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Physician preferences for chemotherapy in the treatment of non-small cell lung cancer in China: evidence from multicentre discrete choice experiments

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ABSTRACT

Objective To evaluate physician risk-benefit preferences and trade-offs when making chemotherapy decisions for patients with non-small cell lung cancer (NSCLC).

Design A discrete choice experiment (DCE).

Settings Tertiary hospitals in Beijing, Shanghai, Guangzhou and Chengdu of China.

Participants The participants were 184 physicians (mean age of 37 years) with more than 1 year of NSCLC chemotherapy practice.

Outcomes The DCE survey was constructed by six attributes: progression-free survival (PFS), disease control rate (DCR), risk of moderate side effects, risk of severe side effects, mode of administration and out-of-pocket costs. Physicians' relative preferences and trade-offs in patient out-of-pocket costs for each attribute level were estimated using a mixed logit model, and interaction terms were added to the model to assess preferences variation among physicians with different sociodemographic factors.

Results Physicians had the strongest preferences for improvements in PFS, followed by reducing the risk of severe side effects. The DCR, risk of moderate side effects and mode of administration were ranked in decreasing order of importance. There was little variation in preferences among physicians with different sociodemographic characteristics. Physicians were willing to trade $4814 (95% CI $4149 to $5480) of patient out-of-pocket costs per month for a chemotherapy that guaranteed 11 months of PFS, followed by $1908 (95% CI $1227 to $2539) for reducing the risk of severe side effects to 2%.

Conclusions With regard to chemotherapy for patients with NSCLC, prolonging PFS, reducing severe and moderate side effects were primary considerations for physicians in China. The mode of administration and treatment costs significantly influenced physicians' therapeutic decision. The current findings could add some evidence to inform NSCLC chemotherapy implementation and promote shared decision-making.

Strengths and limitations of this study

- Our study is the first to quantify physician preferences for non-small cell lung cancer chemotherapy in China, which can add informative and applied data to this field.
- We applied the discrete choice experiment which allows to simultaneously analyse the relative importance of multiple factors on medical decision-making.
- Generalisability may be limited as we only sampled tertiary hospitals.
- The six key attributes in this study may not fully reflect physician treatment decision in the real world.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer and is also the most common cause of cancer-related mortality in China.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of primary lung cancer.[2] Its disease burden on society is also significant. According to the Surveillance, Epidemiology and End Results registry in the USA, the incidence of NSCLC is 42.6 per 100 000 population.[3] In China, the age-adjusted incidence of NSCLC in 2013 was 39.05 per 100 000 people, and its incidence has continued to increase.[4]

The treatment of NSCLC is guided by disease stage. In general, surgery is the first choice for early-stage NSCLC, whereas multimodality therapy, including chemotherapy, radiotherapy, molecular targeted therapies, and so on, remains the norm for patients with advanced NSCLC.[5–7] Adjuvant chemotherapy is recommended in most clinical guidelines for patients with NSCLC with stage II and III diseases.[8] Based on various studies, doublet regimens combining cisplatin or carboplatin with vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed are administered.[7] The choice of combination drugs varies in different countries, in China, cisplatin and vinorelbine are preferred.[8] Cytotoxic chemotherapy treatments, however, are commonly associated with evident side effects. In contrast, molecular targeted therapies, such as epidermal growth factor receptor tyrosine

kinase inhibitors (EGFR-TKI) and anaplastic lymphoma kinase (ALK) inhibitors, are characterised to be more tumour specific in efficacy and have fewer toxicities.[9–11] In China, gefitinib and crizotinib represent the first-choice EGFR-TKI and ALK inhibitor, respectively.[8]

Different chemotherapy regimens offer different clinical outcomes in terms of efficacy, potential risks, dosing options and administration modes, with different expenditures for patients as well. Therefore, from physicians' perspectives, regimen selection of NSCLC chemotherapy involves trade-offs among the benefits, potential risks and convenience of the treatment. Although guidelines recommend that regimens should be chosen based on efficacy and tolerability criteria, other factors, including optimisation of adherence, monitoring of adverse side effects and in patient out-of-pocket costs, may also influence the physicians' therapeutic decision-making in the context of increasing physician–patient interaction.[12]

However, no previous studies have investigated the physician risk-benefit preferences and trade-offs when making chemotherapy decisions for patients with NSCLC in China. Most discrete choice experiment (DCE) studies were conducted from patients' perspectives to understand their treatment preferences.[13–18] The objective of this study is to evaluate physicians' risk-benefit preferences and trade-offs when making chemotherapy decisions for patients with NSCLC.

2. METHODS

2.1 Study population

From 30 September 2017 to 31 December 2017, multicentre face-to-face surveys with physicians were conducted at four tertiary hospitals, namely from Beijing, Shanghai, Guangzhou and Chengdu, China.

We aimed to recruit 200 respondents (50 from each hospital) in the survey. The inclusion criteria were as follows: (1) physician from an oncology, respiratory or thoracic surgery department; and (2) more than 1 year of NSCLC chemotherapy practice. The final sample in our study included 184 physicians in our study. Earlier studies have shown that this number of respondents is sufficiently large for reliable statistical analyses.[19 20]

Copies of written informed consent were provided to participants on recruitment. All eligible participants were informed about the purpose of the study and their right to refuse.

2.2 The DCE questionnaire

DCEs have been extensively used to assess individuals' preferences and risk-benefit trade-offs of healthcare intervention in healthcare.[21–24] In DCEs, a sequence of hypothetical scenarios (choice sets) consisting of defined attributes with different levels is presented to respondents. For each choice set, respondents are asked to choose their preferred scenario between two or more options. Thus, the relative importance and of the given attributes can be determined and the trade-offs that respondents make can be quantified.

Table 1 Attributes and their levels

Attributes	Levels	
Progression-free survival	High	11 months
	Medium	8 months
	Low*	5 months
Disease control rate	High	90%
	Medium	75%
	Low*	60%
Risk of moderate side effects	High	50%
	Medium	25%
	Low*	10%
Risk of severe side effects	High	8%
	Medium	5%
	Low*	2%
Cost	High	CN¥50 000/month
	Medium	CN¥25 000/month
	Low*	CN¥10 000/month
Mode of administration	Infusion	
	Oral*	

*Reference level.

There are several checklists available for the design of DCE studies.[21 24–27]

2.3 Selection of attributes and their levels

Three criteria were considered when we selected attributes: relevance to physicians' choice of NSCLC chemotherapy treatment, ease of quantifying the attribute within a DCE framework and overlap or correlation with other attributes.

Based on a critical literature review,[12–14 18 28 29] consultation with oncology experts and reference to selection criteria above, we ultimately identified six attributes: progression-free survival (PFS), disease control rate (DCR), risk of moderate side effects (levels I and II), risk of severe side effects (levels III and IV), administration mode and out-of-pocket costs to patients. We included out-of-pocket costs as a value attribute to explore physician trade-off in patient out-of-pocket costs. Each of these attributes was then assigned two or three levels (table 1). For this study, the levels of PFS and DCR were based on evidence from clinical trials or real-world data.[30–33] Levels of risk of moderate side effects, levels of risk of severe side effects and levels of out-of-pocket costs were identified by published literature and calibrated by physicians.[34 35]

2.4 Construction of the DCE questionnaire

The combination of these attributes and levels (five attributes with three levels, one attribute with two levels) resulted in 486 hypothetical scenarios (3^5*2^1), which obviously could not be used in a questionnaire. Therefore, we applied fractional factorial design (SAS (version 9.4) OPTEX procedure) to generate optimal scenarios in this study.[36–38] The resulting experimental design consisted

Attributes	Regimen A	Regimen B
Time without tumour progression	5 months	8 months
Disease control rate	90%	60%
Risk of moderate side effects during treatment	25%	50%
Risk of severe side effects during treatment	2%	5%
Treatment cost	CN￥10,000/month	CN￥50,000/month
Mode of administration	Infusion	Oral
Which regimen do you prefer to take? Select the box to show your choice	□	□

Figure 1 Sample of discrete choice experiment (DCE) survey question.

of 16 choice sets. Each respondent answered 16 trade-off questions (see figure 1 for a DCE survey example). No opt-out option was included.

In addition to DCE questions, the survey instrument included questions on physicians' demographic characteristics (eg, gender, age, education level and area of expertise), NSCLC treatment experience (eg, years of NSCLC chemotherapy practice) and an open-ended question for other factors influencing physicians' chemotherapy decision-making for NSCLC. We also conducted a pilot test on a focus group of physicians to ensure the understandability of the DCE questionnaire before implementing the study.

2.5 Data analysis

A mixed logit model was used to estimate the relative importance of the different levels of attributes. The coefficients from the mixed logit model represented estimates of the probability of choosing a chemotherapy for NSCLC treatment.[24 39] Effects coding was applied to represent a categorical variable in the mixed logit model to ensure that all attribute levels can be estimated including the inference level.[40]

For this study, we first estimated the main effects of the mixed logit model, and then estimated models with interaction terms to assess potential differences in preferences across groups with different sociodemographic characteristics including physician age, area of specialty and years of treatment of NSCLC. All analyses were performed using Stata statistical software (V.14 SE, StataCorp).

2.6 Patient and public involvement

The aim of our study was to evaluate physician preferences for NSCLC chemotherapy. The research question and outcome measure were not informed by patients' priorities, experience and preferences. The data used were from surveys on physicians; therefore, patients were not involved in the design or the conduct of the study.

3. RESULTS

3.1 Study participants

Among the 184 physicians who completed the survey, 49 were in Beijing, 48 were in Shanghai, 42 were in Guangdong and 45 were in Chengdu. The sociodemographic characteristics of the participating physicians are summarised in table 2. In our sample of the 184 physicians, 113 were women (61%), and 159 received a master's degree or above (86%). The mean age of the respondents was 37 years, spanning a range of 24–67 years. Most physicians were from the oncology department (73%) and had more than 5 years of experience of treating NSCLC (63%).

Table 2 Sociodemographic characteristics

Characteristics	Subjects n=184
Gender, n (%)	
Male	71 (38.6)
Female	113 (61.4)
Age (years)	
Mean	36
Range	24–67
Education, n (%)	
Bachelor's degree	25 (14)
Master's degree and above	159 (86)
Clinical departments, n (%)	
Oncology	134 (73)
Respiratory	30 (16)
Thoracic surgery	20 (11)
Years for NSCLC chemotherapy practice	
Less than 5 years	68 (37)
5–10 years	69 (38)
10–20 years	37 (20)
More than 10 years	10 (5)
Professional title, n (%)	
Resident physician	49 (27)
Attending doctor	84 (46)
Deputy chief physician	33 (17)
Chief physician	12 (7)
No title	6 (3)

NSCLC, non-small cell lung cancer.

Table 3 Physician preferences for treatment of NSCLC: main effects of mixed logit model results

Attributes	Coefficient*	SE	P value	95% CI LB	95% CI UB	Z
Progression-free survival						
11 months	1.283	0.090	<0.001	1.105	1.460	14.18
8 months	−0.061	0.045	0.175	−0.150	0.027	−1.36
5 months	−1.222	0.090	<0.001	−1.397	−1.046	−13.63
Disease control rate						
High (90%)	0.371	0.051	<0.001	0.271	0.472	7.25
Middle (75%)	−0.010	0.044	0.829	−0.096	0.077	−0.22
Low (60%)	−0.362	0.055	<0.001	−0.469	−0.255	−6.64
Risk of moderate side effects						
High (50%)	−0.336	0.078	<0.001	−0.490	−0.183	−4.30
Middle (25%)	−0.100	0.136	0.463	−0.367	0.167	−0.73
Low (10%)	0.436	0.085	<0.001	0.270	0.602	5.15
Risk of severe side effects						
High (8%)	−0.131	0.089	0.141	−0.305	0.043	−1.47
Middle (5%)	−0.378	0.136	0.005	−0.644	−0.112	−2.78
Low (2%)	0.508	0.086	<0.001	0.340	0.677	5.93
Administration mode						
Infusion	−0.109	0.030	<0.001	−0.168	−0.050	−3.63
Oral	0.109	0.030	<0.001	0.050	0.168	3.63
Cost	−0.039	0.003	<0.001	−0.045	−0.033	−11.99

*Coefficients represent the change in utility for a respondent for a specific level of a given attribute.
LB, low bound; NSCLC, non-small cell lung cancer; UB, upper bound.

3.2 Physician preferences for treatment of NSCLC

Statistical analyses of physician preferences

The main effects of the mixed logit model results are displayed in table 3. The cost variable was modelled as continuous variables, and the other five variables were modelled as categorical variables. For this study, the coefficients were significant ($p<0.05$) for nearly all attributes, which means the attributes were relevant to physician therapeutic decision-making.

In details, physicians had aggressive preferences for better efficacy and tolerability control when performing NSCLC chemotherapy. Specifically, they had strong positive preferences for gaining a longer PFS (11 months), higher DCR (90%) and lower risk of moderate or severe side effects. Physicians reported a negative preference for a shorter PFS (5 or 8 months), lower DCR (60% or 75%), higher risk of moderate side effects (25% or 50%) and higher risk of severe side effects (5% or 8%). Oral administration was preferred to infusion.

Relative preferences for attributes and their levels

The relative preferences intensity results are illustrated in figure 2, with 10 representing the most preferred attributes and 0 representing the least preferred attributes. The vertical bars around each level mean estimate denoted the 95% CI of the point estimate. In relation to the level of the other attributes, the physicians' strongest positive preference was to prolong PFS by 11 months (coefficient 1.283 (SE 0.090); $p<0.001$), followed by a reduction in the risk of severe side effects to 2% (coefficient 0.508 (SE

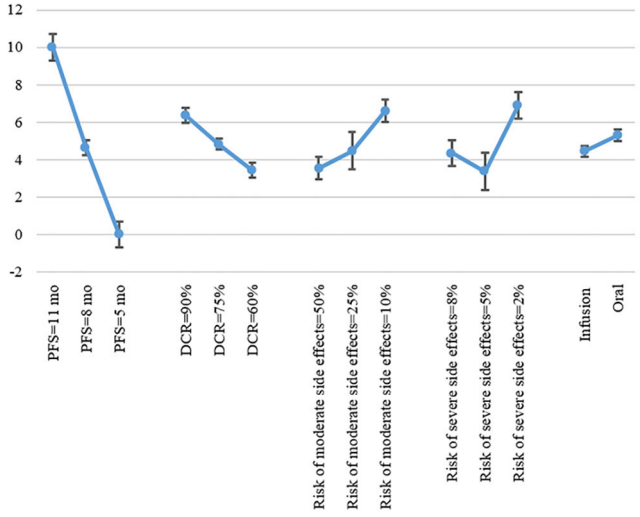

Figure 2 Physician preferences intensity. DCR, disease control rate; PFS, progression-free survival.

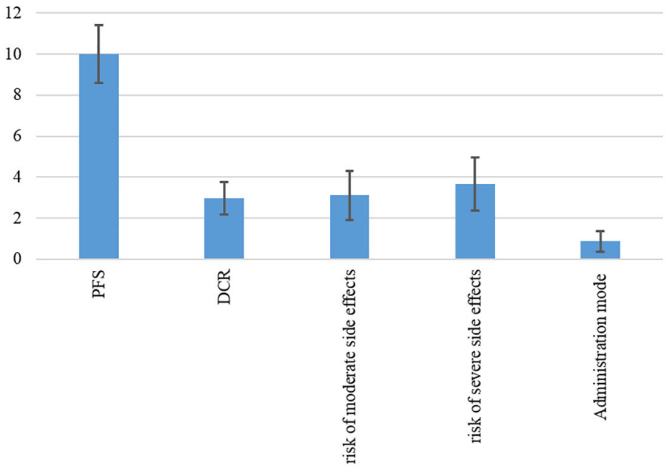

Figure 3 Mean relative preferences intensity. DCR, disease control rate; PFS, progression-free survival.

0.086); p<0.001). They also had stronger preferences for a 90% of DCR (coefficient 0.508 (SE 0.086); p<0.001), and controlling the risk of moderate side effects was also important to physician treatment decisions, such as a 10% risk of moderate side effects (coefficient 0.436 (SE 0.085); p<0.001).

Figure 3 illustrates the mean relative preference intensity with a 95% CI. The mean relative preferences for each attribute were estimated as an improvement from the worst level to the best level (over the ranges presented in this study). In this study, having an improvement in PFS from 5 to 11 months was the most important (10.0; 95% CI 8.6 to 11.4), followed by a reduction of improvement for 6% (from 8% to 2%) in the risk of severe side effects (3.7; 95% CI 2.3 to 5.0). Next were the risk of moderate side effects (3.1; 95% CI 1.9 to 4.3), DCR (3.0; 95% CI 2.2 to 3.8) and mode of administration (0.9; 95% CI 0.4 to 1.4).

Variation in physician preferences for treatment of NSCLC

We estimated the interaction terms between physicians' sociodemographic characteristics (eg, age, specialty and NSCLC treatment years) and preference for different levels of chemotherapy attributes, and we found that there was little significant variation (results are available on request).

Younger physicians had a stronger preference for the DCR than did older physicians. Respiratory physicians tended to favour moderate disease PFS. Physicians with less than 5 years of NSCLC chemotherapy practice had weaker preferences for 90% DCR. Despite being statistically significant, the magnitude of differences in preferences across groups was small.

Physician trade-offs of patient out-of-pocket costs

Based on the stated preference DCE, our study found that physicians were willing to trade \$4814 (95% CI \$4149 to \$5480) of monthly patient out-of-pocket costs for a chemotherapy that guaranteed 11 months of PFS, followed by \$1908 (95% CI \$1227 to \$2539) for reducing the risk of severe side effects to 2% (table 4). The value for 90% DCR was \$1394 (95% CI \$1017 to \$1771) and the value for 10% risk of moderate side effects was \$1637 (95% CI \$1014 to \$2259). Physicians preferred oral administration and the reported value was \$410 (95% CI \$188 to \$631).

Table 4 Physician trade-offs of patient out-of-pocket costs

	WTP*† (95% CI), average $ per month		
Attributes	**Value**	**LB**	**HB**
Progression-free survival			
11 months	4814	4149	5480
8 months	−230	−561	102
5 months	−4585	−5244	−3925
Disease control rate			
High (90%)	1394	1017	1771
Middle (75%)	−36	−361	289
Low (60%)	−1358	−1760	−957
Risk of moderate side effects			
High (50%)	−1262	−1837	−686
Middle (25%)	−375	−1377	626
Low (10%)	1637	1014	2259
Risk of severe side effects			
High (8%)	−490	−1143	163
Middle (5%)	−1418	−2417	−419
Low (2%)	1908	1277	2539
Administration mode			
Infusion	−410	−631	−188
Oral	410	188	631

*Willingness-to-pay calculations are mean estimates derived from mixed logit model without interactions.
†Negative values represent the average amount of cost that would have to be decreased for a physician to choose a treatment with that characteristic.
HB, high bound; LB, low bound; WTP, willingness to pay.

Other factors influencing physicians' chemotherapy decision-making

All of the respondents answered an open-ended questionnaire. The results showed that, in addition to the factors included in the DCE questionnaires, patient factors (such as preference, age, adherence and performance status), disease prognosis, complexity of treatment protocols and recommended guidelines had an impact on physicians' NSCLC therapeutic decision-making.

4. DISCUSSION

In the current study, we applied a multicentre DCE to investigate physicians' risk-benefit preferences and trade-offs when making chemotherapy decisions for patients with NSCLC. To our knowledge, this is the first study to evaluate risk-benefit preferences and trade-offs in NSCLC chemotherapy from physicians' perspectives in China. We

found that prolonging PFS and reducing side effects were the primary considerations for physicians, while improvement in DCR, mode of administration and out-of-pocket costs had a statistically significant influence on physicians' choice. The strength of these preferences was similar among physicians with different sociodemographic characteristics. Furthermore, we investigated the extent to which physicians were willing to trade-off in patient out-of-pocket costs for an improvement in efficacy or reduction in potential side effects from the chemotherapy, and the results showed that the highest trade-off was obtained for 11 months of PFS, followed by a reduction in the risk of severe side effects to 2%.

The findings of this study were consistent with those of some earlier studies. Benjamin *et al*[12] reported that both therapeutic efficacy and economic considerations play significant roles in physicians' prescription of anticancer drugs. Ettinger *et al*[29] found that physicians are concerned more about patient symptom management when prescribing chemotherapy regimens. In the study of Blinman *et al*,[41] most doctors judged moderate survival benefits sufficient to make adjuvant chemotherapy worthwhile in NSCLC. Similarly, McMullen *et al* and Bridges *et al* reported that estimating the benefits versus the risks of therapies is critically needed when making treatment decisions for patients with NSCLC.[28 42]

The implementation of NSCLC therapy aims to prolong the survival time, control tumour-related symptoms and improve patients' quality of life.[43] In the current study, we found that there is little variation in the preferences of physicians with different sociodemographic characteristics, which revealed the consistent attitudes of physicians for the goal of cancer treatment. Studies conducted by Kearney *et al* and Woodmass *et al* also reported the similar attitudes of physicians for cancer treatment.[44 45] However, implementation of interventions designed to improve the quality of medical care often proceeded differently from what was planned, and a large gap was observed between actual practice and clinical practice guidelines in quality of care for NSCLC.[46 47] For example, Potosky *et al* and Younis *et al* reported that many patients with early-stage NSCLC did not receive any surgeries or adjuvant chemotherapies, which is explicitly suggested by most guidelines of NSCLC.[48 49] Physicians were the main source of information about therapy options and were almost always strongly involved in the decision-making process.[42] Therefore, the opinions, judgements and prejudices of physicians often determine which treatment is provided.

Clinical decision-making for NSCLC is complex and difficult in the real-world context. First, patient age has a significant impact on physicians' treatment decision-making process. Older patients with NSCLC are less likely to receive guideline-recommended treatment at diagnosis, independent of comorbidity.[50 51] Second, the patients' general condition should be considered. Physicians used the Fried Frailty Index to characterise frailty before treatment and to help guide treatment decisions.[52] In addition, comorbidity commonly exists among patients with lung cancer, so comorbidity assessment should be included in protocols studying locally advanced-stage NSCLC.[53] Since chemotherapeutic treatment was mostly decided by the physicians, it is important to evaluate their preferences and biases, in order to improve the eligibility and desirability of patients.

The results of physician trade-offs in patient out-of-pocket costs were higher than the real-world NSCLC treatment costs. For example, some Chinese researchers reported that patient expenditures for NSCLC therapy (chemotherapy and target drugs included) per cycle ranged from $731 to $2924.[54–56] Additionally, in Italy,[57] the monthly costs per patient with NSCLC ranged from €1471 to €1788. Thus, more analyses could be needed to further understand physician trade-offs in patient out-of-pocket costs. Because cost input was determined by the literature and a physician focus group, further sensitivity analysis is needed. Moreover, the estimated trade-off value did not consider side effects and patient adherence, which may have impacts on trade-off estimation, so further research should include these potential factors.

Some limitations should also be noted in this study. First, the samples were all from tertiary hospitals in China and lacked data from primary and secondary hospitals. Second, since clinical decision-making for NSCLC is complex, the six key attributes, which are also used in previous studies,[12 29] may not comprehensively reflect the physician treatment decision in the real world. Finally, the DCE survey was conducted in China, and the results may not be representative for other countries.

5. CONCLUSION

Our study is the first attempt to examine physician preferences for NSCLC chemotherapy in China. Our results highlighted the relative importance of NSCLC chemotherapy and physician willingness to trade patient out-of-pocket costs for each attribute level. The findings of the current study added evidence to inform NSCLC chemotherapy implementation and promote patient-centred care.

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