Author’s response to reviews

Title: Venetoclax in combination with carfilzomib and dexamethasone in relapsed/refractory multiple myeloma harboring t(11,14)(q13;q32); a report of two cases and review of literature

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Reviewer reports:

Reviewer #1: 1. Do you believe the case report is authentic?
Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.
Comments: no ethical concerns.

3. Does the Introduction explain the relevance of the case to the medical literature?
Yes

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:
- De-identified demographic information (age, gender, ethnicity)  yes
- Main symptoms of the patient  yes
- Medical, family and psychosocial history  yes
- Relevant past interventions and their outcomes  yes

b. The relevant physical examination findings  yes
c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month.

yes
d. Diagnostic assessments, including:

- Diagnostic methods
- Challenges (e.g., financial, language/cultural)
- Reasoning and prognostic characteristics (e.g., staging), where applicable

yes
e. Types and mechanism of intervention: use of new drug in R/R myeloma patients

f. A summary of the clinical course of all follow-up visits: provided

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

yes
6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

   Yes

7. Is the Abstract representative of the case presented? yes

   Comments:

8. Does the case represent a useful contribution to the medical literature?

   Comments:

   yes

9. Additional comments for the author(s)? Use of venetoclax is relatively new to the field of myeloma. Author describes two cases in which short term response can be achieved through this therapy in R/R myeloma. There are few publications of such use in literature. I think publication of this report will help for clinical use of this drug in R/R myeloma patients with t(11;14).

   Reviewer #2: an interesting and enlightening report to read real life experience of outcomes of bcl-2 inhibiton in MM.

   one or two suggestions:

   1) in the second case "Venetoclax was dosed at mg per day, page 8, line 49-50", you forgot to write the dose of venetoclax.

   Response: Thank you very much for your observation. The venetoclax dose is entered in the revised manuscript.
2) Karyotyping and FISH and molecular analysis is challenging in MM as it should be done preferably with plasma cell sorting and if possible in new acquired plasmocytomas as well. (which is of course mostly not possible). So in case 1, it may be that during the 2014 investigations t(11,14) may have been overlooked due the technical difficulties. Thus it may not be an acquired anomaly, but maybe rather you got more luck to catch it in 2018.

Response: Thank you very much for your comment; this could very well be the case.

3) It is known that additional mutations must accompany everytime a malignant disease progresses or develops resistance to a therapy; thus Non-response to bcl-2 inhibiton tells us that RR-MM is not a disease with one target mutation, but rather a composition with multiple mutations and maybe different mutations in different subclones. FISH analysis can only show us really the top of an iceberg. So the lack response or rapid loss of response could be further discussed in the anarchical mutational status of RR-MM. More brave suggestion would be to test the drug in newly diagnosed 11,144 MM, which would be expected to harbour less additional mutations then RR-MM.

Response: Thank you very much for your comment; cannot agree more.