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Review Article

Landscape of Genetic Alterations in Patients with Acute Myeloid Leukemia and the Implications in Personalized Medicine

Hwei-Fang Tien[1,2]

[1]Department of Internal Medicine, National Taiwan University, Taipei, Taiwan
[2]Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei, Taiwan

Abstract

Genetic alterations play important roles in the pathogenesis of acute myeloid leukemia (AML). With advances in genomics, many gene mutations have been detected in AML, and some specific mutations are included in international classifications and risk stratification. Gene mutations can be targets for the development of novel agents and biomarkers for monitoring measurable/minimal residual disease (MRD). Personalized medicine according to the genetic risk at presentation and MRD after treatment can not only improve survival but also reduce toxicity from therapies. This review focuses on the landscape of gene mutations and their clinical implications in patients with AML.

Keywords: Acute myeloid leukemia, gene mutation, measurable/minimal residual disease

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of neoplastic diseases with great variability in the pathogenesis, clinical presentations, and treatment responses.[1] It is characterized by the uncontrolled proliferation of hematopoietic progenitors and the inability of cells to differentiate. Patients usually present with anemia, infection, and bleeding. About 60%–70% of patients can achieve complete remission (CR) after intensive chemotherapy (IC), but most relapse within 1 year, indicating that there is still minimal/measurable residual disease (MRD) after chemotherapy[2] even though the patients are in morphological CR.

Personalized treatment according to the AML pathogenesis and risk factors of individual patients is needed to improve the survival of AML patients while reducing the side effects from treatment. The risk factors include those that are related to the patient such as age and factors related to the disease such as white blood cell count, cytogenetics,

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Address for correspondence: Prof. Hwei-Fang Tien, Department of Internal Medicine, National Taiwan University, No. 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail: hftien@ntu.edu.tw

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and molecular gene mutations.[3-5] This review focuses on molecular gene mutations and their implications in personalized treatment.

Landscape of Genetic Alterations in Acute Myeloid Leukemia

Recurrent cytogenetic abnormalities, such as t (15;17)/*PML*::*RARA*, t (8;21)/*RUNX1*::*RUNXT1*, inv (16)/*CBFB*::*MYH11*, and del/t (11)(q23)/*KMT2A* fusion, have long been known to play important roles in the pathogenesis of AML and are closely associated with clinical outcomes.[3] With advances in genomic techniques, a variety of molecular mutations which cannot be detected by conventional chromosomal analysis have been found. Some of these mutations have been shown to contribute to the development and progression of AML and predict clinical outcomes.[4]

More than 90% of AML patients have molecular aberrations, including mutations in *ASXL1*, *CEBPA*, *DNMT3A*, *EZH2*, *FLT3*-internal tandem duplication (ITD), *IDH1/IDH2*, *NPM1*, *PTPN11 RUNX1*, *WT1*, *TET2*, *TP53*, RNA splicing factor genes (such as *SF3B1*, *SRSF2*, and *U2AF1*), cohesin complex genes (such as *STAG1*, *STAG2*, and *RAD21*), etc.[6-17] Table 1 summarizes the common gene mutations in AML according to functional categories, and Figure 1 shows the distribution of gene mutations in newly diagnosed AML patients from the National Taiwan University Hospital (NTUH). The two most common mutations are *FLT3*-ITD and *NPM1* mutation, followed by *DNMT3A* mutation. It is common to observe two or more mutations occurring in the same patient, consistent with the two-hit theory. Some mutations frequently co-occur, such as *NPM1* mutation, *FLT3*-ITD, and *DNMT3A* mutation, indicating their concert interaction in the pathogenesis of AML. Conversely, others such as *IDH* and *TET2* mutations

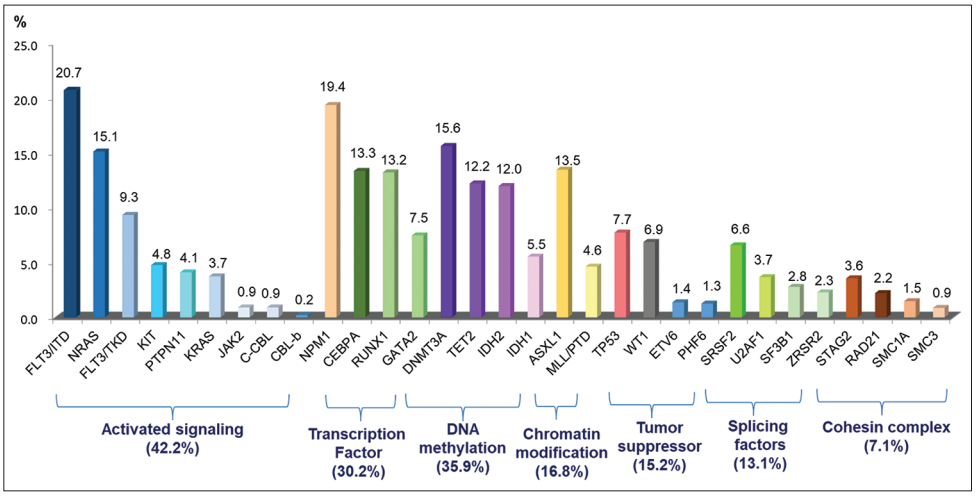

Figure 1: Common molecular gene mutations and their incidence rates (from the acute myeloid leukemia cohort at National Taiwan University Hospital, $n = 763$). ITD: Internal tandem duplication

Table 1: Common genetic alterations in acute myeloid leukemia according to functional categories

Functional category	Gene members	Role in AML leukemogenesis
Myeloid transcription factors	Transcription factor fusions by chromosomal rearrangements, such as t(8;21)(q22;q22)/*RUNX1*::*RUNX1T1* and inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* *GATA2, RUNX1*, and *CEBPA*	Transcriptional deregulation and impaired hematopoietic differentiation
NPM1	*NPM1*	Aberrant cytoplasmic localization of *NPM1* and its interacting proteins
Tumor suppressors	*TP53, WT1, PHF6*	Transcriptional deregulation and impaired degradation via the negative regulator (MDM2 and PTEN oncogenes)
Signaling pathways	*FLT3, KIT, PTPN11, RAS*	Proliferative advantage through the RAS-RAF, JAK-STAT, and PI3K-AKT signaling pathways
DNA methylation	*DNMT3A, TET2, IDH1, IDH2*	Deregulation of DNA methylation and oncometabolite production
Chromatin modifier	*ASXL1, EZH2* and *KMT2A*	Deregulation of chromatin modification and impairment of methyltransferase function
Cohesin complex	*STAG1, STAG2, RAD21, SMC1A, SMC3*	Impairment of accurate chromosome segregation and transcriptional regulation
Splicing factors	*SRSF2, SF3B1, U2AF1, ZRSR2*	Deregulated RNA processing and aberrant splicing patterns

NPM1: Nucleophosmin, AML: Acute myeloid leukemia

are mutually exclusive, indicating their redundant action in AML cells.

Incorporation of Molecular Gene Mutations into the Classification of Acute Myeloid Leukemia

In the 2001 World Health Organization (WHO) classification of myeloid neoplasms, only cytogenetic abnormalities were included as recurrent genetic abnormalities in AML.[18] With molecular mutations detected in the following years, the 2008 WHO classification first included AML with two molecular mutations, *NPM1* mutation and biallelic *CEBPA* mutation, respectively, as provisional entities.[19] The list of AML entities with molecular mutations increased in the 2016 WHO classification[20] and expanded further in the latest 2022 WHO classification[21] [Table 2]. There are some differences between the 2022 International Consensus Classification (ICC) of myeloid neoplasms and the 2022 WHO classification[22] [Table 3]. The major difference is the reclassification of myelodysplastic syndrome (MDS) with 10%–19% blasts in the blood or bone marrow to MDS/AML. The purpose of this change is to allow MDS/AML patients to be eligible for both MDS and AML trials to optimize their management. AML with specific recurrent gene fusions or *NPM1* mutation shows distinct clinical and biological characteristics irrespective of blast counts in the bone marrow or peripheral blood (BM or PB), so the cutoff level of blast count for the diagnosis of AML was reduced from ≥20% in the 2016 WHO classification to ≥10% in the 2022 ICC [Table 3], and there is no lower limit in the 2022 WHO classification [Table 2] in these AML categories, with the exception of AML with *BCR*::*ABL* fusion in which a blast cutoff of 20% is required to avoid overlap with chronic myeloid leukemia [Tables 2 and 3]. The same blast cutoff of 10% is applied for AML with *CEBPA* mutation in the ICC classification; however, the cutoff is 20% in the WHO classification, because the WHO panelists considered that there are insufficient data to support any change in the blast cutoff criterion for AML with *CEBPA* mutation.

Table 2: The 2022 World Health Organization Classification

AML with defining genetic abnormalities
APL with *PML*::*RARA* fusion*
AML with *RUNX1*::*RUNX1T1* fusion*
AML with *CBFB*::*MYH11* fusion*
AML with *DEK*::*NUP214* fusion*
AML with *RBM15*::*MRTFA* fusion*
AML with *BCR*::*ABL1* fusion
AML with *KMT2A* rearrangement*
AML with *MECOM* rearrangement*
AML with *NUP98* rearrangement*
AML with *NPM1* mutation*
AML with *CEBPA* mutation
AML, myelodysplasia-related**
AML with other defined genetic alterations
AML, defined by differentiation
AML with minimal differentiation
AML without maturation
AML with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia

*Blasts <20% in the marrow or PB is acceptable for the diagnosis of AML with defining genetic abnormalities except AML with *BCR*::*ABL1* fusion and AML with *CEBPA* mutation, **Defining cytogenetic abnormalities: Complex karyotype (≥3 abnormalities); 5q deletion or loss of 5q due to unbalanced translocation; Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation; 11q deletion; 12p deletion or loss of 12p due to unbalanced translocation; Monosomy 13 or 13q deletion; 17p deletion or loss of 17p due to unbalanced translocation; Isochromosome 17q; idic(X)(q13). Defining somatic mutations: *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *or ZRSR2*. Khoury *et al*., 2022.[21] AML: Acute myeloid leukemia, APL: Acute myeloid leukemia

Risk Classification Based on Gene Mutations

There are close associations of specific molecular mutations with the clinical and biological features of AML. For example,

Table 3: The 2022 International Consensus Classification

APL with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥10%*
APL with other RARA rearrangements ≥10%*
AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥10%*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥10%*
AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥10%*
AML with other *KMT2A* rearrangements ≥10%*
AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥10%*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2;MECOM(EVI1)* ≥10%*
AML with other *MECOM* rearrangements ≥10%*
AML with other rare recurring translocations ≥10%*
AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
AML with mutated *NPM1* ≥10%*
AML with in-frame bZIP *CEBPA* mutations ≥10%*
AML and MDS/AML with mutated *TP53*
AML and MDS/AML with myelodysplasia-related gene mutations**
AML with myelodysplasia-related cytogenetic abnormalities#
AML and MDS/AML NOS
Myeloid sarcoma

*The diagnosis of AML with these recurrent genetic alterations can be made when blasts (or so-called "blast equivalents" including promonocytes and neoplastic promyelocytes) account for 10% or more in the blood or marrow, **Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *or ZRSR2*, #Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), 18, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities. Arber *et al*., 2022.[22] APL: Acute promyelocytic leukemia, AML: Acute myeloid leukemia, *NPM1*: Nucleophosmin, MDS: Myelodysplastic syndrome, NOS: Not otherwise specified, bZIP: Basic leucine zipper

CEBPA in-frame basic leucine zipper domain mutations and *NPM1* mutation in the absence of *FLT3*-ITD predict longer survival; in contrast, *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2* mutations (all belonging to myelodysplasia-related gene mutations), and *TP53* mutations predict poorer outcomes.[7,23] After the publication of the 2022 WHO and ICC classifications, European LeukemiaNet (ELN) updated the prior 2017[24] ELN recommendations for the diagnosis and management of AML in 2022.[25] In the recommendations, AML is risk stratified according to cytogenetic abnormalities and gene mutations into three categories: favorable, intermediate, and adverse [Table 4]. Patients with different risks have distinct clinical outcomes. Figure 2 shows overall survival curves stratified by the 2022 ELN risk classification of 809 AML patients from NTUH.[26]

Gene Mutations as Targets for the Development of Novel Agents

Gene mutations can be targets for novel therapies, and several agents targeted to specific genetic alterations have been developed.[27-35] Some are available in Taiwan, including the FLT3 inhibitors midostaurin and gilteritinib[28,29] for FLT3-mutated AML, while some others have been approved by the US Food and Drug Administration (FDA) but not yet by the Taiwan FDA, such as the IDH1/IDH2 inhibitors, ivosidenib and enasidenib, respectively, for IDH-mutated AML.[33,35] In November 2024, the US FDA approved the first menin inhibitor, revumenib, for relapsed or refractory acute leukemia with *KMT2A* translocation (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-revumenib-relapsed-or-refractory-acute-leukemia-kmt2a-translocation). More novel agents are under clinical trials, including other menin inhibitors for *KMT2A*-rearranged or *NPM1*-mutated AML, eprenetapopt, a reactivator of p53, for *TP53*-mutated AML,[30] and H3B-8800, an orally active modulator of SF3B1 splicing complex, for spliceosome-mutant cancers.[36]

Table 4: 2022 European LeukemiaNet risk classification by genetics

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
	Mutated *NPM1* without *FLT3*-ITD
	bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD
	Wild-type *NPM1* with *FLT3*-ITD
	t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/*DEK*::*NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged
	t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	t(8;16)(p11;p13)/*KAT6A*::*CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2,*MECOM*(*EVI1*)
	t(3q26.2;v)/MECOM(EVI1)-rearranged*
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype, monosomal karyotype#
	Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*
	Mutated TP53

*t(3q26.2;v)/MECOM(EVI1)-rearranged: 3q26.2 fusions with partners than GATA2, such as t(3;8)(q26.2;q24.2)/MYC::MECOM; t(3;12)(q26.2;p13.2)/ETV6::MECOM; t(3;21)(q26.2;q22.1)/MECOM::RUNX1MYC, etc., are also associated with poor prognosis, #Monosomal karyotype: Presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML). Döhner *et al*., 2022.[25] AML: Acute myeloid leukemia, *NPM1*: Nucleophosmin, ITD: Internal tandem duplication, bZIP: Basic leucine zipper

Gene Mutations as Biomarkers for Monitoring Measurable/Minimal Residual Disease

Most AML patients can achieve cytomorphological CR; however, approximately 50% eventually relapse, indicating the presence of MRD that escapes the detection of conventional morphological examinations. Mounting evidence has shown that a persistently high level of MRD or a rising level after an initial response invariably predicts relapse.

Traditionally, MRD is detected by multicolor flow cytometry, which recognizes leukemia-associated or a different from normal aberrant immunophenotype as a leukemia-specific marker.[37] Quantifying MRD by reverse quantitative polymerase chain reaction is based on AML-specific fusion genes such as *PML*::*RARA*, *RUNX1*::*RUNXT1*, and *CBFB*::*MYH11* or gene mutations such as *NPM1* mutation. Next-generation sequencing is a more powerful technique which can simultaneously detect various mutations and be applied to most AML patients.[38]

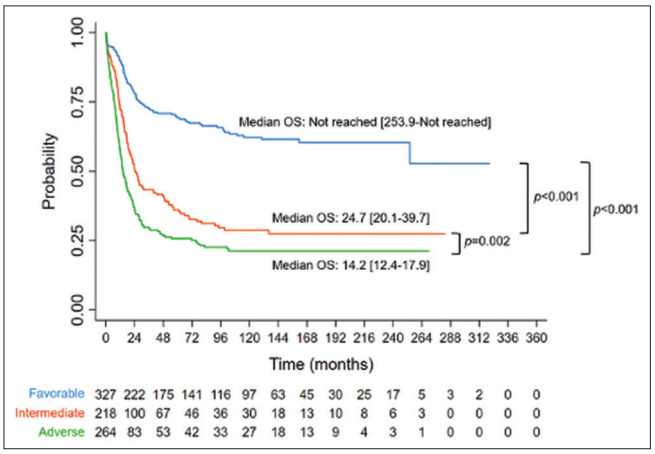

Figure 2: Overall survival of acute myeloid leukemia (AML) patients stratified by the European LeukemiaNet 2022 risk classification (from the AML cohort at National Taiwan University Hospital, $n = 809$).[26] OS: Overall survival

Implications of Gene Mutations on Personalized Treatment

Identifying the prognostic factors for patients with AML is the first step of personalized medicine. Conventionally, AML patients are categorized into favorable-, intermediate-, and unfavorable-cytogenetic risk groups according to cytogenetic changes [Figure 3]. However, patients with intermediate-risk cytogenetics represent a largely heterogeneous population regarding treatment response and clinical outcome. Integrating gene mutations with cytogenetic abnormalities can better stratify AML patients into different risk groups as recommended by the ELN.[25] Patients with favorable-risk AML can be treated with consolidation chemotherapy after achieving CR with no need to proceed to allogeneic hematopoietic transplantation (allo-HSCT). However, the treatment strategy should be changed if MRD is detected during follow-up, even if the patient has good-risk genetic aberrations. On the other side, patients with adverse-risk AML can benefit from IC followed by allo-HSCT. For example, AML patients with *RUNX1* mutation have poorer outcomes than those without the mutation; however, we previously showed that *RUNX1*-mutated patients had similar survival to *RUNX1*-wild patients if receiving allo-HSCT.[40] Similarly, allo-HSCT has been shown to ameliorate the poor prognosis of AML patients with myelodysplasia-related mutations.[23]

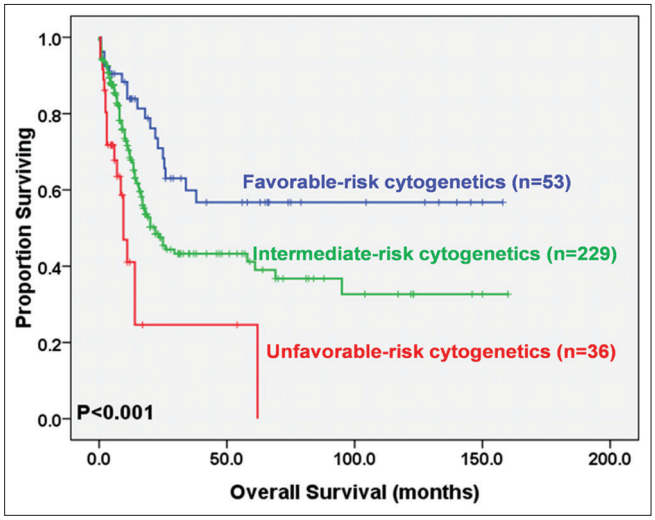

Figure 3: Overall survival of acute myeloid leukemia patients from National Taiwan University Hospital stratified by cytogenetic risk. Favorable-risk cytogenetics: t (8;21), inv (16), t (15;17); unfavorable-risk cytogenetics: Complex, -5/5q-, -7/7q-, 3q-, t (9;22)/(Ph); intermediate-risk cytogenetics: Normal karyotype or all other abnormalities[39]

MRD after treatment is an important biomarker to monitor treatment response, detect early relapse, and predict the prognosis in AML patients. We previously showed that MRD positivity detected by NGS at first morphological CR after induction chemotherapy [Figure 4, left] as well as first consolidation chemotherapy [Figure 4, right] predicts poorer outcomes in AML patients,[38] especially at the latter time point. The poor prognosis of patients with NGS MRD after consolidation chemotherapy can be mitigated by allo-HSCT. Preemptive treatment with azacitidine[41] or venetoclax, an oral BCL-2 inhibitor,-based treatment[42] when MRD is detected is effective to reduce or eliminate MRD.

The use of novel agents targeting specific gene mutations is expected to improve the treatment response and clinical outcomes of AML patients.[43] *FLT3*-mutated AML patients have been shown to have longer survival if receiving frontline IC plus the FLT3 inhibitor midostaurin, compared to IC alone.[28] Furthermore, the addition of ivosidenib, an IDH1 inhibitor, to the hypomethylation agent azacitidine has been shown to improve overall survival in newly diagnosed *IDH1*-mutated AML patients who are illegible for IC compared

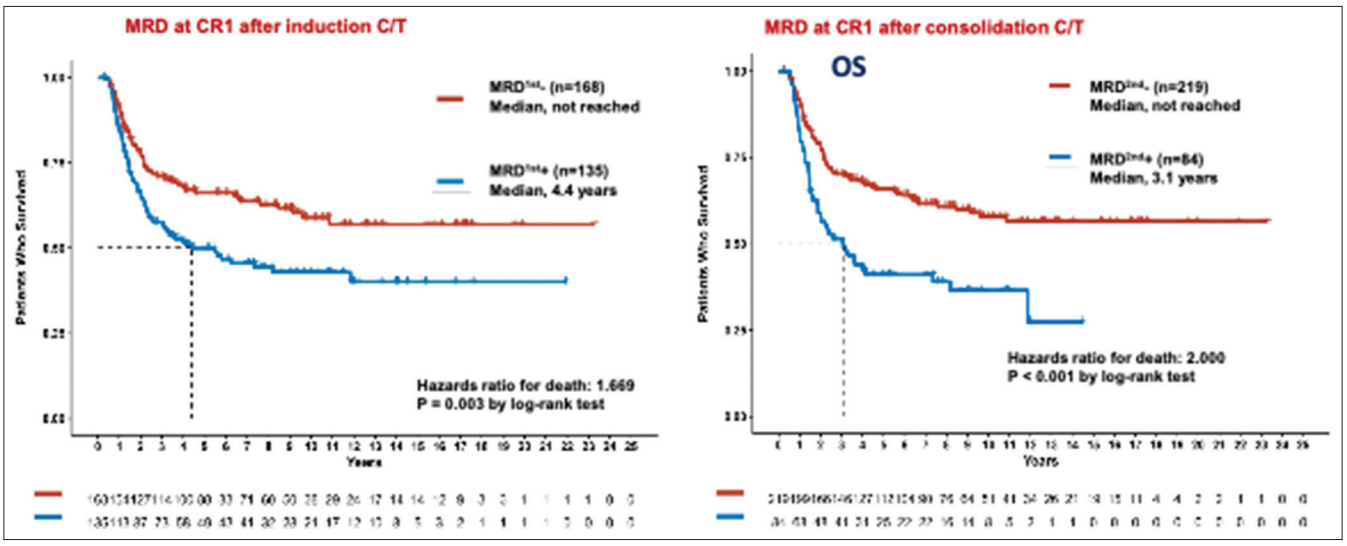

Figure 4: Overall survival curves stratified by the status of measurable/minimal residual disease (MRD) detected by next-generation sequencing at the time of morphological complete remission after induction chemotherapy (left) and first consolidation chemotherapy (right). MRD positivity predicts poorer overall survival, especially after first consolidation chemotherapy.[38] OS: Overall survival

to treatment with azacitidine alone.[44] Issa *et al*. reported that treatment with the menin inhibitor revumenib in patients with heavily pretreated relapsed/refractory acute leukemia with *KMT2A* translocation resulted in a rate of CR or CR with partial hematologic recovery of 22.8%.[34] To achieve the goal of precision medicine, the development of more novel mutation-targeted agents is needed.

Conclusion

Genetic alterations are useful biomarkers to risk-stratify AML and guide treatment choice. They can also be targets for the development of novel agents and markers to monitor MRD. According to the 2022 ELN recommendation, in addition to searching for specific cytogenetic abnormalities/fusion genes such as *RUNX*::*RUNX1T1*, *CBFB*::*MYH11*, and *KMT2A* gene fusions, it is mandatory to screen for gene mutations that are important for AML classification and risk stratification, such as *NPM1, CEBPA, TP53, ASXL1*, *RUNX1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2* mutations, and those that are druggable, such as *FLT3* and *IDH1/2* mutations. Personalized medicine based on the risk at diagnosis, MRD after treatment, and proper use of mutation-targeted novel agents can improve the survival of AML patients while reducing the toxicity from the treatment.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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