Author’s response to reviews

Title: The clonal evolution of two distinct T315I-positive BCR-ABL1 subclones in a Philadelphia-positive acute lymphoblastic leukemia failing multiple lines of therapy: a case report

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Author’s response to reviews:

Dear Dr Solera,

please find herewith enclosed the revised version of the manuscript entitled "The clonal evolution of two distinct T315I-positive BCR-ABL1 subclones in a Philadelphia-positive acute lymphoblastic leukemia failing multiple lines of therapy: a case report" by De Benedittis et al, for consideration for publication in BMC Cancer.

We thank the reviewers for their thoughtful evaluation of our manuscript. We agree with all their comments and we have revised our manuscript accordingly. All changes to the manuscript are highlighted in red. A point-by-point description of such changes in response to reviewers’ comments is detailed below.
Reviewer reports:

Reviewer #1: (page 3 line 24) there is no BCR-ABL1/ABL1 level at diagnosis, therefore the reduction of the copies after treatment can't be compared. As suggested by Reviewer #1 we have now indicate the BCR-ABL1 transcript level at page 3 line 22 and also in Table 1.

(page 3 line 36) what is the meaning of transient hematological response? and did the patient achieve complete hematological response? The term transient indicates that the patient had achieved a very short-lived complete hematologic response. We decide to eliminate this word.

(page 4 line 1-8) what was the gap between the 1st and second Blinatumomab treatment? As required by protocol schedule the second course of Blinatumomab was started two weeks after the end of the first one. No treatment was performed over this time. We have now indicate this information at page 4 line 8

(page 4 line 23) again what is transient hematological response? see answer to first comment.

(page 6 line 19 to 31), this part should be under the subtitle of discussion, line 32-46 under the subtitle of conclusion. We decide to create a brief final summary with our conclusion.

It will be clearer with a chart/graph of the BCR-ABL transcripts level through out the timeline. As suggested by Reviewer #1 we have now illustrate the evolution of the BCR-ABL1 transcript levels through out the timeline with Figure 3

there are too many brackets in the article, example, page 3 line 55: A severe cardiac toxicity (reduction of ejection fraction up to 46%). The authors should try to compose it into a proper sentence. As suggested by Reviewer #1 we have now eliminate the brackets in the majority of the pages.

Overall, this is an interesting case to discuss.
Reviewer #2: This is an interesting case report that furthers our understanding of bcr/abl mutations and their impact on response to bcr/abl inhibitors and other therapeutics.

Comments

Major

The concept of TKI resistant bcr/abl mutations existing prior to exposure because they are 'fitter' oncogenic proteins has been muted before and should be referenced here. We looked for the 315 and other mutation at diagnosis prior to Dasatinib start, but deep sequencing didn’t find evidence of any mutations. We have now indicate this data at page 4 line 46.

Minor

The depth of sequencing (mean and range) should be described in the text. As suggested by Reviewer #2 we now indicate the depth of sequencing (mean and range) at page 4 line 32.

Figure 2 need a label on the Y axis. We have now add the label on the Y axis of Figure 2.

After 11 months from first submission, we now hope that our manuscript will undergo a rapid second round of revision and will soon be accepted for publication in BMC Cancer.

Thank you in advance for your assistance.

Kind regards

Caterina de Benedittis, on behalf of all co-authors