Author’s response to reviews

Title: Exploring the characteristics of patients with mesothelioma who chose active symptom control over chemotherapy as first-line treatment: a prospective, observational, single centre study

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Author’s response to reviews:

Dear Editors

Many thanks for taking the time to review our manuscript, ref PCAR-D-17-00003, entitled “Exploring the characteristics of patients with mesothelioma who chose active symptom control over chemotherapy: a prospective, observational, single centre study”.

We are grateful to the reviewers for their comments, and have made the changes they recommend. We feel this changes strengthen the manuscript, and we hope you will now consider it acceptable for publication.

Our responses to each reviewer’s comment are detailed below.

With best wishes

Anna Bibby
Jacobus Burgers (Reviewer 1):

This paper tells about the retrospective analysis of the patient records of 200 mesothelioma patients from one hospital. The eligibility for chemotherapy has been discussed in a multidisciplinary team. Eligible patients did or did not choose for chemotherapeutic treatment. Groups were compared, Reasons to abstain from active treatment were given.

The paper is well written.

Author’s response (AR) – Thank you.

Major point:

The discussion gives a good oversight of the strenghts and weaknesses of the study. Unfortunately, the role of the medical doctor and the interaction between the doctor and patient seems underexposed. The impression is given that all patients who seem eligible for chemotherapy according to the MDT can choose for them selves whether or not to receive chemotherapy. It might rather well be that this decision is greatly influenced by the (implicit) advice of the medical doctor.

AR – The discussion section has now been amended to include a paragraph about the doctor patient interaction and acknowledgement of the possibility that this may influence patients’ decision (page 15, paragraph 2).

Minor point:

reference 5: The data have been updated at ASCO 2005 reveiling an survival gain of 4 months...

AR – This reference, and updated results, have been included in the introduction (page 5, paragraph 1, line 7-8).

Charles B. Simone (Reviewer 2): The authors performed a 200 patient query into reasons why patients chose active symptom control over chemotherapy for malignant mesothelioma. This is an interesting and novel study, as it is the first such analysis to describe the characteristics of mesothelioma patients who chose active symptom control. These findings are important and have implications for discussions with patients regarding decision making, as well as the design and implementation of future systemic therapy trials.

AR – Thank you. We agree that these finding are important, and have relevance for the implementation of future trials of therapy. We feel strongly that patients who choose not to receive chemotherapy are under-represented in current research, and think it is important this is recognised by the mesothelioma community.
Abstract

1) In the background section, the authors state that "the only treatment that extends survival is chemotherapy." There have not been phase III trials in surgery, radiation therapy, or currently used immunotherapy agents, so this statement cannot be said. I suggest changing the sentence to something more along the lines of 'chemotherapy is the current standard of care to improve survival.'

AR – This sentence has now been changed (page 5, para 1, line 2-3).

Introduction

1) The authors state that "chemotherapy with pemetrexed and cisplatin is the only treatment that has been shown to extend survival." In fact, in the past year, results of the phase III MAPS trial have demonstrated that the addition of bevacizumab significantly prolongs survival. The authors cite this trial later in the Background section. Perhaps reword to clarify something to the order of 'chemotherapy has been the only treatment that has consistently been shown to improve survival for mesothelioma' and not limit the statement to pemetrexed and cisplatin.

AR – The introduction has now been re-worded to clarify the role of bevacizumab alongside chemotherapy (page 5, para 1, lines 8-11).

2) It is implied that chemotherapy offers only a 2.8 month median survival benefit, but time is the benefit of adding pemetrexed to cisplatin. Please reword to clarify that the actual magnitude of chemotherapy over no chemotherapy is greater than 2.8 months.

AR – This has now been made more explicit (page 5, para 1, lines 5-7 and page 6, para 1, line 2-5).

3) Replace "the alternative to chemotherapy" with "an alternative to chemotherapy" given that a standard and likely preferred alternative treatment to chemotherapy is clinical trial enrollment.

AR – This has now been clarified (page 5, para 2, line 1)

Methods

1) The authors call this a prospective longitudinal study, but the reasons for choosing active symptom control were obtained retrospectively by review of the medical record system. Clarify what was actually performed prospectively and if (and which) an institutional review board or ethics committee approved of the study.
AR – Patient characteristics, eligibility for chemotherapy and the decision to receive chemotherapy or ASC were collected prospectively. Patient’s reasons for choosing ASC were obtained retrospectively. This has now been stated. (Page 8, para 2, line 2. Page 8 para 3, line 2-3 and line 4, page 9 para 3). Data was collected as part of the Investigating Pleural Disease Study, which was approved by Central Bristol REC, ref 08/H0102/11. This is stated in the manuscript (page 8, para 1, line 3-4 and page 17 para 2).

2) Why was survival censored nearly a full year ago when the median survival is so limited in this cohort? Valuable data could be missed and should be updated.

AR – the main reason for this is that the paper has been under review with the journal for almost 7 months! However, we agree that updated survival data is necessary and have re-run the analysis and presented the updated survival data, censored 26/06/17.

Results

1) Add actual quantitative information on the performance status for both groups in the manuscript text in addition to the p value that is already listed.

AR – this has now been added. (page 10 para 3 lines 3-6)

2) Among the 22 patients who chose active symptom control after discussion with a respiratory physician, how many saw a medical oncologist?

AR – All 46 patients were seen by a respiratory physician to receive the diagnosis and discuss treatment. 22/46 chose not to receive chemotherapy at this point, and consequently were not referred to see an oncologist, however the remaining 24/26 were referred on, and discussed chemotherapy with an oncologist before deciding not to receive it. This has been clarified in the text. (page 10, para 4). The referral and decision-making process has also been explained in greater detail in the methods section (Page 6, para 2, line 7-14).

3) For both the 24 and 22 patients that are quoted in the text, I suspect that several were seen by both providers. Clarify how patients who saw both providers were stratified for the decision analysis.

AR – See answer to above point.

4) Explain fewer than one-third of medical records contained the reason for treatment decision, as I would have thought this standard of care decision should be in every single patient's medical record regardless of clinical trial participation.
Unfortunately the software for collecting MDT data does not capture patients’ reasons and medical notes are often missing in clinic, or incompletely documented. Consequently, and because this outcome was not collected prospectively as part of the research study, this data was missing or unobtainable in a large number of cases. This is a recognised limitation of retrospective data collection, and has been commented on in the discussion (page 13, para 3).

Our centre has now changed its practice in response to the study findings and patients’ reasons for declining treatment are now collected routinely (in both study patients and non-study patients). This prospectively collected data will be more robust, and will be published as and when sufficient numbers exist.

5) How did previous negative experiences of chemotherapy influence the decision to receive chemotherapy? Did these patients have a prior cancer for which they received chemotherapy? Did they receive chemotherapy for their mesothelioma previously and now refuse second or third line chemotherapy?

AR – One of these patients had received chemotherapy for previous ovarian cancer, whilst the other had cared for his brother whilst he received chemotherapy for lung cancer. This information has now been included on page 12, para 1, line 7-9.

6) Furthermore, clarify that the decision point being assessed in this study is for first line chemotherapy vs. active symptom control or if any refusal of chemotherapy at any line is counted as refusal.

AR – This study examined patients offered first-line chemotherapy only. This has now been clarified throughout the manuscript.

7) PS ≥2 is listed as a factor associated with poor survival, but according to Table 1, there are no patients with a PS >2. Clarify or review to PS of 2 and not ≥2.

AR – this has been corrected – page 12, para 4, line 2.

8) Survival is listed, but the median follow-up and follow-up range are not provided.

AR – All patients were followed up until death, or censored on 26/6/17. Median follow up for surviving patients was 22.7 months (range 12.6 – 102.5 months). This has now been included in the manuscript (page 12, para 2).

Table 1
1) Classify all stage I patients as IA or IB
Discussion

1) Again, the authors misinterpret the findings in reference #5. The survival difference of 7.2 months seen in their study should not be equated to the survival difference of adding pemetrexed to cisplatin since both arms of reference #5 received chemotherapy.

AR – This has now been corrected (page 14, para 1, lines 2-5).

2) Discuss that among patients for whom there were able to report on reasons for a treatment decision, these reasons were not defined a priori and/or asked to patients, and that the reasons were strictly identified by a chart review that introduces inherent bias.

AR – The fact that reasons were collected retrospectively from review of medical records and not defined a priori is now stated in the methods (page 8, para 3, lines 3-6). The effect of missing data, the potential for bias, and the limitation of interpreting this result has been included in the discussion (page 13, para 5 and page 14 para 1).

Figure 1

1) The median survival for active symptom control patients appears to be 9.9 months, not 6.7 months that is listed in the manuscript text for this cohort. The 9.9 months is what is listed in the manuscript text as the median survival for all 200 patients

AR – thank you for bringing this typographical error to our attention. For clarity, the manuscript has now been amended so that survival is reported only in the 139 patients who were offered chemotherapy rather than all 200 patients with meso.

Martine Puts (Reviewer 3): Thank you for allowing me to review this interesting paper addressing an important and understudied topic, why patients choose not to accept recommended therapy.

The paper is very well written and I only have 2 questions.

1) Is the reference to the 2007 BTS the latest? It seems odd to have a professional society statement that does not reflect the current treatment standard, one would expect it would be updated.

AR - The BTS has updated its mesothelioma guidelines in 2017, but these are currently under review prior to publication later this year and therefore cannot be referenced here at present.
2) Could you describe the data collection from the chart in more detail. Was a standardized form used? Who abstracted the data? Did you determine in advance what reasons would be abstracted?

AR – This information has now been added to the methods section (Page 9, para 3) and the data collection form has been included as Appendix 2. Reasons for choosing ASC were not pre-specified. This has also been stated in the methods, (page 8, para 3, lines 3-6).

It seems there is a lot of oncology data but no date on for example travel needs for treatment that lead older adults to refuse treatments, financial barriers, mood disorders etc. These reasons have been documented in the literature but there is nothing mentioned about any of these. Please clarify.

AR – This data was not collected, however a paragraph has been added to the discussion, reviewing these findings in the existing literature, and encouraging prospective collection of this information in future studies. (page 15 para 3 & page 16 para 1).