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MOLECULAR TESTING AND DIAGNOSTICS (J KHOURY, SECTION EDITOR)

Acute Myeloid Leukemia: from Mutation Profiling to Treatment Decisions

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Abstract

Purpose of Review Awareness of the molecular landscape of AML has improved AML care over the last 5 years. This review summarizes updates regarding the diagnostic and therapeutic relevance of key mutations in AML.

Recent Findings Molecular mutations in genes including NPM1, CEBPA, FLT3, IDH1/2, TP53, RUNX1, and ASXL1 provide important prognostic and/or therapeutic information in AML, including best treatment strategies, transplant recommendations, and significance of MRD detection. Mutational analysis has led to the recognition of new entities including hereditary leukemia syndromes and clonal hematopoiesis of indeterminate potential (CHIP). FLT3 and IDH1/2 mutations are the focus of targeted therapies in the treatment of AML.

Summary Advances in the molecular characterization of AML have provided an improved understanding of leukemogenesis and AML risk stratification, improved disease monitoring techniques, optimized therapeutic strategies, and have led to the development of novel molecular-targeted therapeutics. Ongoing genomic advances will continue to improve upon the outcome of patients with AML.

Keywords Acute myeloid leukemia · Targeted therapy · Minimal residual disease · Risk stratification · Molecular prognostication

Introduction

Acute myeloid leukemia (AML) treatment has relied on a backbone of cytotoxic induction chemotherapy since the 1980s for the majority of patients [1]. However, the landscape of genomic sequencing, disease monitoring, and targeted therapy is rapidly evolving and leading to advances in molecular profiling, improved understanding of the genomic heterogeneity of AML, and the development of novel targeted therapies. Clinical benefit from targeted therapy is now realized in patients with *IDH1/2*, *FLT3-ITD*, and/or CD33+ AML [2, 3, 4••, 5, 6]. Advancements in molecular sequencing have improved prognostication, individualized treatment, and provide dynamic utility via minimal/measurable residual disease (MRD) analysis [7, 8]. This review characterizes the landscape of AML as it relates to genomic analysis, including updates to current guidelines and emerging diagnostics and therapeutics.

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Specific Mutations

NPM1

Nucleophosmin-1 (NPM-1) mutations (> 95% within exon 12) occur in ~ 30% of AML patients overall and 40–60% of patients with normal karyotypes (NK) [9, 10]. Mutated NPM1 (mNPM1) is associated with a higher complete remission (CR) (58–60%), improved overall survival (OS; median 16.2 months), and a lower cumulative incidence of relapse (CIR) [9]. ELN guidelines incorporate NPM1 screening at diagnosis given its favorable prognostication, particularly in the absence of co-occurring transmembrane fms-like tyrosine

kinase (FLT3) internal tandem duplication (FLT3-ITD) mutations with a high allelic ratio (AR) [11••].

Co-occurring mutations in FLT3-ITD occur approximately twice as often in patients with mNPM1 compared with wild-type (wt) NPM1 (40.2% vs. 13.7%) [12–14]. When co-mutated, mNPM1 mutants typically have a higher variant allele frequency (VAF) respective to FLT3-ITD mutations, and 15–20% of mNPM1 patients harbor multiple FLT3-ITD mutant clones, supporting the early leukemogenic role of mNPM1 compared with FLT3. Mutated NPM1 is also observed in approximately 60–70% of cases with DNTM3A mutations [14–16]. The presence of either a FLT3-ITD mutation with a high AR or a DNMT3A mutation appears to negate the beneficial effect of mNPM1 [14, 17].

NPM1 appears to be a stable marker for assessment of MRD. Specifically, the presence of detectable mNPM1 following a second cycle of intensive chemotherapy was identified to be the optimal timepoint for MRD discrimination and associated with a relapse risk (RR) of 82% vs. 30% in MRD negative patients [18]. In a validation cohort of 91 patients, MRD following a second cycle of chemotherapy was associated with a CIR of 70% vs. 31% and inferior OS (40% vs. 87%) [18]. Rising mNPM1 levels in the peripheral blood reliably predicted relapse amongst patients in morphologic CR, suggesting a future role for targeted interventions upon MRD detection to prevent relapse. RT-qPCR of bone marrow specimens demonstrated increased sensitivity (median 1-$\log_{10}$/month), and a longer time from analysis to relapse compared with peripheral blood [18].

CEBPA

Mutations of the transcription factor CCAAT/enhancer binding protein alpha (CEBPA) gene are found in approximately 10–20% of patients with cytogenetically normal AML (CN-AML), with biallelic mutations (biCEBPA—most commonly in the N-terminal and C-terminal domains on separate alleles) accounting for approximately 50% [9, 19–21]. WHO recognizes biCEBPA as a unique entity, and ELN guidelines recommend upfront screening for CEBPA given the favorable prognosis of biCEBPA mutations with standard therapy [10]. Biallelic CEBPA mutations are associated with improved event-free survival (EFS) and OS (HR 0.41 and 0.37, respectively) compared with all AML patients, when treated with standard cytarabine-based chemotherapy [19], and independent of consolidation strategies received, including hematopoietic stem cell transplant (HSCT). This benefit is notably exclusive to biCEBPA mutations; patients with single or monoallelic CEBPA (moCEBPA) do not share this favorable genotype [19–21].

Recent work has highlighted clonal heterogeneity within CEBPA mutants [9]. Patients with biCEBPA are more likely to have co-mutations in TET2 and GATA2 (seen in ~30% of biCEBPA patients) [9, 22]. Conversely, moCEBPA patients have a higher frequency of co-mutations in NPM1, FLT-3 ITD/TKD, and IDH2 [9]. TET2 mutations appear to confer an inferior prognosis amongst biCEBPA patients [9]. While CEBPA is not currently recommended as a marker of MRD, a specific leukemia-associated immunophenotype (LAIP) associated with biCEBPA mutations may serve as a valuable tool for screening and disease monitoring [23].

FLT-3

FLT3-ITD mutations within the juxtamembrane domain (JMD) are seen in approximately 25% of cases of AML and are associated with refractory disease, increased relapse risk, and poor OS [24–27]. Mutations within the tyrosine kinase domain (TKD) are seen in approximately 7% of patients and unlike FLT3-ITD are not prognostic in isolation [28]. Interestingly, patients with co-mutated NPM1 and FLT3-TKD may have an exceptionally favorable prognosis based on a recently published analysis [29]. ELN guidelines recommend upfront testing for FLT3 and measurement of AR when available, given the poor prognosis associated with $FLT3^+$, its imperative role in risk stratification [11••], and the importance of incorporation of targeted FLT3 inhibitors for improved patient outcomes (discussed below).

Amongst $FLT3^+$ patients, the presence of an increased AR, often defined as AR > 0.5, associates with higher relapse rates, refractory disease, and decreased OS [26]. Patients with an AR > 0.5 receiving an allogeneic HSCT (allo-HSCT) in CR1 had improved relapse-free survival (RFS) and OS compared with patients receiving cytotoxic chemotherapy or autologous-HSCT (auto-HSCT). This impact was not seen amongst FLT3-ITD^+ patients with an AR < 0.5 [25].

FLT3-ITD^+ patients with an AR < 0.5 and NPM1 mutation are reported to have survival similar to intermediate risk patients without FLT3 mutations, with comparable rates of relapse risk (RR) (38 ± 6% vs. 20 ± 9%), OS (56 ± 5% vs. 47 ± 10%), and leukemia-free survival (LFS) (56 ± 6% vs. 53 ± 11) [30]. Conversely, patients with co-mutations in NPM1 and FLT3-ITD^+ and an AR > 0.5 were at increased risk of relapse and benefited from HSCT compared with alternative consolidation therapies (5-year RR 20 ± 13% vs. 80 ± 9%, 5-year OS 22 ± 10% vs. 70 ± 14%). This benefit was applied to patients with wtNPM1 and any AR of $FLT3^+$, but not patients with mutated NPM1 and low $FLT3^+$ AR or wtFLT-3 [30].

Of note, a recent retrospective validation study of the 2017 ELN guidelines found no significant survival impact of AR in $FLT3^+$ patients irrespective of NPM1 mutational status, and regardless of whether they were treated with intensive chemotherapy with or without a FLT3 inhibitor—a result that is discordant from the current ELN guidelines [31]. The authors suggested the high rate of allo-HSCT amongst $FLT3^+$ patients with a high AR and the institutional use of high-dose

cytarabine compared with standard induction therapies may negate the prognostic effects of high vs. low $FLT3^+$ AR [31].

TP53

Mutations in transcription factor TP53—important in cell cycle arrest for DNA mismatch repair, base excision repair, and nucleotide excision repair—are present in < 10% of patients with de novo AML, 20–37% of patients with sAML/tAML, up to 70% of patients with a complex karyotype and are increasingly prevalent with relapsed or refractory disease status [32–37]. TP53 mutations are more frequent in older patients, patients with 17p mutations, aberrations in chromosomes 5 and 7, and are associated with poor response to standard therapy, and particularly dismal OS [14, 34–36]. ELN guidelines recommend upfront screening for TP53 at diagnosis for risk stratification given its poor prognostic implications [11••].

TP53 mutations have been associated with a CR of 28.6% vs. 80.2% compared with patients without TP53 mutations, representing a significantly higher likelihood of primary refractory disease [36]. The dismal response to therapy appears irrespective of age [36]. TP53 is associated with decreased OS regardless of therapy (high-dose cytarabine, hypomethylating agent, or low-dose cytarabine), with a median OS of only 6–8 months [36]. Even in the post-HSCT setting, patients with TP53 mutations experience a high rate of relapse and toxicity; patients with TP53 mutations who underwent HSCT demonstrated a median OS of 8 months, a 1-year OS of 35%, and a relapse rate of 53% at 1 year [38], and with no evidence of impact of post-HSCT azacitidine maintenance [38, 39]. One notable recent study suggests patients with TP53 may be particularly sensitive to prolonged (10 days) decitabine therapy, with higher rates of CR seen with these agents amongst TP53-mutated cohorts (62% and 100%) than wtTP53 despite evidence of incomplete leukemia clearance [36, 39]. Though not a primary objective, TP53 mutation patients had OS comparable to intermediate and favorable risk patients (11.6 vs. 10 months) [36].

Part of the dismal prognosis with TP53 mutations is in part due to the resistance to chemotherapy amongst this population, and novel therapeutic agents are needed. While clinical data is only available in TP53-mutated MDS patients to date, responses to the novel TP53 modulator APR-246 as presented at ASH 2018 are encouraging (CR 82%, median OS not reached at 7 months) and results of the ongoing randomized trial are eagerly anticipated (NCT03588078) [40].

Molecular Prognostication

Molecular markers prove useful for both prognostication and disease monitoring. Current ELN guidelines recognize favorable risk mutations including NPM1 and biCEBPA, in addition to the core-binding factor leukemias RUNX1-RUNX1T1 and CBFB-MYH11. Unfavorable mutations now include FLT3-ITD and TP53 as discussed above, as well as provisional entities for RUNX1- and ASXL1-mutated leukemias [11••].

The prognostic significance and molecular heterogeneity of AML were nicely highlighted by Metzeler et al., who evaluated genetic information on 664 AML patients to identify driver gene mutations. Ten genes were mutated in more than 10% of patients and a driver mutation identified in 97% [14]. Intermediate risk cytogenetic patients harbored more mutations (median 4 driver mutations) than favorable or adverse risk patients, as did patients with secondary (sAML) [14]. As anticipated, patients harboring NPM1 or biCEBPA mutations had improved OS compared with patients with mutations in DNMT3A, RUNX1, ASXL1, SRSF2, TP53, BCOR, U2AF1, and SF3B1 [14]. Mutations in DNMT3A and RUNX1 were associated with inferior survival in younger (age < 60), but not older patients [14]. Mutations in NPM1, DNMT3A, and FLT3-ITD were found at higher rates in patients with intermediate risk cytogenetics, highlighting the complex cytogenetic and molecular interaction of AML. Analysis of VAF identified heterozygous mutations with median VAF near 0.5 (TP53, IDH2, DNMT3A, CEBPA, TET2, and NPM1) compared with other mutations with significantly lower VAF's (FLT3, KIT, NRAS, KRAS, and PTPN11), implicating some mutations as frequent founder clones, and others developing later in clonal evolution, in more sub-clonal populations [14].

A perhaps unexpected discovery within the NGS-era has been the recognition of recurrent germline mutations in patients with myeloid malignancies [41]. The current WHO classification schema now recognizes germline mutations in CEBPA, DDX41, RUNX1, GATA2, ETV6, and ANKRD26 as AML predisposition syndromes [11••]. While some AML predisposition syndromes may be predicted by life-long thrombocytopenia or platelet defects (RUNX1, ETV6, ANKRD26) or immunologic/immunodeficiency disorders (GATA2, SAMD9, SAMD9L), others lack identifying clinical characteristics and/or may present at older ages such that a family history is not revealing (CEBPA, DDX41) [41–43]. On NGS profiling, the VAF of a gene of potential germline inheritance may be the first indication of a predisposition syndrome, with a VAF of 40–60% indicating a potential heterozygous variant [41]. For patients with multiple mutations, differences in VAF at diagnosis and clinical re-assessment of mutation burden in remission may help isolate and identify persistent clones with a VAF suggestive of a germline mutation [41]. Patients with suspected germline mutations require confirmatory genetic testing on an alternative histology (i.e., skin fibroblasts, hair follicles) and should be referred to genetic counseling for evaluation, as this has direct implications for the patient (for example, identification of appropriate stem cell donors), as well as screening and identification of family members [7, 41].

Minimal Residual Disease

AML historically was classified morphologically using the French-American-British classification scheme [44]. The World Health Organization (WHO) expanded the classification system with a 2002 update subclassifying AML to include clinical factors (i.e., AML arising from a precursor disease state such as myelodysplastic syndrome (MDS)), and clonal cytogenetic abnormalities [12, 13, 18]. Improved next-generation sequencing (NGS) techniques have further advanced not only the understanding of the complex clonality and mutational burden in AML, but now offer increasingly sensitive and specific methods to identify low levels of residual disease. AML specimens on average harbor approximately only 13 mutations; however, these mutations occur across multiple functional genetic classes and subgroups, have distinct interactions and clonal kinetics, thus confer unique challenges to both molecular risk stratification and monitoring [11••, 45–48]. As discussed above, mutations in genes encoding NPM1, and CEPBA confer favorable risk and are also suitable for MRD monitoring, while mutations in FLT3 confer adverse risk and have unstable clonal kinetics, historically making it unsuitable for MRD monitoring [48, 49]. Other molecular markers such as TP53 appear to correlate with disease activity and may be suitable markers for MRD [36, 39].

The 2017 ELN guidelines recommend assessment for MRD via multiparameter flow cytometry (MFC) or via molecular analysis using real-time quantitative PCR (qPCR) or NGS [4••]. Evaluating molecular MRD requires nuanced consideration regarding the sensitivity and stability of a particular mutation throughout treatment, consideration of clones that may be associated with age-related clonal hematopoiesis (ARCH), and early recognition of germline clones (*RUNX1*, *GATA2*, *CEBPA*, *DDX41*, and *ANKRD26*) based on changes in variant allele frequency (VAF) throughout the treatment course [7, 11••]. Current recommended molecular markers suitable for assessment include *NPM1* and the fusion genes *RUNX1-RUNX1T1*, *CBFB-MYH11*, and *PML-RARA* [7]. Current guidelines recommend against the sole use of *FLT3-ITD*, *FLT3-TKD*, *NRAS*, *KRAS*, *IDH1*, *IDH2*, *MLL-PTD*, and *EVI1* due to the often-unstable nature of these clones following therapy; however, such mutations may be suitable for MRD when used in combination with other mutations [7].

The detection of any persistent mutation during CR is associated with a 4-year incidence of relapse of 48.2% vs. 32.4% [50]. Patients with mutations in epigenetically active genes associated with age-related clonal hematopoiesis (ARCH) (i.e., DNMT3A, TET2, ASXL1) did not have an increased 4-year risk of relapse (RR) regardless of allelic frequency; however, when occurring with co-mutations not associated with ARCH in CR, an increased RR was observed (66.7% vs. 39.4%) [50]. Amongst a validation cohort, detection of mutations not associated with ARCH in CR was associated with 4-year RR and OS of 55.1% vs. 26.5% and 67.6% vs. 37.1%, respectively, highlighting the prognostic importance of MRD [50]. A recent presentation found similar results, observing no difference in median OS between AML patients with or without ARCH mutations (12 vs. 11 months, $p = 0.564$) [51].

Targeted Therapies

FLT3 Inhibitors

Numerous tyrosine kinase inhibitors (TKI) targeting the ATP-binding site in the intracellular domain of the FLT3 receptor tyrosine kinase (RTK) have been developed (Table 1). Type 1 inhibitors (which bind the RTK ATP-binding site in the active conformation) include sunitinib, lestaurtinib, midostaurin, crenolanib, and gilteritinib. Type 2 inhibitors (bind to the hydrophobic region in juxtaposition to the ATP-binding domain when the RTK is in the inactive state and prevent receptor activation) include sorafenib, quizartinib, and ponatinib [52].

Sorafenib

The multi-kinase inhibitor sorafenib demonstrated modest efficacy in $FLT3^+$ AML as monotherapy; however, resistance (i.e., D835 mutations in the TKD domain leading to constitutive activation of the RTK, negating the effectiveness of type 2 inhibitors) limit its use as a single agent [52, 53]. In combination with standard chemotherapy in patients under the age of 60, sorafenib prolongs survival with modestly increased toxicity (increased grade 3 or higher adverse events including fever, diarrhea, bleeding, cardiac events, hand-foot reactions, and rashes) [54]. The survival benefit is less clear in patients over the age of 60 when added to standard induction chemotherapy [55, 56]. Sorafenib maintenance following allo-HSCT resulted in improved OS (2-year OS 81% vs. 62%), and progression-free survival (PFS) (82% vs. 53%) [57–59]). Sorafenib added to induction therapy and maintenance following allo-HSCT leads to superior 3-year LFS (80.4% vs. 69.4%, 78.1%, and 34.8%) and 3-year OS (84.6% vs. 74.9%, 78.1%, and 50.9%) compared with patients receiving sorafenib pre-transplant, post-transplant, or no FLT3-directed therapy [60]. Early results of the sormain trial evaluating the efficacy of sorafenib maintenance post-HSCT also demonstrated significant improvement in 2-year RFS (53.3% vs. 85%) [61].

Midostaurin

The type 1 FLT3 inhibitor midostaurin demonstrated modest efficacy as monotherapy in R/R AML. The CALGB10603 (RATIFY) trial was the first large multicenter study investigating the addition of midostaurin to induction and consolidation

Table 1 Approved targeted therapies for AML

Inhibitor	Comments
Type 1 FLT 3 inhibitors	Inhibition of FLT-3 ATP-binding site in active formation; effective even in presence of D835 mutations
Midostaurin	Indication: FLT-3$^+$ AML; dose 50 mg twice daily on days 8–21 of induction, and days 8–21 of consolidation
Gilteritinib	FLT-3 and ASXL inhibitor; indication: R/R* FLT-3$^+$ AML; dose 120 mg daily.
Type 2 FLT 3 inhibitors	Inhibit via binding hydrophobic region of FLT-3 in inactive formation
Sorafenib**	Multi-kinase inhibitor; indication: FLT-3$^+$ AML; dosing regimens include 200 to 400 mg twice daily as tolerated in clinical trials
Quizartinib**	Indication: R/R* FLT-3$^+$ AML; dose 30–60 mg daily in clinical trials
IDH inhibitors	
Ivosidenib	IDH-1 inhibitor; indication: IDH-1 mutated R/R* AML; dose 500 mg daily
Enasidenib	IDH-2 inhibitor; indication: IDH2 mutated R/R* AML; dose 100 mg daily
BCL-2 inhibitors	
Venetoclax	Used in combination with hypomethylating agent or low-dose cytarabine (LDAC) in patients unfit for standard induction therapy; dose: ramp up (100 mg day 1, 200 mg day 2, 400 mg day 3). Maintenance 400 mg daily (used in combination with azacitidine or decitabine) or 600 mg daily (used in combination with LDAC)

*R/R, relapsed or refractory AML

**Not currently FDA approved for treatment of AML

and continued as maintenance therapy for 1 year in patients not proceeding to allogeneic transplant [5, 28]. This was the first randomized study to demonstrate a survival benefit with the incorporation of FLT3 inhibitor therapy into standard intensive chemotherapy for FLT3$^+$ disease; 4-year OS was 51.4% in the midostaurin arm and 44.3% in the placebo arm with a HR for death of 0.78 [5]. More patients in the midostaurin arm had improved EFS (time to relapse, death, or failure to achieve CR) (median 8.2 months vs. 3.0 months) and disease-free survival (DFS) (26.7 months vs. 15.5 months) [5]. Though no statistically significant OS benefit was seen amongst patients who underwent consolidative HSCT (median OS 69.8 months vs. 21.8 months), there was a trend towards improved 4-year OS (63.7% vs. 55.7%). A sensitivity analysis demonstrated a 24.3% lower risk of death in patients treated with midostaurin when censored at transplant [5]. This survival benefit may be due to the higher albeit non-significant rate of CR_1 achieved in the midostaurin arm compared with placebo (58.9% vs. 53.5%, p value 0.15) or improved DFS secondary to deeper remissions—unfortunately, no MRD assessment was performed on study. A study evaluating the role of midostaurin consolidation therapy following HSCT has recently been completed (CTN: NCT01883362) to specifically evaluate the role of post-HSCT midostaurin maintenance, since RATIFY was not powered to assess this specific question.

Quizartinib

The type 2 FLT-3 inhibitor quizartinib is effective in FLT3$^+$ AML. A phase 2 study demonstrated the potency and efficacy of quizartinib amongst FLT3$^+$ patients with a minimum AR of ≥ 10% with relapsed/refractory AML within 1 year of induction therapy or who had undergone salvage chemotherapy or HSCT [62]. Quizartinib was associated with a composite CR (CR_c) (defined here as complete remission, complete remission with incomplete platelet recovery, and complete remission with incomplete hematological recovery) of 56% in the FLT3$^+$ versus 36% amongst the FLT3$^-$ cohort [62]. The recently reported phase III QUANTUM-R study further substantiated quizartinib's efficacy [63]. Patients with relapsed/refractory FLT3$^+$ AML were randomized to receive quizartinib or one of three standard of care (SOC) chemotherapy regimens. Patients were able to continue on quizartinib maintenance following allo-HSCT [63]. Amongst the intention to treat population, CR_c was 48% with quizartinib vs. 27% with SOC. Median OS was 6.2 months with quizartinib vs. 4.7 months with SOC ($p = 0.0177$). Thirty-two percent of patients receiving quizartinib monotherapy proceeded to HSCT, with 62% of quizartinib patients receiving post-HSCT maintenance therapy [63]. A phase 1, multicenter dose-escalation study assessing the safety/tolerability of quizartinib maintenance post-HSCT in FLT3$^+$ AML demonstrated the safety of this approach, with potentially promising results in the first 13 patients treated and no reported increase in GVHD [64].

Gilteritinib

Gilteritinib is a FLT3 and AXL inhibitor that has demonstrated potent in vivo inhibition of FLT3 phosphorylation amongst patients with relapsed/refractory AML [65]. In the original

dose-escalation and tolerability study, 40% of patients responded to therapy: 8% achieving CR, 4% CR_p, 18% CR_i, and 10% PR [65]. Gilteritinib demonstrated efficacy against both FLT3-ITD$^+$ and FLT3 D835 (TKD) relapsed/refractory patients with an ORR of 49% versus 12% amongst wtFLT3 patients, and patients previously treated with TKI therapy (ORR 42%) or without (ORR 56%) [65, 66]. Additionally, a phase 1 trial evaluating the safety of gilteritinib added to anthracycline-based induction and consolidation with gilteritinib maintenance in FLT3$^+$ patients demonstrated a CR_c of 91.3%, compared with 56% in wtFLT3$^-$group [67]. FLT3$^+$ patients receiving ≥ 80 mg/day of gilteritinib had CR_c rates of 90% versus 60% in controls [67]. Based on these trials and interim results of the ADMIRAL trial (NCT02421939), an ongoing trial of 138 patients with relapsed/refractory AML was treated with gilteritinib which demonstrated a CR_c (composite of CR or CR with partial hematological recovery) of 21% in the treatment arm and transfusion independence in 31.1% of previously transfusion-dependent patients—the FDA approved gilteritinib for the treatment of FLT-3$^+$ relapsed/refractory AML (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm627045.htm). A phase 3 trial of gilteritinib as maintenance therapy following HSCT is ongoing, along with multiple other studies evaluating the role of FLT3 inhibition as a component of induction or maintenance therapy pre- or post-transplantation [68, 69].

IDH1/2 Targeted Therapy

Mutations in the isocitrate dehydrogenase gene (IDH), specifically IDH2 mutations R140 and R172, and R132 mutations in IDH1, are another substrate for targeted therapy [70]. *IDH1* and *IDH2* are commonly mutated in cytogenetically normal AML (IDH1 6–16%, IDH2 8–19%) and impart a critical role in cellular metabolism by catalyzing the conversion of alpha-ketoglutarate to the oncometabolite R enantiomer of 2-hydroxyglutarate (R-2HG) [70–73]. R-2HG inhibits cellular differentiation and promotes proliferation via TET2 inhibition and the downstream effects of demethylation in vitro, highlighting the pivotal role of IDH mutations in leukemogenesis [10, 74]. Though currently not a component of the ELN guidelines for prognostication, IDH1/2 assessment should now routinely occur given the availability of targeted therapy with the IDH1 and IDH2 inhibitors ivosidenib and enasidenib.

Ivosidenib

The first-in-class mutant IDH1 inhibitor ivosidenib demonstrated overall safety and efficacy in a phase 1 dose-escalation and dose-expansion study amongst patients with *IDH1*-mutated relapsed or refractory AML leading to FDA approval of ivosidenib [4]. In the primary efficacy population, including 174 patients with a median age of 67 and 2 prior therapies, CR or CR_h was achieved in 30.4% of patients, with a CR in 21.6% and a median time to response of 2 months. The median duration of CR/CR_h was 8.2 months and 9.3 months for CR. Median OS was 8.8 months with 50.1% of patients achieving CR/CR_h surviving a median of 18 months. Approximately 20% of responding patients were noted to achieve IDH1 mutational clearance, to a level of 10^{-4} by digital droplet PCR. Amongst patients achieving mutational clearance of *IDH1*, median CR was 11.1 months vs. 6.5 months, and OS was 14.5 months vs. 10.2 months, suggesting a trend of improved durability of response. Ivosidenib was well tolerated at doses of 500 mg daily. Notable grade 3 or higher adverse events included QT prolongation and the IDH differentiation syndrome (akin to ATRA syndrome and treated with corticosteroids, diuretics, and hydroxyurea if concurrent leukocytosis) [4]. Interestingly, amongst IDH1-mutated MDS patients who were refractory to therapy with hypomethylating agents, ivosidenib appeared to have a substantial response, though this subgroup was small ($n = 12$) [4]. Another IDH1 inhibitor FT2102 is also in development in hematologic malignancies, with interim reported results demonstrating safety and efficacy overall similar to ivosidenib [75].

Enasidenib

The first-in-class mutant IDH2 inhibitor enasidenib has demonstrated safety and efficacy in a first in human phase 1/2 dose-escalation and dose-expansion study [3]. Clinical efficacy was evaluated in 285 patients with relapsed/refractory AML treated with enasidenib, with a median of 2 prior therapies and a median age of 67 [3]. Amongst patients treated with enasidenib, ORR was 40.3% (R140 mutations 35.4%, R172 mutations 53.3%), with 19.3% obtaining CR (R140 17.7%, R172 24.4%) [3]. Median OS was 19.7 months in patients achieving CR and 14.4 months for a partial CR. Grade 3/4 adverse events occurred in 41% of patients, the most common (> 5%) being indirect hyperbilirubinemia, the IDH differentiation syndrome (approximately 10% of patients), anemia, and thrombocytopenia [3]. Enasidenib is currently approved for the treatment of relapsed/refractory AML at a dose of 100 mg oral daily.

Interim results from front-line studies with IDH inhibitors in combination with both intensive chemotherapy for newly diagnosed younger patients (Stein ASH 2018) and azacitidine for newly diagnosed older or unfit AML patients (DiNardo ASCO 2018) have been presented and demonstrate encouraging results suggesting the future benefit of these combinations.

Conclusion

The molecular landscape of AML is undergoing rapid evolution with improved sequencing techniques identifying new

prognostic mutations, improved disease monitoring techniques, novel molecular-targeted therapeutics, and recognition of germline predisposition syndromes. While these advancements have improved risk stratification and disease monitoring via MRD, many challenges still exist, such as how to best incorporate ARCH mutations into the prognostic algorithms and a nuanced understanding of the clinical significance of mutations depending on the specific mutational variant, and the interactions with other co-occurring mutations. Despite these challenges, such advances have enabled improvements in the understanding of leukemogenesis and identified molecular substrates suitable for both disease monitoring and targeted therapy—thereby improving efficacy while minimizing toxicity—in a disease that has relied on cytotoxic regimens for the last 3 decades. Such advancements will only continue to improve survival and quality of life amongst patients with AML.

Compliance with Ethical Standards

Conflict of Interest Courtney DiNardo reports personal fees from Agios, Abbvie, Celgene, Karyopharm, Medimmune, and Jazz.

Curtis Lachowiez declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review committees of participating sites and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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