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The increasing genomic complexity of acute myeloid leukemia

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Therapy of acute myeloid leukemia (AML) is impacted by the increasing genomic complexity of the disease. Multiple targets as expressed by genetics and mutations and the relationships between them add another layer of intricacy to the prognosis and treatment of the disease. It is becoming increasingly apparent that the interactions between mutations are of utmost importance, particularly from a prognostic standpoint. For example, inv(16) or 6(16; 16) AML frequently involves a second genetic lesion that significantly impacts prognosis. In addition, epigenetic changes, including DNA methylation, are becoming increasingly integrated into the genetic landscape and may also have prognostic impact. Despite increased understanding of the genetic and epigenetic aspects of AML, the outcome for AML patients has not changed significantly. Until it does, further inquiry into the genomic complexity of the disease and advances in drug development are needed.

In recent years, the work of the Cancer Genome Atlas Research Network has demonstrated the increasing genomic complexity of acute myeloid leukemia (AML). The Network analyzed the genomes of 200 adult patients with de novo acute myeloid leukemia (AML) and found that 23 genes were significantly mutated (Fig. 1) and 237 genes were mutated in 2 or more people [1]. They were able to identify the numbers of recurring, tier 1 mutations in each of the 200 samples (Fig. 2).

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We have learned from this and other work that what is most important prognostically is the interaction between mutations. For example, a German study of almost 170 patients with inv(16) or t(16; 16) AML found that more than 90% of patients had secondary genetic lesions that significantly impacted their prognosis [2] (Fig. 3).

The genomic complexity continues to unfold, as the integration of genetics and epigenetics becomes better defined. A recent study described a novel 7-gene expression score that encompasses both genetic and epigenetic information for prognostic purposes and treatment response prediction [3]. The researchers used cytogenetically normal AML patients and next-generation sequencing of methylated DNA to develop the score. The number of differentially methylated regions (DMRs) found in distinct genomic groups are depicted in Fig. 4. The authors found that for all 7 genes (*CD34*, *RHOC*, *SCRN1*, *F2RL1*, *FAM92A1*, *MIR155HG*, and *VWA8*), high methylation and low expression levels conferred a better outcome. They concluded that the score, which includes epigenetic and genetic information, identified novel AML subsets that are meaningful in guiding treatment decisions.

Nevertheless, the crux of the problem is that overall results for AML, apart from select small subgroups, have not changed significantly, as can be seen in the most recently published data from the large cooperative groups [4–8]. When it comes to older adults, clearly more receive remission-inducing chemotherapy nowadays and more achieve a complete remission. However, long-term survival remains elusive for the majority of patients. The survival curves for younger adults less than 60 years of age are virtually superimposable (Fig. 5), despite the fact that each group uses different treatment strategies. And the similarity is not due to a lack of new ideas, as there are many new drugs in multiple stages of development (Table 1) [9]. In fact, since the development of therapy for AML over 40 years ago, there have never been so many potential targets, representing the increasing understanding of the biology of the disease. Given the genomic complexity just described, it is probably not surprising that there has still not been a fundamental difference in outcome of AML, as there is a small chance that a single drug will make a difference. Furthermore, some AMLs may originate from a preleukemic progenitor harboring the DNMT3 or IDH mutations, which confer clonal expansion and, with additional mutations, can transform into AML [10]. In this regard, the preliminary data using an inhibitor to mutant IDH2 present, in the mitochondria, which blocks normal cellular differentiation [11], are intriguing, and hopefully may usher in a new era of more successful therapy of AML [12].

Even with our increased understanding, it appears that we still need to better identify the most important driving mutations in AML. This, the proceeding of the18th consecutive Acute Leukemia Forum, examines many of the issues in the biology and therapy of AML, acute lymphoblastic leukemia, and myelodysplasia. The articles that follow in this issue are based on presentations made at the Forum, which took place April 25, 2014, in San Francisco, California.

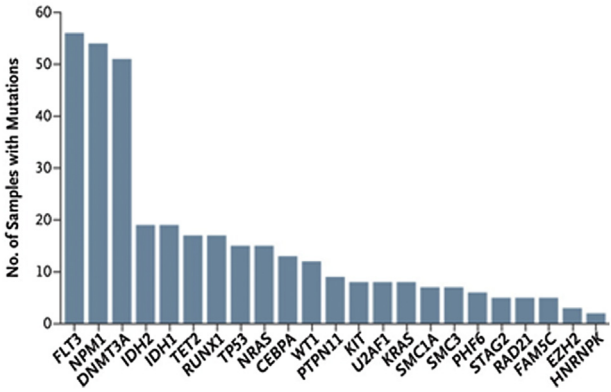

Fig. 1. Significantly mutated genes in de novo adult AML [1]. Significantly mutated genes in 200 AML samples and the number of samples with each mutation. From N Engl J Med, Cancer Genome Atlas Research Network, Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia, Vol No. 368, Page No. 2064, Copyright© 2013 Massacusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.