Great expectations in acute myeloid leukemia

“With the advent of next-generation sequencing approaches, recurrent somatic mutations in acute myeloid leukemia have been identified...”

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Acute myeloid leukemia (AML) represents a heterogeneous hematopoietic stem cell malignancy, characterized by the lack of normal differentiation and proliferation of myeloblasts, leading to the accumulation of abnormal immature myeloid precursors at the expense of normal hematopoietic elements. While the past 10 years have witnessed dramatic progress in the scientific understanding of leukemogenesis and AML biology, the treatment of patients with AML has changed little in over 30 years. With our title referencing the fundamental theme of hope in the penultimate novel by Charles Dickens, we present a forward-looking strategy toward AML diagnosis and treatment.

Toward an improved diagnosis

Patient age, performance status and karyotype have historically been the three most important prognostic factors at AML diagnosis, with cytogenetics providing the first of the ‘genetic’ prognostic markers [1,2]. Patients with newly diagnosed AML are routinely classified into three groups based on their pretreatment karyotype

into those with favorable cytogenetics, those with adverse cytogenetics and the remaining ~50% of AML falling into an intermediate-risk category. Patients with favorable risk disease are typically younger and are treated with cycles of high-dose cytarabine-based chemotherapy with curative intent, whereas the generally older patients with adverse cytogenetics have significantly reduced remission and cure rates with induction/consolidation treatment approaches, and investigative options are prioritized in this population [3].

With the advent of next-generation sequencing approaches, recurrent somatic mutations in AML have been identified, with approximately a dozen genomic alterations present per AML sample analyzed, and >95% of AML cases harboring at least one somatic alteration [4,5]. Improved awareness of genetic abnormalities at the time of diagnosis has improved the prognostic classification of patients, particularly allowing for the improved characterization of patients with intermediate-risk AML, with mutational status of *FLT3-ITD*, *CEBPA* and *NPM1* mutational status

KEYWORDS

- AML • maintenance
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“Currently, no approved or standard maintenance strategies for acute myeloid leukemia patients in complete remission exist...”

now part of the updated European LeukemiaNet classification system [6]. Beyond providing a simply improved classification schema, evaluations of co-occurring mutations, mutually exclusive mutations and improved insight regarding the mechanistic roles of various mutations have allowed for an improved understanding of functional AML subsets to inform rational treatment strategies [7,8]. For instance, clinical trials with tyrosine kinase inhibitors for patients with activating *FLT3* mutations are well underway, and demonstrate effectiveness in combination therapeutic approaches [9]. Remarkably, the identification of an *IDH1* mutation in an AML genome in 2009, followed by the detection of recurrent *IDH1* or *IDH2* mutations in approximately 20% of patients with AML, followed shortly thereafter with promising *IDH*-mutant targeted therapies in early investigation has impressively demonstrated the ability of scientific discoveries to translate into valuable therapies in a fraction of the time previously required [10,11].

Recurrent mutations in genes involved in epigenetic regulation (i.e., DNA methylation and histone modifications) are frequent in AML, and in addition to *IDH1/2* mutations include *DNMT3a*, *TET2*, *EZH2*, *MLL* and *ASXL1*, among others [12–14]. The frequency of mutations involved in epigenetic pathways supports the fundamental role of aberrant epigenetic modulation in AML, and has led to AML treatment with the hypomethylating agents (HMA) azacitidine and decitabine. HMA-based therapy now provides an important treatment approach in patients with AML, irrespective of the presence of identified epigenetic mutations and future HMA-based combination strategies will hopefully provide curative options, in particular for elderly patients [15].

Outside of genomic alterations, other promising strategies are well under way to improve upon current AML diagnosis and treatment options. As a particularly promising example, biomarker-driven determination of response to particular therapies may be evaluated prior to the initiation of therapy, based on the results of a patient's leukemia cells to specific chemotherapeutic agents or combinations. Measurement of the degree of change in proapoptotic mitochondrial signaling induced *in vivo*, that is, the ‘Dynamic BH3 Profiling’ technique has shown the ability to determine patients most likely to respond to a certain therapy, and predict the therapy that would be most effective for real-time personalized treatment decision-making [16].

Another invaluable strategy for AML therapy includes antibody-based treatment, with monoclonal antibodies against commonly expressed myeloid antigens, for example, CD33 and CD123 (IL-3R). While the conjugated anti-CD33 immunotoxin gemtuzumab ozogamicin is unfortunately no longer clinically available, other monoclonals and innovative bispecific T-cell-engaging therapies are currently in clinical trials, and may prove to be instrumental in AML therapy for the majority of patients who express these surface proteins [17,18].

A complete and comprehensive diagnosis of AML will forever be lacking without an improved appreciation of the leukemia microenvironment and bone marrow niche. Our current paucity of understanding regarding the interplay of the AML genome (and epigenome and transcriptome) directly with the tumor microenvironment has substantially hampered the simple translation of promising compounds from *in vitro* studies into effective AML therapies. Recent analysis confirms the profound deregulation of both innate and adaptive immune responses in AML, and certainly the favorable graft-versus-leukemia effect of allogeneic stem cell transplant demonstrates the importance and curative therapeutic potential of an augmented and functioning immune system [19]. Aberrant upregulation of immune markers such as PD-1, PD-L1, PD-L2 and CTLA4 in AML patient samples has notably been demonstrated, suggesting a pathway of immune evasion, and providing the rationale for immunotherapeutic evaluation in AML, which is now ongoing in clinical trials [20].

Toward improved AML monitoring during & after treatment

Confirmation of a complete remission in AML has traditionally depended on routine bone marrow morphology and immunohistochemistry analysis. Additionally, minimal residual disease (MRD) status by cytogenetic analysis (i.e., a complete cytogenetic remission) has long been feasible in the approximately 50% of patients with abnormal cytogenetics at diagnosis, as determined by conventional karyotype. Increasingly sensitive methods for MRD detection are now available, including real-time quantitative PCR for known fusion transcripts and/or genomic mutations, which have improved the sensitivity of MRD detection to one leukemic cell in 100,000 normal cells (i.e., 0.001%) [21,22].

In addition, multiparameter flow cytometry-based leukemia-associated immunophenotypes can be detected in nearly all patients with AML, with a sensitivity of approximately 0.01% and demonstrating powerful independent prognostic information in AML [23].

The improved sensitivity of MRD analysis now allows for improved prognostication at diagnosis and at the time of complete remission. Yet moving forward, with the dual goals of improving both efficacy and minimizing toxicity, active MRD assessment during and post-therapy should provide more than prognostic information, but should influence and lead to risk-adapted and individualized consolidation and maintenance therapy decisions [24].

Currently, no approved or standard maintenance strategies for AML patients in complete remission exist, despite the poor long-term disease free survival, particularly among older patients and/or those in higher-risk prognostic categories. This is likely due in part to the toxicity of standard AML therapy, which is unable to be continuously administered in a manner akin to POMP acute lymphoblastic leukemia maintenance therapy. An avenue of rapidly emerging research and understanding surrounds the identification of leukemia stem cells (LSCs) and leukemia initiating cells (LICs), which are primarily resistant to standard chemotherapy [25,26]. Thus, effective AML therapy and/or post-therapy maintenance strategies must be designed with the goal of targeting residual LSC and LICs through various strategies affecting LSCs including NF- κ B inhibition, monoclonal antibody-based therapies, inhibitors of nuclear export proteins and immunotherapeutic approaches. Moreover, an enhanced scientific understanding of molecularly and epigenetically abnormal preleukemic HSCs will not only provide improved therapeutic strategies for

successful LSC/LIC elimination, but may ultimately prove effective in AML screening and preventative measures.

Toward a future AML treatment paradigm

Thanks to the speed of scientific discovery within this 'genomic era', we are now uniquely poised to see our research-based innovations translate directly into the care of our patients with AML. Through a detailed understanding of the specific aberrations and pathways gone awry in each particular patient with AML, in concert with insight into the LSC/LICs, AML niche and altered microenvironment, and with a continually expanding armamentarium of valuable and well-tolerated therapies to offer in effective combinations to our patients at all stages of therapy (i.e., induction, consolidation and maintenance), the future of AML therapy will ensure not only improved diagnosis and risk stratification of patients with AML, but improved patient outcome as well.

Disclosure

This manuscript represents original research, which has not been previously published or submitted for publication elsewhere.

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