Author's response to reviews

Title: Regional differences in performance of bone marrow transplantation, care-resource use and outcome for adult T-cell leukaemia in Japan

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Author's response to reviews: see over
Dear Editorial Board and BMC Health Service Research

Thank you very much for the opportunity to revise our paper. We found both reviewers’ comments to be helpful. We believe that the quality and depth of the reviews reflect the importance of, and interest in, our research question in this controversial area. The similarity of the reviews enabled us to focus on the important changes called for by the reviewers.

We have attached a point-by-point response to the reviewers’ comments. We believe that we have fully responded to every comment and that the paper is now much improved because of the changes suggested by the reviewers.

If you feel that additional changes are necessary, of course, please let us know. My contact information is noted on the title page of the manuscript.

Thank you again for your time and interest. We look forward to hearing from you soon.

Sincerely,

Toshiki Maeda, MD, MPH
Note
In the revised manuscript, we revised the multivariate analyses related to care resource use and outcomes to obtain more rigorous and reasonable results. Although we analysed data separately by chemotherapy and BMT in the original version, we aggregated them for analysis in the revised version. In addition, we changed the age category and added extra variables to the previous model for analyses. Therefore, the final results of the analyses and the contents of the discussion were partly changed.

RESPONSES TO REVIEWERS’ COMMENTS

Reviewer's report
Reviewer: Helen Parsons

Reviewer's report:
Major compulsory Revisions

Introduction:
1) It may be helpful to describe modes of communication and highlight the high mortality rate after diagnosis. This could help place the extent of disease and challenge of treatment into context.

Response
We added the following sentences as suggested:

HTLV-1 infection is transmitted to newborns by breast milk from HTLV-1 carrier mothers [2]. ATL occurs in less than 5% of people with HTLV-I infection, with a mean latency period of more than 30 years [3]. ATL is classified into four categories [4]. The median survival time ranges from 3.7 to 6.0 months for the acute and lymphomatous forms while the median survival is two years or more in indolent smouldering and chronic forms [3]. The median survival time of those treated by chemotherapy was 13 months [5], thus it is unfavourable compared to other hematologic malignancies. Accordingly, bone marrow transplantation (BMT) is a promising therapy associated with long-term survival [5].

Methods (my main concerns):
2) Please provide a brief description of the Japanese healthcare system for readers who are not familiar. Who is the primary payer of insurance? How is care
typically delivered? This could also go in the introduction. This will help us understand whether the data set actually provides a comprehensive overview of the study population of interest that the authors would like to make an inference about, or whether it may provide a biased sample.

Response
The DPC programme covers more than 90% of acute in-patient care where cancer care is provided in Japan.
Therefore, we added the following sentences to the revised manuscript:

Japanese universal health care insurance is a system that provides every Japanese citizen with insurance benefits in cases of disease, injury, death, and childbirth. Every citizen must belong to one of the social insurance plans that are composed of three categories: Employee Health Insurance, District Health Insurance, and Elderly Health Insurance [12]. The health insurance funds gather premiums from their members and reimburse the costs of treatment. The reimburse system has long been based on a fee-for-service (FFS) using a national fee schedule. The enforcement of the same fee schedule for all insurance plans and almost all providers has maintained equity and contained costs, and the co-payment rate has become the same for all, except for elderly people and children [12].

3) Please provide additional information regarding the data source. It seems like the total N is quite small. Who is included in the DPC/PDPS? Is it a 100% sample of hospitals in Japan or only select facilities? How could this affect the representativeness of the study? In this respect, what percentage of all ATL diagnoses during the study period do you think are captured by this dataset?

Response
The numbers of patients newly diagnosed with ATL annually was estimated to be approximately 1000/year (Yamaguchi K. The comprehensive survey of HTLV-1 infection and HTLV-1 associated diseases. Ministry of Health, Labour and Welfare science research grant report 2009 (in Japanese)). However, ATL has 4 subgroups, all of which do not require immediate therapy. The subtypes of ATL that require chemotherapy are acute, lymphoma and some chronic types. In addition, some patients are treated with oral chemotherapy rather than with hospital chemotherapy, especially for some chronic types, and as older people who are diagnosed with ATL are chemoresistant, care
providers have withdrawn chemotherapy for patients’ QOLs. Therefore, our study was limited to ATL patients treated with chemotherapy within hospitals. In addition, this data was provided for only 6 months, thus the sample size is small. As to representativeness, although the sample size is small, almost all patients requiring chemotherapy were admitted to acute care hospitals in Japan. The DPC programme covers more than 90% of acute in-patient care thus the subject could represent ATL with chemotherapy in Japan.

4) I’m also confused by the statement “This study represented the secondary use of DPC/PDPS survey data collected from June 1st to December 31st 2010, conducted by MHLW”. My reading of the study design was that you used hospital administrative data to obtain the information, not survey data. Please clarify.

Response

As the data we used was hospital administrative data and was used for health service research, we eliminate the word ‘survey’.

5) Using claims data alone to study patterns of cancer care and treatment has been demonstrated to be quite challenging as the claims were not designed to provide information on many critical cancer characteristics such as date of diagnosis and other factors that might influence treatment (grade, stage, histology- not all of which apply to ATL of course). What information does the database contain regarding cancer characteristics besides ICD-10 codes? How do you know that these truly are diagnoses and not potentially a code where patients were being tested for the presence of the disease and later found to not have it? This has been a problem with using claims data only and has typically been addressed by linking cancer registry data to claims for care.

Response

We could not link DPC/PDPS data with cancer registry data. This therefore is a critical study limitation. In addition, DPC/PDPS did not contain detailed data (e.g. histology, stage or clinical data), therefore, the application of DPC/PDPS to clinical research had several limitations. However, DPC/PDPS did include diagnosis with procedures, thus it kept accurate study data. Study subjects were cases who underwent chemotherapy; thus, we considered the accuracy of diagnosis was maintained.
6) In this same respect, how do you know on page 5 that patients were admitted for chemotherapy? What codes did you use to determine this? During what time periods?

Response
The subjects were patients admitted to hospitals for chemotherapy, whose primary diagnosis was classified as ‘C915’, corresponding to ATL in ICD10. Chemotherapy was defined as the use of chemotherapeutic agents used by ‘quality indicators programs’ in Japanese national hospitals.

7) How did you determine someone had a BMT in the data? It is not described. As this is a critical variable in the analysis, it is important to describe the codes and time periods used to identify BMT.

Response
The definition of BMT corresponded to ‘K922’ in the Japanese standardized fee-for-service payment system during hospitalization.

Results
8) In the discussion of results, it would be helpful to put the reference group into the text when describing the AOR.

Response
Thank you. We have added it to the revised manuscript.

9) For the results of logLOS and IHM, it would be helpful to describe the results in terms a direction of the relationship (higher IHM in X vs. Y, etc.)

Response
We have added it to the revised manuscript as suggested.

Conclusion:
10) It’s difficult to figure out what to take away as the main message of the paper. It would be helpful if you could reframe the discussion more into how you could use the information on regional differences in care and outcomes for ATL to plan
programs, create interventions, etc. Right now, it seems more descriptive and less like a focus on what to take away to implement quality improvement initiatives. Additionally, the main title of the paper suggests that you are looking at regional differences, but this doesn’t seem to be the highlight of the discussion. 

What does it mean when there are regional differences? How can this aid in future resource, care planning. Are there lessons some regions may learn from others? All would be helpful to highlight and tie together the discussion with the study purpose inferred from the title.

Response

We have significantly revised the discussion section to focus on regional differences and recommendation for care planning in Japan as suggested.

There were significant regional differences in performance of BMT as Kanto and Kansai regions had significantly higher rates of BMT performance. Although the Kyushu/Okinawa regions had a high prevalence of ATL, a lower proportion of patients were treated with BMT. Additionally, the Kanto and Kansai regions had high care resource use while there was no significant difference in IHM between regions. Previous studies in Western countries reported regional differences in the use of BMT were related to the prevalence of related diseases [11], per capita gross national income and per capita health care expenditures as economic factors, and the availability of BMT teams as care resources [19-20]. However, the current study found no significant relationship between the prevalence of ATL and the performance of BMT in Japan. Regarding economical factors, the health care expenditure per capita in the Kanto and Kansai regions where higher numbers of BMTs were performed was not high. Reasons for relative lower health care expenditures observed could be age structure, that is, a lower proportion of elderly individuals in the Kanto and Kansai regions leading to lower health care expenditure, especially as there was no association between health care expenditure and performing BMT. However, there might be a relationship between household income and BMT, as demographic data showed Kanto and Kansai regions were densely inhabited and their incomes seemed to be higher. There was no relationship between care resources, including the number of hospitals or BMT team density and performing BMT, which was in contrast to prior findings. However, the discrepancy between high numbers of BMTs performed and equivalent care resources in Kanto and Kansai regions might be attributed to the type of health care delivery system in Japan. The health care plan determined by local government in Japan was revised 5
years ago. The aim of the health care plan is to allocate health care resources equally in Japan. However, it focused on quantity rather than quality, in general. Thus, care resources in the Kanto and Kansai regions were almost equivalent to other regions. However, the number of BMTs performed per team was higher in the Kanto and Kansai regions. Thus, the efficiency of care might be superior in the Kanto and Kansai regions although the quantity of care resources was equivalent between all regions.

11) Also, are there other examples of cancer studies that you could compare to rather than stroke. It doesn’t seem quite comparable when describing regional variation, but maybe I’m missing the link.

Response
We deleted the indicated examples because they were less comparable when describing regional variations.

12) Minor Essential Revisions
Tables:
Table 2: should state goodness of fit

Response
We used Hosmer-Lemeshow's test as a goodness of fit and added it to Table 4 as follows:
Hosmer-Lemeshow's test: $p = 0.738$

In addition, we combined Table 2 and Table 4 to create a new Table 4 in the revised version, with the aim of showing the results more clearly.

Level of interest: An article of limited interest
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests

Reviewer's report
Reviewer: Alois Gratwohl
Reviewer's report:

Major Compulsory Revisions
1) Information is essential about the general policy of hospital choice. Can patients choose their hospital; eg can they travel from one region to another to obtain their bone marrow transplant. If this is possible, numbers about such out of region treatments need to be known. Rich patients from poor regions could travel to richer regions with “better” hospitals. Since, in general, affluent patients are better educated, have a better general condition, their outcome is likely to be improved. It could falsify the results and the conclusions.

Response

The Japanese health care system enables patients to have free access to any health care facility with reasonable cost. However, few patients with ATL travelled outside their own region for treatment. We have added the results of patient travel to Table 2.

2) Information on health care settings in the different regions needs to be provided. This includes specifically: N total population, N hospitals, community and academic in absolute numbers and per N inhabitants; annual health care expenditures per capita; N T-cell leukemias in absolute numbers and per N inhabitants; N transplants for T-cell leukemia in absolute numbers and per N inhabitants.

As a comparison, information on BMT in general is needed for each region: N transplants in 2010 for all indications and transplant rates (N transplants per 10 million inhabitants) and on team density (N BMT teams in absolute numbers and per 10 million inhabitants). This information should be easily available from the Japanese society for hematopoietic stem cell transplantation.

Response

We showed the total population number, the number of hospitals and number of hospitals per inhabitants, the number of academic hospitals and number of academic hospitals per inhabitants, and annual health care expenditures per capita, because these were collected nationwide. Moreover, we obtained number of transplants in 2010 and transplant rates (the number of transplants per 10 million inhabitants) and team density (the number of BMT teams per 10 million inhabitants). In addition, we added population density, proportions of aging, income per capita, the number of beds and number of beds per inhabitants, and the number of DPC hospitals to describe the characteristics of each region clearly.

All these data were added to Table 1.
However, we could not obtain the number of T-cell leukaemia individuals and number of T-cell leukaemia individuals per inhabitants, and the number of transplants for T-cell leukaemia and number of transplants per inhabitants. Therefore, we could not add this to the revised manuscript.

3) The authors must clearly state that “in house mortality” is not an accepted endpoint for patients with allogeneic stem cell transplantation in general, for several reasons. Patients may have an initial early uneventful course, be discharged and then die after readmission, to the primary hospital or to another. Similarly, patients with very severe complications and minimal chances for recovery might be transferred to a hospital or a hospice close to home of the patient, or even at home for their final phase. They would not account for “in house mortality”. Day 100 mortality is generally accepted for comparisons but only if the major pretransplant risk factors for individual patients are known.

Response

We could not obtain day 100 mortality, and it is therefore a study limitation. We used in hospital mortality as an alternative measure for the study endpoint. Although in hospital mortality is not regarded as an endpoint for patients with malignancy in general, we used it as a surrogate marker for the quality of health care. Thus, we added the following sentence:

Although IHM was not regarded as an endpoint in general, we assumed that skilled experts could identify successful BMT compared with non-skilled individuals, thus in hospital mortality might be lower.

In addition, we added the following sentence to the discussion section:

This might be explained, as IHM used in this study were not relevant as outcome measures. Outcome measures used in hemato-oncologic research are generally overall survival [21], or day 100 mortality, especially for BMT [22].

- Minor Essential Revisions

4) The quality of the manuscript would substantially win if the primary evaluation, prevalence of the disease, transplant rate and proportion of patients with
transplant vs no transplant could be extended to a disease with homogeneous distribution in Japan, eg acute myeloid leukemia.

**Response**

Unfortunately, we could not obtain the suggested data (primary evaluation, prevalence of the disease, transplant rate and proportion of patients with transplant vs no transplant) by region. Therefore, we added the following sentences describing the study limitations:

Furthermore, we could not obtain data related to primary evaluation, prevalence of disease, transplant rate and proportion of patients with transplantation that would allow a comparison of ATL with other diseases with homogeneous distribution in Japan.

- Discretionary Revisions
  there are several minor misspellings

**Response**

We have asked an English editing service to correct all grammatical and spelling errors in the manuscript.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
'I declare that I have no competing interests'