Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer: a systematic review and cost-effectiveness analysis

Marie Westwood,[1]* Manuela Joore,[2] Penny Whiting,[1] Thea van Asselt,[2] Bram Ramaekers,[2] Nigel Armstrong,[1] Kate Misso,[1] Johan Severens[3] and Jos Kleijnen[4]

[1]Kleijnen Systematic Reviews Ltd, York, UK
[2]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands
[3]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands
[4]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, the Netherlands

*Corresponding author

Declared competing interests of authors: none

Published May 2014
DOI: 10.3310/hta18320

Scientific summary

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Health Technology Assessment 2014; Vol. 18: No. 32
DOI: 10.3310/hta18320

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Scientific summary

Background

Lung cancer is the most commonly diagnosed cancer in the world and the most common cause of cancer-related death. The likelihood of surviving 1 year after diagnosis is around 30% and of surviving 5 years is < 10%. Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. Some epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations make tumours more responsive to treatment with EGFR-TK inhibitors (EGFR-TKIs) but less responsive to treatment with standard chemotherapy. Patients with NSCLC are therefore tested for EGFR-TK tumour gene mutations to inform treatment decision. There are a variety of tests available to detect these mutations. These vary in the specific mutations that they detect, the amount of mutation they detect, the amount of tumour cells needed, the time to give a result, the error rate and cost.

Objectives

To compare the performance and cost-effectiveness of EGFR-TK mutation tests used to identify previously untreated adults with locally advanced or metastatic NSCLC who may benefit from first-line treatment with TKIs.

Methods

Assessment of clinical effectiveness

Twelve databases (including MEDLINE, EMBASE, research registers and conference proceedings) were searched to August 2012. A web-based survey, conducted in October 2012, gathered data on technical performance of EGFR-TK mutation tests. Search results were screened for relevance independently by two reviewers. Full text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Randomised controlled trials (RCTs) were assessed for quality using the Cochrane risk of bias tool. Diagnostic accuracy studies were assessed using QUADAS-2. There were insufficient data for meta-analysis. For accuracy studies, we calculated sensitivity and specificity together with 95% confidence intervals (CIs). Survival data were summarised as hazard ratios (HRs) and tumour response data as relative risks (RRs) with 95% CIs.

Assessment of cost-effectiveness

We considered the long-term costs and quality-adjusted life-years (QALYs) associated with different tests followed by treatment with either standard chemotherapy or a TKI. Direct sequencing was taken as the comparator. The de novo model consisted of a decision tree and a Markov model. The decision tree was used to model the test result (positive, negative or unknown) and the treatment decision. Patients with a positive test result received an anti-EGFR-TKI and patients with a negative test or unknown tumour mutation status received standard chemotherapy. The long-term consequences in terms of costs and QALYs were estimated using a Markov model with a cycle time of 21 days (one cycle of chemotherapy), and a time horizon of 1 year. Health states in the Markov model were 'progression free', 'disease progression' and 'death'. We present three analyses: 'evidence on comparative effectiveness available', 'linked evidence' and 'assumption of equal prognostic value'.

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

Eleven studies (33 publications) were included in the review.

What is the technical performance of the different epidermal growth factor receptor mutation tests?

One study assessed technical performance of EGFR mutation tests. The test failure rate was 19% (29/152 samples) in year 1 for Therascreen® EGFR polymerase chain reaction (PCR) Kit (Qiagen, Venlo, the Netherlands) alone but was lower (5%) in year 2, when a combination of Therascreen EGFR PCR, fragment analysis and direct sequencing were used.

Thirteen laboratories completed the online questionnaire (response rate 93%). The Therascreen EGFR PCR Kit (version 1 or 2) was the most commonly used test (six laboratories), followed by fragment length analysis (three laboratories) and Sanger sequencing (two laboratories); other tests were used in single laboratories. There were no clear differences between tests in terms of batch size, turnaround time, number of failed samples or test cost. Laboratories using the Therascreen EGFR PCR test reported that between < 1% and 10% of tumour cells were required and laboratories that used fragment length analysis reported that a minimum of 1–5% of tumour cells were required, whereas Sanger sequencing needed > 30% of tumour cells; other methods required up to 10% of tumour cells.

What is the accuracy of epidermal growth factor receptor mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors?

Six studies provided data on the accuracy of EGFR mutation testing for predicting response to treatment in patients treated with TKIs. Five studies assessed direct sequencing and one assessed the Therascreen EGFR PCR Kit using objective response (OR) as the reference standard. The sensitivity and specificity estimates for the Therascreen EGFR PCR Kit were 99% (95% CI 94% to 100%) and 69% (95% CI 60% to 77%), respectively. Four of the five studies that used direct sequencing methods to identify EGFR mutations reported high estimates of specificity (> 80%) and sensitivities ranged from 60% to 80%.

How do outcomes from treatment with epidermal growth factor receptor inhibitors vary according to which test is used to select patients for treatment?

Five RCTs provided data on the clinical effectiveness of TKIs compared with standard chemotherapy; one additional study reported data for a subgroup of patients from one of the trials whose samples had been re-analysed using a different EGFR mutation testing method. Three studies used direct sequencing methods, one used fragment length analyses and one used the Therascreen EGFR PCR Kit; the re-analysis of the existing trial used the Roche cobas® EGFR Mutation Testing Kit (Roche Molecular Systems, Inc., Branchburg, NJ, USA).

All studies reported improvements in OR and improvements or trends towards improvement in progression-free survival (PFS) for patients with EGFR mutation-positive tumours who were treated with TKIs compared with those with EGFR mutation-positive tumours who were treated with standard chemotherapy. There were no clear differences in the treatment effects reported by different studies, regardless of which EGFR mutation test was used to select patients.

What is the cost-effectiveness of the use of the different epidermal growth factor receptor mutation tests to decide between standard chemotherapy or tyrosine kinase inhibitors?

'Evidence on comparative effectiveness available' analysis

Direct sequencing of all exon 18–21 mutations could not be included owing to a lack of information. Testing with the Therascreen EGFR PCR Kit was compared with direct sequencing of all exon

19–21 mutations (as an approximation of direct sequencing of all exon 18–21 mutations) in order to estimate lifetime cost and QALYs using the observed response to treatment and the available relative PFS and overall survival (OS) data. Therascreen EGFR PCR Kit was both less effective and less costly than direct sequencing of all exon 19–21 mutations at an incremental cost-effectiveness ratio (ICER) of £32,167 per QALY lost. Sensitivity analyses resulted in similar outcomes. The key drivers behind this result were the differences in the proportion of patients with EGFR mutation-positive tumours, unknown tumour mutation status and mutation-negative tumours, and differences in OR, PFS and OS. In particular, the predicted OS for mutation-negative patients differed substantially between the studies using the Therascreen EGFR PCR Kit and the study that was used for direct sequencing of all exon 19–21 mutations. OS for patients with mutation-negative tumours, after testing using the Therascreen EGFR PCR Kit, was substantially lower than after testing using direct sequencing of all exon 19–21, whereas PFS was similar. Hence, patients survived longer with progressive disease after testing with direct sequencing of all exon 19–21 mutations. As a result, although testing using the Therascreen EGFR PCR Kit resulted in a high accuracy, it appeared less effective in terms of QALYs and was also less costly, as the gained life-years for direct sequencing of all exon 19–21 mutations were mainly spent in the relatively expensive disease progression health state.

However, it should be noted that this analysis was based on a number of assumptions, of which the following two are particularly problematic:

- The proportion of patients with a positive or negative test result, after the use of these tests in the UK NHS population, was estimated based on the proportion of EGFR mutation-positive patients in England and Wales, the proportion of patients with an unknown test result and test accuracy for the prediction of treatment response derived from two separate trials.
- The differences in relative treatment response, PFS and OS, between the results of the First-SIGNAL trial, which were used to model direct sequencing of all exon 19–21 mutations, and the results of the IPASS trial, which were used to model testing using the Therascreen EGFR PCR Kit, were assumed to be solely attributable to the different tests used to distinguish between patients whose tumours are EGFR mutation positive (and who receive TKI treatment) and patients whose tumours are EGFR mutation negative (and who receive doublet chemotherapy).

‘Linked evidence’ analysis

Two other direct sequencing tests [direct sequencing of all exon 18–21 mutations and direct sequencing or WAVE-HS (Transgenomic Inc., Omaha, NE, USA) for inadequate samples (< 50% of tumour cells)] for which accuracy data to predict response to treatment with TKIs were available were included in the analysis. The results of this analysis showed that the relevant strategies to be compared were direct sequencing of all exons 18–21 mutations and testing using the Therascreen EGFR PCR Kit. Therascreen EGFR PCR Kit was less expensive and less effective than direct sequencing of all exons 18–21 mutations at £32,190 per QALY lost. Sensitivity analyses did not show any substantial changes to these results. However, it should be noted that this analysis is also based on a number of substantive assumptions, including those described for the ‘evidence on comparative effectiveness’ analysis. The following additional assumption should be noted:

- For direct sequencing of all exon 18–21 mutations and for direct sequencing or WAVE-HS for inadequate samples (< 50% of tumour cells), the relative PFS and OS for mutation positives and mutation negatives were assumed to correlate perfectly with relative PFS and OS as observed for direct sequencing of all exon 19–21 mutations in the First-SIGNAL trial.

‘Assumption of equal prognostic value’ analysis

This included all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales. This included the tests for which neither comparative effectiveness nor response data were available. Therefore, in this analysis, the costs of the tests were assessed given an assumption of equal prognostic value and test-specific information on costs only. For this purpose, the prognostic value of all tests was based on the Therascreen

EGFR PCR Kit, as this was the only test for which prognostic data were available on patients with positive, negative and unknown tumour mutation status. In addition, tests used in NHS laboratories in England and Wales were considered to have technical characteristics (low limit of detection and similar proportion of tumour cells required for analysis), which were more similar to this test than to direct sequencing methods and would therefore be more likely to have similar prognostic value to the Therascreen EGFR PCR Kit than to direct sequencing. The results of this analysis indicated that the effectiveness of the strategies was equal (as a consequence of the above assumption) and the costs were almost equal. The lowest total strategy cost was [commercial-in-confidence (CiC) information has been removed] (Sanger sequencing or Roche cobas) compared with (CiC information has been removed) for the most expensive strategy (fragment length analysis combined with pyrosequencing). The sensitivity analysis, in which the number of unknowns was based on results from the online survey of NHS laboratories in England and Wales, instead of being assumed equal based on literature, showed a slightly larger range of costs (CiC information has been removed) and a small range of QALYs (0.871–0.886) for the included mutation tests.

Conclusions

Implications for service provision

There was no strong evidence that any one EGFR mutation test had greater accuracy than any other test, although there was a suggestion that Therascreen EGFR PCR Kit may be more accurate than direct sequencing for predicting response to treatment with TKIs. There was a suggestion that Therascreen EGFR PCR Kit may be more accurate than direct sequencing for predicting response to treatment with TKIs, although it should be noted that only one data set was available for this test and no studies reported direct comparisons between the Therascreen EGFR PCR Kit and other tests conducted in the same population. The clinical effectiveness of TKIs in patients whose tumours are positive for EGFR did not appear to vary according to which test was used to determine EGFR mutation status.

The results of the 'evidence on comparative effectiveness available' analysis and the 'linked evidence' analysis both indicated that the Therascreen EGFR PCR Kit was less effective and less expensive than direct sequencing (all exon 19–21 mutations and all 18–21 mutations, respectively) at £31,000–35,000 per QALY lost. The lower QALYs for the Therascreen EGFR PCR Kit seem counterintuitive, as the accuracy data show a higher accuracy for Therascreen EGFR PCR Kit. This contradiction possibly results from the problematic and substantial assumptions made to arrive at the economic results, in particular the assumption that the differences in treatment response and survival between tests as observed between the different studies are solely attributable to the different tests used. This ignores all other factors that can explain variations in outcomes between the studies. Therefore, these outcomes of the assessment of cost-effectiveness should be interpreted with extreme caution.

The results of the 'assumption of equal prognostic value' analysis (including all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales) showed that the costs of the EGFR mutation tests were very similar [ranging from (CiC information has been removed) for Sanger sequencing or Roche cobas for samples with insufficient tumour cells to (CiC information has been removed) for fragment length analysis combined with pyrosequencing].

There are no data on the clinical effectiveness or cost-effectiveness of Therascreen EGFR Pyro Kit (Qiagen, Venlo, the Netherlands) or next-generation sequencing. No published studies were identified for either of these two methods and neither method is currently in routine clinical use in any of the NHS laboratories in England and Wales that responded to our survey; one laboratory is currently developing and validating a next-generation sequencing method.

Suggested research priorities

Re-testing of stored samples from previous studies, where patient outcomes are already known, could be used to provide information on the relative effectiveness of TKIs and standard chemotherapy in patients with EGFR mutation-positive and EGFR mutation-negative tumours, where mutation status is determined using tests for which adequate data are currently unavailable. Should quantitative testing become part of routine practice, longitudinal follow-up studies relating the level of mutation and/or the presence or rarer mutations to patient outcomes would become possible. Studies of this type could help to assess which features of EGFR mutation tests are likely to be important in determining their clinical effectiveness.

As the uncertainties associated with clinical effectiveness forced the major assumptions in the economic evaluation, this type of research would also facilitate economic analyses of EGFR mutation testing.

Study registration

This study is registered as PROSPERO CRD42012002828.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 12/34/01. The protocol was agreed in July 2012. The assessment report began editorial review in February 2013 and was accepted for publication in August 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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