

Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Lung cancer is the most common cancer worldwide and is the second most diagnosed cancer in the UK after breast cancer (12.9% of all cancer cases). It is also the most common cause of death in the UK. In 2010, 42,000 people in the UK were diagnosed with lung cancer and there were 35,000 registered deaths from lung cancer. The majority of cases (80%) are diagnosed in people over 60 years of age. The treatment options for patients with non-small cell lung cancer (NSCLC) depend on the stage of disease, disease histology, epidermal growth factor receptor (EGFR) mutation status, performance status, comorbidities and patient preferences. Patients with stage III or IV disease, good performance status and for whom curative treatment is not an option, may be initially offered chemotherapy to improve survival, disease control and quality of life. A proportion of this group of patients (33%) will go on to receive further chemotherapy treatment following disease progression after first-line therapy. It is this patient group that is of relevance to this appraisal. Two oral anticancer treatments, used within their licensed indications are the focus of this review: erlotinib [Tarceva®, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca). Both are EGFR tyrosinase inhibitors that block the signal pathways involved in cell proliferation.

Objectives

The remit of this review is to appraise the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC after disease progression following prior chemotherapy [review of National Institute for Health and Care Excellence (NICE) technology appraisals TA162 and TA175].

Methods

Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations (EEs). Studies that compared the use of erlotinib or gefitinib with each other or with the use of docetaxel or best supportive care (BSC) were considered. Patients with NSCLC whose disease had progressed following prior chemotherapy were included. Outcomes for clinical effectiveness included overall survival (OS), progression-free survival (PFS), response rate (RR) and adverse events (AEs). Cost-effectiveness outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including EEs, applied inclusion criteria to relevant publications and quality assessed the included (clinical) studies. The results of the data extraction and (clinical) quality assessment are summarised as a narrative description. No meta-analysis or network meta-analyses were undertaken.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Results of the literature review

Clinical effectiveness

Twelve trials were identified for inclusion in this review, only one of which (BR.21) was included in the previous review of erlotinib (NICE TA162). Seven trials compared the use of gefitinib with chemotherapy or BSC, four trials compared the use of erlotinib with chemotherapy or BSC, and one trial compared the use of gefitinib with the use of erlotinib.

No trials were identified that were conducted in a population of solely EGFR mutation-positive (EGFR M+) patients. EGFR mutation data were derived retrospectively from six subgroup analyses of RCTs that included patients of unknown EGFR mutation status at the time of randomisation for OS, PFS and RR. Seven trials reported subgroup data describing EGFR mutation-negative (EGFR M-) patients; however, only one trial [TArceva Italian Lung Optimization tRial (TAILOR)] was conducted in a population of solely EGFR M- patients. Ten studies presented quantitative data describing the EGFR unknown population; the results of the Bhatnagar *et al.* trial (Bhatnagar AR, Singh DP, Sharma R, Kumbhaj P. Docetaxel versus gefitinib in patients with locally advanced or metastatic NSCLC pretreated with platinum-based chemotherapy. *J Thorac Oncol* 2012;**3**:S159) and the Docetaxel and Erlotinib Lung Cancer Trial (DELTA) were described in an abstract in narrative format only.

Epidermal growth factor mutation positive

No trials were identified that were conducted in a population of solely EGFR M+ patients. Limited EGFR mutation status data were derived retrospectively from relatively small subgroup analyses from RCTs that included patients of unknown EGFR mutation status at the time of randomisation. Four studies reported OS outcomes, none of which was statistically significantly different for any of the comparisons described. Four studies reported PFS but only one trial, IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST), showed a statistically significant improvement for any comparison considered; the results favoured gefitinib over docetaxel.

Epidermal growth factor mutation negative

Key clinical data were derived from the results of TAILOR and DELTA. However, EGFR mutation status data were also derived retrospectively from subgroup analyses carried out in the BR.21, Tarceva In Treatment of Advanced NSCLC, INTEREST and IRESSA Survival Evaluation in Lung cancer (ISEL) trials and the study by Kim *et al.* (Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, *et al.* Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;**75**:82–8). The only statistically significant differences identified for any treatment were in the comparison of erlotinib with docetaxel; in both TAILOR and DELTA, PFS improved in patients in the docetaxel arm.

Epidermal growth factor mutation unknown

Clinical data were available from 10 trials in populations in which EGFR mutation status was not a factor in the recruitment process, or in which overall trial results were presented (with the exception of TAILOR, in which only EGFR M- patients were recruited). The only statistically significant OS benefit for any treatment was reported in BR.21. However, this finding was based on an adjusted rather than an unadjusted analysis of the data (favouring erlotinib over placebo). Only one of the four trials (IRESSA as Second-line Therapy in Advanced NSCLC – Korea) reported a statistically significant PFS benefit for the comparison of gefitinib with docetaxel favouring gefitinib, although this was based on 90% confidence intervals. For the comparison of gefitinib with BSC, gefitinib was reported to have a statistically significant benefit (ISEL), and in BR.21 a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis) when compared with a placebo.

Cost-effectiveness

Eleven studies containing economics information were identified. However, the Assessment Group (AG) concluded that the results of the systematic review were of limited value to decision-makers in the UK NHS. This is a result of (1) relatively recent changes in the price of docetaxel and (2) the increased significance of EGFR mutation testing for patients with NSCLC.

Manufacturer's submissions (economics)

Neither of the manufacturers submitted a review of cost-effectiveness literature. Only Roche (UK) Ltd, the manufacturer of erlotinib, submitted economics evidence. Roche (UK) Ltd's base-case analysis compared the use of erlotinib with BSC in patients whose EGFR mutation status is unknown and who are unsuitable for docetaxel or who have previously received docetaxel. In a separate subgroup analysis, Roche (UK) Ltd also considered the use of erlotinib compared with BSC for patients with EGFR M- tumours. The AG provides a summary and critique of the EE that is presented in Roche (UK) Ltd's submission.

Summary of the Assessment Group's cost-effectiveness results

To allow all therapy options for the post-progression treatment of patients with NSCLC to be compared using a consistent framework, the AG developed a de novo cost-effectiveness model. Costs and outcomes were assessed from the perspective of the UK NHS and Personal Social Services. Wider indirect costs and benefits (e.g. loss of productivity, value of informal care and impact on utility of patients' family) were not considered.

Relevant patient populations

Three distinct populations were modelled as follows:

1. previously treated adult patients with locally advanced or metastatic NSCLC and who exhibit EGFR-activating mutations (referred to as the EGFR M+ population)
2. previously treated adult patients with locally advanced or metastatic NSCLC and who do not exhibit EGFR-activating mutations (referred to as the EGFR M- population)
3. previously treated adult patients with locally advanced or metastatic NSCLC and for whom EGFR mutation status is unknown or indeterminate (referred to as the EGFR unknown population).

Epidermal growth factor mutation-positive population

In the absence of any relevant clinical trial evidence in the EGFR M+ population, the AG concluded that there was no reliable basis on which to assess the clinical effectiveness or cost-effectiveness of available treatments for this patient population.

Epidermal growth factor mutation-negative population

Using data from TAILOR for patients who are EGFR M-, in the AG's comparison of erlotinib with docetaxel, erlotinib was found to be dominated by docetaxel, yielding a reduced mean survival and fewer QALYs while also involving a greater net cost of treatment. A univariate sensitivity analysis indicated that the use of generic docetaxel in place of the branded product is the major factor in establishing docetaxel as the preferred option. The incidence rate of febrile neutropenia (FN) has a larger influence on the estimated incremental cost-effectiveness ratio (ICER) than other model parameters, but for none of model parameters is the known parameter uncertainty sufficient to alter the conclusion that erlotinib is dominated by docetaxel in the EGFR M- population. The only model input which could alter this conclusion is the incidence rate of FN in docetaxel-treated patients. The probabilistic sensitivity analysis (PSA) strongly indicated that erlotinib is less cost-effective than docetaxel. The AG's estimated ICER when comparing erlotinib with docetaxel is -£5112 per QALY gained.

Using subgroup data from the BR.21 trial for patients who are EGFR M-, the AG's comparison of erlotinib with BSC yielded an ICER of £54,687 per QALY gained, which is above the range normally considered cost-effective. The results of univariate sensitivity analyses indicated that these results are most affected by projective survival model parameters (especially for the OS model), utility model parameters and the incidence of key AEs. Examination of the PSA scatterplot and the cost-effectiveness acceptability curves indicated strong general confidence that erlotinib exhibits a high ICER when compared with BSC in this subgroup (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained and 12% favour it at a threshold of £50,000 per QALY gained).

Epidermal growth factor mutation status unknown population

Using data from the BR.21 trial for patients whose EGFR status is unknown, the AG's comparison of erlotinib with BSC yielded an ICER of £61,132 per QALY gained, which is well beyond the range normally considered cost-effective. The results of univariate sensitivity analyses indicated that these results were unaffected by uncertainty in almost all model parameters. The only exceptions were the intercept parameter value in the Nafees *et al.* (Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non-small-cell lung cancer. *Health Qual Life Outcom* 2008;**6**:84) utility model (i.e. the baseline NSCLC population utility value in patients with stable disease) and the incidence of FN when docetaxel was used. Examination of the PSA scatterplot and the cost-effectiveness acceptability curves indicated strong

general confidence that erlotinib is not more cost-effective than BSC in this population (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained).

Discussion

Strengths and limitations of the analyses

A key strength of this review is that it has brought together all the available evidence relevant to the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib in patients who have progressed following prior chemotherapy. The review has also highlighted the importance of EGFR mutation status for the selection of effective treatments for patients with NSCLC. In addition, the AG's cost-effectiveness analyses have incorporated the most up-to-date cost and benefit information available (i.e. the off-patent price of docetaxel and clinical results from TAILOR) and, therefore, offer relevant economic evidence to inform decision-making in this complex clinical area.

The main limitation of the assessment is the lack of clinical data available for distinct patient populations. The gaps in the evidence base have precluded the assessment of clinical effectiveness and cost-effectiveness of relevant treatments. Specifically, the AG was unable to carry out an EE of treatments for patients with EGFR M+ tumours.

Uncertainties

The results of the recent TAILOR trial demonstrate that docetaxel has a statistically significant PFS benefit when compared with erlotinib in a European EGFR M- population. However, it is not yet certain whether or not the reported PFS benefit seen in an Italian population would be achieved by NHS patients in England and Wales.

The cost-effectiveness analyses rely on the QALY values modelled from data obtained from a sample of the general population; however, these values do not directly reflect patient experience or patients' preference for the mode of treatment (oral vs. intravenous treatments). This is most important in the comparison of docetaxel with erlotinib. The AG carried out a sensitivity analysis to assess the effect of applying the maximum possible patient health utility increment (bonus) on the estimated ICER. This extreme sensitivity analysis indicates that any realistic assessment of utility advantage due to oral therapy is very unlikely to have more than a minor impact on the size of the estimated ICER.

Conclusions

Implications for service provision

The largest group of patients to whom the results of this appraisal apply is the EGFR M- patient population. The results of the AG's cost-effectiveness analysis comparing erlotinib with docetaxel in patients whose disease has progressed favour the use of docetaxel. Switching from an oral therapy (erlotinib) to an intravenous therapy (docetaxel) would have substantial implications for service provision for both patients and staff in the UK NHS.

Suggested research priorities

It is suggested that any future trials in this area should distinguish between patients who have EGFR M+ and EGFR M- disease. To date, the evidence base supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations is weak and is not sufficiently robust to inform decision-making.

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