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Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations

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The European LeukemiaNet (ELN) genetic risk classifications were developed based on data from younger adults receiving intensive chemotherapy. Emerging analyses from patients receiving less-intensive therapies prompted a proposal for an ELN genetic risk classification specifically for this patient population.

Introduction

European LeukemiaNet (ELN) genetic risk classifications have been used widely in clinical practice and in clinical trials.[1,2] These classifications were based exclusively on data from patients who received intensive chemotherapy and were not intended for prognostic stratification of older and/or unfit patients receiving less-intensive therapeutic options. Recent attempts to validate the 2017 and 2022 ELN risk classifications in older patients treated with less-intensive regimens have proven suboptimal, with most individuals classified as adverse risk.[3,4] This supported the need for a new genetic classifier relevant for stratifying prognostic outcomes in patients receiving hypomethylating agent (HMA)–based regimens alone or in combination with either the B-cell leukemia/lymphoma 2 inhibitor venetoclax (VEN) or azacitidine (AZA) with the IDH1 inhibitor ivosidenib (IVO) for *IDH1*-mutated acute myeloid leukemia (AML).[5,6]

HMA monotherapy

Regarding the prognostic impact of genetic factors in patients treated with HMA monotherapy, analysis of cytogenetic data from the phase 3 clinical trial evaluating AZA vs standard of care indicated a 31% to 46% reduced risk of death for patients with adverse-risk karyotype treated with AZA compared with conventional care.[7] Gene mutation analyses were only available in one-third of patients and were largely inconclusive.

A recently published analysis of 604 patients treated in a randomized clinical trial evaluating guadecitabine vs treatment with either AZA, decitabine, or low-dose cytarabine demonstrated that both the 2017 and 2022 ELN risk classifications had suboptimal utility in predicting clinical outcome.[3] Remodeling and multivariable analysis identified 3 distinct prognostic risk groups based on the genomic status of 3 genes: a low-risk group identified by *DDX41*^{mut} (germ line in 61% cases); a high-risk group characterized by the presence of either *FLT3*-ITD^{pos} or *TP53*^{mut}; and an intermediate-risk group defined by the absence of *DDX41*^{mut}, *FLT3*-ITD and *TP53*^{mut}.

HMAs plus VEN

There has been a steady increase in the number of studies investigating the role of genomic factors in determining response and survival outcomes after HMA/VEN-based

therapy.[4,8-16] Similar to the HMA monotherapy study,[3] a pooled analysis of 279 patients treated with AZA/VEN in phase 1b and phase 3 trials demonstrated an inability of either the 2017 or 2022 ELN risk classifications to clearly stratify prognostic outcomes.[4] Reanalysis using a bioinformatic-based approach delineated 3 novel risk groups based on a 4-gene classifier: a higher-benefit group defined by *TP53*^{wt}, *KRAS/NRAS*^{wt}, and *FLT3*-ITD^{neg} (52% patients); an intermediate-benefit group by *FLT3*-ITD^{pos} and/or *KRAS*^{mut} and/or *NRAS*^{mut} (25.4%); and a lower-benefit group defined solely by *TP53*^{mut} (22.6%).[4] The median overall survival (OS) times for the 3 risk groups were 26.5 months, 12.1 months, and 5.5 months, respectively. The adverse prognostic impact of *TP53*^{mut} or *FLT3*-ITD^{pos} after treatment with AZA/VEN and failure to improve survival above AZA alone has been reported previously.[9,10] Importantly, an external validation of this 4-gene predictive signature was provided recently by a single-center study of 159 patients treated with HMA/VEN.[15]

Within these newly defined higher- and intermediate-benefit groups, the most frequently occurring International Consensus Classification disease entities were AML with myelodysplasia-related (MR) gene mutations (corresponding to AML, MR in the World Health Organization fifth edition classification[17]), followed by AML with mutated *NPM1*, and AML not otherwise specified.[4] In patients with *NPM1*- or *IDH2*-mutated AML, exploratory analyses identified a negative prognostic impact in the setting of concomitant signaling gene mutations (*FLT3*-ITD^{pos}, *KRAS*^{mut}, and *NRAS*^{mut}), which is consistent with their biological associations as mediators of VEN resistance. For example, *NPM1*^{mut} AML without signaling gene mutations had a median OS of 39 months compared with only 9.9 months in the presence of a co-occurring *FLT3*-ITD^{pos}, *KRAS*^{mut}, and/or *NRAS*^{mut}. Similar trends were found for *IDH2*^{mut} (median OS, 36.9 vs 12.2 months), *RUNX1*^{mut} (median OS, 32.5 vs 9.3 months), and AML with MR gene mutations (median OS, 22.9 vs 12.9 months), if an activated kinase pathogenic variant was absent or present, respectively.

DDX41 mutations identify a particularly favorable-risk group among patients treatment with HMA therapy[3] and similarly appear to demonstrate a favorable prognosis in patients treated with AZA/VEN, with 2 recent studies reporting a high response rate and favorable outcome for patients with *DDX41*^{mut} AML.[13,14] At 2 years, *DDX41*-mutated AML was associated with an OS probability of 60.1% (median OS, 27.8 months) after HMA monotherapy[3] and 91.1% (median OS, not reached) after HMA plus VEN–based therapy.[13]

AZA and IVO

A randomized phase 3 study established AZA/IVO as a new treatment standard for patients with *IDH1*^{mut} AML, with improved OS for AZA/IVO, compared with AZA/PBO (24.0 vs 7.9 months).[6] With additional follow-up, the median OS in the AZA/IVO arm has extended to 29.3 months.[18] Although this compares favorably with 10.2 months for *IDH1*^{mut} patients treated with AZA/VEN,[19] such uncontrolled crosstrial comparisons should be interpreted cautiously. Genes frequently comutated with *IDH1* include *DNMT3A*, *SRSF2*, and *RUNX1*.[20] Ad hoc subgroup analyses suggest that AZA/IVO has favorable outcome in *IDH1*^{mut} AML even if co-occurring with either these or receptor tyrosine kinase mutations.[20] Therefore, based on the available data, it is appropriate to categorize all patients with *IDH1*^{mut} AML as favorable in the context of AZA/IVO therapy.

Genetic risk classification

Table 1 outlines a proposed ELN genetic risk classification framework for patients with newly diagnosed AML receiving less-intensive HMA-based therapies (2024 ELN Less-Intensive). The 2024 ELN Less-Intensive genetic risk classification is applicable to patients receiving HMA monotherapy, HMA/VEN, or AZA/IVO (for *IDH1*^{mut} AML). For patients with favorable-risk disease, the median OS times have been reported to be >24 months. For adverse-risk patients, OS ranges between 5 to 8 months, whereas the remaining patients are categorized as intermediate risk. Table 2 gives an overview of reported survival times for selected genetic subgroups.

Although patients with *NPM1*^{mut} or *IDH2*^{mut} AML appear sensitive to VEN treatment,[8] favorable clinical outcome appears limited to cases lacking activated signaling gene comutations. *DDX41*^{mut} (two-thirds of germ line origin) has increasingly been linked to favorable outcomes in AML, after both HMA monotherapy or VEN-based combination therapies.[3,13] Finally, all patients with *IDH1*^{mut} have favorable outcomes after AZA/IVO.

TP53^{mut} are universally associated with adverse clinical risk, with poor outcomes for HMA therapy alone or in combination with VEN.[3,4,10,14-16] Complex karyotype is present in the majority (80%-90%) of *TP53*^{mut} cases. Although the median OS for cytogenetic adverse-risk AML without concurrent *TP53*^{mut} treated with AZA/VEN is 23.4 months,[10] additional confirmatory studies in the setting of less-intensive therapies are needed.

AML with MR mutations as defined by the International Consensus Classification has established specificity for

Table 1. ELN risk classification for patients receiving less-intensive therapies (ELN 2024 Less-Intensive)

Risk category	Genetic abnormality
Favorable	Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH1** (*TP53*^{wt}) Mutated *DDX41*† Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	Mutated *TP53*

This classification does not apply to patients who have received prior treatment with an HMA.

*Favorable risk applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signaling gene mutations.

†Identification of a *DDX41* mutation at near-heterozygous frequency should prompt consideration of germ line *DDX41* mutation.

‡For many cytogenetic and molecular abnormalities, single or as coaberrations, no data are currently available; they are tentatively categorized as favorable and intermediate-risk depending on the absence or presence of activating signaling gene mutations.

Table 2. Overview on median OS times by genetic marker

Genetic marker	Median OS, mo	Reference
Favorable-risk group		
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39	4
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37	4
Mutated *IDH1** (*TP53*^{wt})	29	6,17
Mutated *DDX41*	>24	3,13
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23	4
Intermediate-risk group		
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13	4
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12	4
Adverse-risk group		
Mutated *TP53*	5-8	3,4,7,10,14-16

*Favorable risk (median OS time) applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signaling gene mutations.

secondary AML.[21] A recent study indicates that patients with AML and MR mutations are particularly responsive to HMA/VEN[22]; consistent with other reports linking splicing factor variants or *ASXL1* mutations to improved outcomes after HMA/VEN.[23,24] However, even within this category, the copresence of signaling gene mutations is associated with inferior prognosis.[4]

This iteration of the 2024 ELN Less-Intensive AML classification was based on currently available genetic data from less-intensively treated patients, which still remain limited. For AML subgroups with specific gene rearrangements (eg, translocations and inversions), characterization of their impact on prognosis was not possible, owing to their rarity in older age patients, resulting in a paucity of available data. The current classification also has limited relevance to patients with prior myeloproliferative neoplasm or prior exposure to HMA therapies, including AML after an antecedent myelodysplastic syndrome, because such patients were generally excluded from clinical trials of VEN in AML. In terms of low-dose cytarabine/VEN-based treatment and genomic determinants of outcome, we have not included specific comments in the current ELN Less-Intensive classification, because these analyses have yet to be published.

The 2022 ELN recommendations additionally emphasize the role of measurable residual disease (MRD) assessment for comprehensive risk assessment, which has become integral to the management of patients treated with intensive chemotherapy. In patients treated with HMA-based therapies, MRD data are just emerging, and they suggest that MRD monitoring also plays an important and complementary role in informing prognosis.[25,26]

Acknowledging its limitations, this ELN genetic risk classification provides a basis for consensus stratification of patients receiving less-intensive therapies. It will be important for these 2024 ELN Less-Intensive recommendations to be validated in future clinical trials, as well as large real-world data sets. With the treatment landscape in older/unfit patients continuing to evolve (eg, with addition of FLT3 and menin inhibitors), it is expected that this classification will continue to undergo iterative future refinement.

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Footnote

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