A systematic review of health economic evaluation of targeted therapies for first-line treatment of metastatic non-small cell lung cancer (NSCLC): Quality evaluation

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Abstract

Backgroud: Evolving practice in non-small cell lung cancer (NSCLC) therapy inevitably impacts health care budgets, especially the introduction of targeted therapies. This results in a rise of health economic evaluations (HEEs) in this domain. The objective of this article is to review the quality of the economic evidence of targeted therapies in metastatic NSCLC.

Methods: A literature search using Pubmed, Cochrane, Embase and CRD (University of York Centre for Reviews and Dissemination) database was conducted to identify original articles published between 1/1/2000 and 31/3/2019. A quality of reporting assessment using CHEERS (Consolidated Health Economic Evaluation Reporting Standards statement) was translated into a quantitative score and compared with QHES (Quality of Health Economic Studies) evaluation.

Results: Twenty-one HEEs were analyzed. In CHEERS assessment, method description integrity (including setting, perspective, time horizon and discount rate), justification of data sources and heterogeneity description were often absent or incomplete. Only four studies reach the standard of good quality. Modeled articles were mainly evaluated by the QHES instrument, lack of illustrated structure, formula of the transitioning probability and justification for the choice of the model were the most frequent problems in selected studies. After quantification, the CHEERS-scores did not differ significantly from QHES-scores.

Conclusion: The overall quality of HEEs in NSCLC targeted therapies is not high. In addition, further efforts are needed to improve the standardization of the model application and the transparency of data description, which is indispensable for valid decision-making on scarce health care resource allocation.

Introduction

In the clinical therapy for advanced non-small-cell lung cancer (NSCLC), the past two decades brought important treatment change: the use of targeted anti-cancer drugs in the context of inoperable treatment has been established. Since the landmark I-PASS trial has established the role of first-generation Epidermal Growth Factor Receptor tyrosine kinase inhibitors (EGFR-TKIs) as preferred first-line therapy for EGFR mutant tumors, gefitinib and erlotinib gained global approval in this setting, and afatinib has been developed then as another treatment option for first-line therapy in EGFR mutant NSCLC [22]. Lung cancer is the most common cancer and the leading cause of cancer mortality worldwide, accounting for 1.7 million cancer-related deaths each year [23], such evolutions will inherently have an impact on health care budgets.

In addition, ample evidence shows that the cost of cancer is becoming unaffordable in many countries [24]. In the light of the limited nature of health resources, systematic analysis of various medical projects will clearly identify each relevant options. The methodology applied to analyze the inputs and outputs of medical activities as well as to make explicit whether a new intervention or strategy is worthwhile from an economic point of view, can be defined as health economic evaluation (HEE). It is no wonder that the interest in HEE has surged year after year. The identification of various costs and the measurement in

monetary units in most HEEs are similar, but the nature of the results of various alternatives may be quite different, which decides the different techniques of HEEs. In short, cost-effectiveness analysis (CEA) relates a change in costs to the difference in health effects, expressed in natural units such as life years gained (LYG); whereas a cost utility analysis (CUA) express the health effect as quality adjusted life years (QALYs) gained.

Transparency of reporting is an essential factor to evaluate methods, assumption, model and possible bias of HEE results. To address this question, a lot of instruments were developed to evaluate the methodological quality of health economics researches. The 'British Medical Journal', the 'Drummond' and the 'CHEC' checklists are well-known instruments for qualitative evaluation [25–27]. Then the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) issued the Consolidated Health Economic Evaluation Reporting Standards statement (CHEERS), with the objective to guide and further standardize the reporting of economic evaluations [28]. In contrast, the Quality of Health Economic Studies (QHES) is an instrument intended and validated for quantitative scoring [29].

We performed a qualitative and quantitative scoring assessment of HEE publications focusing on non-small-cell lung cancer, undertaken by a systematic literature review. The quality of reporting of the selected studies was appraised using the CHEERS checklist, of which the results were applied as a scoring system compared with the QHES evaluation. This article reports on the results of both instruments evaluation and comparison, and describes remaining shortcomings and methodological questions in the available literature of HEEs in NSCLC targeted therapy.

Methods

Search strategies and study selection

Search strategies were designed for Pubmed, the Cochrane Library, EMBASE and the University of York Centre for Reviews and Dissemination (CRD) Database, published between 1/1/2000 and 31/3/2019, as a consideration of the novelty of the targeted therapies. Search strategies were restricted to publications written in English or Chinese (the first author is a native Chinese speaker). A detailed description included both index terms and free-text words can be found in Additional file1.

Table 1 describes the study selection criteria. After removal of duplicates, titles and abstracts were screened based on presence of both economic aspects and treatment of NSCLC. Final selection required comparison of different analytical strategies in NSCLC, specifying targeted drug cost as a result of real costing exercise. Only original studies published in a full text were included. Conference aticles, reviews and position papers were excluded. The eligibility of the studies for review was assessed independently, any uncertainties were resolved in discussion.

Quality evaluation

The CHEERS checklist is a 24-item checklist, used to optimize and improve reporting quality of health economic evaluations [28]. All 24 items were cheked each article by two reviewers independently (ZJ and LY). In case of disagreement, we reached a consensus through discussion. Furthermore, in order to compare CHEERS results with the qualitative QHES evaluation, we assigned a quantitative score of '1' if the fulfilled the requirement of reporting for that item completely, '0.5' for partial report and '0' for not mentioned [30], equal weights were allocated.

The QHES instrument is a dichotomous scoring system, which was designed to evaluate three common types of health economic analyses: cost-minimization (CMA), cost-effectiveness (CEA), and cost-utility (CUA) [31]. Each study was scored in 16 items, allocating a Yes (fulfilled) or No (not fulfilled) per item, and each score is multiplied by a weight, varying between 1 and 9, to obtain a total score on 100 points [32]. No partial points per item are intended [31]. Also, the QHES evaluation was conducted independently by the same two researchers for addressing interpretational problems.

Resulting scores of the two instruments were then converted into percentages to allow comparison.

Statistical analysis

Instruments were compared using the paired Wilcoxon rank test for continuous variables. The R statistical environment (version 3.5.3, TUNA Team, Tsinghua University, China) was used to develop and solve the comparison. A p-value of <0.05 is considered as statistical significance.

Results

Systematic review

The database search identified 492 publications, yielding 357 after removal of duplicates, 181 after screening titles and abstracts. 21 full text articles were identified that fulfilled the inclusion criteria. The CONSORT diagram is illustrated in Fig. 1.

Detailed characteristics of these 21 publications is summarized in Additional file 2. All selected studies represented a full economic evaluation, examining both costs and effectiveness (CEA) or utilities (CUA). Eighteen out of the 21 publications took variable estimates in the analysis from randomized control trials (RCTs), most were derived from the LUX-Lung 3,6 and 7, OPTIMAL, EURTAC, SATURN, GFPC and BR.21 trials, the other three publications were based on hospital medical records. Nine studies demenstrated specifically the patient population, the study sample size varied from 41 to a cohort of 731 patients.

The majority of articles compared different targeted therapies to chemotherapy (n = 16), being afatinib versus chemotherapy (n = 2) and erlotinib versus chemotherapy/placebo/best surpportive care (BSC) (n = 12), gefitinib versus chemotherapy/routine care (n = 2) in addition. Eight articles evaluated the cost-effectiveness of treatments between the three first line strategies among NSCLC patients harboring EGFR mutations, four of which compared afatinib to gefitinib in three countries, two studies estimated the

economic impact between afatinib and erlotinib in two countries, another two publications addressed the effectinveness and cost-effectiveness of erlotinib versus gefitinib in one country.

CHEERS checklist

The results of the assessment of reporting quality per study is summarized in Table S2.1. Figure 2 shows a visual representation of the fulfilment of the CHEERS criteria and a sorting of completeness of the items. The score on the CHEERS checklist ranged from 12 to 21among the selected studies. According to Hong et al [33], the publications were categorized as being of good reporting quality if they were scored 20–24, and were deemed to be of moderate and low reporting quality if they were scored 14–19.5 and <14, respectively. Only four (19%) studies were of good quality based on the CHEERS checklist, 16 were of moderate quality, and two were of low quality. The quality ranking of these studies were of no relation with publication years.

Treatment comparators were always described in the title, except 5 papers did not describe the interventions compared [15,16,19–21]. In addition, setting, perspective, time horizon and discount rates were not always included; results of uncertainty analyses, choice for health outcomes, findings and conflicts of interest were also not provided in all articles. As most studies were using data from RCTs, characterizing heterogeneity was generally unprovided, only Wang et al [18] reported explicitly by variations between subgroups of patients with different genotype baseline. Although some studies described the base case population, most of them presented no characteristics and the reason they chosen. For measurement and valuation of preference based outcomes, only two papers based on a systematic review [1,14], the others referred to the source of utilities used, without justifying the selection.

Quality evaluation (QHES)

The results of the quality assessment using the QHES instrument are presented in Table S2.2. The table shows how often each criterion was met by the 21 studies. According to Spiegel et al [34], studies are grouped by the following quartiles: (1) extremely poor quality (0–24); (2) poor quality (25–49); (3) fair quality (50–74); and (4) high quality (75–100). Less than half publications (38%) are classified as high quality and 3 studies (14.3%) are of poor quality [1,11,17]. There are five studies presented no economic model used through their manuscript [1,7,11,17,20].

For the rest of CEA/CUAs, ten articles developed a Markov model to compare the cost-effectiveness of first-line targeted therapies and chemotherapy, among them two articles [14,15] created both the Decision tree and the Markov model. While three studies [2,9,16] just use decision tree to estimate the costs and the utilities, the model is displayed in an in-transparent manner by three studies [5,12,13]. For the articles used Markov model, there was no illustrated structure of the model in three studies [6,8,19], and three were showed by the Markov model tree [4,10,21]. Only two studies [4,18] manifested the formula of the transitioning probabilities specifically from each stage to the next, most others usually demonstrated the

rates or the probability which were calculated from clinical trials. No justification for the choice of the model was given by six articles [2,9,12,13,15,19]. We also evaluated the source of utility values that all selected studies extracted, 13 out of 21 papers were obtained from previously published literature, five studies derived utility data from EQ–5D or other quality of life survey [2,3,5,7,16], and three studies used survival data from a single medical institution [9] or clinical trials [12,13]. The effectiveness value was calculated in quality-adjusted life years (QALYs) for fifteen studies, life year (LY) was measured by four studies [12,13,20,21], one article [1] used median survival time (MST) to evaluate the therapeutic effect of the regimens. Statistical pairwise comparison between CHEERS and QHES did not result in significant differences (Fig 3).

Discussion

This review mainly analyses the quality of articles on health economic evaluations (HEEs) of first-line targeting agents (afatinib, gefitinib and erlotinib) in the treatment of patients with metastatic NSCLC. Based on the CHEERS and QHES results, less than one in three studies are of good quality. While for supporting decision-making in healthcare, it is important to ensure the reliability and consistency of pharmacoeconomic evaluation results. Among the different instruments evaluating the quality of HEEs, the CHEERS checklist have been widely used since its publication in 2013, and over 40 review articles in different medical territories checked the adherence of economic evaluations to the CHEERS checklist.

According to Zhang [35], a quality review may serve two basic objectives: it may intend to determine a minimum quality threshold or study design threshold. Furthermore, it may be intended for interpreting the differences in the results of selected studies, indicating the shortcomings and how to improve quality.

In treating non-small cell pulmonary carcinoma, about eight systematic review of HEEs have previously been performed, three of them have been conducted for quality assessment. Bongers et al [36] evaluated the methodological quality of 11 full published studies between 2001 and 2010 by Drummond checklist, consisting assessment of content structure and data identification, but they signaled there was no question that addresses the inclusion of all relevant cost items. Lange et al [37] and Nguyen et al [38] used the QHES instrument to evaluate the quality of the included studies. The scoring method of the two reviews are different: a three-level scale (zero score, full score and half of full score) was modified by Nguyen et al, which only reviewed the economic evaluations of erlotinib in the first-line treatment, while there was no partial points per item with Lang et al and for most quality reviews.

Both the CHEERS and the QHES checklist we utilized for reviewing the 21 studies, and the quality review of the selected publications in our study revealed some common shortcomings.

Studies generally characterized uncertainty about the sampling and the effects on the results, however, the heterogeneity are rarely discussed. As already indicated by many researchers, NSCLC may exhibit substantial heterogeneity, encompassing a spectrum of clinical and physiological manifestations, which may also influence the results. Therefore, heterogeneous groups and report differences in effects should

be considered or explained. In addition, since the limitation of RCT researches, the source from real-world data and large-scale clinical observation trials should be incorporated more into economic evaluations.

Neither scale related to threshold issue, which has been discussed frequently in recent years. In Table S1, a large degree of studies stated the willingness to pay (WTP) threshold, and determinants of threshold were not specified in six articles. There is no uniform criteria of threshold range in each country, except the NICE from the UK and the ICER from the US. Meanwhile, some problems remain unresolved. NICE typically recommends treatment for use in the NHS where their cost-effectiveness threshold range between £20000 and £30000, which has been criticized by some experts that “the threshold is indeed to high”. However, Khan et al [7] reported that erlotinib had about 80% chance of being cost-effective at thresholds between £50000 and £60000, twice as much as NICE threshold. As for ICER (Institude for Clinical and Economic Review), an independent and non-partisan research organization to translate clinical and economic value evidence into policy decisions, defined the US cost-effectiveness threshold between $50000 and $175000 per QALY gained. Although nearly all research papers set their WTP threshold under this range, it does not have the same legal effect as NICE. Like Zhu et al[15] and most other Chinese scholars cited three times the per capita gross domestic product(GDP) as a WTP threshold, experience with the use of such GDP-based thresholds in decision-making processes at country level shows them to lack country specificity and this—in addition to uncertainty in the modelled cost–effectiveness ratios—can lead to the wrong decision on how to spend health-care resources [39]. For these reasons, we consider that it is feasible and probably desirable to operate a threshold range. An elasticity index may suitable for the supply side, and a WTP threshold from the societal perspective may be appropriate for the demand side estimates.

A declaration of funding sources and conflict of interests in the domain of health economics is important to avoid all doubt on bias [40]. Six studies included in our review did not disclose their source of funding, while almost all the studies declared the conflict of interest. This discrepancy may be explained by the presumption that a negative declaration on conflict of interest encompasses both topics [41]. Whereas explicit statements would avoid all doubt.

This study has several limitations. First, the differences in scoring could potentially be related to interpretation of reviewers. Discriminating between partially or fully reported was difficult for some items. Second, the CHEERS checklist accorded an equal weight to each item, one may question if every item is of the same importance, from the title to uncertainty analysis. The application of the QHES instrument is based on observer-dependent which does not permit intermediate scores [42], and intermediate measure values are missing, such a solution results in some important information in practical applications will lose. Consequently, it is arbitrary to carry out quality classification according to Hong et al [33] and Spiegel et al [34]. Third, we allocated a score of 0.5 for partial reporting when using CHEERS checklist and may lead to an upgrade of the overall score of the selected studies; using a dichotomous rating (the QHES checklist) would have decreased the reporting quality likewise. Finally, the validity of the model itself along with the adaptability of the results in the own health economic environment should be considered.

Conclusion

In conclusion, this review found an increasing number of published cost-effectiveness analyses of targeted therapies in the treatment of NSCLC. The overall quality of the literature included is not high. The standardization and refinement of the model application, as well as the consideration and measurement of each parameter need to be improved. Obviously, reliable cost-effectiveness result is essential, especially for its data sources, demographic heterogeneity, sensitivity analysis and threshold selection. Evaluating the relevance, reliability and generalizability of these results is an indispensable support for valid decision-making on scarce health care resource allocation.

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Declarations

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None.

Competing interests

All authors declared no conflict of interest.

Authors' contributions

ZJ: study design, literature search, literature selection, quality assessment of studies, drafting the manuscript. LY: literature search and selection, quality assessment of studies,

reviewing of the manuscript. LJL and MXH: literature search, literature selection, reviewing of the manuscript. LHC and CF: quality assessment, interpretation and reflection, reviewing the manuscript. DSZ and ZXJ: study rationale and design, interpretation and reflection, reviewing of the manuscript.

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Availability of data and materials

Not applicable. Search strategy available in supplement.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Table

Table 1. Paper selection criteria

Population	Studies of participants diagnosed with NSCLC, restricted based on the first-line treatment.
Intervention/Comparison	Studies about treatments with specific targeted agents: afatinib, gefitinib and erlotinib
Outcomes	Costs Clinically relevant outcome measures (QALY or Life year gained)
Study design	Economic evaluations (cost comparison, cost effectiveness, cost utility), health technology assessments

Figures

Fig. 1. Consort diagram

Figure 1

Consort diagram

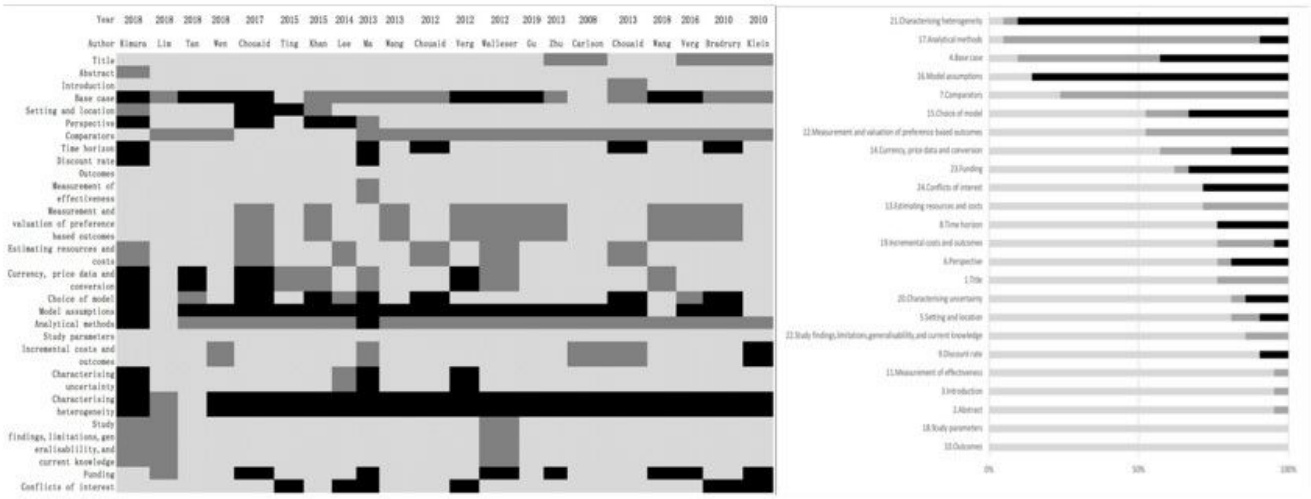

Fig. 2. Overview of evaluation using CHEERS criteria, per article (left) and per item (right)

2a (left): Visual representation of the 24-item CHEERS evaluation applied on the 21 selected studies.

Completely fulfilled Partially reported Not mentioned

(right): Ranking of completeness of sub-items. Same code was applied as in figure 2a.

Figure 2

Fig. 2. Overview of evaluation using CHEERS criteria, per article (left) and per item (right) 2a (left): Visual representation of the 24-item CHEERS evaluation applied on the 21 selected studies. Completely fulfilled Partially reported Not mentioned 2b (right): Ranking of completeness of sub-items. Same code was applied as in figure 2a.

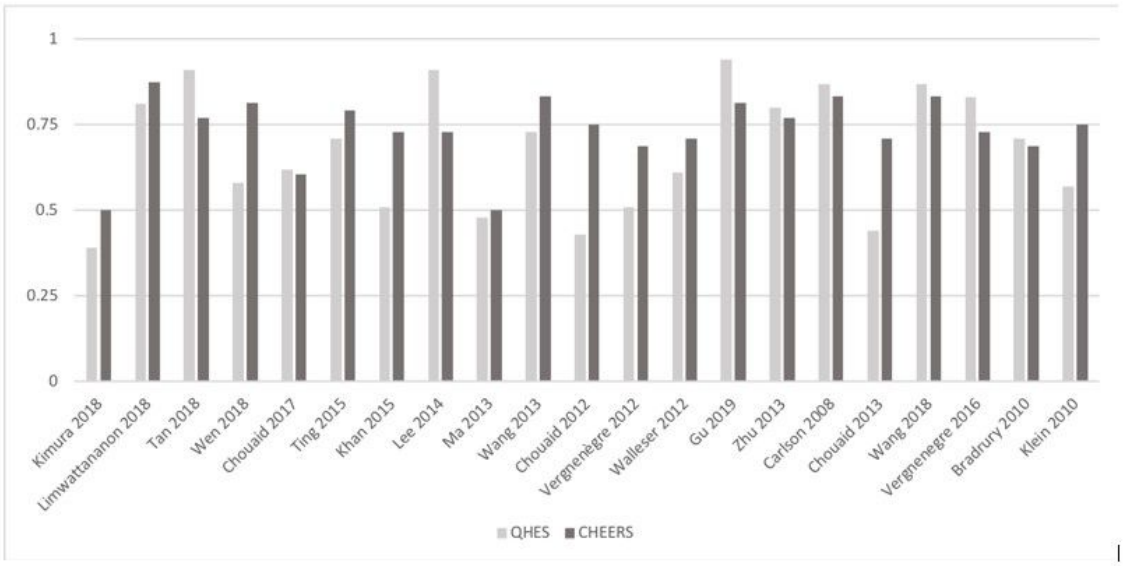

Fig. 3. Comparison of qualitive sores for CHEERS and QHES

Statistical comparison (paired Wilcoxon rank test) of CHEERS with QHES scores did not result in a significant difference between instruments (CHEERS vs. QHES: p=0.14). Scores per article are illustrated in percentages to allow comparison. Light grey=CHEERS, dark grey=QHES.

Figure 3

Comparison of qualitive sores for CHEERS and QHES Statistical comparison (paired Wilcoxon rank test) of CHEERS with QHES scores did not result in a significant difference between instruments (CHEERS vs. QHES: p=0.14). Scores per article are illustrated in percentages to allow comparison. Light grey=CHEERS, dark grey=QHES.

Supplementary Files

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

- Additionalfile2.docx
- Additionalfile3.docx
- Additionalfile1.docx