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Kendra Sweet, Jeffrey Lancet

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State of the Art Update and Next Questions: Acute Myeloid Leukemia

Kendra Sweet[1] and Jeffrey Lancet[1]

1 Moffitt Cancer Center, Tampa, Florida

Background

The past decade has witnessed major advances in our comprehension of the biological heterogeneity of acute myeloid leukemia (AML); however, translating this knowledge into better outcomes for AML patients has lagged. Over the past year, two large, randomized phase III clinical trials with novel therapies produced positive results that are expected to lead to the first new drug approvals in AML in over 40 years.[1, 2] Many other promising drugs are currently under investigation, offering hope that even more novel treatments will be added to the armamentarium in the near future.

Enhanced knowledge about the prognostic significance of common genomic alterations, both at diagnosis and at the time of minimal residual disease (MRD) assessment, have begun to inform management decisions.[3] As such, routine testing for molecular mutations, and MRD monitoring of patients in morphologic remission are becoming commonplace in general practice.[4, 5] Here we will review the data on genomics, MRD monitoring and new therapeutic options in AML.

Incorporation of Genomic Analysis in AML

In recent years, whole-genome sequencing has provided the field with a wealth of data on the role of driver mutations and clonal evolution in AML.[3, 6-8] Although this information has shed light on the biological complexity of AML, the clinical utility of much of this genomic data remains debatable. In 2013, The Cancer Genome Atlas AML sub-study published results from whole-genome and whole-exome sequencing of 200 cases of de novo AML. The authors identified 23 commonly mutated genes, and 237 additional genes that were mutated in at least 2 cases. These mutations were seen in patterns of co-occurrence and mutual exclusivity. Nine distinct categories of genetic alternations were identified from this study, and all are believed to play a role in leukemogenesis.[6] This study set the stage for others to begin incorporating genetic data into disease classification, prognostication and therapeutic decision making.

Whole-exome sequencing has shown that numerous somatic mutations are detected in patients with AML, and most have more than one identifiable driver mutation. Multiple leukemic clones exist simultaneously, and compete with each other as leukemia evolves.[6, 7] Certain mutations are known to frequently co-occur, implying a synergistic functionality that propagates the leukemic clones.[3, 6, 9] Clonal relationships and AML ontogeny can be inferred based on the allele frequencies of specific mutations. Mutations in genes that encode epigenetic modifiers such as DNMT3A, ASXL1, IDH1/2 and TET2 are typically found in pre-leukemic stem or progenitor cells and are rarely found in isolation, indicating the development of these particular mutations is an early event which takes place before transformation to overt leukemia. Ordinarily, the variant allele frequency (VAF) of these genes is close to 50% which is expected when a heterozygous mutation is present in nearly all cells, as would be the case for a founding clone. Mutations in growth-factor signaling genes such as FLT3, KIT, NRAS, KRAS and

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