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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.

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]

After evaluating sunitinib under its Priority Review policy, Health Canada approved this drug on 26 May 2006.[21] Health Canada Priority Review policy is a 'fast-tracking' review process with a shorter target evaluation timeframe for eligible new therapies intended for serious, life-threatening or severely debilitating diseases or conditions.[22] Based on the review of the quality, safety and efficacy data, Health Canada concluded that sunitinib had a favourable risk/benefit profile for the treatment of GIST after failure or intolerance of imatinib treatment, despite the fact that a long-term survival benefit had not been demonstrated. The decision to approve sunitinib recognised the potential of sunitinib to increase PFS fourfold with a low risk of serious toxicity.[21]

3.2. Cost-effectiveness model: methods

An evaluation of the cost-effectiveness of sunitinib for the treatment of GIST after failure or intolerance of imatinib was conducted to meet the CDR submission requirements. A Markov model was constructed to simulate disease progression and death and to estimate QALYs and LYG over the lifetime of patients who received sunitinib, compared with those receiving only BSC. The analysis took the perspective of a provincial health ministry, considering only direct medical costs.

A lifetime horizon was adopted in the Markov model. The sunitinib treatment cycle duration was 6 weeks, matching the recommended therapeutic cycle of 4 weeks on treatment followed by 2 weeks off treatment. Clinical effectiveness parameters were derived primarily from the interim analysis of the pivotal Phase III trial.[20] The following trial endpoints were used for valuation of the model's outcomes: (1) PFS, defined as the time from randomisation to tumour progression or death due to cancer; (2) OS; (3) utility, as measured by the EuroQol 5 dimensions (EQ-5D) questionnaire and (4) treatment-related adverse events. Mean PFS and OS were estimated by fitting exponential curves to empirical Kaplan–Meier survival curves to predict the survival of patients beyond the period when follow-up data were available. Table 1 shows the health-state utilities used to calculate QALYs.

Table 1 – Utilities for health states associated with sunitinib treatment or BSC

Health state	Mean utility ± SD
No progression: during the 4 weeks on sunitinib treatment	0.712 ± 0.2
No progression: utility improvement during the 2 weeks off sunitinib treatment	0.081 ± 0.02
No progression: BSC	0.781 ± 0.2
Progression	0.577 ± 0.3

SD: standard deviation.

Table 2 – Cost of health care resources

Component	Cost per 6-week cycle (2005 Can$)
Sunitinib treatment – recommended standard dose	6947.99
Sunitinib treatment – reduced dose for adverse event management	5210.99
Sunitinib treatment medical follow-up, cycle 1	2275.13
Sunitinib treatment medical follow-up, cycle 2	726.47
Sunitinib treatment medical follow-up, cycles 3+	277.91
Routine BSC	1072.11
Terminal phase (end-of-life cost)	3752.00
Serious adverse events with sunitinib	42.84

Model costs included the acquisition cost of sunitinib and health-care resources for BSC, cost of routine follow-up for patients receiving sunitinib, cost of treatment for clinically significant adverse events and end-of-life costs. Relevant health-care resources and corresponding unit costs were derived from the published literature, Canadian government benefit schedules and medical oncologists. Costs were standardised to 2005 Canadian dollars. Table 2 shows the cost of each different health state, derived by combining the quantity of health-care resources used, the unit costs of resources and event probabilities. Costs and outcomes that occur beyond 1 year were discounted at 5% annually. The impact of parameter uncertainty on results was explored with one-way sensitivity analyses using extreme values for all model parameters except acquisition cost of sunitinib, which was considered certain.

3.3. Cost-effectiveness model: results

Model results are summarised in Table 3. The reference case results indicated a difference of $34,493 in the total average per-patient lifetime cost of treatment with sunitinib versus BSC. This difference was accounted for mainly by the acquisition cost of sunitinib. Patients treated with sunitinib spent an average of 0.5 years in the progression-free health state and 1.1 years with progressive disease, resulting in a mean survival of 1.6 years. BSC patients spent an average of 0.2 years in the progression-free health state and 0.7 years in

Table 3 – Cost-effectiveness of sunitinib versus BSC[a]

Treatment	Mean cost ($)	Mean PFS (years)	Mean OS (years)	Mean QALYs	ICER ($/LYS)	ICUR ($/QALY)
Sunitinib	46,125	0.49	1.56	0.97	49,826	79,884
BSC	11,632	0.21	0.87	0.54		

ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; LYS: life-year saved; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life-year.
a Costs are in 2005 Can$; costs and benefits were discounted at 5% annually.

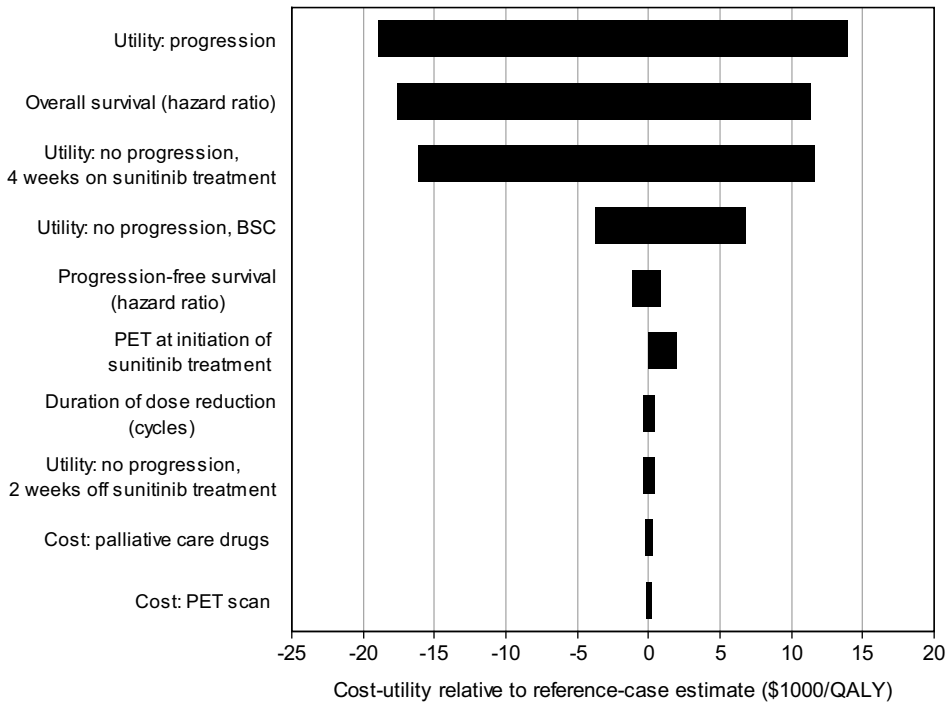

Fig. 1 – Univariate sensitivity analyses: incremental net benefits associated with variations in the 10 most influential model parameters.[d]

progression, resulting in a mean survival of 0.9 years. Compared to BSC, sunitinib treatment was associated with an estimated gain of 0.7 years and 0.4 QALYs. The incremental cost-effectiveness ratio (ICER) and cost-utility ratio (ICUR) of sunitinib versus BSC were $49,826 per LYG and $79,884 per QALY, respectively.

Sensitivity analyses indicated that results were robust to variation in most model parameters. Fig. 1 shows the incremental cost that would be required to reach the reference-case ratio of $79,884/QALY when varying values for the 10 most influential model parameters. These results indicate that the cost-utility ratio was most sensitive to variation in health-state utility values and survival hazard ratio.

3.4. *Cost-effectiveness model: discussion*

No cost-effectiveness analysis of sunitinib has been published previously. However, two different models of imatinib versus BSC for advanced GIST in the UK yielded 5 year cost-utility ratios of £41,219/QALY and £36,479/QALY.[23] Comparison of results of these models with the present model for sunitinib is hampered by differing study populations and methodologies, including how values were assigned to key parameters such as survival and utilities. Nevertheless, the true cost-effectiveness of imatinib is probably better than projected by the UK models since real-life data from British Columbia Cancer Agency (BCCA) patients with advanced GIST indicated that the impact of imatinib on OS is much higher than predicted from preliminary data. Based on an evaluation of 46 imatinib-treated patients and 47 historical patients in BCCA, the median OS in the imatinib group was 66.7 months compared to 7.7 for historical controls, leading to a cost-effectiveness ratio of $15,882 per LYG.[24]

A major limitation of the sunitinib economic evaluation (and the UK economic models of imatinib[23]) was the need to extrapolate survival outcomes beyond clinical trial follow-up.

Sensitivity analyses highlight the fact that the present model was highly sensitive to uncertainty in the OS advantage for sunitinib relative to BSC. This is particularly problematic because patients in the placebo group had the opportunity to switch to sunitinib at time of disease progression. As a result, the intent-to-treat (ITT) analysis would be expected to underestimate the survival benefit of patients randomised to sunitinib. Since treatment crossover does not represent usual clinical practice, the cost of the subsequent sunitinib therapy in patients assigned to placebo could not be accounted for in the economic evaluation. Moreover, with a crossover rate of 70% at the time of the first interim analysis, it would be virtually impossible to adjust for the effect of crossover on survival outcomes in the analysis without compromising the internal validity of the model.

Based on ethical considerations, the study was unblinded after the interim analysis had revealed significantly longer time to tumour progression in the sunitinib group. All patients on placebo were then allowed to crossover to open-

[d] BSC: best supportive care; PET: positron-emission tomography. Utilities and hazard ratios varied between ± 2 standard deviations of the reference-case value. Duration of dose reduction to manage sunitinib-related adverse events varied between 0 and 2 cycles (1 cycle in reference case). PET scan at baseline varied between 0 and 1 (1 PET scan in reference case). Costs varied between ± 10% of the reference-case value.

label sunitinib.[20] As a consequence, further trial data analysis will not improve the certainty in the survival benefit assessment.

Caution is warranted when interpreting the cost-utility results because of the demonstrated sensitivity of the model to uncertainty in utility valuation. Utilities were valued from the clinical trial patients using the EQ-5D, a generic quality of life questionnaire that has not been validated for its responsiveness to changes in health state clinically relevant to a GIST population. Similar concerns apply to utility valuations in the UK studies.[23] Moreover, the high standard deviations for all utility values highlight the large inter-patient variability in this outcome and suggest a high level of uncertainty in the assessment.

As opposed to the UK National Institute for Clinical Excellence (NICE), no provincial health ministry in Canada has established an explicit threshold for acceptable cost-effectiveness. However, Laupacis et al. proposed in 1992 that interventions with cost-utility ratios below $20,000/QALY (in 1990 Can$) should be strongly recommended for adoption within the Canadian health-care system, whereas those costing more than $100,000/QALY should probably not be considered cost-effective.[25] Adjusted to 2005 dollars using the health and personal care component of the Canadian Consumer Price Index,[26] these thresholds would be $26,433 and $132,166, respectively. The estimated cost-utility of sunitinib in the economic analyses lies between these two boundaries, in a zone characterised by Laupacis et al. as showing moderate evidence for adoption. Nonetheless, there is no objective rationale for selecting any given ICER threshold above which a therapy is unacceptable.[27] Laupacis et al. acknowledged this fact and suggested that their recommendations were reflective of 'the current *gut feeling* about the cost-effective attractiveness of technologies.[28]

The initial CDR recommendation based on this economic evaluation was 'not to reimburse' sunitinib in Canada. This decision was reversed on Manufacturer's appeal, likely due to the fact that patients who are resistant to imatinib have no other treatment options. This led to an 8 month delay between reimbursement submission and the final CDR recommendation that sunitinib should be funded for patients with unresectable, recurrent or metastatic GIST who would meet provincial drug plans' eligibility criteria for imatinib but who have failed or are intolerant to imatinib.[29]

4. Discussion

The economic evaluation presented here was based on the equity principle that a QALY gained is equivalent regardless of who gains it, implying that the society values all health gains equally. The underlying assumption for QALY valuation is that the value of health benefits is equal for all people and is directly proportional to the absolute gain, irrespective of baseline health state and life expectancy. From a decision-making perspective, patient needs are considered equal across diseases, and health benefits are valued equally. Some might argue that the value of a given life gain should be higher for a patient diagnosed with a condition such as GIST with a poor short-term prognosis since this diagnosis may increase the perceived value of each remaining day of life. Inherent in this perspective is the acknowledgment that societal values favour access to therapy for life-threatening conditions such as metastatic cancers, specifically when other therapeutic options are unavailable.[30] By approving oncology medicines on surrogate endpoints, the regulatory authorities support the societal values and avoid undue delays in the licensing of effective drugs. Policy-makers and the public in industrialised countries have also converged on the principle that disease severity is an ethically legitimate basis for prioritising health-care.[31]

Sunitinib received accelerated approval from Health Canada. This decision was based on the recognition of sunitinib's clinical benefits on surrogate outcomes in imatinib-resistant or intolerant GIST, a life-threatening condition with no other therapeutic options. The clinical trial design favoured patient access to sunitinib but this was at the expense of a survival advantage demonstration with longer follow-up. In this context, reliance on traditional cost-effectiveness methodology is unsatisfactory. Current Canadian guidelines for economic evaluations do not take into account situations when improvement in appropriate surrogate outcomes makes it unethical to maintain patients on the comparator therapy. By requiring that submissions include LYG and QALYs, these guidelines cannot be applied without compromising the internal validity of the model estimates. Guidance is needed on how to better reconcile the best available clinical trial data with cost-effectiveness requirements and the objective of prompt access to oncology medicines when no other options are available. This could potentially translate into the acceptance of surrogate endpoints in economic models.

Beyond the ethical questions inherent to the funding of drugs for metastatic cancer, there is a clear need to improve consistency between regulatory decisions, clinical practice guidelines and reimbursement decisions. Reflecting the need for 'a more timely, effective and efficient review and evaluation of cancer drugs,' an interim process was introduced on 1 March 2007, to replace the role of the CDR in reviewing cancer drugs in Canada.[32] Manufacturer submissions to this Joint Oncology Drug Review (JODR) are considered as submissions to all participating provinces (except Québec) with the hope of greater concordance in reimbursement decisions across Canada. The JODR process relies on the development of evidence-based practice guidelines. A revision of the pharmacoeconomic guidelines for evaluating oncology drugs to acknowledge ethical considerations and other inherent constraints in the design of oncology clinical trials would also improve the process.

Conflict of interest statement

Isabelle Chabot is an employee of Pfizer Canada Inc. and owns Pfizer stock. Dr. LeLorier has received honoraria for consultancy, speaker's fees, outcomes research grants and travel assistance from Pfizer. Dr. Blackstein has received honoraria from Pfizer for Advisory Board consultancy, and speaker's fees; he also received financial compensation for providing clinical advice in the development of the economic model presented in this article.

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