Reviewer's report

Title: Constitutional mutation in CDKN2A is associated with long term survivorship in multiple myeloma

Version: 0 Date: 17 Jul 2017
Reviewer: Douglas Sborov

Reviewer's report:

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Shah et al present a patient with MM that had a profound response to melphalan with sustained complete response for over 30 years. Development of other malignancies led to investigation for a germline CDKN2A mutation, and the authors argue that this germline mutation may be associated not only with development of MM, but also with profoundly chemo-sensitive disease.

Page2 Line42 - Statement "subsequent introduction of IMiDs, PIIs, and autoHSCT" is dated, and would be strengthened by mention of 1) maintenance therapy, 2) new therapies including monoclonal antibodies and HDACIs, and 3) references to recent trials supporting the use of autoHSCT/MEL in the era of novel therapeutics.

Page2 Line45 - The statement "significant variation in outcome" would be strengthened by a very brief discussion of R-ISS staging and associated median OS rates as a means to identify those patients that we currently think have a possibility of long term remission.

Page3 Line12 - If available, can you provide the percentage of PCs in the initial biopsy?

Page3 Line 39 - Has a repeat bone marrow biopsy been completed to evaluate for MRD?

Page4 Line6 - Wording needs to be fixed, "with by"

Page4 Line18 - "described a (not an) MM"
Page4 Line17 - 1st paragraph of discussion, a more thorough discussion is warranted here. In addition to the mention of the Dilworth et al, Blood, 2000 article, discussion of recent GWAS studies and the association between PC dyscrasias and CDKN2A-related risk loci would be interesting.

Page4 Line25 - 2nd paragraph of discussion. In the latter part of the paragraph, an abbreviated list of mechanisms is provided. A more detailed explanation is warranted, including how CDKN2A and related mutations are directly associated with myeloma (development and treatment).

Page4 Line47 - Provide rationale for incorporation of the MDM2 inhibitor discussion; ie. how is this associated to the discussion about CDKN2A mutations. The link presented is ARF but it is not very clear how it's presently written.

This patient provides an extremely interesting case that supports the possibility that a CDKN2A germline mutation may be associated with development of MM, and potentially increased susceptibility to melphalan therapy. That being said, a more clear and potentially hypothesis driven explanation and discussion would strengthen the manuscript.

Are the methods appropriate and well described? 
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls? 
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown? 
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review? 
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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