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NCCN Guidelines Panel: Acute Lymphoblastic Leukemia (Adult and AYA)

On behalf of Adaptive Biotechnologies, we request that the NCCN Acute Lymphoblastic Leukemia (Adult and AYA) Guideline Panel review and consider the following modifications for the ALL Guidelines.

Rationale

In 2018, the clonoSEQ® Assay was granted De Novo designation by the FDA as the first and only test for the assessment of minimal (measurable) residual disease (MRD) in the bone marrow of patients with MM and acute lymphoblastic leukemia.[1] The analytical and clinical validation studies included more than 40,000 unique MRD measurements demonstrating the precision and reproducibility of the clonoSEQ Assay. The FDA has publicly recognized the rigor of clonoSEQ validation[2] and has restated the need for a standardized MRD tool to aid in clinical management. Additionally, the FDA published a draft guidance for the use of MRD in hematologic malignancies to support drug development,[3] and this guidance follows three new drug labels that incorporate MRD data.

To ensure that all patient populations have access to the most standardized and specific technology, Adaptive Biotechnologies has secured a positive coverage determination by Medicare[4] and currently covers 165 million lives through private payer policies, thus removing a patient access barrier.

In addition to the specific requests below, we would like to request the consideration of additional data that demonstrates the utility of MRD assessment to the discussion section. Specifically, the SWOG 033 study used next generation sequencing (NGS) to evaluate residual disease in 32 patients with adult B-cell ALL. Results were compared to multi-parameter flow cytometry (mpFC). There was a strong concordance (82%) between the methods. However, in 17% (N=9) of cases, leukemia was detected by NGS, but not by mpFC. 1 patient was identified as mpFC MRD-positive and NGS-MRD negative. In 54 bone marrow (BM) and peripheral blood (PB) paired specimens, the burden of leukemia detected by NGS was lower in PB than BM, although still detectable in 68% of the 28 paired specimens with positive BM. Lastly, patients without disease detected by NGS or FCM had a 5-year relapse free survival (RFS) of > 80%. The results suggest that residual disease detection by NGS is an extremely sensitive technique and may identify patients that might benefit from transplant. Moreover, the increased sensitivity of the method may allow frequent peripheral blood testing to supplement marrow sampling to measure disease response.[5]

Requested Modifications

- Page 30 (ALL-F), Version 2.2019: Update MRD section with additional content from the MRD page of the recently released NCCN Pediatric ALL Guidelines (add entire bullet; suggested addition in red):
  MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.

- Page 30 (ALL-F), Version 2.2019: Update text to include information about FDA-clearance of an NGS-MRD assay (3rd bullet; suggested addition in red): MRD is an essential component of patient evaluation over the course of sequential therapy. If a patient is not treated in an academic center, there are

commercially available tests available that should be used for MRD assessment. One commercially available NGS-MRD assay is FDA- cleared (clonoSEQ®).

- Page 30 (ALL-F), Version 2.2019: Update MRD section with additional content from the MRD page of the recently released NCCN Pediatric ALL Guidelines (5th bullet; suggested addition in red): The most frequently employed methods for MRD assessment include at least 6-color flow cytometry assays specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, BCRABL1), and next-generation sequencing (NGS)-based assays, to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes (does not require the creation of patient specific primers).

- Page 30 (ALL-F), Version 2.2019: Update MRD section with additional content from the MRD page of the recently released NCCN Pediatric ALL Guidelines (add as a sub-bullet under bullet 5; suggested addition in red): Prior treatment with immunotherapy or HSCT can affect interpretation of flow cytometry-based MRD results. MRD should be performed in a laboratory with experience performing MRD in this setting and/or with a methodology less subject to alteration by these therapies.

- Discussion section, Version 2.2019: Update the discussion section to include recent data relating to the utility of NGS-MRD assessment in the adult setting.[5]

References

1. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2018. https://www.clonoseq.com/technical-summary
2. FDA authorizes first next generation sequencing-based test to detect very low levels of remaining cancer cells in patients with acute lymphoblastic leukemia or multiple myeloma [press release]. September 28, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622004.htm
3. FDA. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM623333.pdf. Published 2018. Accessed September 9, 2019.
4. CMS. Local Coverage Article: MolDX: Clonoseq® Assay for Assessment of Minimal Residual Disease (MRD) in Patients with Specific Lymphoid Malignancies (A56270). https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56270&ver=5&Cntrctr=374&ContrVer=1&CntrctrSelected=374*1&DocType=Active&s=48&bc=AhAAAAIAgAAA&. Updated January 17, 2019. Accessed September 9, 2019.
5. Sala Torra, et al. Next-Generation Sequencing in Adult B Cell Acute Lymphoblastic Leukemia Patients. *Biology of Blood and Marrow Transplantation.* 2017;23(4):691-696.