OHTAC Recommendation

KRAS Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer

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

December 2010

OHTAC Ontario Health Technology Advisory Committee

Issue Background

In February 2010, the Medical Advisory Secretariat (MAS) began work on evidence-based reviews of the literature surrounding three pharmacogenomic tests. This project came about when Cancer Care Ontario (CCO) asked MAS to provide evidence-based analyses on the effectiveness and cost-effectiveness of three oncology pharmacogenomic tests currently in use in Ontario.

Evidence-based analyses have been prepared for each of three technologies. These have been completed in conjunction with internal and external stakeholders, including a Provincial Expert Panel on Pharmacogenetics (PEPP). Within the PEPP, subgroup committees were developed for each disease area. For each technology, an economic analysis was also completed by the Toronto Health Economics and Technology Assessment Collaborative (THETA) and is summarized within the reports.
The following report is a systematic review of the evidence of one of the three reviews and is specific to determining the predictive value of KRAS testing in the treatment of metastatic colorectal cancer (mCRC) with two anti-EGFR agents, cetuximab and panitumumab.

Metastatic colorectal cancer (mCRC) is usually defined as stage IV disease according to the American Joint Committee on Cancer tumour node metastasis (TNM) system or stage D in the Duke's classification system. Patients with advanced colorectal cancer (mCRC) either present with metastatic disease or develop it through disease progression. In Ontario, patients with advanced colorectal cancer who are refractory to chemotherapy may be offered the targeted anti-EGFR treatments cetuximab or panitumumab. Eligibility for these treatments is based on the KRAS (Kristen-RAS, a member of the rat sarcoma virus (ras) gene family of oncogenes) status of their tumour, derived from tissue collected from surgical or biopsy specimens.

KRAS (is frequently mutated in epithelial cancers such as colorectal cancer, with mutations occurring in mutational hotspots (codons 12 and 13) of the KRAS protein. Involved in EGFR-mediated signalling of cellular processes such as cell proliferation, resistance to apoptosis, enhanced cell motility and neoangiogenesis, a mutation in the KRAS gene is believed to be involved in cancer pathogenesis. Such a mutation is also hypothesized to be involved in resistance to targeted anti-EGFR (epidermal growth factor receptor with tyrosine kinase activity) treatments such as cetuximab and panitumumab, hence, the important in evaluating the evidence on the predictive value of KRAS testing in this context.

Both cetuximab and panitumumab are indicated by Health Canada in the treatment of patients with metastatic colorectal cancer whose tumours are WT for the KRAS gene. Cetuximab may be offered as monotherapy in patients intolerant to irinotecan-based chemotherapy or in patients who have failed both irinotecan and oxaliplatin-based regimens and who received a fluoropyrimidine. It can also be administered in combination with irinotecan in patients refractory to other irinotecan-based chemotherapy regimens. Panitumumab is only indicated as a single agent after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Research Question

To determine if there is predictive value of KRAS testing in guiding treatment decisions with anti-EGFR targeted therapies in advanced colorectal cancer patients refractory to chemotherapy.

The Evidence

In total, 14 observational studies were identified for inclusion in this EBA: 4 for cetuximab monotherapy, 7 for the cetuximab-irinotecan combination therapy, and 3 to be included in the review for panitumumab monotherapy.

Inclusion Criteria

- English-language articles, and English or French-language HTAs published from January 2005 to May 2010, inclusive.
- Randomized controlled trials (RCTs) or observational studies, including single arm treatment studies that include KRAS testing.
- Studies with data on main outcomes of interest, overall and progression-free survival.
- Studies of third line treatment with cetuximab or panitumumab in patients with advanced colorectal cancer refractory to chemotherapy.
- For the cetuximab-irinotecan evaluation, studies in which at least 70% of patients in the study received this combination therapy.

Exclusion Criteria

- Studies whose entire sample was included in subsequent publications which have been included in this EBA.
- Studies in pediatric populations.
- Case reports, comments, editorials, or letters.

Outcomes of Interest

- Overall survival (OS), median
- Progression-free-survival (PFS), median.
- Response rates.
- Adverse event rates.
- Quality of life (QOL).

Summary of Findings

Cetuximab or Panitumumab Monotherapy

Based on moderate GRADE observational evidence, there is improvement in PFS and OS favouring patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

Cetuximab-Irinotecan Combination Therapy

There is low GRADE evidence that testing for KRAS may optimize survival benefits in patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

However, cetuximab-irinotecan combination treatments based on KRAS status discount any effect of cetuximab in possibly reversing resistance to irinotecan in patients with the mutation, as observed effects were lower than for patients without the mutation. Clinical experts have raised concerns about the biological plausibility of this observation and this conclusion would, therefore, be regarded as hypothesis generating.

Economic Analysis

Cost-effectiveness and budget impact analyses were conducted incorporating estimates of effectiveness from this systematic review. Evaluation of relative cost-effectiveness, based on a decision-analytic cost-utility analysis, assessed testing for KRAS genetic mutations versus no testing in the context of treatment with cetuximab monotherapy, panitumumab monotherapy, cetuximab in combination with irinotecan, and best supportive care.

Of importance to note is that the cost-effectiveness analysis focused on the impact of testing for KRAS mutations compared to no testing in the context of different treatment options, and does not assess the cost-effectiveness of the drug treatments alone.

Conclusions

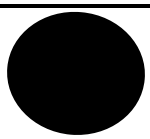
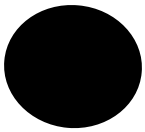
KRAS status is predictive of outcomes in cetuximab and panitumumab monotherapy, and in cetuximab-irinotecan combination therapy.

While KRAS testing is cost-effective for all strategies considered, it is not equally cost-effective for all treatment options.

Decision Determinants

OHTAC has developed a decision-making framework that consists of seven guiding principles for decision making and a decision-making tool, called the Decision Determinants (DD) tool. The evaluation of the four explicit main criteria (overall clinical benefit, value for money, feasibility of adoption into health system, and consistency with expected societal & ethical values) are reported in using 1 of 4 symbols. For more information on the Decision-Making Framework and the meaning of the symbols below, please refer to the Decision Determinants Guidance Document or visit: www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html
Based on the deliberations of OHTAC on July 31, 2009 pertaining to this evidence, OHTAC made the following ratings with respect to the decision determinants criteria:

Table 1: Overall Clinical Benefit

	Technology KRAS Mutation Test
Effectiveness	
Safety	
Burden of Illness	
Need	
Overall Clinical Effectiveness	

Effectiveness

Moderate for test, but treatment effects are small.

Safety

Risk of biopsy and toxicity of treatments considered here.

Need

Given that approximately 43% of patients are mutated for KRAS and will likely not benefit from the anti-EGFR treatments cetuximab and panitumumab, it is an important issue.

Table 2: Consistency with Societal and Ethical Values

	KRAS Testing
Expected Ethical Values	?
Expected Societal Values	?
Society and Ethical Values	?

Not assessed but some issues may be the convenience of administering panitumumab (every 2 weeks) compared to cetuximab (weekly), patient preference, and marketing of treatments by pharmaceutical companies.

Table 3: Value for Money

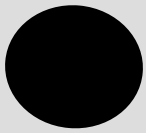
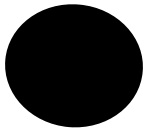
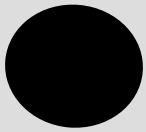
	KRAS Mutation Testing
Value for Money	

Table 4: Feasibility of Adoption into the Health System

	KRAS Mutation Testing
Economic Feasibility	
Organizational Feasibility	
Feasibility of Adoption into the Health System	

OHTAC Recommendations

KRAS testing has predictive value in the treatment of advanced colorectal cancer patients with cetuximab and Panitumumab monotherapy, or cetuximab-irinotecan combination therapy. Therefore, these treatment options should be given to patients with KRAS wildtype mutation status.

OHTAC wishes to point out that any test that overall avoids unnecessary exposure to potentially harmful effects should be a welcome addition to patient care.