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by Donna Przepiorka and Emily Y. Jen

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Implications of the EHA/ELN guidelines for reporting blast percentage. Comment on: "Reporting blast percentage for response assessment in acute leukemias: recommendations from an EHA/ELN expert panel"

Donna Przepiorka[1] and Emily Y. Jen[1]

From the [1]US Food and Drug Administration, Silver Spring, MD.

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Address correspondence to: Donna Przepiorka, MD, PhD
US Food and Drug Administration
10903 New Hampshire Ave,
Silver Spring, MD 20993
Tel: 301-796-5358
Email: donna.przepiorka@fda.hhs.gov

The EHA/ELN recommendations for reporting blast percentages for acute leukemia response assessments from Wang et al[1] contained an overview of the challenges in identifying blasts by morphology and other methods, strategies for communicating the resulting uncertainties, and a framework for deriving and reporting the blast percentage in the face of these uncertainties. While the suggested approach to handling the difficult cases is quite sound, we have concerns with the recommendations for how to derive and report the blast percentage across all cases, and how these recommendations may complicate clinical trial analysis and interpretation.

Our concern stems from the authors' recommendation to use results from different platforms as the marrow blast percentage depending on the leukemia subtype, morphological blast count, and measures of residual disease (see for example Figure 2 in Wang et al[1]). Thus, the morphological blast percentage, flow blast percentage, and molecular measures of residual disease burden could be used to report the blast percentage. Although an assessment integrating results from all platforms may help the pathologist make a call of "in remission" vs "not in remission", the clinical trialists will immediately recognize the recommended reporting framework as a conflation of different efficacy endpoints (i.e., CR vs MRD-negative CR, etc.) and not a measure consistent with the current criteria for complete remission.[2] Additionally, the technical specifications for acute leukemia data sets in marketing applications require that results from each of these platforms be reported separately.[3] Moreover, there is a potential for bias due to missing data when the MRD testing is not performed consistently for all study participants. Thus, reporting blast percentage from inconsistent platforms as recommended by the EHA/ELN guidelines, rather than identifying the results from each platform individually, has the potential to

complicate data extraction by the data managers using the pathology reports, to delay or preclude review of marketing applications for new drugs due to data quality issues, and to increase the costs of clinical trials if a central laboratory is needed to review all response testing to ensure that the trial results have no biases.

Nonetheless, the authors also make a good case for routine use of flow cytometry for reporting blast percentage. Acknowledging that the blast percentage by morphology has only a modest correlation with that by flow cytometry,[4] any flow-based endpoint (i.e., flow CR) would be considered novel at this time. Advantages of a flow-based endpoint are that flow cytometry is widely available, there are consensus technical recommendations for quantifying leukemia burden by flow cytometry,[5] and there is a quality assessment program to ensure consistency between laboratories.[6] The main disadvantage is that there is not a qualified cut-point to identify the population of interest by flow cytometry. Even the recommendations from the ELN-DAVID MRD Working Party[7] cite levels of evidence largely in the 3-4 range despite enthusiastic agreement among the participants. Although available data are consistent with the recommended cut-point of 0.1% to identify patients at high risk of imminent relapse for patients with acute leukemias, preliminary analyses have not consistently excluded lower levels of residual disease to identify that target population.[8,9] Given the heterogeneity of AML and ALL subtypes, the different disease settings under study, and the range of intensities of the treatment regimens, qualification of a new flow-based remission assessment is likely to require an international effort.

Thus, although a standardized approach to reporting blast percentages for response assessments for acute leukemias could potentially improve the reliability of reported clinical trial outcomes, the mixing of platforms for quantitating blasts as recommended in the EHA/ELN guidelines precludes their applicability for use in clinical trials, and it would seem more advantageous to develop new single-platform measures of disease, such as a flow-based criteria, instead. Additionally, while highly sensitive molecular measures of residual disease are clearly needed to guide risk-adapted treatments for acute leukemias, the results of such molecular testing should not be confused with blast percentage.

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