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Title	Cancer treatment on financial aid in a publically funded system: a retrospective cohort study on the Ontario Trillium Drug Program
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Reviewer 1	Waseem Sharieff
Institution	Department of Radiation Oncology, Faculty of Medicine, Dalhousie University, Halifax, NS
General comments (author response in bold)	<p>The authors use administrative database to estimate cost of drugs funded through the public fund for cancer treatment. They found the cost has significantly increased over the past two decades. The authors address an important issue. I have following suggestions for further improvement of the manuscript,</p> <ol style="list-style-type: none"> 1. Cost of drugs could be grouped under a) cytotoxic, b) biologic/targeted agents, c) hormonal, and d) supportive. Thank you for your suggestion. We have modified Figure 2 such that the treatment drugs are grouped as: cytotoxic chemotherapy, LHRH agonist, aromatase inhibitor, antiandrogen, other treatment and supportive therapy. 2. In addition to presenting absolute costs, it may be helpful to present costs as a percentage of annual budget. Thank you for your comment. However we were not able to gain access to the annual budgets for the TDP for the purposes of our research. 3. Graphs need a legend with brief interpretation. We have created a new Figure 2, which we hope will be more easily understood as a standalone graph. 4. Discussion section should address the questions why the study was done, what was found, how results compared with other studies, and what is implication of results on public policy. Thank you for your comment. We feel that the first paragraph of the Interpretation on page 7-8 explains what was found. We have added a sentence to this paragraph (line 229 – 230) to elaborate more on why the study was conducted. Throughout the remainder of the Interpretation, we have further discussed study results and how they compare with other studies. The final paragraph of the Interpretation on page 9 discusses possible implications of the study.
Reviewer 2	David Stock
Institution	Community Health and Epidemiology, Dalhousie University, Halifax, NS
General comments (author response in bold)	<p>This manuscript is a very well written, relatively concise description of the cost of Ontario's Trillium Drug Plan. It presents a timely and effective perspective on the financial burden of chronic disease – particularly cancer - through documenting not only the rise in cost of prescribed treatments, but also the increasing dependency on such publicly-funded programs.</p> <p>Minor Revisions</p> <p>Title</p> <ol style="list-style-type: none"> 1. Suggest changing the title to something along the lines of: "Cost of cancer treatment in a publicly funded system among an Ontario-wide cohort".

a. First, this study does not assess “impact”. It describes and compares costs of TDP claims and cancer treatments (i.e., there is no effect measure that would normally convey an epidemiological or population-based assessment of impact).

b. Second, this is not a “cohort study” according to the epidemiological definition which studies exposure-outcome associations and should be changed for clarity. Due to this, the STROBE is largely not applicable as this is a descriptive study (and the STROBE mostly pertains to cross-sectional, cohort or case-control-based observational designs – the key shared attributes of all being that these designs assess the effect of an exposure on an outcome). [Ed note: we believe that STROBE is applicable]

Thank you for your comment. As per the editor’s comment above, we have updated the title to read: “Cancer treatment on financial aid in a publically funded system: a retrospective cohort study on the Ontario Trillium Drug Program”

Abstract

2. Results: “Although the proportion of claims remained constant” If the denominator is total number of TDP claims (as apparent in Results), suggest stating this more transparently to the reader: “Although the number of cancer-related relative to all claims remained constant...”.

Thank you for the suggestion. We have made the clarification as suggested on page 7, line 191: “Although the proportion of cancer-related claims relative to all TDP claims remained constant”

Results

3. Adjustment for inflation. (Results paragraph 1; pg 6; Ln 17-21). Might be informative to provide an inflation-adjusted change in cost of cancer treatments billed through TDP over the study period.

Thank you for your comment. We have decided to include inflation in our primary analysis. All figures and in-text values have been updated throughout the Results section (pages 6-7).

4. More specific study period ranges? (pg 6; Ln 30-31). “first several years (80% of the annual total), imatinib and temozolomide throughout the 2000s (70% of the annual total) and finally dasatinib and lenalidomide upon their introduction in the last several years (40% of the annual total).”

Thank you for your comment. We have updated this sentence to be more specific to the years. It now reads as follows (page 7 lines 196 – 199): “Different treatment drugs dominated total annual TDP costs throughout our study period: interferon made up the highest proportion (upwards of 60% of the annual total) from 1997 to 2002. Dominance shifted to imatinib at that time, and finally dasatinib and lenalidomide made up approximately 40% of the annual total from 2014 to 2016 upon their introduction. More details on year-over-year costs for select high-cost cancer treatment drug costs can be found in eFigure 1.”

5. Probably clearer to define a specific interval and state “approximately X% of annual total” for this range.

Please see comment 4 above.

Table 1

6. Possibly redundant to include all 3 columns (as the third is a sum of the first 2).

Thank you for the comment. We have elected to retain the third column, as we thought it was worth noting the difference in age between the first two columns.

7. Suggest omitting p-value column from Table 1. The use of hypothesis testing (e.g., t-tests) and corresponding p-values for Table 1 is somewhat dubious as the data include all TDP claims for the study period (i.e., not a sample thereof). Therefore, the calculated differences in means and proportions are the true differences. Further it is becoming increasingly recommended to forgo multiple crude hypothesis testing in descriptive tables*. **“Inferential measures such as standard errors and confidence intervals should not be used to describe the variability of characteristics, and significance tests should be avoided in descriptive tables” Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014 Dec;12(12):1500-24.

Thank you for your response. We have removed the p-values column in Table 1.

Figure 2.

8. Suggest using inflation-adjusted dollars for easier comparison across study period.

Thank you for your comment. We have decided to include inflation in our primary analysis. All figures and in-text values have been updated throughout the Results section (pages 6-7).

eFigure 1

9. Suggest having Y-axis as “proportion of annual cost” (given that costs were aggregated annually) rather than dollar amount. (This is mainly to adjust for inflation to present a better comparison across study period)

The y-axis in this figure is the proportion of total annual cost. We have modified the title of this figure for clarity and included an axis label.

eFigure 2.

10. As above, suggest using inflation-adjusted dollars.

We have decided to include inflation in our primary analysis, therefore the updated Figure 1, will be the same as the previous eFigure 2, and thus 2Figure 2 will no longer be included in the manuscript.

Interpretation

11. Pg 11; In 2-18. A very brief description of how the TDP works would allow the reader to better evaluate the propensity for “financial toxicity”. Eg, What is the

	<p>deductible, and how is it calculated and paid by the client? One or two sentences should suffice.</p> <p>We have now added a sentence to page 9 lines 285-288 as follows: “However, when on TDP, the patient is only required to pay an annual deductible (about 4% of one’s household income after taxes) before the TDP coverage can begin, after which the patient is only required to pay up to \$2 for each drug that is filled or refilled.”</p> <p>12. And related to financial toxicity, the sentence “However, it is our hope that improved access to TDP will positively affect patient outcomes and reduce their burden of financial toxicity.” Is there reason to believe that there are substantial barriers to accessing the TDP currently? If so, briefly justify. If not, what is the function of this statement? If it can’t be materially improved, then what is the potential for a positive effect on outcomes, etc?</p> <p>Thank you for your comment. We have decided to remove this sentence from the manuscript. Once we added background on how cancer treatments are subsidized in other jurisdictions (see comment below), we felt that this sentence was no longer needed and added unnecessarily to the manuscript word count.</p> <p>13. Despite length constraints, it would strengthen context to briefly discuss how treatments for cancer and other chronic conditions are subsidized in other jurisdictions with access to public insurance.</p> <p>Thank you for your comment. We had added a few sentence on this on page 9 lines 288-297 as follows: “In contrast, the cost of cancer in the US is often subsidized by insurance, managed care or public health care programs, however the cost of cancer drugs are often higher than prices in Canada as it is up to the private market to set appropriate prices. Alternatively, cancer drugs are subsidized in the UK through the National Health Service (NHS) or through private cancer treatment; drugs will be available to the patient based on treatment approved by the National Institute for Health and Care Excellence (NICE) based on budgetary process or patients must pay out-of-pocket for treatments not approved by NICE, which is a common concern for patients in the UK. Therefore, cancer treatments are subsidized in different ways across the world; however the burden of cancer remains high, which suggests that more needs to be done to make cancer treatment more affordable and equitable for patients.”</p>
Reviewer 3	Kednapa Thavorn
Institution	Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ont.
General comments (author response in bold)	<p>The authors describe the characteristics and the cost of Trillium Drug Program (TDP) for patients with cancer. The study reports constant volume of TDP claims but increased total cancer treatment costs over the observation period. TDP claims for cancer and associated costs are found to be varied by cancer diagnosis. The manuscript is based on a simple descriptive analysis, and it reads well. I have a few minor questions.</p> <p>1. The authors indicated that the ODB database was used to identify prescriptions that claimed through TDP. Could the authors please clarify how the TDP claims were identified from the ODB? Is there a flag in the ODB database indicating TDP enrollees? What percentage of Ontario’s residents that have been</p>

covered by TDP? Did the number of TDP enrollees change over the study period? Of these enrollees, what was the percentage of cancer patients?

We have added clarification to the methods on page 5 line 121 to describe how TDP claims were identified: “the program by which the drug is funded (used to identify a TDP claim)”. We have also added a few sentences to the end of the first paragraph of the introduction (page 4) to describe the TDP program in more detail.

2. The authors performed a sensitivity analysis by applying a consumer price index. Please specify a currency year that the costs were adjusted to. Please also add a currency year for eFigure 2.

We have decided to include inflation in our primary analysis, therefore the updated Figure 1, will be the same as the previous eFigure 2, and thus 2Figure 2 will no longer be included in the manuscript. However we have updated the other figure titles to include the currency year.

3. On Page 6 (Line 21), please add standard deviations after the mean costs. **Please see our response to Editor comment #15 on page three.**

4. On Page 9 (Line 34 – 40), for patients who enrolled in the TDP before cancer diagnosis, to what extent the number of TDP claims and the average cost per claim increased after cancer diagnosis?

We have added this information to the Results on page 7 lines 214 – 219 as follows: “In the twelve months prior to cancer diagnosis, patients’ TDP claims were fairly stable, no matter the eventual cancer diagnosis, averaging \$300-\$400 per month (data not shown). However in the first month after cancer diagnosis, we observed a significant increase in the average TDP monthly claims compared to the month prior to diagnosis, for patients with brain cancer (over 500%), leukemia (over 70%), prostate cancer (over 30%) and myeloma (nearly 30%) (data not shown).”

5. Figure 1 and eFigure 2, there is no bar representing cancer treatment utilization. Is this due to a small number of claims? Please re-label the legends from “supportive and treatment” to “Cancer supportive therapy and Cancer treatment” Did the other category refer to treatments for other conditions or other treatments for cancer?

That is correct. The utilization was sufficiently low, that the bars were not displayed graphically in the figure. We have added a footnote to Figure 1 to explain this. We have also re-labeled the legends as suggested.

6. Figure 2, did -\$ refer to 0\$? It would be great to indicate that costs were reported as nominal Canadian dollars. This Figure would be easier to read if it is presented as stacked bars as they show how the proportion of the amount paid for each treatment changed over time.

Thank you for your suggestion. We have changed Figure 2 into a stacked bargraph as the reviewer has suggested.

7. Figure 3, there was a typo in the x-axis label.

Thank you for noticing this error and it has been changed in the manuscript.

8. eFigure 1, please fix the y-axis. The current form only has \$0.

	<p>We apologize for this error. It seems that once the figures were changed into a PDF through the online submission process, the labels in the figure became misaligned and the percentages were removed from the y-axis. This will look correct when we submit the editable figures to CMAJ Open.</p>
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