Lung Cancer 120 (2018) 91–97

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Cost-effectiveness analysis of policy options on first-line treatments for advanced, non-small cell lung cancer in Thailand

Chulaporn Limwattananon[a,*], Supon Limwattananon[b], Onanong Waleekhachonloet[c], Thananan Rattanachotphanit[c]

[a] Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, 40002, Thailand
[b] Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand
[c] Department of Clinical Pharmacy, Faculty of Pharmacy, Mahasarakham University, Thailand

ARTICLE INFO

Keywords:
Cost-effectiveness
Non-small cell lung cancer
Tyrosine kinase inhibitor

ABSTRACT

Objectives: Tyrosine kinase inhibitors (TKIs) have shown to be better for progression-free survival than chemotherapy as the first-line treatment for advanced, non-small cell lung cancer (NSCLC), especially in patients with epidermal growth factor receptor mutation (EGFR M+). This study evaluates under the Thai health system context, cost-effectiveness of (A) the use of platinum doublets for all without EGFR testing, and (B) an EGFR test followed by TKIs or platinum doublets conditional on test results.

Materials and methods: A decision analysis model was constructed to estimate quality-adjusted life years (QALYs) and total cost for each option. Cancer progression and death were pooled from randomized, controlled trials. Quality of life was obtained from patient interview, using the European Quality-of-Life, 5-Dimension questionnaire. Costs associated with treatment outcomes were derived from patient chart reviews.

Results: Combining the EGFR test with each TKI, gefitinib, erlotinib and afatinib if M+ or otherwise platinum doublets, resulted in higher effectiveness than the use of platinum doublets for all by 0.15, 0.19 and 0.21 QALYs, respectively. Among the three TKIs, gefitinib was dominated economically by erlotinib, which incurred an incremental cost-effectiveness ratio (ICER) of $46,783/QALY over the platinum doublets for all. Moving to the next best, afatinib resulted in the ICER of $198,961/QALY over erlotinib. Probabilities for any TKIs being cost-effective when compared with platinum doublets over a wide range of willingness to pay were modest.

Conclusion: In Thailand, the first-line treatment for advanced NSCLC with TKIs conditional on EGFR test results was not cost-effective as compared with platinum doublets for all.

1. Introduction

Lung cancer, the second- and fifth-ranking solid tumor among male and female populations in Thailand has a global age-standardized rate of 22.7 and 10.1 per 100,000, respectively [1]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases and is mostly diagnosed beyond early stages [2,3]. Tyrosine kinase inhibitors (TKIs), novel chemicals, target the human epidermal growth factor receptor (EGFR) and patients who have EGFR mutation (M+) tend to have a better prognosis, and respond well to the TKIs [4–6]. Certain practice guidelines recommend the EGFR testing before starting the first-line treatments [7,8]. The National Institute for Health and Care Excellence in the UK and the European Society for Medical Oncology recommend TKIs as the first-line monotherapy for patients with metastasis NSCLC who had EGFR M+ [9,10].

Initial phase-III randomized, controlled trials (RCTs) in treatment-naïve patients with EGFR M+ or M− have revealed better clinical and quality-of-life outcomes for monotherapy with the first two TKIs, gefitinib and erlotinib, than for platinum-based chemotherapy in combination with cytotoxic drugs [11–14]. Findings among the M− subgroup in those trials, however, favored the platinum doublets on both progression-free survival (PFS) and overall survival (OS) endpoints.

Abbreviations: AUC, area under the curve; CE, cost effectiveness; CEAC, cost-effectiveness acceptability curve; CI, confidence interval; DMSIC, Drug and Medical Supply Information Center; DRG, diagnosis-related group; DSA, deterministic sensitivity analysis; EGFR, epidermal growth factor receptor; EQ5D, European Quality-of-Life 5-Dimension; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IP, inpatient; LY, life year; M−, mutation negative; M+, mutation positive; MST, median survival time; NLEM, National List of Essential Medicines; NMA, network meta-analysis; NMB, net monetary benefit; NSCLC, non-small cell lung cancer; OP, outpatient; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; UCS, Universal Coverage Scheme; WTP, willingness to pay

* Corresponding author.
E-mail address: limw0002@kku.ac.th (C. Limwattananon).

https://doi.org/10.1016/j.lungcan.2018.04.003
Received 25 January 2018; Received in revised form 4 March 2018; Accepted 3 April 2018

Follow-on RCTs of first-line gefitinib and erlotinib plus afatinib, the third TKI, have been conducted in selective patients with EGFR M+ and mainly in Asia [15–23]. In these trials, all TKIs contributed a longer PFS than the first-line platinum doublets. A recent meta-analysis of those 10 RCTs confirmed a significantly higher efficacy of the first-line TKIs on PFS but not OS, when compared with the platinum doublets [24]. A very recent, phase-IIb RCT comparing afatinib with gefitinib found a better outcome of the former than the latter on PFS, however, a trend for benefit in OS was statistically nonsignificant [25].

In Thailand, none of the three TKIs are included in the National Lists of Essential Medicines (NLEM), the national formulary guiding medical reimbursement for health insurance. Instead, platinum-based chemotherapy (carboplatin and cisplatin) and cytotoxic drugs (paclitaxel, gemcitabine, etoposide and docetaxel) are included in the current NLEM [26]. Due to prohibitive costs, neither TKIs nor EGFR tests are at present reimbursable by the Universal Coverage Scheme (UCS), the largest public insurance scheme that covers 73% of the 67 million Thai population. For drugs to be included in the NLEM they must meet this cost-effectiveness (CE) criterion: the total cost incurred per one year gained with full quality of life should not exceed 160,000 Baht (approximately $4500), which is Thailand's Gross National Income per capita.

Previous studies in patients with EGFR M+ reported a wide CE range of TKIs when compared with chemotherapy; cost-saving (lower cost with higher effectiveness), higher in both cost and effectiveness by varying degrees, and higher cost with lower effectiveness [27–30]. The present study evaluated cost and effectiveness of two distinct policies towards use of first-line treatments for advanced NSCLC. One is in accordance with the UCS benefits at present, platinum doublets without a prior EGFR test. The alternative is the EGFR test followed by TKIs or platinum doublets after a known test result on gene mutation. Information on additional costs incurred by TKIs per effectiveness gained could shed light on policy decision towards an inclusion of the drugs into the NLEM for insurance reimbursement.

2. Materials and methods

2.1. Target population and interventions

The target population was defined as patients with stage IIIB/IV, advanced NSCLC, who previously had neither chemotherapy nor TKIs. A hypothetical, 60–65 year old elderly cohort, similar to those enrolled in the TKI RCTs, was followed for 5 years. The study interventions composed of two treatment options. The first option consisted of the *status quo* – first-line treatment by platinum doublets for mixed M+/M− patients without the EGFR test. The option of interest was the use of EGFR test, followed by the first-line treatments conditional on known test results, including daily treatment with gefitinib, erlotinib, or afatinib if the test shown M+ and otherwise platinum doublets if the test shown M−. Use of TKI for known M− was not considered since evidence from the RCTs revealed worse PFS and OS than platinum doublets [11–14]. Certain fractions of patients who failed to respond to TKI therapy were allowed to switch to platinum doublets, but not *vice versa*. In both options, fractions of failure to the platinum doublets were followed by the second- or third-line docetaxel.

2.2. Models

A decision tree for the two combined test-treatment options: (A) no EGFR test but platinum doublets and possibility (+/−) of docetaxel for all and unknown M+/M− mix; and (B) EGFR test followed by known M− with platinum doublets +/− docetaxel and by known M+ with each TKI with possibility of switching to platinum doublets +/− docetaxel was illustrated in Fig. 1A. For the sake of simplicity, the no-test option (A) was called "Platin M+/M−", whereas the second option (B) was called "TKI M+/Platin M−".

A Markov model was constructed for further outcomes of the combined treatments and possible gene mutation: (1) platinum doublets in M−, (2) platinum doublets in M+, and (3) gefitinib, erlotinib or afatinib in M+ (Fig. 1B). To resemble the fast pace of cancers in the advanced stages, transitions across three mutually, exclusive health states, including stable disease (no progression), disease progression, and death, were defined in a monthly cycle.

Total effectiveness as a result of each policy option was calculated in life years (LYs) and quality-adjusted life years (QALYs) over a 5-year time horizon. Total cost incurred was estimated under societal and healthcare perspectives, as recommended in the Thai Health Technology Assessment Guideline [31] and valued at 2016 in Thai Baht which was converted to US$ ($1 = 35.5 Baht). Costs and effectiveness that occurred in the second year onwards were discounted to present values, using an annual rate of 3% for a base-case analysis, and 0–5% for its variant.

The cost incurred by the combined test and treatment with TKIs per additional effectiveness gained (if any) as compared with the no-test but platinum doublets was presented as an incremental cost-effectiveness ratio (ICER), which was further subject to sensitivity analysis. The price of each TKI was determined for its threshold if it would meet the country's willingness to pay (WTP) at $4500 for cost-effective medical technology.

2.3. Natural history of the disease and treatment effectiveness

On a monthly basis, risk of disease progression and death from the no-progression state was first estimated for a cohort, treated with platinum doublets. Data were derived from 10 phase-III RCTs, published during 2009–2015 that compared platinum doublet chemotherapy with TKI monotherapy as the first line for advanced NSCLC (Table A.1). All trials, except for three [14,18,22] were conducted entirely in Asia. Three trials reported median survival time (MST) on PFS and OS in the platinum doublet arms for patients with EGFR M+ mixed with EGFR M− subgroup [11–14]. Seven trials reported the MST for the whole groups of patients who had EGFR M+ [15–23]. All individual studies, except First-SIGNAL [13], WJTOG 3405 [16,17] and ENSURE [19] followed patients for the median of less than 2 years. The MST on PFS, ranging from 4.6 to 6.9 months (pooled estimate, 5.8 months) among patients with EGFR M+ in the 10 RCTs [11–23] and 4.6–6.4 months (pooled estimate, 5.2 months) among patients with EGFR M− in the 3 RCTs [11–14] was relatively longer than the median time to progression (3–4 months) found in a very recent study of 54 Thai patients with unknown EGFR mutation in a university hospital [32].

For each study, data on the MST were converted into instantaneous rates, then to probabilities over a one-month period. Risks of disease progression and death for platinum doublets in the EGFR M+ were pooled across 10 trials, using a meta-analysis for proportions [33]. The pooled analysis was repeated for the EGFR M− subgroup, based on data from 3 RCTs of mixed M−/M+ patients [11–14]. Tests for heterogeneity of the pooled risks resulted in an inconsistency value (I^2) of zero for both M+ and M− subgroups [34]. Ratios of the 3-trial pooled risks between M− and M+ subsets were used as multipliers of the 10-trial pooled risks in M+ so as to generate the risks for patients with EGFR M−. As patients with the EGFR M− responded less often to medical treatments than those with EGFR M+, the resulting multipliers were greater than 1.0.

For TKIs, risks of the disease progression and death were derived using relative efficacy of the TKIs as compared with platinum doublets under an intention-to-treat analysis. Hazard ratios (HRs) on the PFS and OS from the 10 RCTs [11–23] plus LUX-Lung 7 [25], the most recent trial that directly compared afatinib with gefitinib, were pooled together, using a network meta-analysis (NMA). An overall chi-square test for inconsistency between the indirect and direct (afatinib-gefitinib) comparison revealed statistical non-significance for both OS (P = 0.94) and PFS (P = 0.64) endpoints. Cisplatin plus gemcitabine was the only