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The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: The example of sunitinib for gastrointestinal stromal tumour

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ABSTRACT

This paper examines the challenge of conducting economic evaluations to support patient access to cancer therapies when the cost-effectiveness estimation is hampered by crossover trial design.

To demonstrate these limitations, we present the submission to the Canadian Drug Review (CDR) of a cost-effectiveness evaluation of sunitinib versus best supportive care (BSC) for the treatment of gastrointestinal stromal tumour in patients intolerant or resistant to imatinib.

The economic model generated an incremental cost-effectiveness ratio for sunitinib versus BSC of $79,884/quality-adjusted life-year gained. Eight months after initial submission, CDR granted a final recommendation to fund sunitinib following the manufacturer's appeal against their first recommendation. Although cost-effectiveness is an important consideration in reimbursement decisions, there is a need for improved decision-making processes for cancer drugs, as well as a better understanding of the limitations of clinical trial design.
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1. Introduction

Patient access to new cancer drugs depends on regulatory approval and, in most cases, third-party payer coverage. In Canada, regulatory approval of new drugs is based on evidence of safety and efficacy relative to standard therapy and is the responsibility of the Federal Department, Health Canada. Public drug coverage decisions, in contrast, are based on a review of the clinical value and cost-effectiveness of the drug compared to alternative therapies, and coverage decisions are made by the provincial and territorial drug plans. Since September 2003, the Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR) has informed all provincial drug plan decisions (except for the province of Québec) by providing expert advice on the available clinical evidence, a critical appraisal of the pharmacoeconomic evidence submitted by the manufacturer, and a detailed funding recommendation.[1] While the CDR streamlines the submission process for manufacturers, participating provincial drug plans retain final coverage decisions, and are not bound by the CDR recommendations.[1]

The expected timeframe for a review is 19–25 weeks, not including 3–4 weeks for CDR administrative tasks.[2] In the event that manufacturers do not agree with the funding recommendation and reasons for the recommendation made by CDR, they may appeal. A request for reconsideration from

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the manufacturer adds another 6 weeks to the review process. Provincial drug plans will then make their decisions based on their own timetable.

Integral to the CDR process is the submission by the manufacturer of a pharmacoeconomic analysis comparing the new treatment option to usual care. Manufacturers are instructed to adhere to Canadian guidelines for the economic evaluation of health-care technologies, revised in 2006.[3]

Using a cost-effectiveness analysis comparing sunitinib malate (Sutent) and best supportive care (BSC) in the treatment of gastrointestinal stromal tumour (GIST) in patients intolerant or resistant to imatinib mesylate (Glivec) as an example, this paper examines the challenges of conducting pharmacoeconomic evaluations of oncology drugs using outcomes derived from crossover trials.

2. Differences between regulatory and reimbursement requirements for outcomes in trials of drugs for cancer

Oncology clinical trial endpoints have traditionally been a source of debate between patients, physicians, regulators and payers.[4] While these parties all agree that survival is the most reliable cancer endpoint, the sample sizes and trial durations necessary to detect a difference in this endpoint are often incompatible with ethical and practical considerations. Also, the treatment effect on survival may be confounded by crossover to the comparator treatment. As a consequence, several tumour-assessment measures have been used as primary endpoints in oncology trials to support marketing approval.[4]

A number of these surrogate endpoints are considered acceptable bases for regulatory approval in Canada, the US, Europe and Japan, such as disease- and progression-free survival (PFS), objective tumour response rate and time to progression.[5–7] In fact, endpoints other than overall survival (OS) were the approval basis for 68% of oncology drug approved by the FDA between 1990 and 2002; by definition, 100% of the FDA accelerated approvals were based on surrogate endpoints in that same period.[7,8]

In contrast, surrogate endpoints are often considered as inappropriate outcome measures for economic evaluation by reimbursement agencies.[9] Canadian health-economic guidelines prescribe the use of final outcomes, preferably quality-adjusted life-years (QALYs) gained or life-years gained (LYG); surrogate outcomes are acceptable only when they have a well-established relationship to QALYs or LYG.[3]

Ethical issues may also limit the suitability of some clinical trials for economic analysis. Drug trials for advanced cancers often have a crossover design in which patients are allowed to receive the alternative therapy following disease progression on assigned treatment.[10] Paradoxically, when the study protocol allows crossover at time of disease progression, the more successful a new treatment is in delaying disease progression, the more difficult it will be to demonstrate a significant difference in OS.

Very often, regulatory approval is based on the interim analysis of trial data and the duration of follow-up available is rarely sufficient to observe the outcomes of interest in the entire study population. In these circumstances, parametric functions must be used to extrapolate the survival curves forward in time.[10] For rare cancers, the small numbers of patients available to participate in trials may make it difficult to demonstrate statistically significant benefits from therapy.[11] These considerations all contribute to a high level of uncertainty in economic analyses of oncology drugs in the treatment of uncommon cancers.[10]

To illustrate these issues, we describe the pharmacoeconomic analysis of sunitinib, a new therapy for GIST, and its passage through the CDR process.

3. Case study: economic evaluation of sunitinib for the treatment of GIST in Canada

3.1. Background

GISTs are uncommon mesenchymal neoplasms that occur primarily in the stomach, small intestine, and colon or rectum.[12] GISTs most often arise during the late sixth or early seventh decade of life. A review of clinical records and histological samples from patients in western Sweden from 1983 to 2000 yielded an estimated population prevalence of GIST of 129 per million, of which 17% (22.2 per million) were high risk and 7% (8.7 per million) were overtly malignant.[13]

Approximately 85% of GISTs exhibit activating mutations in the gene for the KIT receptor tyrosine kinase.[14] Prior to the introduction of the tyrosine kinase inhibitor imatinib, surgery was the only viable therapy, because response to chemotherapy was poor and radiation therapy was typically impractical. The median survival for patients with metastatic GIST in the pre-imatinib era was only 15 months.[15] In clinical trials, 48–71% of patients with metastatic GIST responded to imatinib with an additional percentage achieving disease stabilisation for at least 6 months, for an overall clinical benefit in up to 85% of patients.[12] Currently, imatinib is the primary treatment for unresectable and/or metastatic GIST and is recommended by Canadian,[16] US[17] and European[18] clinical practice guidelines.

Approximately 15% of patients never respond to imatinib therapy,[19] and of those who have an initial response or a stabilisation of disease, 50% develop secondary resistance and progress by 23 months.[12] For patients with imatinib-resistant GIST or those who experience life-threatening adverse effects with imatinib, US treatment guidelines published in 2006 recommend the new TKI, sunitinib malate.[17] A pivotal randomised, double-blind, placebo-controlled Phase III study (ClinicalTrials.gov registration number NCT00075218) found that amongst imatinib-resistant or intolerant patients with GIST, sunitinib resulted in improved time to tumour progression (median 27.3 weeks, 95% CI 16.0–32.1) compared with placebo (6.4 weeks, 4.4–10.0; $p < 0.0001$).[20] Duration of PFS, and tumour response rate were also significantly greater in the sunitinib group than in the placebo group. Because of crossover, the effect of sunitinib on OS cannot be quantified. However, as more than 70% of patients in the placebo group crossed over to sunitinib, a hazard ratio for OS of 0.491 (95% CI 0.290–0.831; $p < 0.007$) appeared promising even though the pre-specified level of statistical significance was not met. Adverse events were generally mild to moderate, and manageable.[20]

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