Reviewer’s report

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

Version: 1 Date: 24 Sep 2017

Reviewer: Amer Zeidan

Reviewer's report:

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In this systematic review by Shapiro et al, the authors compared the different azacitidine administration schedules used in MDS as no randomized controlled trial has been done directly comparing all three dosing regimens. They were able to conduct a systematic review but not a meta analyses due to heterogeneity of the included studies. A Pooled analyses of ORR was performed but comparisons between groups were not attempted due to the heterogeneity of study designs. The pooled proportion of ORR was 44.4% with 95% CI (42.4%, 45.1%) for 7-0-0, 41.2% with 95% CI (39.2%, 41.9%) for 5-0-0, and 45.8% with 95% CI (42.6%, 46.4%) for 5-2-2 schedule. The authors concluded that comparison of alternative azacitidine dosing regimens in MDS shows a benefit for the 7-day regimen in attaining ORR.

The work by the authors addresses a very important question given that population level studies showed the 7-0-0 is rarely used in USA with more than 85% of patients receiving either 5-2-2 or 5-0 due to logistical challenges of weekend administration. However clinical trial data regarding long term outcomes with these regimens are lacking as only the 7-0-0 been shown to be associated with a survival advantage. Despite below limitations, I think this is important work that is worthy of publication.

Major comments:

- One of the problems in this study is that most studies that used 5-0 regimen included patients with lower risk mds including the only randomized prospective study against 5-2-2 by Lyons et al. Therefore it is not clear how valid is the comparison against higher risk mds patients for whom 5-2-2 is more commonly used at is does not appear risk categories of MDS were adjusted for in these analyses
Recent data (Jabbour et al, Blood. 2017 Aug 3. pii: blood-2017-06-788497. doi: 10.1182/blood-2017-06-788497. [Epub ahead of print] A randomized phase II study of low-dose decitabine versus low-dose azacitidine in lower risk MDS and MDS/MPN.) suggested even shorter course of aza and decitabine could result in high ORR responses-in this study for exam aza for 3 days had 49% ORR, this study and other studies of shorter regimens were not included in this analysis and raise the question if 5-0 is as good as 3-0 in lower risk mds and cast a question on whether longer regimens are better than shorter ones.

- Direct comparison between the ORR associated with the different couldn't be performed which limits the significance of the findings.

- There could be a disconnection between other important endpoints such as CR and OS and the ORR and not clear how do the different regimens compare in these endpoints. 7-0-0 remains the only regimen associated with OS benefit in randomized trials.

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?
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Yes

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