Coverage of Genotype-Directed Therapy for Non-Small Cell Lung Cancer in Canada: An Update

BY JAIME MCDONALD, BSCPHARM, PHARMD

Introduction

Previous editions of the Report Card have reported on the sporadic reimbursement of companion diagnostic tests for oral tyrosine kinase inhibitors (TKIs) for non-small cell lung cancer (NSCLC). As of the writing of this article, it is our pleasure to report that for the therapies in question, notably crizotinib (Xalkori), afatinib (Giotrif), erlotinib (Tarceva), and gefitinib (Iressa), genotype testing for anaplastic lymphoma kinase (ALK), in the case of crizotinib, and epidermal growth factor receptor (EGFR) mutations is now available to all eligible patients free of charge. However, the mechanism for funding the costs of testing still varies across provinces.

Funding of EGFR and ALK Genotyping

Genotyping for EGFR mutations is now considered standard of care in patients with NSCLC and is publicly funded in all provinces. However, this is not necessarily the case for newer agent coming to market. Traditionally, albeit not exclusively, the manufacturer of the pharmaceutical or companion diagnostic in question has taken on the responsibility of establishing genotyping networks via various pilot programs and laboratories. To make matters worse, these drugs are often launched to market without long-term plans for coverage of testing.

In the case of EGFR, funding of these networks has gradually transitioned from patchwork coverage (via the pharmaceutical industry, manufacturers of companion diagnostics, cancer organizations, interprovincial agreements, etc.) to provincial coverage.[1] At one point in the lifespan of erlotinib and gefitinib, patients were even paying for EGFR testing out of their own pocket.[2] But, as of September 2014, the province of Ontario became the final province to offer provincial funding for EGFR testing.[1] However excellent the news, this announcement comes nearly 10 years after Health Canada's initial approval of erlotinib and gefitinib for NSCLC.

This start-up approach is likely unsustainable for several reasons. Under relatively few circumstances in medicine are pharmaceutical companies, or even patients, responsible for diagnostic costs, nor is their willingness to fund diagnosis likely to continue. Most importantly, an ethical dilemma emerges where the pharmaceutical manufacturer, who is set to profit from use of the drug, is funding the definitive test to determine a patient's eligibility. Needless to say, the convoluted path to provincial coverage for EGFR testing must be streamlined if we are to keep up with the flood of new drugs entering the market. The number of genotype-directed agents in clinical trials has nearly quadrupled in recent years,[3] therefore a systematic approach to coverage for testing must be developed before we reach critical mass.

Testing for ALK fusions, via both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), is funded in each Canadian province as is crizotinib, the companion oral TKI. The territories usually have health agreements with other provinces (British Columbia, Alberta or Ontario), therefore testing will be performed for these patients at an out of province site. The approval of crizotinib through the pan-Canadian Pricing Alliance was dependent on simultaneous coverage of ALK testing,[4] representing a novel approach to coverage similar to the drug approval process adopted by the Food and Drug administration (FDA) in the United States.[5] The source of funding and type of ALK genotyping still varies across provinces,[1] with Abbott Canada, makers of the Vysis FISH assay, currently funding the cost of FISH testing. This approach provides more security that patients will be eligible for both ALK testing and subsequent treatment with crizotinib without unnecessary delays, representing a definite improvement over the path taken by EGFR testing.

In August 2014, the FDA finalized their guidance for industry that now requires the simultaneous submission and approval of companion diagnostics for genotype-directed therapies; a drug is generally not approved without the simultaneous approval of its companion diagnostic.[5] As companion diagnostics are considered class III medical devices, their approval is required by Health Canada, however these submissions, reviews and approvals do not always occur in tandem with the drug. Although the American model of healthcare reimbursement for both test

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and drug differs significantly, the take-home message is that co-development and approval of drug and diagnostic will ideally expedite time to approval, ensure immediate availability of testing, promote standardization of methods across testing centers, and permit universal access to the same diagnostic testing methods used in clinical trials.

Under the new FDA approval process, product labeling regulations specify that the safe and effective use of the drug can only be guaranteed when used in conjunction with the approved diagnostic.[5] Use of a specific test is not currently a mandatory requirement of Health Canada however, general suggestions for specific testing are usually recommended for the product monograph. Medico-legally, these suggestions may be left open for interpretation and therefore may vary according to site and even by product monograph. As an example, the product monograph for vemurafenib (Zelboraf), an oral therapy for metastatic melanoma targeting the BRAF V600E mutation, simply states that a validated test must be used.[6] However, the product monograph for crizotinib (Xalkori) lists the specific FISH assay (Vysis) to be used.[7]

Provincial Drug Coverage

Under the current model of Canadian funding, it is possible that a drug may be approved for coverage on a provincial formulary without guaranteed access to companion diagnostic testing. However, it is becoming evident that the opposite is also occurring. While access to diagnostic genotyping is improving, patients now have access to testing without the guarantee of drug coverage. Such is the case for crizotinib in the Northwest Territories, Yukon and Nunavut. Afatinib, which differs from erlotinib and gefitinib in that it irreversibly inhibits EGFR tyrosine kinase and HER2, was approved for the first-line treatment of NSCLC by Health Canada in November of 2013. A year later, most provinces were still debating coverage, while some had already

Table 1 **Provincial coverage of targeted therapies for NSCLC**
Source: Information retrieved from individual provincial formularies

Province	Crizotinib	Afatinib	Erlotinib	Gefitinib
NL	✓	X	✓	X
PEI	✓	X	✓	X
NS	✓	✓	✓	X
NB	✓	✓	✓	X
QC	✓	X	✓	✓
ON	✓	✓	✓	✓
MB	✓	✓	✓	✓
SK	✓	✓	✓	X
AB	✓	X	✓	✓
BC	✓	✓	✓	✓
NU	X	X	✓	X
NWT	X	X	✓	X
YT	X	✓	✓	✓

approved its use (Table 1). This is a clear example of how the lag-time to coverage of new treatments can differ greatly, depending on the province of residence. For rapidly progressive cancers, such as NSCLC, any delays to effective treatment can be costly.

In March 2014, Ontario approved afatinib for coverage under the special access program[8] and now British Columbia does the same. Since then, patients in provinces not offering the drug could theoretically have moved to another province, waited for provincial health coverage and received the drug, all before their home province listed the drug on formulary. In a country that promotes universal healthcare, this should not be necessary.

As outlined in Table 1, gefitinib coverage is also sporadic across Canadian provinces while erlotinib is available ubiquitously. Clinical experience and evidence for efficacy likely favor erlotinib,[9] however the National Comprehensive Cancer Network guidelines list gefitinib as interchangeable with erlotinib[10] and there is limited evidence that the former may be better tolerated.[9]

This problem is not unique to NSCLC. Such is the case for vemurafenib, an oral BRAF kinase inhibitor used in the treatment of melanoma. Testing for the BRAF V600E mutation, which the drug targets, is available free of charge to every Canadian.[11] However, Prince Edward Island has yet to list the drug on its provincial formulary.

Owing to the cost of the oral TKIs, which is about $90,000 per year for crizotinib,[12] they are available almost exclusively through special access programs. Canadian cancer patients find themselves once again in a postal code lottery of drug coverage.

Summary

It is clear that some work remains to be done in terms of optimizing access to oral genotype-directed therapies in NSCLC. The first barrier to treatment is timely access to genotyping. Thankfully, for the agents in question, funding is no longer a short-term issue. However, this is not necessarily the case for other disease states with new molecules entering the market. Therefore, it is imperative that provincial governments and Health Canada strike a balance in terms of approval, standardization and funding of testing.

The final frontier is ultimately ensuring that once a patient is deemed eligible for treatment they do not experience treatment delays due to drug coverage.

Recommendations

1. **The funding of diagnostic genotyping for targeted chemotherapies should not be sustained by private industry or third parties. As is the standard of care in medicine, the funding of diagnostic medicine should remain public.**
2. **The American model of co-development and approval of a drug and its companion diagnostic should be considered by Health Canada in order to expedite access to standardized testing across Canada.**
3. **Provincial approval of funding for both drug and companion diagnostic should occur simultaneously.**
4. **Provinces should make every effort to follow similar timelines for formulary review to avoid interprovincial discrepancies in drug coverage.**
5. **Exceptional use criteria for genotype-directed therapies should be evidence based and reviewed regularly to reduce interprovincial differences in coverage.**

Jaime McDonald BPharm, MScPharmD, is a pharmacist in Ottawa, ON and a Director of the CACC.

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