OHTAC Recommendation

Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Prediction of Response to EGFR-Targeting Tyrosine kinase Inhibitor (TKI) Drugs in Patients with Advanced Non-Small-Cell Lung Cancer

Presented to the Ontario Health Technology Advisory Committee in August, 2010

December 2010

OHTAC Ontario Health Technology Advisory Committee

Issue Background

The Medical Advisory Secretariat undertook a systematic review of the evidence on the clinical effectiveness and cost-effectiveness of epidermal growth factor receptor (EGFR) mutation testing compared with no EGFR mutation testing to predict response to tyrosine kinase inhibitors (TKIs), gefitinib (Iressa®) or erlotinib (Tarceva®) in patients with advanced non-small cell lung cancer (NSCLC) in Ontario.

Clinical Indication

With an estimated 7,800 new cases and 7,000 deaths last year, lung cancer is the leading cause of cancer deaths in Ontario. NSCLC accounts for approximately 80-85% of all cases of lung cancer. Approximately 50 to 70% of patients with NSCLC present with advanced stage disease or present with early-stage disease that has subsequently relapsed.

Those with unresectable or advanced disease are commonly treated with platinum-based combination chemotherapies. Although response rates to the current cytotoxic chemotherapies for advanced NSCLC are approximately 30 to 40%, all patients eventually develop resistance and have a median survival of only 8 to 10 months. Treatment for refractory or relapsed disease includes single-agent treatment with docetaxel, pemetrexed or EGFR- targeting tyrosine kinase inhibitors (TKIs). The two most widely used TKIs that approved by Health Canada are gefitinib (Iressa®) and erlotinib (Tarceva®). TKIs have been shown to be either non-inferior or superior to chemotherapy in the first- or second-line setting (gefitinib), or superior to placebo in the second- or third-line setting (erlotinib). However, TKIs use can be costly up to C$ 2000 to C$ 3000 per month, and have only approximately a 10% chance of benefiting unselected patients. The combination of these factors can create a situation in which the value of predictive markers of response, before the use of TKIs for patients with advanced NSCLC, needs to be determined.

Somatic mutations in the tyrosine kinase domain of EGFR are associated with increased sensitivity to gefitinib and erlotinib. Several other EGFR-related molecular predictive markers have been investigated and somatic mutations in the EGFR gene found as the most robust biomarkers for EGFR-targeting therapy selection.

Technology

The EGFR gene sequencing by polymerase chain reaction (PCR) assays is the most widely used method for EGFR mutation testing. PCR assays can be performed at pathology laboratories across Ontario. According to experts in the province, sequencing is not currently done in Ontario because this method is not sensitive enough. A variety of new methods has been introduced to increase the sensitivity of the mutation assay. Some technologies such as single-stranded conformational polymorphism, denaturing high-performance liquid chromatography, and high-resolution melting analysis have the advantage of allowing for rapid mutation screening of large numbers of samples and have high sensitivity but require direct sequencing to confirm the identity of the detected mutations. Other techniques have been developed for the simple but highly sensitive detection of specific EGFR mutations, such as the amplification refractory mutations system (ARMS) and the peptide nucleic acid-locked PCR clamping; others selectively digest wild-type DNA templates with restriction endonucleases to enrich mutant alleles by PCR. Experts have commented that currently PCR fragment analysis for deletion and point mutation in PCR fragment analysis and restriction digest conducts in Ontario, with sensitivity of 1% to 5%.

Evidence

The MAS evidence search on EGFR mutation testing identified 11 published papers. Six were prospective analysis of phase III RCTs; and five were published results from retrospective studies. Of the 6 prospective studies, 4 were compared the effectiveness of EGFR mutation testing with gefitinib compared to chemotherapy in the first-line setting in patients with advanced NSCLC; 2 compared clinical effectiveness of EGFR mutation testing with gefitinib compared to placebo or chemotherapy in the second- or third-line setting in patients with advanced NSCLC. Of the 5 retrospective studies, 1 was retrospective analysis of sub-sample of phase III RCT; 4 were retrospective phase II trials compared the effectiveness of erlotinib in patients with EGFR mutation versus patients with wild-type EGFR. The results of the evidence-based review on EGFR mutation testing are summarized below.

OHTAC Findings

EGFR mutation testing in patients with advanced NSCLC in the first-line setting

Based on moderate quality of evidence, patients with advanced NSCLC with adenocarcinoma histology being treated with gefitinib in the first-line setting are highly likely to benefit from to gefitinib if they have EGFR mutations compared to those with wild-type EGFR. This advantage is reflected in improved PFS, ORR and QoL in patients with EGFR mutation who are being treated with gefitinib relative to patients treated with chemotherapy

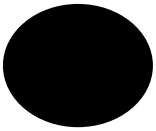
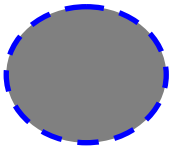
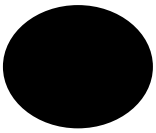
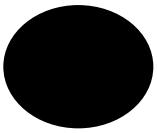
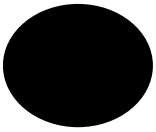
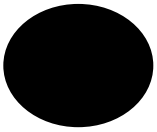
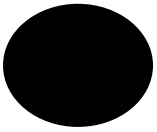
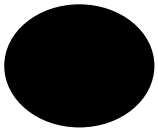
EGFR mutation testing in patients with advanced NSCLC in the second- or third-line setting

In patients with locally advanced or metastatic NSCLC, who are being treated with erlotinib relative to patients treated with placebo in the second- or third-line setting:

- Based on low quality of evidence, the identification of EGFR mutation status may help to select patients who are highly likely to benefit from erlotinib.

Decision Determinants

Based on the evidence reported in the MAS EGFR mutation testing for prediction of response to EGFR-targeting TKIs in patients with advanced non-small-cell lung cancer review and the deliberations of OHTAC on August 27th, 2010 pertaining to this evidence, OHTAC made the following ratings with respect to the decision determinants criteria:

	EGFR mutation testing		
	Gefitinib first-line	**Erlotinib second- or third-line setting**	**Gefitinib second- or third-line setting**
Overall clinical benefit			
Consistency with expected societal and ethical values			
Value for money			
Feasibility of adoption into the health system			

For additional information on the decision determinants criteria, please refer to the OHTAC website at http://www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html .

OHTAC Recommendations

- EGFR mutation testing should be a prerequisite for the first-line treatment of advanced NSCLC with gefitinib.

- Given the uncertainty (i.e. low quality of evidence) regarding the effectiveness of EGFR Mutation testing for erlotinib use in the second- or third-line treatment of advanced NSCLC, patient outcomes data should be collected and reported through a field evaluation.