Reviewer's report

Title: Systematic Review of Azacitidine Regimens in Myelodysplastic Syndrome and Acute Myeloid Leukemia

Version: 1 Date: 18 Jul 2017

Reviewer: Vu H. Duong

Reviewer's report:

The authors present a systematic review of the available literature and a direct comparison of different dosing schedules of azacitidine in patients with MDS and AML. The study and the results are of interest, but there are some issues that I think need clarification before publication.

Major Points:

1) For systematic reviews and meta-analyses, PRISMA guidelines have become the standard. Although this manuscript follows most of these guidelines, some items from the checklist are missing and the authors do not state explicitly that these guidelines were followed.

2) Table 1 - the numbers for references (#62-69) do not all match the numbers in the reference list and this must be corrected.

3) The inclusion of studies involving patients with both MDS and AML is problematic. It is not clear to me how response criteria were applied. Throughout the text, the authors refer to IWG criteria for MDS, and in particularly the revisions published in 2006; however, several of the included studies were for patients with AML exclusively. There are separate IWG criteria for AML (published in 2003), which do NOT include hematologic improvement. AML studies therefore rarely, if ever, report on HI. In addition, the definitions of CR and PR differ significantly from the MDS 2006 criteria. Thus, in the studies involving AML patients exclusively, did the authors apply MDS response criteria? The authors touch a bit on this subject in the discussion, but again reference the IWG MDS response criteria from 2006 only - I think this issue need clarification in the manuscript.

4) Stable disease has been associated with improved overall survival in patients with MDS treated with azacitidine (Gore SD, Haematologica 2013) and therefore it would be helpful to analyze this "response" in this study. If this is not possible, this issue and the implications of this should be mentioned in the discussion.

5) As the authors concluded, indeed randomized trials are indeed needed to assess the impact of different dosing regimens. However, I disagree with the authors' comment that "at the very
least a standardization of outcome data reporting in the literature must be agreed upon" and "standardization of reporting of outcomes of azacitidine treatment is essential." Again, I think part of why there was heterogeneity in reporting of outcomes is because there are several different diseases studied here, each with different response criteria. In addition, the IWG response criteria for MDS and AML (and more recently an international consortium standardization of responses in MDS/MPN including CMML) were developed specifically for the purpose of standardization of reporting. As the authors point out, many of the studies being retrospective in nature and therefore may lack the ability to report on all of the outcomes desired by the authors. I think this is inherent when studying ANY disease, not just MDS or AML. These concluding remarks, I feel, need to be softened.

Minor point:

Last sentence of the 1st paragraph in the introduction is slightly imprecise - the FDA recognized the survival benefit in patients with highER-risk MDS (int-2 and high) by the IPSS, not just high-risk MDS.

**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?**
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No

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