

EGFR inhibitors and availability of KRAS testing in Canada

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As discussed in the Landmarks commentary by Drs. Lim and Gill on pages 9–12 of this issue of *Oncology Exchange*, KRAS testing helps to determine the approximately 40% of patients with metastatic colon cancer (mCRC) for whom the anti-epidermal growth factor receptor (EGFR)-based therapies cetuximab and panitumumab provide no benefit.

Cetuximab (ERBITUX®) was approved by Health Canada in September 2005. It is currently indicated for use in combination with irinotecan for treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to other irinotecan-based chemotherapy regimens, and as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy. However, cetuximab was never marketed in Canada, and access to this therapy has been very uneven. Factors such as province of residence, type of private insurance coverage and income level have played important roles in determining whether eligible patients obtain treatment. Many patients have received cetuximab via Health Canada's Special Access Program, for which funding sources can include the manufacturer, the patient and family or an insurance plan (provincial or private).^{1,2} Ontario has funded administration of the drug in US hospitals for selected patients, and some patients have financed their own treatment in the US. An application for a revised Notice of Compliance (NOC) for cetuximab is currently under review by Health Canada, and it is unknown what changes will be made to the product monograph regarding approved indications, requirement for KRAS testing or other modifications. A decision and revised monograph are hoped for by the end of 2008 or early 2009. It is likely that funding bodies and/or individual institutions will require KRAS testing even if it is not specifically mandated in the mCRC indication.

Another EGFR inhibitor, panitumumab (VECTIBIX™) was approved by Health Canada in April 2008 as monotherapy for EGFR-expressing mCRC with non-mutated

(wild-type) KRAS, after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The logistics of offering KRAS testing to appropriate mCRC populations are manageable. A number of US laboratories provide KRAS testing.

Toronto's Mount Sinai Hospital and the University Health Network (UHN, Princess Margaret Hospital, Toronto General Hospital and Toronto Western Hospital) have been offering the test for some time. Canadian research laboratories involved in clinical trials for KRAS testing have the necessary technical capability, and once funding issues are worked out these centres should be able to offer it on a more widespread basis. To promote a uniform standard of testing across Canada, UHN is offering training and validation to 1 laboratory in each of the other 9 provinces.

With this very important development we will now be able to identify patients with metastatic CRC who will likely benefit from anti-EGFR targeted therapies. We will thus be able to optimize treatment in a group for whom it was previously difficult to determine whether the therapeutic benefit outweighed the potential toxicities and expense.

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The buck stops here: oncologists' role in managing expectations

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The fact that healthcare cost increases exceed overall inflation is well recognized, as is the fact that healthcare costs are consuming an ever-increasing proportion of gross domestic product (GDP) in most Western countries. The Conference Board of Canada calculates that public health expenditures are expected to rise from 31% of total provincial revenues in 2000 to 42% by 2020.¹

Between 1996 and 2007, the allocation of funding for healthcare in British Columbia rose from \$7 billion to \$13.7 billion² (taking inflation into account, an increase to \$8.79 billion would have indicated no change). Many factors contribute to this phenomenon, including growth in the cancer drug budget from \$37.5 million in 2000 to over \$100 million in 2007³ (again, with increase due to inflation

only, the 2007 drug budget would have been \$43.77 million). Many political and medical commentators have written about possible responses, even “solutions,” to this growing problem, including in this journal.⁴ Most suggestions in Canada have centred on moving our system away from publicly-funded, comprehensive healthcare towards incorporating an increasing role for privately-funded healthcare — either as a parallel system as seen in some European countries, or even by switching to a predominantly private system as in the United States.

But as costs are ultimately borne by citizens, these systems only shift the relative levels of funding between direct taxation and “discretionary” spending: they are not mechanisms to constrain overall costs. In 2003, total healthcare spending as a proportion of GDP was 7.8% in the UK and 9.9% in Canada, and in the most privatized healthcare system in the western world — the US — it was 15.2%.⁵ Clearly, such “radical” solutions are really not radical at all.

Rather than concentrating on how to find more money, perhaps we should debate whether all of the money now being spent is necessary. In the final analysis, there are only 3 ethical reasons for a physician to offer any treatment to a patient with cancer (or any disease), and the same 3 reasons for a patient to consider seeking or accepting treatment:

- **Cure:** Is there convincing evidence that the treatment being considered has a realistic chance of curing the patient, at an acceptable cost in risks and side effects?
- **Extending survival:** If cure is not possible, is there convincing evidence that treatment has a realistic chance of improving the patient’s survival time by a meaningful amount, at an acceptable cost in risks and side effects?
- **Improving quality of life:** If cure or extended survival is not possible, is there convincing evidence that treatment has a realistic chance of improving the patient’s quality of life at an acceptable cost in risks and side effects?

A fourth possible reason could be inclusion in a clinical trial in order to further knowledge. Every trial is reviewed by an institutional ethics board that gives approval if there is a rational basis (rather than convincing evidence) to believe that at least one of the tests above may be met.

Following are some common reasons often given for administering a potentially unpleasant or dangerous treatment:

- **“The patient (and/or family) is treatment-seeking.”**
What these patients want is to be cured, to live longer or to live with better quality of life. They may express that wish as a demand for treatment, most likely because of unrealistic expectations of what treatment can achieve.
- **“The patient is only 36 years old and has 3 small children.”**
If anyone reading this does not understand why this is not a good reason to give treatment, it is unlikely I could convince you.
- **“It is the standard of care.”**
If the standard of care is rigorously evidence-based, it will meet the valid reasons to treat. The problem is that “standards of care” sometimes simply reflect what most people are doing, and the motivation for adhering to them may be more about risk management for physicians and organizations than about what is best for the patient. For example, the most common fractionations in Canada

for bone metastases are 20 Gy in 5 fractions and 30 Gy in 10 fractions, despite ample Level 1 evidence that in the vast majority of circumstances, 8–10 Gy in a single fraction has equal efficacy and is no more toxic.^{6,7}

- **“There is a 30% chance of response.”**
Response may translate into cure, survival extension or improvement in quality of life — but not necessarily. Evidence is required, except in the context of a clinical trial.
- **“We have to give the patient something to hope for.”**
Time spent in striving for realistically achievable goals like control of pain and other distressing symptoms is also an affirmation of hope, and much more likely to have a worthwhile outcome than colluding with patients’ unrealistic expectations.

Oncologists are responsible for evaluating the evidence and for advising patients that a particular management strategy is appropriate based on that evidence. Oncologists and other members of the care team are — or should be — available to help patients understand the situation. Oncologists are responsible for obtaining informed consent, which includes ensuring that patients understand any potential benefits of treatment in a real-world sense, i.e. absolute as well as relative risk reduction rates, and also that they understand the risks and unpleasant effects.

It is entirely appropriate to debate healthcare funding models — and physicians should be a vigorous part of that debate. More important than funding models, however, is that significant amounts of money are wasted in our health services. Worse than the waste of money is the disservice we do to our patients if we put them through potentially toxic or even dangerous treatments for no good reason. We can argue about how often this happens but we all know it happens. The limited time that a patient with metastatic cancer has left should be put to better use than wasting it on treatments that are very unlikely to achieve anything worthwhile. **EB**

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