pemetrexed, and gemcitabine.^{5,6,8} Patients with advanced metastasis may benefit from palliative chemotherapy.⁶ Different chemotherapy regimens offer different clinical outcomes in terms of efficacy, potential risks, dosing option and administration mode, with different expenditures for patients as well.

Patient engagement in prioritizing their treatment preferences can have an impact on the treatment effects.^{9–12} Understanding patient preferences is important to inform the regimens selection, as well as promote patient-centered health care.^{13–15} However, in China, studies of NSCLC were mainly concerned about the efficacy, safety, cost of different therapies,^{16–18} there are very few studies that investigating patient preferences in the treatment of NSCLC. The objective of this study is to quantify patients' risk-benefit preferences for chemotherapy in the treatment of NSCLC, and to elicit the WTP they make. For this study, the discrete choice experiment (DCE) was applied with data collected from multicenter settings in China.

Methods

Sample And Study Design

Multicenter face-to-face survey was conducted in four tertiary hospitals each from Beijing, Shanghai, Guangzhou and Chengdu between September 30, 2017 and December 31, 2017. The inclusion criteria were: 1) participants were required to be at least 18 years old with a physician diagnosis of NSCLC. 2) participants had received chemotherapy practice. We aimed to recruit 400 respondents (100 in each region) in the survey, the final sample included 361 respondents in our study. Earlier studies have shown that this number of respondents is sufficiently large for reliable statistical analyses.^{19,20}

For this study, after detailed explanations of the questionnaire by interviewers, participants were invited to participate in a 10 mins structured interview (based on a questionnaire) with one trained interviewers. Copies of their written informed consent were provided to participants upon recruitment. All eligible participants were informed of the purpose of the study and their right to refuse to participate. The study protocol and questionnaires were approved by the Fudan University School of Public Health Institutional Review Board (IRB#2017-09-0638, September 8, 2017–December 31, 2018). All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

The Discrete Choice Experiment Questionnaire

The discrete choice experiment (DCE) is a quantitative survey-based method, which has been extensively used to assess patient preferences, and marginal rates of substitution (e.g. marginal willingness to pay) in health care.^{21–24} In a DCE, respondents are presented with a sequence of hypothetical scenarios (choice sets) composed by defined attributes (efficacy, safety, mode of administration, costs, etc.) that are assigned with different levels. For each choice set, respondents are asked to choose their preferred scenario. Thus, relative preferences of given attributes can be determined and the trade-offs that respondents make can be quantified. There are several checklists available during the design of DCE study.^{23,25–28}

Selection Of Attributes And Their Levels

Three criteria were considered when we selected attributes: relevance to patient concern about the NSCLC chemotherapy, ease of quantifying the attribute within a DCE framework, overlap or correlation with other attributes.

Based on a critical literature review,^{29–34} consultation with clinical experts and patients focus group, key attributes were identified with different levels to describe the NSCLC treatment alternatives, with each of these attributes assigned two or three levels (Table 1). The key attributes in the survey are progression-free survival (PFS), disease control rate (DCR), side effect of skin, nausea and vomiting, tiredness and mode of administration. We used out-of-pocket costs per month as a value attribute to explore patients' marginal willingness to pay for each attribute level. For this study, the levels of

Table 1 Attributes And Their Levels

Attributes	Levels
Progression free survival	11 months 8 months 5 months ^a
Disease control rate	High, 90% Middle, 75% Low, 60% ^a
Rash	None, no rash Moderate, rash covers less than 10% of your body Severe, rash covers more than 1/3 of your body ^a
Nausea and vomiting	Mild, once a day Moderate, 2 to 5 times a day Severe, more than 6 times a day ^a
Tiredness	Mild, daily activities little influenced, some difficulties on exercising, climbing several flights of stairs, or running Moderate, daily activities somewhat influenced, some difficulties on shopping, house working, travelling Severe, daily activities severely influenced, you do not have the energy to get out of bed ^a
Out-of-pocket costs	CNY50,000/month CNY25,000/month CNY10,000/month ^a
Administration mode	Infusion Oral ^a

Note: ^aReference level.

Abbreviation: CN, Chinese yuan.

progression-free survival, levels of disease control rate, and levels of side effects were based on evidence from clinical trials or real-world data.^{35–41} The levels of out-of-pocket costs and administration mode were identified by published literature and calibrated by physicians and patients.^{42–44}

Construction Of The DCE Questionnaire

The combination of these attributes and levels (six attributes with three levels, one attribute with two levels) resulted in 1458 hypothetical scenarios ($3^6 \times 2^1$), which obviously could not be used in a questionnaire. Therefore, we applied fractional factorial design (SAS OPTEX procedure) to generate optimal scenarios. We firstly applied macro %Mktruns to calculate reasonable design sizes, then macro %Mktex was used to create the combinations.^{45–47} The resulting experimental design

Attributes	Regimen A	Regimen B
Progression free survival	8 months	5 months
Disease control rate	60%	75%
Rash	Moderate	None
Nausea and vomiting	Mild	Moderate
Tiredness	Moderate	Mild
Out-of-pocket costs	CNY50,000/month	CNY25,000/month
Administration mode	Infusion	Oral
Which regimen do you prefer to take? select the box to show your choice.	<input type="checkbox"/>	<input type="checkbox"/>

Figure 1 Sample of DCE survey question.

consisted of 18 choice pairs. The survey instrument included an introduction to choice sets with a description of the attributes and their levels. Each respondent answered 18 trade-off questions under the interviewers' assistance (Figure 1 for a DCE survey example).

In addition to DCE questions, the survey instrument included questions on demographic characteristics (e.g. gender, age, education level, and household income) and patients' treatment experience (e.g. time since diagnosis, cancer type, cancer stage, and past treatment). We also conducted a pre-test with 10 patients at one hospital to test the understandability of the survey instrument.

Data Analysis

Mixed logit model was used to estimate the relative preferences of the attributes and patient WTP for each attribute level. The mixed logit model controlled for clustering and unobserved preference heterogeneity among patients by estimating a distribution for each preference parameter.⁴⁸ The coefficients from the mixed logit model represented estimates of the probability of choosing a chemotherapy for NSCLC. Then, WTP was calculated to resemble the real-world situation, where patients' valuation for obtaining improvement in certain treatment outcome. Effects coding was applied to represent a categorical variable in the mixed logit regression model to assure all attribute levels can be estimated including the inference level.⁴⁹

In the current study, we firstly estimated the mixed logit model, then the results from the model were used to calculate the marginal WTP for each attribute level. All analyses were performed in Stata statistical software (version 14 SE, Stata Corp).

Results

Study Participants

Three hundred and sixty-one patients participated in and completed the survey, Beijing (95), Shanghai (87), Guangzhou (90), Chengdu (89). The socio-demographic characteristics of participating patients are summarized in Table 2. Of the 361 patients, the majority were male (63%) and had received senior high school education (51%). The mean age of the patients was 58 years, spanning a range of 31 to 82 years. Most patients were diagnosed as having adenocarcinoma NSCLC histology (62%), with the time since diagnosis of less than 1 year (74%).

Table 2 Demographic Characteristics Of The Study Sample

Characteristics	Subjects N=361
Gender – No.(%)	
Male	228(63)
Female	133(37)
Age – Years	
Mean	58
Range	31–82
Education – No.(%)	
Less than high school	176(49)
High school	91(25)
Bachelor's degree or higher	94(26)
Family Per Capita Income < Per Capita GDP In 2016	151(42)
Cancer Type – No.(%)	
Adenocarcinoma	223(62)
Squamous cell carcinoma	118(33)
Large cell carcinoma	20(5)
Cancer Stage – No.(%)	
Stages I, II	102(28)
Stage III	131(36)
Stage IV	128(35)
Time Since Diagnosis – No.(%)	
Less than 1 year	266(74)
1 year or more	95(26)
Treatments Received – No.(%)^a	
Chemotherapy	361(100)
Surgery	142(39)
Radiation	66(18)
Other	14(4)

Note: ^aPatients could have more than one treatment.

Abbreviation: GDP, gross domestic product.

Patient Preferences For Treatment Of NSCLC

The main effects mixed logit model results are displayed in Table 3. The coefficients were significant for nearly all attributes regarding PFS, DCR, nausea and vomiting, tiredness, mode of administration and treatment costs, meaning that these attributes played significant roles when patients engaging in the treatment decisions. The coefficient of rash, however, had no significant impact on patients' decision.

For this study, 11 months of PFS (coefficient, 0.59 [standard error (SE), 0.05]; $P < 0.001$) was the most preferred for patient, followed by 90% disease control rate (coefficient, 0.37 [SE, 0.04]; $P < 0.001$). Severe tiredness (coefficient, -0.29 [SE, 0.04]; $P < 0.001$) was judged to be the most important risk, followed by severe nausea and vomiting (coefficient, -0.13 [SE, 0.04]; $P < 0.001$). Oral administration (coefficient, 0.05 [SE, 0.02]; $P < 0.05$) was preferred to infusion. As expected, patients had higher positive preferences for better clinical outcomes. For instance, patient preferences for 11 months of PFS were far greater than 8 months. Meanwhile, patients had negative preferences for side effects.

Patient Preferences Intensity

The relative preferences intensity results are illustrated in Figure 2, with 10 representing the most preferred attributes and 0 representing the least preferred. The vertical bars around each level mean estimate denoted the 95% confidence interval about the point estimate. In relation to the level of other attributes, patients' strongest positive preference was to prolong progression-free survival by 11 months. Patients also had strong positive preferences for improving with a 90% disease control rate, mild tiredness and oral administration.

Figure 2 also illustrates the mean relative preferences intensity score with a 95% confidence interval. The mean relative preferences intensity score for each attribute was estimated as an improvement from the worst level to the best level (over the ranges presented in this study). Taking tiredness as an example, its mean relative preferences intensity was the improvement from severe to mild. In the current study, having an improvement from 5 months of PFS to 11 months of PFS was the most important (10.0; 95% [confidence interval (CI)]: 8.4–11.6), followed by improvement with 30% DCR (4.6; 95% CI: 3.4–5.8). Next were tiredness (3.9; 95% CI: 2.9–5.1), nausea and vomiting (1.9; 95% CI: 0.9–

Table 3 Main Effects Mixed Parameter Logit Model Results

Attributes	Coefficient ^a	SE	P Value	95% CI	
				LB	HB
Progression Free Survival					
11 months	0.59	0.05	0.00	0.49	0.69
8 months	0.11	0.03	0.00	0.04	0.17
5 months	−0.70	0.06	0.00	−0.80	−0.59
Disease Control Rate					
High (90%)	0.37	0.04	0.00	0.29	0.45
Middle (75%)	−0.15	0.03	0.00	−0.21	−0.09
Low (60%)	−0.22	0.04	0.00	−0.30	−0.14
Rash					
None	−0.01	0.03	0.65	−0.08	0.05
Moderate	0.04	0.03	0.23	−0.02	0.05
Severe	−0.02	0.03	0.51	−0.09	0.04
Nausea and Vomiting					
Mild	0.11	0.03	0.00	0.05	0.18
Moderate	0.02	0.03	0.54	−0.04	0.08
Severe	−0.13	0.04	0.00	−0.20	−0.06
Tiredness					
Mild	0.22	0.04	0.00	0.15	0.29
Moderate	0.07	0.03	0.03	0.01	0.13
Severe	−0.29	0.04	0.00	−0.36	−0.22
Administration Mode					
Infusion	−0.05	0.02	0.03	−0.09	−0.01
Oral	0.05	0.02	0.03	0.01	0.09
Costs, CN¥	−0.04	0.00	0.00	−0.04	−0.03

Note: ^aCoefficients represent the change in utility for a respondent for a specific level of a given attribute.

Abbreviations: SE, standard error; CI, confidence interval; CN, Chinese yuan; LB, low bound; HB, high bound.

3.0), oral administration (0.8; 95% CI: 0.1–1.4) and rash (0.5; 95% CI: −0.6–1.5).

Variation In Patient Preferences For NSCLC Treatment

We estimated interaction terms between patients' sociodemographic characteristics (e.g. age, cancer type, tumor stage) and preference for different levels of chemotherapy attributes (Table 4). We found that compared with patients aged over 40, patients aged 30–40 had stronger preference for longer PFS, and they had negative preferences for infusion mode. Squamous cell carcinoma patients tend to favor no rash than patient with other types. Adenocarcinoma patients have positive preference for mild tiredness. As the tumor stage evolved, patients have more demand for longer PFS. Despite being statistically significant, the magnitude of differences in preferences across groups was small.

Patients' Willingness To Pay For Treatment Of NSCLC

Some earlier studies reported patient expenditures for NSCLC treatments in China, and the treatment costs per cycle for NSCLC ranged from \$730 to \$2924.^{42–44} Exchange rate as of September 2018: US\$1= ¥6.84. In the current study, patients' marginal WTP was elicited by stated preference discrete choice analysis. The results revealed patients were monthly willing to pay \$2340 (95% CI, \$1927–\$2754) for obtaining 11 months of PFS (Table 5).

In addition, patients were willing to pay \$195 (95% CI, \$22–\$368) per month for oral administration, \$1,465 (95% CI, \$1163–\$1767) per month to improve their disease control rate by 90%, \$145 (95% CI, \$90–\$381) per month for rash less than 10% on the body, \$571 (95% CI, \$189–\$716) per month to reduce nausea and vomiting to one time a day and \$879 (95% CI, \$600–\$1159) per

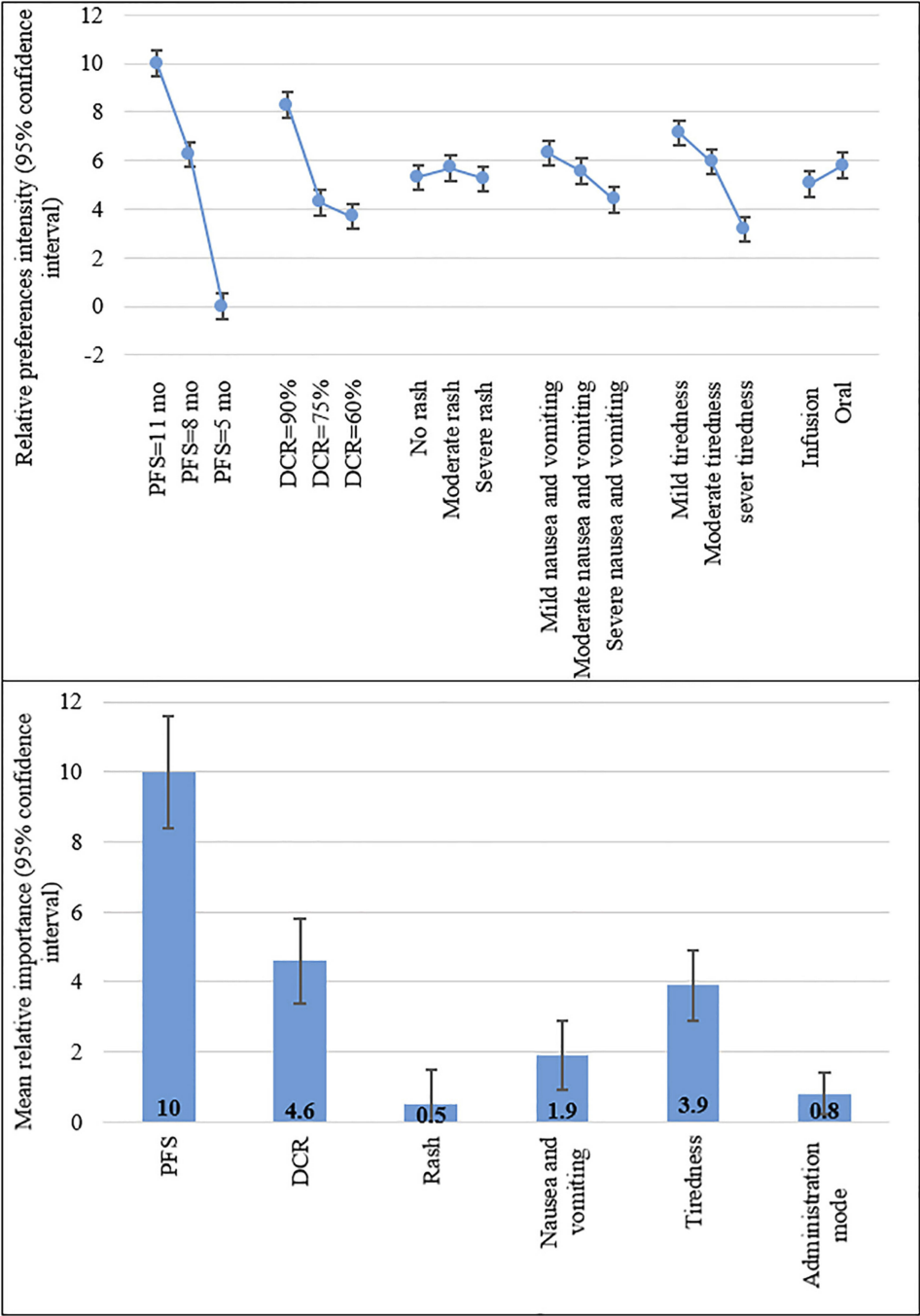


Figure 2 Patient preferences intensity.

month to get mild tiredness. The wide ranges of CIs showed that there were considerable differences in WTP, which proved the existence of preference heterogeneity.

Discussion

In this study with a multicenter sample of patients, we apply a DCE framework to investigate patient preferences for chemotherapy in the treatment of NSCLC. We found that

prolonging progression-free survival, increasing disease control rate and reducing side effects were the primary consideration for NSCLC patients (over the ranges of attributes and levels presented in the survey). Mode of administration and out-of-pocket cost have statistically influence on patient preference. We also estimated interaction terms between patients' sociodemographic characteristics, we found the magnitude of differences in preferences across groups was

Table 4 Variation In Patient Preferences For NSCLC Treatment

Attributes	Coefficient ^a	SE	P Value
Aged 30–40 × 8 month of PFS	0.11	0.08	0.01
Aged 40–69 × None rash	0.10	0.05	0.04
Aged 30–40 × Infusion mode	−0.12	0.06	0.03
Squamous cell carcinoma × None rash	0.13	0.04	0.01
Adenocarcinoma × Mild tiredness	0.21	0.05	0.01
Stage I × 11 month of PFS	−0.23	0.11	0.01
Stage II × 11 month of PFS	−0.12	0.09	0.04
Stage III × 11 month of PFS	0.15	0.07	0.01

Note: ^aCoefficients show estimated utility of each attribute, where positive coefficients indicate positive preference. Positive coefficients for aged 30–40 × <attribute> interaction terms indicate that group aged 30–40 place higher preference on that attribute than other age group.

Abbreviation: SE, standard error.

Table 5 Patients' Marginal WTP For Each Attribute Level

Attributes	WTP ^{a,b} (95% CI), Average \$ Per Month		
	Value	LB	HB
Progression-Free Survival			
11 months	2340	1927	3754
8 months	424	172	675
5 months	−3764	−3193	−2335
Disease Control Rate			
High (90%)	1465	1163	1767
Middle (75%)	−587	−826	−348
Low (60%)	−878	−1183	−573
Rash			
None	−56	−299	186
Moderate	145	−90	381
Severe	−89	−353	175
Nausea and Vomiting			
Mild	452	189	716
Moderate	74	−160	308
Severe	−526	−800	−253
Tiredness			
Mild	879	600	1159
Moderate	269	29	508
Severe	−1148	−1444	−853
Administration Mode			
Infusion	−195	−368	−22
Oral	195	22	368

Notes: ^aWillingness to pay calculations are mean estimates derived from mixed logit model without interactions. ^bNegative values represent the average amount of cost that would have to be decreased for a patient to choose a treatment with that characteristic.

Abbreviations: SE, standard error; WTP, willingness to pay; CI, confidence interval; CN, Chinese yuan.

small. Furthermore, we elicited the extent to which patients were willing to pay for achieving an improvement of efficacy or reduction of potential side effects from the treatment. The result showed that the highest willingness to pay was obtained for 11 months of PFS.

The findings of the current study were consistent with some earlier studies in most countries. Bridges et al³¹ reported that PFS benefit was the most important attribute for patients when considering treatment decisions in the US. In the study of Muhlbacher et al³² in Germany, they found patients had clear preferences for an increase in “progression-free survival,” and “oral administration” preferred to “infusion.” Studies conducted in the US,³⁰ Canada^{50,51} and Japan^{29,52} revealed that most cancer patients (>50%) judged moderate survival benefits sufficient to make chemotherapy worthwhile. In contrast to the study in the Germany, which ranks “tumor-associated symptoms” in the first place of all included side effects,²⁹ the patients in the present study assessed the “tiredness” as the most important side effect in their treatment decision. A possible explanation might be that patient are severely affected by “tiredness” in their daily life and possibly with a reduction in their quality of life. However, through literature reviews in selected Chinese and English databases, no studies have been found in relation to patients' risk-benefit preferences for NSCLC chemotherapy in China, this study could add informative and applied data to this field.

More analysis could be needed to further understand patient' WTP for the treatment outcomes. First, the cost input in this study was determined by literature and calibrated by patients focus group, more sensitivity analysis was needed to validate the WTP value. Second, the estimated WTP did not consider the absence or presence of side effects and risk of drugs abuse that may have impacts on WTP estimation, further research is needed to investigate these potential factors that may have impacts on WTP.

Some limitations should be noted in this study. Firstly, potential selection bias might exist among patients, because the participants were healthy enough to complete the survey. Secondly, although we identified seven key attributes with different levels patient concerned most, the limited number of attributes and levels presented may not reflect the patient treatment decision in real world. However, the attributes used in this study were similar to those used in other studies on patient preferences towards NSCLC chemotherapy,^{29,31,32} incorporating more attributes and levels could increase respondents burden, which could not benefit in DCEs study. Finally, the DCEs survey was conducted at regional large-scale tertiary

hospitals in China. Thus, the patients' relative preferences for NSCLC chemotherapy and their WTP for treatment outcome may not be generalizable to other countries.

Conclusion

The current study is the first attempt to examine patient preferences for NSCLC chemotherapy in China. The findings from this study have provided some useful insight into understanding patients' relative preferences for NSCLC chemotherapy and the willingness to pay they make for achieving a single treatment outcome, which can further help to inform the clinical decision-making and promote patient-centered care.

Acknowledgments

The study was funded by China Medical Board Health Technology Assessment Collaborating Program (Grant No.16-251). We would like to thank all the staff involved in the field survey for their excellent research assistance.

Disclosure

The authors declare no conflicts of interest in this work.

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