Author's response to reviews

Title: Case series discussion of cardiac and vascular events following carfilzomib treatment: possible mechanism, screening, and monitoring

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Author's response to reviews: see over
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Manoj K Pandey, PhD
Associate Editor, BMC Cancer

RE: MS: 9427337321346899

Dear Dr Pandey:

Please find enclosed our revised manuscript entitled “Case series discussion of cardiac and vascular events following carfilzomib treatment: possible mechanism screening and monitoring.” We thank the reviewers for their review of our manuscript and for providing their thoughtful feedback. A detailed response is provided below.

We look forward to your decision regarding acceptance of the manuscript for publication in BMC Cancer.

Sincerely,

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Reviewer's #1 comments:

In this case report, the authors retrospectively examine the records of 67 patients with relapsed and/or refractory multiple myeloma (MM) treated at Mt. Sinai Medical Center, NY. The authors describe 12 patients amongst the 67 who experienced cardiac or vascular-related adverse events subsequent to Carfilzomib-based treatment. While several of the described adverse effects have also been described by other independent observations, the records examined by the authors indicate that most of these patients had a prior history of the specific cardiac or vascular adverse event they exhibited. Thus, this case report falls under 'Findings that shed new light on the possible pathogenesis of a disease or an adverse effect.'

No 'Major Compulsory Revisions' are recommended

Minor Essential Revisions:

From the described case-studies the criteria for the selection of 67 patients is not clear. Were these the total number of patients diagnosed with refractory or relapsed MM and treated with Carfilzomib or were these randomly selected Carfilzomib-treated patients? This needs clarification.

The patients described are consecutive patients treated with carfilzomib at our institution from August 2012 to December 2012. We have revised the manuscript to clarify this point.

Table 2: It is not clear whether the patients who demonstrated grade > adverse event (column1) were the ones who also had a prior history of adverse effects (column2). This needs to be clarified.

Please note that the patients in column 2 are a subset of the patients shown in column 1. We have clarified this in Table 2.

Some of the recommendations provided in Table 3 here have also been provided by Carfilzomib drug-manufacturers (https://urldefense.proofpoint.com/v1/url?u=http://www.kyprolis.com/starting-kyprolis/side-effects&r=mmkjhx4owUAlOiuCX0Hf407CuKAMhbDv5iiWqqS66GM%3D%0A&m=6Mh%2BEKpLNq6n%2B5%2FyuuwDrUjb9EKogurF5%2FupSTIRAw%3D%0A&s=2966978f4f32705cc32643ca51ae5afcf5fbd4d8c4bd71b99abc3d780fb344eb58). The authors should comment on how the recommendations that they provide in this study differ/add to those from the manufacturers.

We have revised the manuscript to include the recommendations for management of cardiac and pulmonary events from the Kyprolis® prescribing information and have noted how our recommendations differ.

Discretionary Revisions:

A brief description of Carfilzomib pharmacokinetics (Drug clearance, metabolism) needs to be provided in the section starting on Line 71.

Per the reviewer’s suggestion, we have added an additional paragraph describing the pharmacokinetics of carfilzomib.
It is recommended that the discussion on 'Potential mechanisms of proteasome inhibition-mediated endothelial dysfunction and heart failure' (line 295) can be shortened. A review (e.g. Kortuem and Stewart, Blood 2013), could be cited.

We have substantially shortened the section on the potential mechanisms underlying these events. We thank the reviewer for their suggested reference but note that the indicated publication does not discuss preclinical mechanisms behind proteasome inhibitor–mediated cardiac events, so we were unable to include it as a reference in this section. We have, however, added the reference within the Conclusions section (p. 14) to support our hydration recommendations.

To be consistent between the different case studies, it would be beneficial to readers if the total cumulative dose of carfilzomib before the occurrence of the described adverse events is listed.

We thank the reviewer for their suggestion and have added information regarding total cumulative dose of carfilzomib received for each patient where it was previously missing.

Reviewer#2 comments:

In the present manuscript authors have reviewed the medical records of 67 patients with relapsed and/or refractory multiple myeloma that were treated with carfilzomib, a proteasome inhibitor. From a comprehensive analysis they report that a significant percentage of patients (12 out of 67) underwent cardiac and vascular related adverse events that were already at the border of cardiac related risk. Further, they describe how patients with cardiac risk factors can be monitored closely during the drug treatment. Finally, the authors put forward the hypothesis that adverse events may be the result of a dose response-dependent perturbation in endothelial nitric oxide synthase (eNOS) activity and NO synthesis that adversely affect cardiac and endothelial cells.

This report is highly significant for treating patients with cardiac complications, especially due to lack of existing published material/reports of such nature.

Minor Essential Revisions/Discretionary Revisions:

1. The authors report that 9 out of 12 patients had prior autologous stem cell transplant. Did the authors come across any patients who had autologous stem cell transplant but did not experience cardiac or vascular related adverse events. If so, it will be beneficial to include this case study as well.

   Approximately 40 of the 67 patients identified in our study had prior autologous stem cell transplant; therefore, approximately 30 patients with prior transplant did not experience a cardiac- or vascular-related adverse event. Given the high proportion of patients who fall into this category, it does not appear that prior transplant is a significant factor in these events.

2. One of the future management plans includes decreasing or eliminating hydration in certain patients. It would be important to explain how decrease in hydration will have beneficial effect.

   Patients received up to 500 mL of intravenous saline or other appropriate fluid before and after carfilzomib dosing as a prophylactic measure against tumor lysis syndrome. However,
decreasing or eliminating hydration may be beneficial in some patients who are at risk for fluid overload, such as those with preexisting congestive heart failure, as overhydration may manifest itself as a severe cardiac or pulmonary event. We have modified the text to clarify this rationale behind the recommendation.

3. It will be useful for a general reader to understand the logic of grading system for the adverse events in patients (for example, what is grade 3 Vs grade 4 etc.)

   Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, including the definitions of grading contained therein. We’ve modified the text to further clarify the grading system utilized.

4. *in vivo* (line 86 and line 318) and *in vitro* (line 311) should be in italics.

   We have modified the text accordingly.

5. In the list of abbreviations, Durie-Salmon and DS are written in two separate lines.

   We thank the reviewer for their close reading of the manuscript and have corrected this in the revised draft.