CURRENT ONCOLOGY
A Canadian Cancer Research Journal

The economic impact of the transition from branded to generic oncology drugs

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ABSTRACT

Background Economic evaluations are an integral component of many clinical trials. Costs used in those analyses are based on the prices of branded drugs when they first enter the market. The effect of genericization on the cost-effectiveness (CE) or cost–utility (CU) of an intervention is unknown because economic analyses are rarely updated using the costs of generic drugs.

Methods We re-examined the CE or CU of regimens previously evaluated in Canadian Cancer Trials Group (CCTG) studies that included prospective economic evaluations and where genericization has occurred or is anticipated in Canada. We incorporated the new costs of generic drugs to characterize changes in CE or CU. We also determined acceptable cost levels of generic drugs that would make regimens reimbursable in a publicly funded health care system.

Results The four randomized controlled trials included (representing 1979 patients) were CCTG BR.10 (early lung cancer, adjuvant vinorelbine–cisplatin vs. observation, n = 172), CCTG BR.21 (metastatic lung cancer, erlotinib vs. placebo, n = 731), CCTG CO.17 (metastatic colon cancer, cetuximab vs. best supportive care, n = 557), and CCTG LY.12 (relapsed or refractory lymphoma, gemcitabine–dexamethasone–cisplatin vs. cytarabine–dexamethasone–cisplatin, n = 619). Since the initial publication of those trials, the genericization of vinorelbine, erlotinib, cetuximab, and cisplatin has taken place or is expected in Canada. Costs of generics improved the CEs and CUs of treatment significantly. For example, genericization of erlotinib ($1460.25 per 30 days) resulted in an incremental cost-effectiveness ratio (ICER) of $45,746 per life-year gained compared with $94,638 for branded erlotinib. Likewise, genericization of cetuximab ($275.80 per 100 mg) produced an ICER of $261,126 per quality-adjusted life-year (QALY) gained compared with $299,613 for branded cetuximab. Decreases in the cost of generic cetuximab to $129.39 and $63.51 would further improve the ICER to $150,000 and $100,000 per QALY respectively.

Conclusions Genericization of a costly oncology drug can modify the CE and CU of a regimen significantly. Failure to revisit economic analyses with the costs of generics could be a missed opportunity for funding bodies to optimize value-based allocation of health care resources. At current levels, the costs of generics might not be sufficiently low to sustain publicly funded health care systems.

Key Words Costs, branded drugs, generic drugs, drugs

Curr Oncol. 2019 April;26(2):89-93 www.current-oncology.com

INTRODUCTION

Although cancer remains the leading cause of death worldwide, prognosis has improved significantly for many patients who are newly diagnosed with cancer today[1]. Such improvements in cancer outcomes can be attributed to a number of factors, including the widespread availability of population-based screening programs, advanced surgical techniques, and innovative new drug therapies[2]. Specifically, the development of novel cancer drugs has led to more favourable toxicity profiles, increased convenience associated with the use of oral agents, and greater adoption of supportive care medications that often result in better symptom control[2].

Unfortunately, significant costs are associated with the design and development of cancer drugs, resulting in new

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therapies that are frequently very expensive and increasingly resource-intensive[2,3]. Between 1995 and 2015, the average cost per life-year gained (LYG) from agents used in hematologic malignancies rose to $200,000 from $50,000. Similar trends have been observed in the costs of other oncologic agents that target solid tumours[4]. Rising drug costs in the face of finite health care budgets are placing significant strains on health care spending and are also creating significant barriers to the accessibility of new therapies for patients in both developed and developing countries[5].

Publicly funded health care systems are particularly affected by increasing drug costs. As cancer drug prices continue to rise, mounting medical literature is suggesting that some novel interventions offer only marginal clinical benefit despite their high cost[6]. In that context, policymakers are increasingly tasked with making difficult funding decisions to ensure that a value-based approach is taken with respect to the allocation of health care resources[7].

Decisions about which oncology drugs should and should not be funded have to be well informed and based on best evidence. That need has contributed to a rapid uptake in the number of cost-effectiveness and cost–utility analyses[2,6,8]. Many organizations have underscored the importance of collecting and evaluating economic data alongside the conduct of clinical trials, especially in situations in which the budget impact is high and clinical benefit is modest. Evaluation is also relevant in settings in which similar treatments are available, but the cost effects are uncertain or different[8]. Thus, economic evaluations are increasingly playing a key role in the development of policies and budgets. Such evaluations can also help to ensure that the funding of drugs is fair, equitable, and transparent[8]. Although economic evaluations of novel therapies certainly provide valuable information, they might not always provide a complete assessment of true drug costs over time[3,9].

Upon successful development of a novel drug, the pharmaceutical company maintains a patent on that drug for a set number of years. The patent creates exclusivity in the market, which in turn allows the company to recuperate the significant monetary investment associated with the initial research and development of the new therapy[10,11]. The expiry of the patent many years later allows for the creation of less-expensive generic versions of the medications. Generics are agents that are bioequivalent to the branded medications with respect to efficacy, potency, and safety[12]. The entry of generic drugs into the market typically has a significant impact on the cost-effectiveness of a drug. Thus, repeating health economic assessments after the transition from branded to generic drugs can provide a more complete understanding of the cost of a drug over time[3,9]. Such assessments are infrequent, however. The main objective of the present proof-of-principle study was therefore to reassess the cost-effectiveness and cost–utility of regimens previously evaluated in Canadian Cancer Trials Group studies, focusing on oncology drugs for which genericization has occurred or is anticipated in Canada.

METHODS

In this retrospective analysis of data available from four clinical trials in the Canadian Clinical Trials Group database, assessments of cost–utility and cost-effectiveness were repeated to incorporate new cost information for drugs whose genericization has occurred or is anticipated.

The clinical trials included in the analysis were

- BR.10, a randomized trial of adjuvant vinorelbine–cisplatin compared with observation in early-stage non-small-cell lung cancer (NSCLC)[13];
- BR.21, a randomized placebo-controlled clinical trial of erlotinib in advanced NSCLC[14];
- CO.17, a randomized trial of cetuximab compared with best supportive care in metastatic colorectal cancer[15]; and
- LY.12, gemcitabine–dexamethasone–cisplatin (GDP) compared with cytarabine–dexamethasone–cisplatin (DHAP) for relapsed or refractory aggressive-histology lymphoma[16].

For all four clinical trials, economic analyses were repeated using the previous costing methods, but replacing the prices of branded drugs with the prices of their generic equivalents. For the BR.10 clinical trial, for example, economic analyses were first conducted by substituting only the cost for generic vinorelbine and holding all other costs constant. A further analysis then varied only the cost of cisplatin to reflect the cost of the generic version of that medication. A subsequent analysis varied the costs of both vinorelbine and cisplatin. In a similar approach for the LY.12 clinical trial, the cost of each individual branded component of the regimen was separately replaced with the cost for the generic version. For the BR.21 and CO.17 clinical trials, similar costing methods were used. Genericization of erlotinib and cetuximab had not yet occurred at the time of the analyses, but was anticipated. The generic prices of those drugs were therefore estimated. For all four clinical trials, the price points at which the cost-effectiveness and cost–utility of treatment would reach less than $150,000, less than $100,000, and less than $50,000 per LYG or QALY were also determined. Because erlotinib and cetuximab are biologics, the unbranded version of those drugs would be called "biosimilars" instead of "generics," but for consistency, "genericization" in this manuscript refers to the transition of all drugs (cytotoxics or biologics) from their branded to unbranded (or "generic") formulation.

RESULTS

The cohort size resulting from the inclusion of the four randomized controlled trials from the Canadian Cancer Trials Groups was 1979 participants: 172 from BR.10[17,18], 731 from BR.21[19], 557 from CO.17[20], and 519 from LY.12[21].

The BR.10 clinical trial assessed the effect of vinorelbine–cisplatin compared with observation on overall survival in patients with completely resected early-stage NSCLC[17]. The 482 eligible participants were randomized to either vinorelbine–cisplatin or observation, and it was found that the experimental treatment group experienced improved outcomes (recurrence-free survival: 94 months vs. 73 months; hazard ratio for recurrence: 0.69; $p = 0.04$). The treatment group also had a superior 5-year overall survival rate of 69% compared with 54% for the control group

($p = 0.03$)[17]. Ng *et al.*[13] conducted a cost-effectiveness analysis of vinorelbine–cisplatin based on a subset of 172 of the trial participants (36% of the entire cohort). Direct costs considered included chemotherapy, emergency room visits and acute-care hospitalizations, outpatient visits, surgery, radiation treatment, laboratory tests, blood transfusions, and other inpatient and outpatient drugs[13]. Re-analysis of BR.10 showed that the cost-effectiveness of treatment would be $150,000 per LYG if the combined cost of vinorelbine and cisplatin were to be $22,872. Further reducing the cost of those therapeutic agents to $12,006 and $386 would result in a cost-effectiveness of $100,000 per LYG and $50,000 per LYG respectively. The cost–utility of the treatments showed similar trends, showing $150,000, $100,000, and $50,000 per QALY being achieved when the combined cost of the therapeutic agents reached $17,872, $9,006, and $218 respectively. Because the costs of vinorelbine and cisplatin have remained very low, this treatment regimen continues to be cost-effective in the re-analysis. Using a simple case estimator, the chemotherapy arm was found to have an incremental cost-effectiveness ratio (ICER) of $465 per LYG; the censored medical costs method produced an ICER of $7,175 per LYG. An ICER of $10,096 was found based on undiscounted mean survivals[13].

In the BR.21 clinical trial, 731 patients with stage IIIB or IV NSCLC who had previously been treated with chemotherapy were randomly assigned in a 2:1 ratio to receive either erlotinib or placebo[18]. Erlotinib was associated with a response rate of 8.9% compared with less than 1% in the placebo group; the median duration of response was 7.9 months for erlotinib and 3.7 months for placebo[18]. Progression-free and overall survival for patients treated with erlotinib were 2.2 months and 6.7 months respectively; they were 1.8 and 4.7 months respectively for patients receiving placebo[18]. A study was subsequently conducted to determine the cost-effectiveness of erlotinib, based on the results of the trial[14]. The analysis was undertaken using costs for erlotinib treatment, diagnostic tests, outpatient visits, acute hospitalizations, adverse events, lung cancer-related concomitant medications, transfusions, and radiotherapy. Branded erlotinib had an ICER of $94,638 per LYG[14]. The generic version of erlotinib is predicted to cost approximately $1,460.25 per 30 days. That decrease in cost would result in a new ICER of $45,746 per LYG.

The phase III clinical trial CO.17 was conducted to determine the effect of cetuximab in the treatment of colon cancer. A total of 572 patients with *KRAS* wild-type tumours were assigned to receive treatment with either cetuximab plus best supportive care or best supportive care alone[20]. Patients treated with cetuximab showed improvements in overall survival, progression-free survival, and quality of life relative to patients receiving best supportive care alone. Based on the CO.17 trial, direct medical costs associated with the use of cetuximab relative to best supportive care alone were calculated by considering medications, physician visits, toxicity management, blood products, emergency department visits, and hospitalizations[15]. The ICER for cetuximab was found to be $299,613 per QALY gained[15]. With the introduction of a generic version of cetuximab that is expected to be priced at $275.80 per 100 mg, the new ICER is anticipated to be $261,126 per QALY. Further reducing the price of generic cetuximab to $129.39 per 100 mg would improve the ICER to $150,000 per QALY. Likewise, $100,000 per QALY would be achieved if the cost per 100 mg were to be lowered to $63.51 per 100 mg.

The LY.12 study was a phase III randomized controlled trial designed to assess whether the GDP regimen was noninferior to DHAP. The latter regimen represented the historical standard for patients with refractory or relapsed aggressive lymphoma[21]. The 519 participants were randomized to receive either GDP and DHAP. Although the differences in event-free and overall survival were nonsignificant, patients treated with GDP experienced less toxicity, less need for hospitalization, and improvement in quality of life[21].

Based on results from LY.12, Cheung *et al.*[16] initially conducted a cost-minimization analysis and found GDP to be the less costly treatment. Costs considered in their analysis included chemotherapy, physician visits, nursing and pharmacist wages, hospital days, emergency department visits, medications, blood transfusions, and the costs of imaging, laboratory tests, and procedures. Treatment was found to cost $19,961 with GDP and $34,425 with DHAP[16]. Compared with branded versions of cisplatin, which were priced at $493.74 per 100 mg, generic versions currently cost $157.50 per 100 mg. Based on that difference, the transition from the branded to the generic drug would reduce the cost of GPD and DHAP for relapsed or refractory lymphoma to $441.32 and $488.42 per cycle respectively.

DISCUSSION

The present study constitutes one of the few attempts to examine the effect of drug genericization on cost outcomes. As expected, the transition from branded to generic cancer treatments resulted in significant improvements in cost-effectiveness and cost–utility. Although ICERs or overall savings related to treatment with generic erlotinib, cisplatin, cetuximab, and vinorelbine were all improved relative to treatment with the branded versions of those drugs, the magnitude of some of the improvements might still not be adequate for public reimbursement based on conventional thresholds.

Our findings could have significant implications for policymakers as they face the increasingly challenging task of making evidence-based decisions about resource allocation. The rising cost of oncology medications combined with limited health care budgets has contributed to a need for a strong foundation on which to base funding decisions[2,6,8,22]. Although the numbers of cost-effectiveness and cost–utility analyses have been markedly increasing, those analyses have, in great proportion, been based on measures from phase III clinical trials and have primarily examined the cost of the treatment at the point of entry of a drug into the marketplace[2,3]. As a result, the understanding of the cost-effectiveness and cost–utility of a treatment over its entire life cycle is likely incomplete[11] .By reassessing the economic impact of various treatment regimens after the entry of generic options into the marketplace, significant areas of cost savings could potentially be ascertained. Such cost savings could facilitate the reallocation of resources to fund costly novel therapeutic agents[2].

The use of generic alternatives in place of branded medications has already been identified as a key area of cost recovery in non-oncology settings, such as primary care and cardiology[10]. In fact, oncology also provides such evidence, with generic versions of the breast cancer drug trastuzumab having been shown to provide substantial cost savings and improvements in ICERs[3]. Likewise, a study by Lu *et al.*[9] found that paclitaxel and docetaxel were both associated with significantly more favourable ICERs after their exclusivity or patents had expired. Thus, our findings are mostly consistent with results from prior studies, demonstrating that generic versions of common cancer drugs such as vinorelbine, erlotinib, cetuximab, and cisplatin could offer similar cost savings and improvements in ICERs. Conversely, our analysis also identified certain cases in which the cost-effectiveness and cost–utility of generic alternatives might have to be further improved for the generics to be economically feasible for reimbursement in a publicly funded health care system. In the case of cetuximab, the price of the generic version must be reduced by more than several magnitudes for the cost per QALY to be reasonable (for example, less than $100,000 per QALY).

Because of their significant costs, oncology drugs have frequently been targeted as areas of potential cost reduction in health care budgets[6]. The results of the present study, in conjunction with other similar analyses by other investigators, suggest a strong need to transition from the use of branded drugs to their generic equivalents whenever possible. However, a number of barriers to the use of generics have been described, including physician preference for branded medications, perceptions by patients of the generic alternatives as less effective, and institutional policies that result in the branded version of a drug being dispensed unless the generic is explicitly specified[12,23,24]. Further research into factors that promote the uptake of generic medications and how misconceptions about those alternatives could be minimized can help to ensure that the full cost-saving potential of generic treatments is realized.

Our study is subject to some limitations. First, we did not account for the possibility that the use of specific cancer drugs could change over time. The entry of generic alternatives into the marketplace is a significant factor in modifying a drug's cost-effectiveness and cost–utility, but other studies have suggested that changes in the population in which a medication is used over time can also influence its economic impact[3,9]. Randomized clinical trials in oncology are often conducted in young and fit participants, whereas the patients encountered in routine clinical practice tend to be older and more frail. Further, changes in the efficacy of a drug over time can also occur as clinicians learn how to better manage its use and side effects[9]. In addition, our analysis was limited to data from Canadian Cancer Trials Group studies. Because laws governing the approval and entry of generics differ and because pricing varies by jurisdiction, our findings might not be directly applicable in other countries.

CONCLUSIONS

In summary, generic versions of costly oncology drugs offer significantly improved cost-effectiveness and cost–utility. Generic versions of vinorelbine, erlotinib, cetuximab, and cisplatin all contributed to improved ICERs or overall cost savings when compared with their branded versions. However, further reductions in the cost of generic options might still be necessary before some treatments become economically viable and sustainable. Revisiting economic analyses before the expiration of a patent, incorporating the actual or anticipated costs of the generic product, can be a useful exercise. Our study suggests that economic reassessments should be performed regularly, because the findings can be used to better inform the effective reallocation of finite health care resources to support emerging novel interventions.

ACKNOWLEDGMENTS

The Ontario Institute for Cancer Research (OICR) is funded by the Government of Ontario through the Ministry of Economic Development, Job Creation and Trade. The Canadian Centre for Applied Research in Cancer Control (ARCC) receives core funding from the Canadian Cancer Society (grant no. 2015-703549). Both OICR and ARCC are proud to support the publication of this costing series.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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