Author's response to reviews

Title: Increased financial burden among patients with chronic myelogenous leukaemia receiving imatinib in Japan: A retrospective survey study

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Author's response to reviews: see over
February 1st, 2012

Dr. Christa Chap,
Executive Editor in BMC Cancer
cc.ed to BMC Cancer editorial team

Dear Dr. Chap

Thank you very much for organizing the review process and for the reviewers’ thoughtful comments. I, along with my co-authors, would like to re-submit the attached manuscript entitled “Increased financial burden among patients with chronic myelogenous leukaemia receiving imatinib in Japan: A retrospective survey” as an original research article for publication in BMC Cancer. The manuscript ID is 2879200736437483.

The manuscript has been carefully rechecked and appropriate changes have been made in accordance with the reviewers’ suggestions and indicated as red sentences. The responses to their comments have been prepared and attached herewith.

Again, there is no conflict of interest in our paper. We state that the manuscript is original, is not under consideration elsewhere, and has not been published elsewhere. All authors agreed with the journal policies of BMC Cancer.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and better account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

I look forward to your reply.

Sincerely,

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Reviewer 1: Dr. Anne Mason,

Comments to the Author:
1-a. My understanding is that the key objective of the study is to establish the relationship between patient income, the financial burden of treatment, and patients’ consequent willingness to continue treatment (p. 6, para 2), using imatinib for CML as a case study. The findings relating to this are summarised in a single sentence (p.11, top) in the results section. The abstract contains mainly descriptive statistics on the population, but does not clearly report these key findings: that whilst around 75% of patients feel financially burdened by treatment costs, only 31% considered discontinuing treatment because of the financial burden, and a tiny percentage (2.6%) actually did discontinue treatment for this reason (albeit temporarily). This information needs to be more prominent: it should appear in the abstract, be positioned earlier in the results and its policy implications considered in the discussion (it’s mentioned on p14, but no policy implications are drawn out).

Our reply:
Thank you very much for your careful review and constructive comments. The abstract, results and discussion were reconstituted as follows:

“A financial burden of their medical expenses was felt by 41.2% (28 of 68) of participants with imatinib treatment in 2000, 70.8% (201 of 284) in 2005, and 75.8% (400 of 528) in 2008. Overall, 182 patients (31.7%) considered its discontinuation because of the financial burden and 15 (2.6%) temporarily stopped imatinib prescription.”

(Line 9 in Page 3, Abstract section)

“Patient perspectives on the financial burden of imatinib treatment and discontinuation of the prescription
In 2000, 28 patients out of 68 who were given an imatinib prescription (41.2%) felt that their medical expenses constituted a heavy financial burden, although not all medical expenses reflected the cost of imatinib because imatinib was not approved in Japan in 2000. This number and ratio have increased more recently, rising to 201 out of 284 (70.8%) in 2005, and 400 out of 528 (75.8%) in 2008.

A total of 261 patients (45.4%) had considered discontinuation of imatinib; 127 (22.1%) for the reason of side effects and 204 (35.5%) for other reason(s) (Figure 1). A total of 182 patients (31.7%) considered its discontinuation because of the financial burden that its use created. Imatinib prescription was actually stopped by 76 (13.2%) patients because of the side effects, and 15 (2.6%) temporarily stopped imatinib prescription.

(Line 4 in Page 10, Result section)

“From the patient perspectives, approximately 90% of the reasons to consider discontinuation of imatinib was their financial issues, and the rate of those who sensed the financial burden was getting higher year by year was approximately 40% in 2000 and 76% in 2008. Actually, 2.6% of the patients stopped imatinib prescription for financial reasons. While the ratio of patients who discontinued imatinib treatment is approximately 10% of that reported in a previous study in the United States, [15] it should be noted that Japan has a universal health insurance system that guarantees all Japanese citizens access to any hospital and standard therapies that are regulated by the national government, regardless of
income or their type of private medical insurance. These findings suggest that a sense of financial burden might affect patients’ compliance with continuing to take the high cost medication, even though they can change their hospitals easily to keep up the medication in cases of conflict between patients and hospital staff. Therefore, medical insurance programs specifically for patients with severe economic conditions who use costly medications should be considered.”

(Line 3 in Page 13, Discussion)

Comments to the Author:
1-b. The current manuscript reports lists of descriptive statistics and is quite difficult to follow. Some of the findings would have a greater impact on readers if they were presented graphically – for instance, the data in Table 4 could be presented as a bar chart (perhaps with error bars). These findings are some very striking, showing that the financial burden on patients – despite the ‘ceiling’ for final copayment imposed by the government – is highly regressive. This is mentioned in the discussion (p14) which then considered the option of 3-monthly prescriptions/hospital visits. Other specific policy recommendations are warranted – e.g. should the ratio of out-of-pocket expenses to medical costs depend not only on age but also on income?

Our reply:
Data on Table 3 and 4 in previous manuscript were converted to Figure 2 and 3 in revised paper, respectively. The policy recommendation is also mentioned as follows: “Supplemental support for low-income patients who are not covered by social security and are treated with expensive drugs for a long term could be a possible direction, because the current refund system was designed for high medical expenses with short-term duration such as surgical operations, not for high-cost medicine using new drugs for the treatment of cancer or rheumatoid arthritis. Although the development of a new support system for low-income patients would cause additional cost, we believe that this new support is still reasonable, since it was reported that non-adherent CML patients prescribed imatinib might be more costly to the health care system than adherent patients [15].”

(Line 10 in Page 15, Discussion)

Comments to the Author:
2-a-1. The authors undertook a questionnaire survey, but asked patients for retrospective data on income, medical insurance, out of pocket costs and final copayments. There are very few responders for the data from 2000, and it is not clear why this is: was the question directed only to those diagnosed before 2000, or does this simply reflect a lack of response?

Our reply:
Our questionnaire was distributed among patients who have ever been treated with imatinib in 2009 so that those who started imatinib therapy after 2000 were also included into this study. To show patient characteristic more clearly, number of patients who were treated with imatinib in 2000, 2005 and 2008 are added in Table 3.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>68 (11.8)</td>
</tr>
<tr>
<td>2005</td>
<td>284 (49.4)</td>
</tr>
<tr>
<td>2008</td>
<td>528 (91.8)</td>
</tr>
</tbody>
</table>
Comments to the Author:
2-a-2. The authors inaccurately describe the retrospective data as coming from ‘patients who were followed through the study’ which implies a prospective approach. This is misleading and needs to be corrected.

Our reply:
We agreed with reviewer’s comment and the name of subtitle was revised as follows:
“Financial situations of patients who were treated with imatinib throughout 2000 to 2008”
(Line 7 in Page 11, Results)

Comments to the Author:
2-a-3. Given the very small numbers of respondents (n=41) who provided data on income in 2000, the finding that income fell by US$13k over the period (p 13) should be interpreted with caution.

Our reply:
We added the caution due to the nature of small cohort study as follows:
“Because imatinib was not approved for sale in Japan until 2001, the data on medical expenditures in 2000 should be interpreted with caution. Unknown bias may be present due to the small population of patients who were treated with imatinib in 2000…”
(Line 1 in Page 14, Discussion)

Comments to the Author:
2-a-4. The authors discuss possible reasons for the drop in income that are related to CML, but these patients could have retired during that period.

Our reply:
We added the following sentences:
“Another possible reason is retirement during study period, because patients aged 56 to 73 years old in 2009 may have retired during the period of interest.”
(Line 3 in Page 15, Discussion)

Comments to the Author:
2-b. The odds ratios (p. 11, bottom) need to be explained for those without a statistical background – talk through one as an example (upper confidence interval below 1 etc). Also, are these ‘conditional’ odds ratios (i.e. the odds ratio for family residence is conditional upon the other factors being held constant)?

Our reply:
We added the following sentences:
“The variables were evaluated with conditional odds ratios (OR) and 95% confidence intervals (CI). A tested variable was considered unlikely to contribute to patients’ consideration to discontinue imatinib if the odds ratio was below 1.0. Conversely, a variable was more likely to contribute when the odds ratio was above 1.0.”
(Line 6 in Page 9, Method)
Comments to the Author:

Minor Essential Revisions
1. Background: p5, para 1. “To lower medical expenses,…” How do the authors know this is the reason for reducing government subsidies? I am not sure cost cutting is the key factor, rather the aim is to curb the rate of increase in medical expenditure. The authors cite our paper from the JCO, but we only discuss increased copayments by private health plans.

Our reply:
We revised the sentence as follows:
“To maintain the financial balance of the insurance system, governmental agencies in many of these nations have carefully reviewed the applications for approval of expensive medications, such as anticancer drugs [1-3].”
(Line 7 in Page 5, Background)

Comments to the Author:
Minor-2. Methods and procedures (p 6): surely ‘Methods’ is sufficient?

Our reply:
We put ‘Methods’ in the head of methodology section. (Line 15 in Page 6, Method)

Comments to the Author:
Minor-3. Methods: p 7, para 2. ‘Payment of medical costs in Japan’: this section is important but doesn’t fit under Methods – it is background. The statement that the ratio of patient payments to medical cost depends on age needs to be explained: what is the nature of this relationship?

Our reply:
We moved the section of ‘Payment of medical costs in Japan’ into Introduction section and revised as follows:
“Japan established a universal public medical insurance system in 1961. By law, all Japanese citizens must join public health insurance programs and can access all hospitals, regardless of income or insurance policy [4]. This system has been revised frequently to adapt to social changes [4]. At present, all patients have to pay a part of their medical costs, these payments vary according to patient age and range from 10% to 30% of the costs: 20% for those under 6 years old, 30% for 6 to 69 year olds, 20% for 70 to 74 year olds, and 10% for those over 75 years old.

The upper limit of self-payment is regulated by patient household income and age; it varies from 76.9 US dollars (USD) to 801.9 USD per month at the timing of writing (Table 1) [5]. If patients exceed this limit, any overpayments are later reimbursed [5]. The final co-payment is defined as the total payment minus the amount of the refund. If the patient receives welfare because of low income or as a survivor of the atomic bombings of Hiroshima and Nagasaki, his or her medical expenses are fully covered by the government and no out-of-pocket charges are required.”
(Line 10 in Page 5, Background)

Comments to the Author:
Minor-4. Language: the paper is generally well written, but needs to be proof-read by a native speaker.

Our reply:
The revised manuscript was carefully revised by the native, professional speaker.

Again, thank you very much for your thoughtful comments and suggestions and for the opportunity to submit a revision. We hope that our reply will be acceptable and the revised manuscript will be approved for publication in *BMC Cancer*.

**Reviewer 2: Dr. Lina Eliasson**

**Comments to the Author:**

1. Clarify why cost/financial burden of imatinib was assessed in 2000, when sales started in Japan in December 2001 (p.9 last paragraph)? The patients who received imatinib at this time, where did they get it from? Did patients pay for it? Was it reimbursed according to the same scheme as after it has gone on sale? Is data collected from before imatinib was sold directly comparable to data collected in 2005 and 2008?

   **Our reply:**
   
   We added the following sentences:
   
   “The patients who were treated with imatinib in 2000 received the medicine by clinical trial or imported it under physicians’ advice. In the clinical trial, patients did not need to pay a medication fee, but did pay other medical costs and received reimbursements for these if they exceeded the ceiling of medical expenditure. If patients imported imatinib, they paid the medication fee as well as the transaction fee, and they could not apply to the reimbursement program.”

   (Line 7 in Page 8, Method)

   “Because imatinib was not approved for sale in Japan until 2001, the data on medical expenditures in 2000 should be interpreted with caution. Unknown bias may be present due to the small population of patients who were treated with imatinib in 2000, as well as the unequal conditions of co-payment/reimbursement in 2000 versus 2005 and 2008. Data on medical costs in 2000 might be modified by these differences in co-payment/reimbursement.”

   (Line 1 in Page 14, Discussion)

2. p.11 In terms of the multivariate analysis, since co-payment is dependent on patients age and upper-limit of co-payments are dependent on household income and age (see background p.5 second paragraph) these factors should all be highly correlated and I therefore question whether it is appropriate to include all three in the model and also wonder if this contributed to these 3 factors all being found to be significant to predict patients considering discontinuing imatinib (because of their interactions)? I am not a statistician though, so please seek further advice on this.

   **Our reply:**
   
   We understood reviewer’s comments; however, all possible variables were equally treated in statistical procedure and multivariate analysis was employed to correct interaction between the variables and to find independently contributed factors.

   “A multiple logistic regression analysis was used to determine the variables that independently affected patient considerations to discontinue imatinib treatment, correcting interactions between the variables.”
Comments to the Author:
Minor Essential Revisions
3. It is stated that one of the aims were to assess patients thoughts about their financial burdens over time – I expected more qualitative data because of this wording and I am not convinced patients’ “thoughts” can be assessed satisfactory by the single item “Do you feel the financial burden of your medical expenses [YES/NO]” (Supp. Table 2) and then whether they have stopped or consider stopping imatinib because of high costs (Supp. Table 1). I assume this may be a translation issue though, so maybe it just needs to be reformulated?

Our reply:
We deleted the word of ‘thoughts’ and revised the sentence on the aim in this study as follows: “To assess the financial burden of taking imatinib, we surveyed annual pre-tax household incomes from all sources in 2000, 2005, and 2008, out-of-pocket medical costs, final co-payments, and their financial burdens over time.”

Comments to the Author:
4. I suggest replacing all instances of “taken” with “prescribed” – e.g. on p.6, instead of writing “In this study we focused on CML patients who have TAKEN imatinib”, write “CML patients who have BEEN PRESCRIBED imatinib” – because patients may be prescribed imatinib but not take it as directed...

Our reply:
We replaced ‘taken’ with ‘prescribed’ in entire manuscript.

Comments to the Author:
5. p.5 please clarify in what way co-payments vary with age and income – e.g. does higher age mean higher or lower co-payments (in particular to help interpreting the multivariate analysis)?

Our reply:
We added the following sentence and Table 1;
“The upper limit of self-payment is regulated by patient household income and age; it varies from 76.9 US dollars (USD) to 801.9 USD per month at the timing of writing (Table 1) [5]. If patients exceed this limit, any overpayments are later reimbursed [5].”

Comments to the Author:
6. p.6 final paragraph – replace “cooperated with our survey” with “participated in our survey”

Our reply:
We corrected the sentence;
“A major patient association for CML participated in our survey and”

Comments to the Author:
7. p.6 final paragraph – it is unclear if the nine associations agreed to take part in the survey or not?
Our reply:
We revised the sentence as follows:
“A major CML patient association participated in our survey, while the other eight did not.”
(Line 6 in Page 7, Method)

Comments to the Author:
8. p.7 first paragraph – replace “patients filled-in questionnaire forms” with “patients completed the questionnaires”

Our reply:
We corrected the sentence:
“A total of 577 CML patients completed the questionnaires”
(Line 9 in Page 7, Method)

Comments to the Author:
9. I would also write that “Two patients were excluded…//… never been PRESCRIBED imatinib.” (unless the case was that they had been prescribed but never actually took the imatinib?)

Our reply:
We corrected the sentence:
“Two patients were excluded from the study because they had never been prescribed imatinib.”
(Line 10 in Page 7, Method)

Comments to the Author:
10. p.10 second paragraph – Clarify if the “medical expenses” that were felt to be a heavy burden by the 28 pts in 2000 was directly due to cost of imatinib?

Our reply:
As mentioned above, imatinib was not approved in Japan in 2000 so that the ‘medical expenses’ in 2000 did not directly reflect the cost of imatinib.
“The patients who were treated with imatinib in 2000 received the medicine by clinical trial or imported it under physicians’ advice. In the clinical trial, patients did not need to pay a medication fee, but did pay other medical costs and received reimbursements for these if they exceeded the ceiling of medical expenditure. If patients imported imatinib, they paid the medication fee as well as the transaction fee, and they could not apply to the reimbursement program.”
(Line 7 in Page 8, Method)

Comments to the Author:
11. p.11 I would like to know how many patients were not considering stopping imatinib and how many considered doing so due to side effects?

Our reply:
To clarify the individual number, we prepared new figure of Venn diagram (Figure 1).

Comments to the Author:
12. p.12 end of first paragraph – A thought: can imatinib still be considered to be “newly developed” having been approved as first line for 11 years and coming off US patent in 3?
**Our reply:**
We deleted the sentence including the phase of ‘newly developed’.

**Comments to the Author:**
13. Elaborate more on what can be done to address high cost of drugs in last sentence – in what way do medical insurance programs need to be different to the medical insurance programs these patients already have? Same comment applies to end of second paragraph on page 14.

**Our reply:**
We addressed as follows:
“Supplemental support for low-income patients who are not covered by social security and are treated with expensive drugs for a long term could be a possible direction, because the current refund system was designed for high medical expenses with short-term duration such as surgical operations, not for high-cost medicine using new drugs for the treatment of cancer or rheumatoid arthritis. Although the development of a new support system for low-income patients would cause additional cost, we believe that this new support is still reasonable, since it was reported that non-adherent CML patients prescribed imatinib might be more costly to the health care system than adherent patients [15].”

(Line 10 in Page 15, Discussion)

**Comments to the Author:**
14. p.12 last paragraph – Rephrase first sentence – maybe by adding “many” or “most” as not all CML patients had financial problems: i.e. “This study showed that most CML patients did not have enough financial resources…”

**Our reply:**
We revised the sentence as follows:
“This study showed that many CML patients did not have enough financial resources for their imatinib treatments.”

(Line 14 in Page 13, Discussion)

**Comments to the Author:**
15. p.14 – rephrase sentence stating that the ratio of patients discontinuing imatinib treatment due to monetary constraints in this study only being 10% of that reported by Darkow et al 2007. As far as I can see, Darkow did not report the ratio of patients stopping imatinib specifically due to monetary constraints?

**Our reply:**
We revised the sentence as follows:
“While the ratio of patients who discontinued imatinib treatment is approximately 10% of that reported in a previous study of the United States,[15]…”

(Line 6 in Page 13, Discussion)

**Comments to the Author:**
16. Clarify the sentence regarding noting that the universal insurance system guarantees all Japanese citizens access to hospitals, regardless of income or insurance policy. In what way is this sentence linked to the previous arguments and in what way is this linked to patients’ access to or affordability of imatinib?
Our reply:
We added the following sentence after the description on Japanese universal insurance system as follows:

“These findings suggest that a sense of financial burden might affect patients’ compliance with continuing to take the high cost medication, even though they can change their hospitals easily to keep up the medication in cases of conflict between patients and hospital staff.”

(Line 10 in Page 13)

Comments to the Author:
17. p.14 last paragraph – rephrase the sentence “Since the summer of 2007, the association has given members an idea of three-month prescription…” In fact, I find this whole paragraph a little difficult to follow.

Our reply:
We revised the paragraph as follows:

“The three-month prescription is beneficial because refunds are calculated on a monthly basis and the maximum limit of the refunds is not affected by medical costs, meaning that prescribing imatinib in a particular month as much as possible can bring higher patient refunds. The refund system can be applied when patients pay medical expenses over the maximum limit four times or more per year; thus a three-month prescription is the most reasonable way to reduce annual final co-payments. This information was shared with CML patients and might be related to the reduction of final co-payments in 2008 by 800 USD compared with 2005 (Figure 2).”

(Line 19 in Page 15, Discussion)

Comments to the Author:
18. p.15 paragraph on limitations – I am not convinced dose level in itself is the only and most important difference between Japan, Europe and USA that make generalizability of the study difficult (in particular as 63% of study sample was prescribed 400mg or more)?

Our reply:
We added the following sentences:

“Importantly, the health insurance system in Japan is different from other countries, meaning that the flow of medical expenditures and refunds in the household budget is different. Thus, careful consideration is needed when comparing the financial burdens of imatinib internationally.”

(Line 14 in Page 17, Discussion)

Comments to the Author:
19. p.25 Table 4 – the classifications are confusing, I think it may be because of the use of both the # “less than or equal to” sign and the < “less than” sign? Also think about not having values that overlap and I assume 74,423 should be marked with the # “equal to or more than” sign?

Our reply:
We agree that Table 4 in the previous manuscript is confusing and converted it into a graph of Figure 3 according to the other reviewer’s comment.
20. p.26 – Change “Odds rate” to “Odds ratio” – write out the exact p-values instead of “n.s.”

**Our reply:**
We revised Table 4 according to the reviewer’s comment.

**Comments to the Author:**
21. Supplement p.4 Table 3 – Change “Odds rate” to “Odds ratio” and add the confidence intervals

**Our reply:**
We revised supplemental Table 3 according to the reviewer’s comment.

**Comments to the Author:**
Discretionary Revisions
22. I think some mentioning of patients-access schemes may be appropriate?

**Our reply:**
We added the following sentences:
“From the perspective of patient accessibility, the Japanese universal health insurance system is beneficial because it guarantees that patients can access any hospital/clinic. However, financial difficulty among low-income patients who are treated with expensive medicines might affect the accessibility of long-term advanced medication, suggesting a limitation of the current universal insurance in Japan. Health care reform to support low-income patients is highly desired.”

(Line 15 in Page 16, Discussion)

**Comments to the Author:**
23. Maybe interesting for European and US readers to have some mentioning of access/cost of second line treatments nilotinib/dasatinib - are these available, are they reimbursed?

**Our reply:**
We added the following sentences:
“Dasatinib and nilotinib, which are newly developed tyrosine kinase inhibitors for CML, were approved in Japan in March 2009 and March 2011, respectively [22,23]. The prices for these medicines regulated by the national institute for approved dosage per day are follows: dasatinib (100mg) 18,448 Yen and nilotinib (800mg) 18,428 Yen [24]. That of imatinib (400mg) is 10,996 Yen for reference. The patients who are treated with dasatinib or nilotinib can also receive reimbursement if their medical expenses exceed the upper limit of co-payment.”

(Line 1 in Page 17, Discussion)

Again, thank you very much for your thoughtful comments, suggestions, and the opportunity to submit a revision. We hope that our reply will be acceptable and the revised manuscript will be approved for publication in BMC Cancer.