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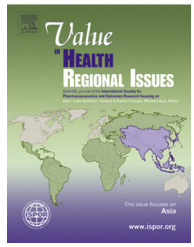

Epidermal Growth Factor Receptor Mutation Testing in Thailand: A Cost-Utility Analysis

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ABSTRACT

Objective: To evaluate the cost utility of epidermal growth factor receptor (EGFR) testing plus first-line gefitinib treatment in patients with activating EGFR mutations in Thailand. **Methods:** The study used a decision tree model considering the provider's perspective. Direct medical costs were included and based on a local Thai database. Effectiveness was measured as quality-adjusted life-year and based on randomized controlled trials. Incremental cost-effectiveness ratio was calculated and presented in 2012. A series of one-way sensitivity analyses were conducted. **Results:** We found that the EGFR testing plus first-line gefitinib alternative gained 0.03 quality-adjusted life-year more, but 62,540 Thailand baht (US $2082.58) less total costs compared with the no-testing alternative. The results were robust when varying most variables in the model except for the duration of gefitinib treatment with activating EGFR mutation, the duration of chemotherapy treatment with activating EGFR mutation, and the utility of second-line chemotherapy. **Conclusions:** EGFR testing should be considered before administering EGFR tyrosine-kinase inhibitor such as gefitinib as first-line treatment in patients with non–small cell lung cancer in Thailand where the incidence of EGFR mutation is high.

Keywords: cost-utility analysis, EGFR, first-line, gefitinib, Thailand.

Introduction

Lung cancer is a major cause of cancer death in Thailand. According to the 2001-2003 cancer registry report in Thailand, the age-standardized rates of male and female lung cancer are 24.9/100,000 and 9.7/100,000, respectively [1]. Approximately 80% of lung cancers are non–small cell lung cancer (NSCLC). Of those with NSCLC, about 60% seek modern medical treatment at a late stage. Chemotherapy is the acceptable standard treatment of advanced NSCLC; however, its outcome is still not satisfactory in terms of adverse events and patients' quality of life. Up until recently, the emergence of epidermal growth factor receptor (EGFR) mutation and the treatment with EGFR tyrosine kinase inhibitor (TKI) have made a significant impact on the treatment outcome of NSCLC. Findings from a meta-analysis of phase III trials confirm that initial treatment with gefitinib is associated with an improvement in objective response rates and progression-free survival as well as less toxicity and better quality of life in nonsmokers with adenocarcinoma with known EGFR mutations or associated with an increased likelihood of EGFR mutations [2]. In Thailand, Sriuranpong et al. [3] reported 57.4% activating EGFR mutations in patients with adenocarcinoma. Based on Mok et al. [4], Maemondo et al. [5], and Mitsudomi et al. [6], first-line gefitinib treatment should be one of the options in patients with EGFR mutations. The cost-effectiveness study conducted by de Lima Lopes et al. [7], which used cost data from Singapore and outcome data from randomized controlled trials, demonstrated that EGFR testing and first-line treatment with gefitinib had lower costs and greater quality-adjusted life-years (QALYs) than did standard care. The incidence or prevalence of EGFR mutation in Asian countries is indifferent based on data from PIONEER [8]. Unfortunately, there are no data from Singapore in this study. We still believe that the incidence or prevalence in Singapore and Thailand are not different. The management pathway of lung cancer in Thailand, especially reimbursement, however, is inferior to that in Singapore. In Thailand, EGFR-TKI has been approved for use as first-line therapy but patients have to pay out of pocket. For using EGFR-TKI as second-line or third-line therapy, the reimbursement is limited on the Civil Servant Medical Benefits Scheme under restricted criteria. Singapore, where the income level is classified as high income, had gross domestic product per capita about 10 times higher than that of Thailand in 2012 (US $51,709.45 vs. US $5,479.76) [9]. Most patients in Singapore compared with those in Thailand are able to afford drug expenses either by their insurance or out of pocket. In addition, the economic burden on the Thai society as a whole when first-line gefitinib is administered to NSCLC has not been clearly examined.

Conflict of Interest: Sumitra Thongprasert is one of the researchers in IRESSA Pan Asia Study.

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Hence, we performed a cost-utility analysis to assess whether EGFR testing plus first-line gefitinib treatment in patients with activating EGFR mutations was cost-effective. This study will provide useful economic evidence for decision makers.

Methods

We conducted a cost-utility analysis using a decision tree model similar to that used in the study of de Lima Lopes et al. [7]. Our decision to use this model structure was due to its uncomplicated tree structure. In addition, the flow of treatment from the model is relevant to the practice of oncologists in Thailand. The study was undertaken from the provider's perspective. Only direct medical costs were included. Outcome was measured as QALYs. The time horizon was based on IRESSA Pan Asia Study (IPASS) [4], which was equal to the overall survival. The total survival time of patients with and without activating EGFR mutations was 27.8 and 12.5 months, respectively. Because of the relatively short duration of each treatment strategy, costs and benefits were not discounted.

Study Model

A decision analytical model compared testing and no EGFR mutation testing alternatives (Fig. 1). Members of the hypothetical cohort stated whether they received the EGFR mutation test. When the test result was positive, gefitinib was selected as first-line treatment followed by second-line chemotherapy, and best supportive care (BSC). On the contrary, chemotherapy was chosen as first-line treatment followed by BSC if the test result was negative. No gefitinib was provided to patients with a negative test result.

For the no EGFR mutation testing alternative, first-line chemotherapy was provided. Gefitinib was selected as second-line treatment followed by BSC. Finally, all patients expired from the disease. We assumed that all members of the hypothetical cohort were Thai with advanced adenocarcinoma of the lung and never or light smokers.

Treatment and Treatment Duration

In this study, the combination of chemotherapy was primarily based on general treatment practice of Maharaj Nakorn Chiang Mai Hospital, which is the largest affiliated medical teaching hospital located in the north of Thailand. We routinely provided the combination of carboplatin and paclitaxel as either first-line treatment or second-line treatment. It is the most commonly used regimen in Thailand due to the availability of generic drugs and reimbursement for all beneficiaries. Moreover, this regimen is more convenient for patients who live quite far from the hospital. The dosage of carboplatin was calculated on the basis of area under the curve of 6. We assumed an average body surface area of 1.5 m^2 for Thai patients. Chemotherapy treatment lasted six cycles (each 21 days). We assumed, however, that time in treatment state under chemotherapy in this study was equal to 6 months. Gefitinib dosage was 1 tablet once daily. Based on IPASS [4], overall survival was not different in patients who were treated with either first-line or second-line gefitinib; hence, we assumed that if patients had tested positive for the EGFR mutation, gefitinib treatment duration would not vary. According to the assumption from the study of de Lima Lopes et al. [7], which was based on IPASS [4], the duration of gefitinib treatment was 9.8 months in patients with activating EGFR mutations and 2.1 in those without activating EGFR mutations. We estimated the time spent in BSC as the difference between median total survival and treatment duration of other strategies. The duration for each treatment is given in Table 1.

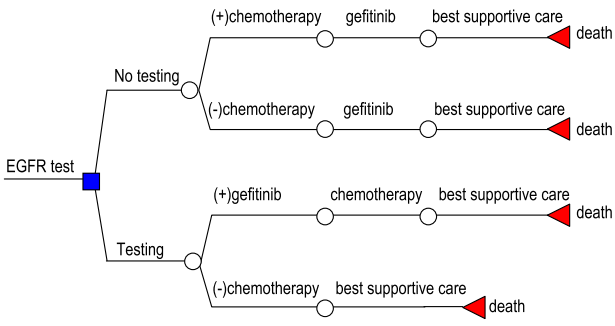

Fig. 1 – Decision analytical model. EGFR, epidermal growth factor receptor.

Outcome

This study measured outcome as QALYs, which was estimated by utility values multiplied by the time spent under each treatment strategy. We used utility values similar to those used in the study by de Lima Lopes et al. [7], which derived utility values from available literature [4–6,10,11]. The percentage of occurrence of each adverse event after receiving each treatment strategy was obtained from IPASS [4], as given in Table 2.

Costs

Considering the provider's perspective, direct medical costs included costs for drugs, EGFR mutation test, administration, outpatient visits, treatment of adverse events, laboratory tests, and BSC (treatment of malignant pleural effusion, palliative radiation, pain control, and nutrition/blood transfusion). All cost data inputs were obtained from Maharaj Nakorn Chiang Mai Hospital and presented in the year of 2012 (Table 1). Treatment costs of each adverse event were the multiplication of the proportion of that event and its unit cost (Table 2). The costs were converted at a rate of 30.03 Thailand baht (THB) per US dollar as the average rate for 2012 [12].

Data Analyses

The finding was presented as incremental cost-effectiveness ratio (ICER), which was the ratio between the difference in cost and difference in QALYs. If the new alternative is more costly and has a higher effectiveness than does usual care, then the ICER is positive. On the contrary, ICER becomes negative for less costly, but more effective new treatment compared with usual care. This means cost saving of the new strategy.

Sensitivity Analyses

To test the robustness of the model, a series of one-way sensitivity analyses were performed. Costs, utilities, time in each treatment strategy, and prevalence of positive EGFR mutation test results were varied within the plausible ranges. When specific ranges or confidence intervals were not available, it was assumed that the range varied by ±50%.

Results

Table 3 presents base-case results. The EGFR testing with first-line gefitinib gained 0.03 QALY more, but 62,540 THB (US $2,082.58) less total costs compared with the no-testing alternative, resulting in a negative ICER or cost saving. The total costs saved attributable to avoiding the ineffective use of gefitinib in