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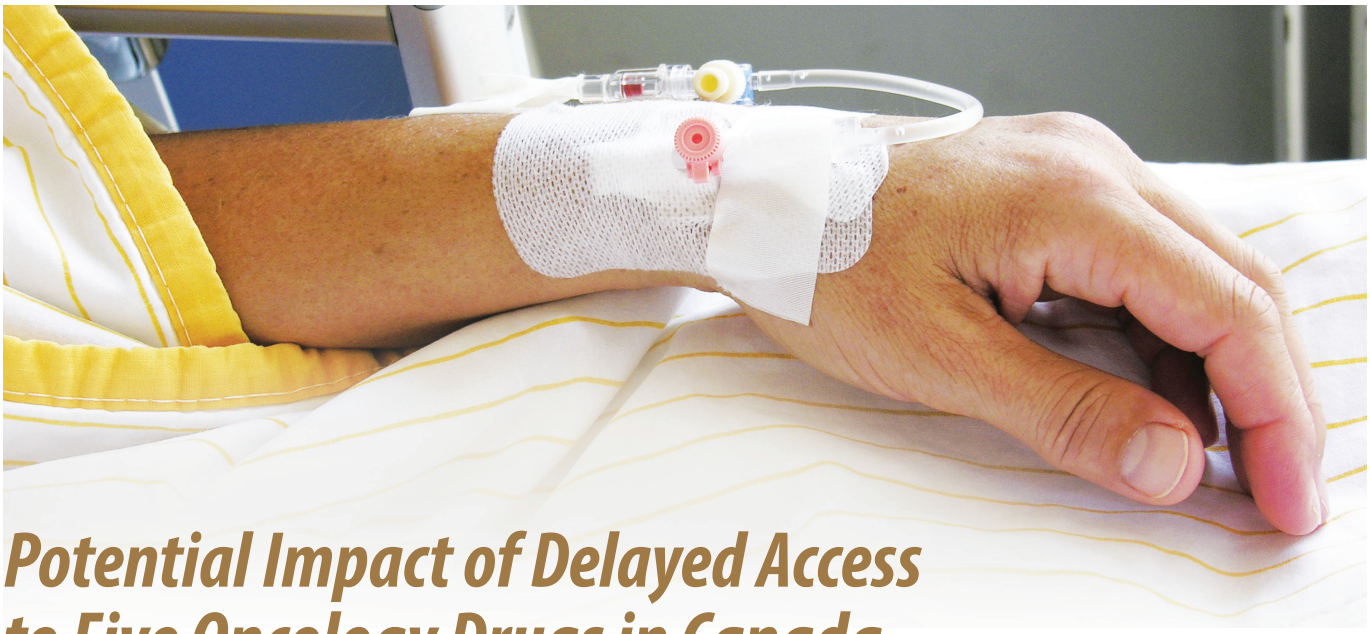

Potential Impact of Delayed Access to Five Oncology Drugs in Canada

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MAIN CONCLUSIONS

Slow regulatory and reimbursement approvals in Canada are affecting cancer survival.

- More than 5,000 patients could have been negatively affected by delayed federal regulatory and provincial reimbursement approval for Avastin, Halaven, Jevtana, Tarceva and Torisel (five new oncology drugs approved in Canada between 2003 and 2011 for the treatment of advanced solid tumours), according to an evaluation that conservatively assumed only 25% of patients would have responded to the drugs.

- If each of these patients had received the drugs and achieved the median survival benefit identified in each drug's pivotal randomized clinical trial, a total extension in survival over standard therapy of 1,696 patient-years would have resulted.

- The monetary value of this extension in life was estimated to be between $339.2 and $559.6 million.

- Since several types of patients for whom the drugs may have been appropriate could not be included, the calculated numbers are almost guaranteed to be underestimates.

- Patients affected by slow regulatory and reimbursement approval procedures are anonymous and receive less attention from decision-makers than victims of adverse drug reactions. This study identifies a substantial number of real people who should not be ignored.

Introduction

A Fraser Institute analysis of 33 new oncology drugs approved between 2003 and 2011 showed that only 24 (73%) of the 33 drugs received approval in Canada, whereas 30 (91%) were approved in the United States (Rawson, 2012). Moreover, the median review time for the drugs approved in Canada (the time within which 50% were approved) was 356 days, compared with 182 days in the United States for the same 24 drugs.

Five of the 24 oncology drugs were Avastin (bevacizumab; Genentech), Halaven (eribulin; Eisai), Jevtana (cabazitaxel; Sanofi-Aventis), Tarceva (erlotinib; Genentech), and Torisel (temsirolimus; Pfizer). This report examines the estimated effects of delayed access to these drugs experienced by Canadians in terms of potential numbers of patients affected.

The report is divided into four sections. In the first, aspects of the cancers treated by the five drugs are reviewed, while the benefits, risks, and regulatory and reimbursement milestones of the drugs are considered in the second. Estimates of the potential numbers of patients affected by delayed access in Canada and the potential economic value of lives lost are presented in the third section. Implications of the estimates are discussed in the final section.

Cancers Treated by the Five Drugs

The original indication for each of the five drugs as approved in Canada is shown in table 1. Four of the drugs are for the treatment of breast, colorectal, lung, and prostate cancers that each account for more than 10% of the total deaths from cancer in Canada in 2013 (CCS, 2013a).

Excluding non-melanoma skin cancers, lung cancer is the most commonly diagnosed cancer and the main cause of cancer-related deaths in Canada (The *Lancet* has called the disease "a global scourge" [2013]). By gender, breast

Table 1: Original approved indication in Canada

Drug	Initial approved use
Avastin	First-line treatment (in combination with fluoropyrimidine-based chemotherapy) of metastatic colorectal cancer patients
Halaven	Treatment of metastatic breast cancer patients previously treated with at least two chemotherapy regimens that should have included an anthracycline and a taxane administered in either the adjuvant or metastatic setting
Jevtana	Treatment (in combination with prednisone or prednisolone) of castration-resistant (hormone refractory) metastatic prostate cancer patients previously treated with a docetaxel-containing regimen
Tarceva	Monotherapy treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen, and whose epidermal growth factor receptor expression status is positive or unknown
Torisel	Treatment of patients with metastatic renal cell carcinoma

Source: Health Canada, 2013.

and prostate cancers have the highest annual incidence in women and men, respectively, and breast cancer ranks as the second most common cause of cancer death in women. Colorectal cancer is the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths in both men and women. Although kidney cancer is less common than the other four cancers, its age-standardized annual incidence has increased over the last 30 years in Canadian men by almost 45% from 11.3 to 16.4 per 100,000 (CCS, 2013a).

All five drugs in this study are for the treatment of solid tumours that have spread (metastasized) to other parts of the body. These are difficult to treat and generally have a poor prognosis. The striking difference between the five-year survival rates for patients with localized and metastasized disease can be seen in table 2.

Screening

Tumours detected early are usually more treatable than those discovered at a later stage of development. Recommended, commonly available, cancer screening programs exist in Canada for the early detection of breast, colorectal, and prostate cancers.

Participation in mammography screening for breast cancer is relatively high and close to the target of 70% in a two-year period. For instance, from 2004 to 2006, the participation was estimated to be 63% over two years, which increased to 70% when the time frame was extended to 30 months (Doyle et al., 2011). Nevertheless, a significant proportion of Canadian women are not being screened regularly or at all.

Screening for prostate cancer is also quite high. A large proportion of men aged 50 years or more receive regular screening via a digital rectal examination and a prostate-specific antigen test (Allard et al., 2012), although controversy surrounds the value of these tests for detecting the disease (Hoag and So, 2012).

The rate of screening for colorectal cancer in Canada is inadequate in spite of the high incidence and mortality associated with this disease. In a 2003 survey of nearly 13,000 people aged 50 years or more who were eligible for screening and at average risk for colon cancer, the proportion of respondents who reported any history of colorectal cancer screening was 23.5%, which dropped to 17.6% when only up-to-date screening (that is, within the time frame recommended in guidelines) was considered (Zarychanski et al., 2007).

Regular screening for lung and kidney cancer is not performed. As a result, these diseases frequently go undiagnosed until the disease has progressed significantly.

Table 2: Five-year survival rate (%) by stage at diagnosis in the United States, 2002–2008

	Breast	Colorectal	Kidney	Lung	Prostate
Localized disease	98	90	91	52	100
Metastasized disease	24	12	12	4	28

Source: ACS, 2013

Disease Staging

At diagnosis, solid tumours are classified using a system known as staging, which is based on (a) the size of the primary tumor, (b) whether cancer cells have spread to nearby lymph nodes, and (c) whether the cancer has metastasized to other parts of the body (NCI, 2013). Tumours are then categorized into four stages (I, II, III, and IV) with higher numbers signifying more extensive disease. Stage IV indicates that the cancer has metastasized to distant tissues or organs. Some cancer registries reduce the categories to three: localized (limited to the organ in which it began with no evidence of spread); regional (extended beyond the primary site to nearby lymph nodes or tissues and organs); or distant (spread from the primary site to distant tissues or organs or to distant lymph nodes).

Staging at diagnosis is important because it is used in estimating the patient's prognosis and assists physicians in planning the appropriate treatment. Since all five drugs in this study are for the treatment of metastatic cancers, it is crucial to know the distribution of patients by stage at diagnosis but this information is not available at the national level in Canada.

The Five Drugs

Benefits

The drugs were chosen because each was tested in a pivotal randomized clinical trial (RCT) that demonstrated a statistically significant increase in overall survival when compared with standard therapy. The same RCT was used as evidence of the overall survival benefits in each drug's application to both Health Canada and the US Food and Drug Administration (FDA).

The increase in the median overall survival time in each trial was small (table 3), although it represented improvements of between 19% and 49%. These figures re-emphasize the poor prognosis for patients with metastasized cancers and how difficult they are to treat.

Benefits have also been demonstrated in other studies for all five drugs. Avastin has been shown in a meta-analysis of six RCTs to improve overall and progression-free survival significantly in metastatic colorectal cancer (Galfrascoli et al., 2011). Halaven is the first monotherapy to demonstrate both significantly and clinically meaningful improvements in overall survival in metastatic breast cancer

Table 3: Median overall survival (in months) reported in each drug's pivotal RCT study

Drug (study authors)	Median overall survival on study drug	Median overall survival on comparator drug	Difference between medians (% of comparator drug median)
Avastin (Hurwitz et al., 2004)	20.3	15.6	4.7 (30%)
Halaven (De Bono et al., 2010)	13.1	10.6	2.5 (24%)
Jevtana (Cortes et al., 2011)	15.1	12.7	2.4 (19%)
Tarceva (Shepherd et al., 2005)	6.7	4.7	2.0 (43%)
Torisel (Hudes et al., 2007)	10.9	7.3	3.6 (49%)

patients (Perry, 2011). Jevtana, which is only the second drug approved in Canada to treat castration-resistant metastatic prostate cancer (most metastatic prostate cancer patients fall into this category), has been shown to improve survival with a predictable, manageable side effect profile (Saad and Asselah, 2013; Sperlich and Saad, 2013). Tarceva has been extensively studied in patients with metastatic non-small cell lung cancer (NSCLC) and found to be particularly efficacious in improving overall survival in those with the epidermal growth factor receptor (EGFR) mutation (Melosky et al., 2008; Piperdi and Perez-Soler, 2012). Torisel has been shown to provide significant overall and progression-free survival benefits and is associated with fewer withdrawals due to adverse effects (Simpson and Curran, 2008). For some, Torisel is now considered the standard for renal cell carcinoma patients with poor prognostic features (Bukowski, 2012). In addition, the introduction of improved oncology drugs has been shown to increase life expectancy and to be worth their high costs (Lichtenberg, 2009, 2011).

Risks

Each of the five drugs is a powerful therapeutic product that can have significant adverse effects, which may be so severe that they result in the patient being unable to complete the treatment. Table 4 shows the most common serious adverse events reported (in no particular order) at the time of their approval. Four of the drugs may have negative effects on the cells of the blood, that is, neutropenia, leukopenia, thrombocytopenia and anemia, and two may cause hemorrhaging.

Estimates of the incidence of adverse events come from pre-marketing RCTs (in which patients are carefully monitored) or post-marketing studies (where patients are less rigorously observed) and, as a result, they vary widely. Moreover, some estimates refer to all occurrences of the adverse event, while others

Table 4: Most common serious adverse events reported at the time of approval

Avastin	Halaven	Jevtana	Tarceva	Torisel
Neutropenia	Neutropenia	Neutropenia	Gastrointestinal hemorrhage	Thrombocytopenia
Hemorrhage	Leukopenia	Hematuria	Diarrhea	Anemia
Arterial thromboembolism	Peripheral neuropathy	Cardiac disorders	Interstitial lung disease	Interstitial lung disease
Gastrointestinal perforation	Asthenia	Diarrhea	Rash	Rash
Impaired wound healing				
Hypertension				

Source: Health Canada, 2013

only consider severe cases. Nevertheless, the incidence of severe cases of several of the events in table 4 is at least 5% to 10%.

Regulatory and Reimbursement Milestones

Table 5 summarizes the type of regulatory review, the submission and approval dates, and the duration of the review in the United States and Canada for each of the drugs. The applications for marketing approval for all five drugs were submitted first to the US FDA. The Canadian applications for the older products were submitted prior to their approval by the FDA, whereas those for Halaven and Jevtana were submitted after their FDA approval. This is consistent with the finding that, in comparison with practice in the United States, new drug applications are being submitted later in Canada more frequently than in previous years (Rawson, 2013).

All five drugs received an expedited review in the United States compared with only three in Canada.[1] Each drug received approval from Health Canada between 205 and 591 days after FDA approval, and the time required to review each drug was 1.5 to 4.5 times longer in Canada than in the United States. The longer review time in Canada was not related to the type of review.

Table 5 also shows the first Canadian province to provide total or partial reimbursement for the drug and the earliest date of reimbursement, which was between 56 and 412 days after the drug received marketing approval from Health Canada. Decisions regarding funding can take a long time in some provinces so that, at the end of June 2013, only Avastin and Tarceva were reimbursed in all 10 provinces, while Torisel was reimbursed in nine. The newer products, Jevtana and Halaven, were funded in three provinces and one province, respectively. The most recent province to reimburse each drug and when it did so is presented in table 5. The time difference between the first and last provinces to approve reimbursement for Avastin, Tarceva, and Torisel was 3.5 to 4.5 years.

Potential Number of Patients Affected by Delayed Access to the Five Drugs

The box, Methodology (page 9), describes details of the methods used to estimate how many patients were likely to have been affected by federal and provincial delays. Federal delay was defined as the time taken for the regulatory review beyond the performance targets of 205 and 345 days for priority and standard review drugs, respectively (Health Canada, 2011). Provinces do not approve a new drug for reimbursement immediately after Health Canada has given its marketing approval. An application must be submitted, reviewed, and a decision made. However, once the first province has approved a drug for reimbursement, the additional time taken by the other provinces constitutes a delay that could be eliminated by a mutual recognition process. Therefore, current provincial delay was considered to be the time taken beyond the date on which the first province approved the

1 The FDA has three approaches to expedite the review of drugs to treat serious conditions that fill an unmet medical need: fast track, accelerated approval, and priority review (Thaul, 2012). Health Canada has only one method: priority review. To qualify for priority review status, a drug must not only be intended for patients suffering from a life-threatening or severely debilitating disease but must also be indicated to treat, prevent, or diagnose a serious symptom or manifestation of the disease (Health Canada, 2009).

Table 5: Regulatory and reimbursement milestones in the United States and Canada for each drug

	Avastin	Halaven	Jevtana	Tarceva	Torisel
Review type in United States	Priority	Priority	Priority	Priority	Priority
Approval date in United States	26/2/2004	15/11/2010	17/6/2010	18/11/2004	30/5/2007
Review time (days), US Food and Drug Administration	149	230	78	111	237
Submission date in Canada	27/1/2004	31/12/2010	2/7/2010	25/10/2004	20/11/2006
Review type in Canada	Priority	Standard	Standard	Priority	Priority
Approval date in Canada	9/9/2005	14/12/2011	16/6/2011	7/7/2005	21/12/2007
Review time (days), Health Canada	591	348	349	255	396
First province to reimburse	British Columbia 1/1/2006	Quebec 1/11/2012	Ontario 1/8/2012	British Columbia 1/9/2005	Nova Scotia 9/4/2008
Days between approval and earliest reimbursement, Canada	114	323	412	56	110
Most recent province to reimburse	Prince Edward Island 1/7/2010	n/a	Alberta, Saskatchewan 4/10/2012	Prince Edward Island 1/3/2009	New Brunswick 4/10/2012
Days between approval and latest reimbursement	1,756	n/a	476	1,333	1,749

Note: n/a: not applicable.

drug for reimbursement until either a province gave reimbursement approval or June 30, 2013, whichever occurred first.

The estimated annual number of new cases of the cancer at the time of the marketing approval of the drug, the proportion of newly diagnosed patients with the appropriate metastatic indication, and the resulting estimated annual and daily numbers of new cases for whom the drug could be appropriate are shown in table 6. It is anticipated that only a proportion of the potentially eligible patients would respond to treatment because the benefits in the tightly controlled, experimental environment of the RCT (efficacy) is usually less than 100%—for example, the overall efficacy was less than 45% in the Avastin pivotal RCT (Hurwitz et al., 2004)—and because how well it works in the less-controlled, real world of the oncologist's clinic (effectiveness) is likely to be even lower (Rawson, 2001; Thaul, 2012). Therefore, to be conservative, it was arbitrarily assumed that only 25% of the patients would respond to each of the drugs and would, consequently, be negatively affected by the delay in access in

Table 6: Potential numbers of Canadian patients affected by delayed regulatory and reimbursement approval, assuming an arbitrary 25% response rate

	Avastin	Halaven	Jevtana	Tarceva	Torisel	Total
Annual new cases of relevant cancer	19,690	23,310	25,520	22,050	4,865	95,435
New cases estimated to match indication	20%	6%	11%	6%	24%	
Estimated new cases for whom the drug could be appropriate: annual (daily)	3,938 (10.8)	1,399 (3.8)	2,807 (7.7)	1,323 (3.6)	1,168 (3.2)	
Number of potential patients negatively affected by:						
Federal delay [1]	1,041	3	8	45	153	1,250
Current provincial delay [2]	2,072	169	305	223	703	3,472
Federal and current provincial delays combined	3,113	172	313	268	856	4,722
Estimated total provincial delay [3]	2,072	349	500	223	704	3,848
Federal and est. total provincial delays combined	3,113	352	508	268	857	5,098

Note 1: Federal delay is the time taken for the regulatory review beyond the appropriate performance standard.

Note 2: Current provincial delay is the time taken beyond the date on which the first province approved the drug for reimbursement until either a province gave reimbursement approval or June 30, 2013, whichever occurred first.

Note 3: Estimated total provincial delay is the time taken beyond the date on which the first province approved the drug for reimbursement until either a province gave reimbursement approval or the estimated date was reached.

Sources: CCS, 2013b; CCM, 2013; Alvi et al, 2011; SEER, 2013; FDA, 2013

Canada. Under this assumption, the potential number of patients affected by the federal and current (that is, as at June 30, 2013) provincial delays are 1,250 and 3,472, respectively (a total of 4,722). The biggest delays were for Avastin and Torisel.

If each of the 4,722 patients had received the relevant drug and achieved the median survival benefit shown in table 3, this would have led to a total extension in survival over standard therapy of 1,619 patient-years. Estimating the economic value of a human life is a complex matter (Viscusi and Aldy, 2003). However, the value of a life lost due to cancer has been estimated to be US$150,000 per year (Cutler et al., 2000; Lichtenberg, 2004; Viscusi and Aldy, 2003) and used to assess the value of lives lost from cancer in the United States (Yabroff et al., 2008). After adjusting for inflation between 1999 and 2012, US$150,000 increases to US$200,000. Assuming parity between the US and Canadian dollars and applying this figure to the 1,619 patient-years gives an estimated economic value for these years of $323.8 million. This amount is based on an averaged value, whereas patients with metastatic disease, whose life expectancy is short, place a higher value on extending survival of $200,000 to $300,000 per year gained (Hirth et al., 2000; Seabury et al., 2012). Taking the middle of this range and inflating from 2000 to 2012 dollars gives a value of $330,000. Using this figure, the estimated economic value is $534.3 million.

Methodology

To estimate the potential number of new patients suitable for each drug, it is necessary to know two pieces of information: (a) the number of new cases of the cancer at the time of the approval of the drug, and (b) the proportion of newly diagnosed patients with metastatic disease. The number of Canadians newly diagnosed with the relevant cancer in each province in the year that the drug was given marketing approval was obtained from the annual publication of the Canadian Cancer Society (CCS, 2013b).

The CCS does not, however, record disease stage. Use was made of information from all available Cancer Care Manitoba annual statistical reports from 2004 to 2010 (CCM, 2013), which list stage at diagnosis in four categories, and from a Saskatchewan Cancer Agency (SCA) report that has data on stage at diagnosis, categorized as localized, regional, or distant, for four of the cancers for the period 2005 to 2007 (Alvi et al., 2011). Since Manitoba and Saskatchewan are relatively small provinces, a request for stage-at-diagnosis data from 2011 for the five cancers was submitted to Cancer Care Ontario (CCO), which uses the four-category system. In addition, stage at diagnosis information from the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER, 2013), which collects stage-at-diagnosis data categorized as localized, regional, or distant from cancer registries in 15 states, was used. Stage-at-diagnosis data from the four sources were all relatively consistent.

For Avastin, Halaven, Jevtana, and Torisel, the median of the percentages of stage-IV patients from the CCM and CCO data and distant category patients from the SCA and SEER data was used to estimate the relevant percentage of newly diagnosed metastatic patients. The same median was calculated for Tarceva, but because this drug is also indicated for patients with locally advanced disease, the median of the percentages of stage-III patients from the CCM and CCO data and regional category patients from the SCA and SEER data was also calculated, and the two medians summed. Tarceva is indicated for patients with non-small cell lung cancer (NSCLC) whose EGFR expression status is positive or unknown. Alvi et al. (2011) reported that NSCLC constitutes 88% of all lung cancers and the FDA has estimated that EGFR gene mutations are present in approximately 10% of NSCLC cases (FDA, 2013). Therefore, the sum of the two median percentages was reduced first by 12% and then by 90%. For each drug, the daily number of new cases for whom the drug could be appropriate was multiplied by the relevant percentage of newly diagnosed patients at the metastatic stage to obtain the daily number of newly-diagnosed metastatic patients.

The dates on which reimbursement was begun by the provinces were requested from the manufacturers. One did not provide them and, consequently, dates were sought from the relevant cancer agencies and internet searches, which resulted in using the date of the announcement of the start of reimbursement in a few cases, but since this date either preceded or was the same as the date on which reimbursement began, the effect was to underestimate the delay. Often dates were only available as month and year, in which case the day was assumed to be the first of the month in order to be conservative in calculating the delay. The date on which the first patient actually received reimbursement in any province is unknown but was likely to be after both the date of the announcement of reimbursement and the date on which it came into effect.

There are two types of access delay. The first is the federal delay due to Health Canada failing to review drugs within its performance standards of 205 and 345 days for priority and standard reviews (Health Canada, 2011). To estimate the impact upon patients of federal delay, the relevant daily number of newly diagnosed metastatic patients was multiplied by the number of days between the date on which approval would have been received if the performance standard had been achieved and the date on which it was actually given.

The second delay is the provincial delay. Where a province had approved reimbursement, the impact upon patients of provincial delay was estimated by multiplying the relevant daily number of newly diagnosed metastatic patients by the number of days between the date on which the first province approved reimbursement and the date when the relevant province approved reimbursement. When reimbursement had not been approved, the time to June 30, 2013 was used as a first estimate ("current province delay"). However, at the end of June 2013, the provincial delay for Halaven and Jevtana is underestimated. The times taken by each province to approve reimbursement for Avastin, Tarceva, and Torisel were averaged and used to provide an estimated date where a drug was yet to be approved. "Estimated total provincial delay" was calculated as the time taken beyond the date on which the first province approved the drug for reimbursement until either a province gave reimbursement approval or the estimated date was reached.

At the end of June 2013, Halaven and Jevtana had been approved for marketing by Health Canada for 564 and 745 days, respectively. Since 52% of the times taken by provinces to approve reimbursement for Avastin, Tarceva, and Torisel exceeded 745 days and 59% were longer than 564 days, it is obvious that the provincial delays for Halaven and Jevtana at June 30, 2013 are underestimated. The times taken by each province to approve reimbursement for Avastin, Tarceva, and Torisel were averaged and used to provide an estimated date where a drug was yet to be approved. Estimated total provincial delay was then calculated as the time taken beyond the date on which the first province approved the drug for reimbursement until either a province gave reimbursement approval or the estimated date was reached. This increased the provincial delay to 3,848 patients and the total federal and provincial delay to 5,098 (table 6). If each of these patients had received the relevant drug and achieved the median survival benefits shown in table 3, the total extension in survival over standard therapy would be 1,696 patient-years and the estimated value of this extended survival would range between $339.2 and $559.6 million.

To evaluate the impact under an assumption of minimal drug effectiveness, the results were re-calculated assuming only a 10% response rate. In this scenario, the total federal and estimated provincial delays would affect 2,250 patients. Even under this extreme assumption, the estimated number remains substantial. The estimated value of extended survival with this response rate would be between $148.3 and $244.7 million.

Discussion

The analysis of these five oncology drugs is consistent with an evaluation of the time taken to review 454 new drugs approved in both Canada and the United States between 1992 and 2011, which showed that, over the 20 years, there has been an increasing delay between the submissions of the marketing applications to the US FDA and Health Canada (Rawson, 2013). The 20-year study also found that, although the difference between the overall median approval times in the two countries decreased from 2007 to 2011 compared with the previous 15 years, oncology drugs continued to take longer to be reviewed and approved in Canada. Furthermore, significantly fewer drugs received priority status in Canada (20% compared with 40% in the United States), a difference that was more profound in oncology drugs (29% versus 77%).

The present analysis demonstrates that, even under conservative assumptions, federal and provincial delays in access to the five drugs could affect a large number of patients who may have received benefit from the drugs. The assumption that only 25% of the patients are likely to receive benefit may be too low for the first-line therapies (Avastin and Torisel), which would increase the estimated numbers of negatively affected patients for these drugs.

The estimated value of the lives lost is huge, ranging from $339.2 to $559.6 million, depending on how one values an extension of a year of life. The substantial costs of the drugs must be set against these estimates but, even if the cost for each patient were $50,000, the economic value outweighs the cost by a significant margin. Moreover, the value placed on drugs by

terminally ill patients is commonly 10 times the cost of the drug (Seabury et al., 2012). In addition, since almost all the provinces have decided to provide reimbursement for the three oldest drugs (Avastin, Tarceva, and Torisel) even if it took them up to 4.5 years to do so, it appears that provincial governments consider these drugs to be worth their cost, which suggests that the delays in approving reimbursement were not due to high prices but to a slow approval process.

Lack of transparency

There are caveats concerning the data used in this study for reasons that include the absence of national information about the stage of new cancers diagnosed each year and, for some drugs and provinces, imprecision about the dates on which they were approved for reimbursement. Stage is recorded at diagnosis in the records of all cancer patients and is documented by some cancer agencies (Alvi et al., 2011; CCM, 2013). However, it seems that only two smaller provinces make any effort to disseminate this information. Ontario, which has staging data, provides them only in response to a special request, which takes several months. It is difficult to understand how the provision of cancer treatment services can be planned efficiently and effectively if decision makers do not have information on important factors such as the distribution by stage of the anticipated number of new cancer patients. Moreover, a societal assessment of the national performance in screening and treating cancer is hindered by the lack of access to this information (*CBC News*, 2013).

Conservative estimates

The lack of precise and transparent of information about when drugs were approved for reimbursement by provincial insurance plans appears to result from either careless record keeping or secrecy. Even if the general public is ignorant of the fact, many cancer patients and others with major diseases resistant to treatment are aware of the absence of transparency and fairness that are frequently part of provincial drug-reimbursement decision-making processes. In the context of this study, it important to note that neither the date on which reimbursement began nor that of the announcement of reimbursement approval (the only date available in a few instances) is likely to be the same as the date on which the first patient received reimbursement, implying that the number of patients potentially affected is further undervalued.

Estimating the potential provincial reimbursement dates for Halaven and Jevtana by averaging those for Avastin, Tarceva, and Torisel may not be reliable. Nevertheless, some assessment of the eventual reimbursement approval dates must be incorporated to avoid significantly underestimating the number of patients that could be affected by delayed provincial access to these two drugs. Avastin, Tarceva, and Torisel were given priority status by Health Canada, while Halaven and Jevtana received a standard review, which may result in these drugs being seen as less important by provincial reviewers. This scenario is supported by the fact that the first provinces to reimburse Halaven and Jevtana took 323 and 412 days, respectively, to do so, compared with 56 to 114 days for the other three drugs (table 5). The slower approval for Halaven and Jevtana suggests that the number of patients potentially affected by provincial delays is likely to be considerably greater than those affected by delayed access to Tarceva or Torisel.

In addition to these caveats, it is important to note that the study only focused on newly diagnosed metastatic disease patients. Although disease frequently progresses during the

waiting time for access to diagnostic tests and oncologists (Barua and Esmail, 2012; Singh et al., 2010), patients commonly remain categorized by their stage at diagnosis. Therefore, patients with disease progression from localized to metastatic and who may have become appropriate candidates for the drugs were not included in this analysis. Similarly, current stage data on patients who were diagnosed at an earlier time (prevalent cases) are not available and they are also not included. Finally, no account could be taken of patients who may have received the drug under a government or manufacturer's compassionate release program, but their numbers are probably small.

The effect of these exclusions is likely to vary by drug. Since screening detects many breast and prostate cancers at an early stage, the proportion of patients with these cancers who progress to metastases may be small. This view is supported by data from Manitoba, where change in stage of breast cancer is monitored, that showed that only 3.5% of patients whose stage at diagnosis was I, II, or III in 2010 subsequently progressed to stage IV (personal communication, Cancer Care Manitoba, 2013). However, the proportion of patients that progress to metastases may be much higher in colorectal, lung, and kidney cancers where screening is inadequate or non-existent, so that the numbers of patients that could be affected by delayed access to Avastin, Tarceva, and Torisel could be markedly underestimated. When drugs are second- or third-line therapies (that is, used after other chemotherapies have been tried) such as Halaven, Jevtana, and Tarceva, the numbers may also be seriously underestimated due to patients with prevalent disease being omitted. Thus, the overall effect of the exclusions almost guarantees that the numbers are significantly underestimated.

Poor access to advances in cancer treatment

A new drug can have a beneficial effect but it may be difficult to demonstrate a favourable benefit-cost ratio because of a high cost. Other factors that influence the cost-benefit assessment are disagreement over the appropriate comparator drugs and health outcomes in the analysis, as well as the analytical methods and the lack of real-world experience with costs and outcomes. Using mainly RCT data, favourable comparative cost-effectiveness outcomes have been demonstrated for Tarceva (Schwander et al., 2012; Vergnenègre et al., 2012; Walleser et al., 2012; Wang et al., 2013) and Torisel (Thompson Coon et al., 2010), but the results for Avastin have been more contentious (Gilligan, 2012; Hedden et al., 2012). Although post-approval data provide a more accurate assessment of cost-effectiveness, reimbursement decisions are based on pre-marketing estimates, which can be unreliable. Consequently, the decision-making process at the provincial level is known to be less than optimal and frequently inequitable. This inequity is highlighted by the fact that, even when approved, not all patients are eligible for reimbursement because, in some cases, benefits are only available to specific patients based on disease, age, or income criteria (Khoo, 2013).

A result of this system is that Canada is one of the countries with "the most restricted access to publicly funded cancer drugs" (Cheema et al., 2012). Moreover, interprovincial differences in the reimbursement of oncology drugs raise serious concerns among patients (Picard, 2009; Chafe et al., 2011; Turner & Associates, 2008). These differences also significantly affect how oncologists practice. In a survey of Canadian oncologists conducted in 2007, only 29% of the physicians felt that they had been using the ideal first-line chemotherapy regimen for

metastatic colorectal cancer and 97% reported concerns about the drug approval and reimbursement processes (Chan et al., 2012).

Methods for assessing new oncology products in Canada are still maturing with the introduction of the pan-Canadian Oncology Drug Review (pCODR) in late 2010 (Walkenshaw, 2011) and disease-specific health technology assessment guidelines in 2012 (Mittmann et al., 2012). The review process continues to be focused on an assessment of cost per quality-adjusted life year, which tends to create a fixed-cost cut-off point for reimbursement decision-making, rather than allowing for other factors, often difficult to enumerate, to be considered in the process (Cohen and Looney, 2010; Gavura et al., 2011). Patient and societal views are two of these less tangible inputs that should be included in decision making (Krol et al., 2007; Gavura et al., 2011). Patient views can be included in the pCODR review process but, when provinces make their decisions regarding reimbursement, they are often more focused on the impact on their drug budget than on patients' desires as a result of the siloed nature of the provincial health-care systems (Deveau, 2013, Sept. 17), which has contributed to access restrictions leading to inequity (LeLorier et al., 2008; Drummond et al., 2009). Moreover, the decision process can take too long. Timeliness is important to patients as well as to their physicians and manufacturers; not making a decision is the same as a decision not to reimburse.

New approaches to evaluate drugs have been proposed, but few, if any, have been put into action. If rationing of high-cost oncology drugs is unavoidable, it should be equitable and based on methods that include both clinical guidelines and patients' input. The results of such decisions should also be monitored to ensure that the drugs are used properly because inappropriate drug use diminishes cost-effectiveness (Bonifazi et al., 2012; Aitken and Valkova, 2013).

Conclusion

The results of this study demonstrate that over 5,000 patients with serious disease, whose options are limited, could have been affected by delays in the federal regulatory review and in provincial reimbursement approval for just five of the 24 new oncology drugs approved in Canada between 2003 and 2011 that may have alleviated their disease. This number was derived under conservative assumptions so that it is likely to be significantly underestimated. The magnitude of the number demonstrates that the slow regulatory and reimbursement approval processes in Canada deny access to drugs that may extend the lives of several thousand terminally ill patients. In contrast to the victims of adverse drug reactions whose identities often become public in both the medical literature and the media (Sibbald, 2001; Chai and Politi, 2013), patients affected by slow regulatory and reimbursement-approval procedures leading to a lack of reimbursed access are anonymous and receive less attention from decision makers. Nevertheless, the numbers in this study represent real people and are substantial. More importantly, their suffering is real and should not be ignored.

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