Introduction to the review series on advances in acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is the most common form of acute leukemia, with an incidence that increases with advanced age. Although it is usually of unknown etiology, it can also develop following exposure to genotoxic agents or following an antecedent hematologic disorder (eg, marrow failure syndrome). The disorder arises in a malignantly transformed multipotential hematopoietic stem cell that acquires successive genomic alterations, ultimately evolving into clinically overt disease. AML is a remarkably complex malignancy, with considerable genetic, epigenetic, and phenotypic heterogeneity.

Molecular and cytogenetic abnormalities in AML involve mutations in critical genes of normal cell development, cellular survival, proliferation, and maturation, adding to the challenge of targeting these pathways without inducing toxicity. Furthermore, in almost every patient with AML, multiple malignant clones coexist. Each one of these subclones is characterized by a unique configuration of genetic and epigenetic abnormalities and may also differ in their response to treatment. The complexity of the molecular, cellular, and clonal structure may explain why advancing the treatment of AML has been an extraordinary challenge. As a result, progress in understanding the pathobiology of AML has far exceeded the progress in translating our understanding into improved therapy. Approximately 35% to 40% of patients younger than 60 years of age may obtain long-term survival with current forms of treatment. However, there is a wide variation in outcome among genetically distinguishable subsets of the disease, with some subtypes having a notoriously poor outcome. Also, in older patients (>60 years), the overall prognosis has remained highly unsatisfactory. Thus, there is an urgent unmet need for therapeutic improvements. It is presumed that successful treatment must effectively eradicate the leukemic stem cell and its subclones so that residual disease cannot act as the source of recurrence.

What have we learned in recent years about the biology of AML, and how does this knowledge impact on our current treatment strategies? The series of 5 reviews on AML that are presented in this issue of *Blood* offers comprehensive updates on the latest insights into the pathobiology of the disease as well as the current and future directions of treatment.

In the first review, Grimwade, Ivey, and Huntly comprehensively describe the dazzling variety of gene mutations in AML that have been discovered as drivers of the development and progression of the disease. They discuss the interrelationships between identified genetic mutations and their biological significance, emphasizing the perspective of their therapeutic relevance. Thus, they create "order" in this apparent "chaos" of abnormalities. In addition to DNA mutations, epigenetic alterations reflecting chromatin changes that affect gene expression may also contribute to AML pathogenesis. In the second review, Wouters and Delwel update our current understanding of epigenetic alterations in relation to disease pathogenesis and highlight their potential value for treatment development. Epigenetic alterations may profoundly disrupt and perturb a variety of key functional intracellular pathways. Because epigenetic modifications are potentially reversible, they appear particularly amenable to therapeutic interventions and offer attractive avenues for targeted treatment development.

As previously noted, therapeutic progress in AML has been modest. Current treatment is still largely based on the classical cornerstones of combination chemotherapy and the appropriate use of stem cell transplantation. What is the current framework for the clinical management of a patient with AML? Although the promise of a fully developed personalized treatment approach has yet to be fulfilled, clinicians need the best possible information to guide the optimal treatment approach in an individual patient. The option of an allogeneic or autologous stem cell transplant has become an integrated part of the current comprehensive treatment strategy. However, who "needs" a transplant, and in whom would it be better to refrain from the risks of an allograft? Diverse transplantation approaches (various transplant sources and donor options, new conditioning regimens) have become available. What type of transplant is the preferred choice in a particular patient, taking into account leukemia-specific and patient-related factors? These issues are critically and lucidly reviewed in the third review by Dombret and Gardin of the clinical management of AML and in a fourth review by Cornelissen and Blaise of the utility of stem cell transplantation in the front-line treatment of AML.

Today, an unprecedented number of novel drugs are in the developmental pipeline. Many of these drugs act through entirely novel mechanisms of action and target particular molecularly defined subsets of disease. In the fifth review, Stein and Tallman discuss emerging drugs that hold clinical promise. Some of these are foreseen to become part of our therapeutic armamentarium in the near future.

We are pleased to introduce the reviews of this series on AML that summarize the current state of the art in this exciting and rapidly evolving area of scientific and clinical hematology:

Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance (David Grimwade, Adam Ivey, and Brian Huntly)

Epigenetics and approaches to targeted epigenetic therapy in acute myeloid leukemia (Bas J. Wouters and Ruud Delwel)

An update of current treatments for adult acute myeloid leukemia (Hervé Dombret and Claude Gardin)

Hematopoietic stem cell transplantation for patients with AML in first complete remission (Jan J. Cornelissen and Didier Blaise)

Emerging therapeutic drugs for AML (Eytan M. Stein and Martin S. Tallman)

We trust that the Review Series on AML will be of value to those interested and involved in leukemia research and the clinical management of patients with leukemia.

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