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Authors

Jonas, BA
Medeiros, BC

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Individualizing Therapeutic Strategies in Acute Myeloid Leukemia: Moving Beyond the 'One-Size-Fits-All' Approach

Brian A. Jonas, MD, PhD¹, Bruno C. Medeiros, MD²

Acute myeloid leukemia (AML) is an aggressive hematopoietic cancer characterized by recurrent genetic lesions and clonal expansion of immature and ineffective myeloid lineage cells, and is associated with a high morbidity and mortality. Recent genomic studies have shown that AML is a highly complex and heterogeneous disease.[1] The most recent edition of the World Health Organization classification addressed the increasing awareness of AML heterogeneity by significantly increasing the number of AML subcategories.[2] Prognostic variables in AML include age and such biologic features as recurrent cytogenetic abnormalities and certain genomic mutations.[3] In fact, recent analyses have demonstrated the value of incorporating gene mutations beyond *FLT3*, *NPM1*, and *CEBPA* (eg, *IDH1* and *IDH2*, *ASXL1*, *MLL*, *DNMT3A*, and *TET2*) into AML risk classifications.[4] Despite these advances in our understanding of the pathogenesis of AML, treatment strategies have not significantly changed over the past 40 years, and age-adapted remission induction with chemotherapy and post-remission consolidation with chemotherapy and allogeneic hematopoietic stem cell transplant remain the standard of care.

In this issue of *ONCOLOGY*, Khaled, Al Malki, and Marcucci contribute a timely and comprehensive review of recurrent genomic abnormalities, current treatment paradigms, and emerging targeted therapeutic approaches in AML.[5] The authors review the incidence and biologic and prognostic impact of both established and emerging recurrent cytogenetic and molecular abnormalities, as well as the current treatment paradigms in both untreated and relapsed and refractory AML. Importantly, the authors review many of the emerging therapeutics for AML, including several novel therapeutics that target recurrent mutations or abnormal biological processes in AML cells. The impact of minimal residual disease (MRD) analysis on post-remission strategies in AML is also discussed. The authors summarize these advances and propose updated treatment algorithms that incorporate newer mutations and MRD testing, and in which patients are stratified by age and fitness for intense therapy.

As highlighted by the authors, our therapeutic approach to



This commentary reflects on the review article on page 318.

AML must evolve to match our increasing understanding of AML pathogenesis and potential associated therapeutic vulnerabilities. Since the advent of next-generation sequencing (NGS), the mutational profiles of large numbers of AML genomes have been described, resulting in a well-characterized AML mutome.[6,7] This information has increased our understanding of AML pathogenesis. For example, data suggest that AML development is often a stepwise process that follows the development of clonal hematopoiesis as early as the fifth decade of life.[8,9] Furthermore, mutational profiling has led to the isolation of phenotypically and functionally normal preleukemic hematopoietic stem cells that serve as a reservoir for the development of AML clones, both at presentation and at relapse.[10,11] Transformation of these preleukemic hematopoietic stem cells leads to the development of AML, and while the field of AML leukemic stem cells is relatively mature, knowledge of AML mutations adds to the potential targets that might be used to eliminate leukemic stem cells (and potentially preleukemic hematopoietic stem cells) and thus improve therapeutic outcomes.[12] In addition, the process by which secondary AML develops and established AML evolves, termed clonal evolution, has been better described now that NGS has facilitated the characterization of AML-associated mutations.[6,13] Similar work has described the role of *TP53* mutations in the very-poor-risk therapy-related AML subtype, and has made it possible to identify which patients have a secondary or secondary-like AML based on mutational profiling.[14,15] Overall, the rapid increase in our molecular understanding of AML has led to refinements in our prognostic models, in addition to paving the way for the development of very promising novel targeted agents, such as *FLT3* inhibitors, isocitrate dehydrogenase (*IDH*) inhibitors, and *BCL-2* inhibitors.[16-18] The impact of AML mutational profiling on MRD analysis is also rapidly evolving. The presence of MRD after initial therapy, detected by either flow cytometry or molecular-based approaches, has significant and independent prognostic value in AML.[19-22] Determination of the optimal method for MRD detection in AML, the choice of molecular or antigen targets, and the signifi-

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¹Department of Internal Medicine, Division of Hematology and Oncology, University of California (UC) Davis School of Medicine, UC Davis Comprehensive Cancer Center, Sacramento, California

²Department of Medicine, Division of Hematology, Stanford University School of Medicine, Stanford Comprehensive Cancer Center, Stanford, California

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cance of MRD cutoff levels remain critical questions in incorporating MRD analysis into AML management.

As highlighted in this review, the antileukemic activity of intensive chemotherapy has likely been maximized, after decades of trials optimizing the choice of chemotherapy, dose intensity, and duration of treatment. The rapid advances in our understanding of AML molecular pathogenesis and in novel targeted drug development provide a unique opportunity to change the design of future clinical trials and to individualize treatment algorithms to improve outcomes for all subgroups of AML, including older unfit patients. For example, two major recent studies have demonstrated that the addition of the tyrosine kinase inhibitors sorafenib and midostaurin improved survival and outcomes for unselected and *FLT3*-mutated younger patients with AML, respectively.[16,23] Furthermore, the addition of the BCL-2 inhibitor venetoclax to standard hypomethylating agent therapy led to promising overall response rates in elderly unfit AML patients.[18] As a field, we now have the opportunity to change the paradigm of clinical trial development by embracing

Our therapeutic approach to AML must evolve to match our increasing understanding of AML pathogenesis and potential associated therapeutic vulnerabilities

ing risk-adapted designs that allow us to answer many questions in a single clinical trial. To this end, the treatment approaches suggested by Khaled et al for younger, older fit, and older unfit AML patients suggest a roadmap for risk-adapted prospective clinical trials with limited selection at baseline, randomization to specific mutationally or biologically based treatment arms incorporating novel agents, and further randomization based on MRD response. Alternative trial endpoints that might be used in place of overall survival, such as MRD negativity, can be readily incorporated into these studies. Such “personalized medicine” trials will require large multi-cooperative group efforts in order to adequately power subset arms. This approach will also require AML clinician-scientists to embrace changes to current trial and academic paradigms, as well as necessitating buy-in and cooperation from multiple pharmaceutical companies and other funding sources. In agreement with Khaled et al, we are ready to move beyond a “one-size-fits-all” approach in AML and join our colleagues treating other malignancies, such as lung cancer, in moving towards a personalized medicine approach. ○

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