

Review Article

Molecular and genomic landscapes in secondary & therapy related acute myeloid leukemia

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Abstract: Acute myeloid leukemia (AML) is a complex, aggressive myeloid neoplasm characterized by frequent somatic mutations that influence different functional categories' genes, resulting in maturational arrest and clonal expansion. AML can arise de novo (dn-AML) or can be secondary AML (s-AML) refers to a leukemic process which may arise from an antecedent hematologic disorder (AHD-AML), mostly from a myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) or can be the result of an antecedent cytotoxic chemotherapy or radiation therapy (therapy-related AML, t-AML). Clinical and biological features in secondary and therapy-related AML are distinct from de novo AML. Secondary and therapy-related AML occurs mainly in the elderly population and responds worse to therapy with higher relapse rates due to resistance to cytotoxic chemotherapy. Over the last decade, advances in molecular genetics have disclosed the sub-clonal architecture of secondary and therapy-related AML. Recent investigations have revealed that cytogenetic abnormalities and underlying genetic aberrations (mutations) are likely to be significant factors dictating prognosis and critical impacts on treatment outcome. Secondary and therapy-related AML have a poorer outcome with adverse cytogenetic abnormalities and higher recurrences of unfavorable mutations compared to de novo AML. In this review, we present an overview of the clinical features of secondary and therapy-related AML and address the function of genetic mutations implicated in the pathogenesis of secondary leukemia. Detailed knowledge of the pathogenetic mechanisms gives an overview of new prognostic markers, including targetable mutations that will presumably lead to the designing and developing novel molecular targeted therapies for secondary and therapy-related AML. Despite significant advances in knowing the genetic aspect of secondary and therapy-related AML, its influence on the disease's pathophysiology, standard treatment prospects have not significantly evolved during the past three decades. Thus, we conclude this review by summarizing the modern and developing treatment strategies in secondary and therapy-related acute myeloid leukemia.

Keywords: Secondary AML, therapy related AML, leukemia

Introduction

Acute myeloid leukemia (AML) is a complex disorder characterized by the development of

malignant myeloid precursors in the blood and bone marrow [1]. AML is the most prevalent out of all acute leukemias diagnosed in adults and the second most common among all acute leu-

kemias diagnosed in children [2]. This disease is delineated by a clonal proliferation of myeloid blasts, suppressing normal hematopoiesis and generally having a high fatality and a low cure rate, especially among older patients [3, 4]. Genetic and molecular evidences suggest that AML is exceptionally varied entity with complicated repetitive genetic modifications such as chromosomal aberrations, DNA methylation patterns, and gene mutations [5-7]. These alterations accumulate and result in the blocking of normal maturation of myeloid progenitor cells and lead to clonal expansion of blast cells in the bone marrow. Despite novel breakthroughs in understanding of the molecular pathogenesis in AML still, the pathophysiology of leukemogenesis of myeloid blasts remains unclear [8, 9]. Although most cases arise de novo, AML can also develop from an antecedent hematologic disorder such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) or as a late complication of previous exposure to cytotoxic therapy including alkylating agents and topoisomerase II inhibitors typically used for a solid malignancy/lymphoma or radiation therapy for other cancers (therapy-related AML, t-AML). Secondary AML (s-AML) accounts for a large proportion of the AML population and is correlated with biological characteristics that contribute to poor outcomes, including unfavorable cytogenetics and multidrug resistance phenotype as compared with de novo AML (dn-AML) [3-7, 10, 11]. Genome-wide and targeted mutational analysis from next-generation sequencing has shown that the most commonly mutated genes were usually those that played a role in DNA methylation (46%), modifications of chromatin (42%), RAS signaling (42%), RNA spliceosome machinery (55%), transcriptional regulation (34%) and proteins that regulate the three-dimensional organization of chromatin in the nucleus (22%) [12]. These mutations may also help to predict the response of hypomethylating agents (HMA) and allogeneic hematopoietic stem cell transplantations (HSCT) to be used for the treatment of different patients with AML. Treating s-AML with traditional chemotherapy or hematopoietic stem cell transplantation (HSCT) is linked with poor prognosis [13-15]. HSCT refers to a medical procedure that infuses hematopoietic stem cells in order to restore bone marrow function in cancer patients whose bone marrow or immune system is damaged or defective. Nevertheless,

HSCT has been proven a treatment option for patients with s-AML. It is extensively utilized in younger patients with adverse-risk cytogenetics [16-22]. HMAs such as decitabine and azacitidine are generally well-tolerated and helpful treatment options in patients with s-AML who are not eligible for intensive chemotherapy due to reduced cytotoxic profile. HMA exerts anti-tumor effects via an epigenetic modification to induce re-expression of tumor suppressor genes. The genetic mechanisms include DNA hypomethylation, chromatin reorganization, and DNA methyltransferase-I depletion. Treatment responses are seen after a few months of therapy. HMA is typically helpful in s-AML, where patients are usually elderly and frequently have TP53 alterations. They are also used to treat high-risk MDS and in AML post-transplant in high-risk patients. The median time to response is 3-4 cycles, and a minimum of 4-6 cycles should be given unless otherwise contraindicated. Median duration of response is 12-18 months. HMA is less toxic than intensive chemotherapy. The side effects seen are commonly related to myelosuppression, including infections and bleeding. Other side effects include nausea, vomiting, and occasional tumor lysis syndrome. Oral analogues have recently become available and used as maintenance therapy in AML patients after consolidation therapy. Of late, they are increasingly combined with other targeted agents, including FLT3 and IDH inhibitors. HMAs can be used in AML irrespective of the underlying genetic status. TP53 mutated AML does not behave worse compared to TP53 unmutated AML when treated with HMAs. Both Decitabine and azacitidine HMAs have proven efficacy, safety and confer an OS benefit in the absence of CR. The management of secondary AML (s-AML) is more complex compared to de novo AML as it is associated with worse clinical outcomes, less hematopoietic stem cell reserve, co-morbidities due to old age, and overall worse survival [23-28]. Hence, a better knowledge of the molecular landscape in secondary and therapy-related AML has significant implications on treatment response, prognostication, and the development of new molecular therapeutic targets. There is a necessity to introduce advanced personalized therapies for s-AML and t-AML [29]. In the light of diversified treatment options available for secondary and therapy-related AML, we also summarize the popular and developing treat-

ment strategies in secondary and therapy-related AML.

Secondary acute myeloid leukemia (s-AML)

The majority of cases of AML are de novo AML without any antecedent hematologic disease or other cancer. Secondary leukemia can be further categorized into leukemia arising out of a prior myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) or that originating from a bone marrow failure state (BMF). Secondary AML (s-AML) is a biologically complex heterogeneous disease that covers 25 to 30% of all AML cases [10, 11]. About 20% of cases of AML are s-AML having an antecedent hematologic disorder (AHD-AML) involving progression from myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), or chronic myelomonocytic leukemia (CMML) as the antecedent disorders. Conventional prognostication depends on clinicopathological correlation and cytogenetic information. Additionally, secondary AML (s-AML) occurs more in the elderly population, responds worse to therapy, and displays worse prognosis and low response rates as compared to de novo AML [13, 30, 31]. Secondary AML is a distinguished unfavorable prognostic factor that confers distinct clinical and biological features characterized by adverse genetic mutations, cytogenetic alterations, and aberrations in TP53; leukemic clones are often more resistant to cytotoxic chemotherapy, contribute to a high relapse rate in s-AML [32-36]. In 2017 FDA authorized CPX-351 (liposomal formulation of cytarabine and daunorubicin), especially for secondary AML. However, current investigations show promising outcomes with high-dose cytarabine or hypomethylating agents [29]. Targeted immunotherapy is likely to evade multidrug resistance mechanisms but is unlikely to give continual remission due to a complicated and rapidly developing clonal disease profile [37]. Secondary AML is considered as an outcome of various somatic mutations that influence genes of different functional categories.

Secondary AML (s-AML), secondary to other myeloid neoplasms

Patients with s-AML developed as a result of an antecedent hematologic disorder (AHD-AML) have approximately 60% of the cases-MDS, 30% of the cases-MPN, and about 10% of the

cases-CMML [30]. The development of s-AML is defined by the progressive evolution of clones [38].

Secondary AML (s-AML) Arising from Myelodysplastic Syndrome (MDS): Secondary AML results from an antecedent hematologic condition (AHD) or previous chemotherapy/radiation therapy with distinct genomic alterations. The most prevalent cause of s-AML is myelodysplastic syndrome (MDS), a group of diverse clonal abnormalities of the hematopoietic stem cells (HSCs) characterized by morphologic dysplasia in the hematopoiesis, and bone marrow failure, resulting in cytopenias and a significant risk of evolving into secondary acute myeloid leukemia (s-AML). Nearly one-third of MDS patients progress to s-AML. MDS and its evolution into s-AML are correlated with the accumulation of various genetic mutations particularly, RUNX1 [30, 39-44]. The International Prognostic Scoring System is used to evaluate the prognosis of MDS [45]. The median time to develop s-AML from MDS is about 17 months, while from a precursor MPN, it's about 43 months. AML resulting from an antecedent MPN displays a lower response to chemotherapy and poorer overall survival (OS) than AML from antecedent MDS [30]. MDS is divided into five prognostic subgroups based on the development of dysplasia, blast counts percentage, and specific cytogenetic abnormalities. A combination of cytogenetics and clinical parameters classifies patients into prognostic risk categories using a Revised-International Prognostic Scoring System (IPSS-R), with a variable uncertainty of disease progression [46, 47]. In higher-risk groups, a substantial overlap of cytogenetic aberrations and mutations was observed between MDS and s-AML [48-50]. Poor prognosis is correlated with a complex karyotype (CK) which significantly raises the risk of progression to s-AML [47, 48]. Cytogenetic abnormalities linked with MDS and s-AML are usually due to copy number alterations, which are more prevalent in dn-AML. Many genetic studies have led us to classify mutations common in MDS and s-AMLs into the following main groups: spliceosome genes, epigenetic modifiers, transcription factors, and activated signaling genes [12].

Mutations in spliceosome genes (e.g., SRSF2, SF3B1, U2AF1, EZH2) are more common in

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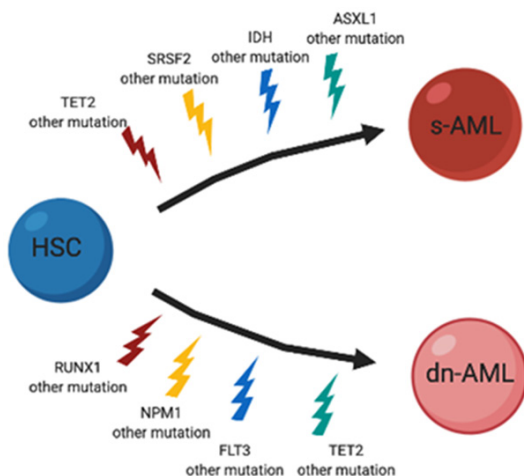


Figure 1. Mutational variation in de-novo and secondary acute myeloid Leukemia. HSC: Hematopoietic Stem cell, s-AML: Secondary acute myeloid leukemia, dn-AML: de novo acute myeloid leukemia.

AML resulting from MDS compared to dn-AMLs [51, 52]. Mutations in epigenetic modifiers (e.g., TET2, DNMT3A, ASXL1) are well-known in multiple clonal hematopoiesis (e.g., CHIP, MDS, s-AML) [53]. This suggests that these mutations occur early in the pathogenesis of MDS before the development of s-AML. While mutations in transcription factors (e.g., RUNX1, GATA2, CEBPA) and signaling pathway genes (e.g., RAS, FLT3) are more frequent in s-AML, implying that these mutations are acquired later during progression to s-AML [54, 55]. Mutational variation in s-AMLs and dn-AMLs is given in **Figure 1**. However, whole-genome sequencing reports suggest that the intrinsic pathophysiology of s-AML progression includes complex stages of clonal evolution [56]. An extensive population-based study has concluded that the risk of transformation is driven by a single genetic or epigenetic event [57].

Secondary AML (s-AML) arising from myeloproliferative neoplasms (MPN): The myeloproliferative neoplasms (MPN) are a group of chronic clonal proliferative disorders of the myeloid series of cells. The development of MPNs in most cases is driven by various mutations, including myeloproliferative leukemia protein (*MPL*), Janus Kinase 2 gene (*JAK2*), and calreticulin (*CALR*) by activating the JAK2-STAT signaling pathway [58-65]. Multiple risk factors, including decreased platelet count, anemia, increasing age, circulating blast forms, have

been proposed to prognosticate the risk of leukemic progression from a myeloproliferative neoplasm [66]. Chromosomal aberrations like del7p were found in cases of MPN linked with progression to secondary AML (s-AML). Furthermore, an adverse karyotype indicates a six-fold higher risk of progression to the MPN-Blast Phase [49, 67]. Exposure to one or more cytoreductive treatments was seen to have enhanced the risk of progression to AML [68]. Various mutations, including SRSF2, IDH1, or IDH2, were exhibited as independent risk factors for leukemic alteration in MPNs [69, 70]. Heterozygous TP53 mutation is usually found early in MPN, but evolution to leukemia correlates with the transition of TP53 from heterozygous to homozygous mutated form [71]. Post-MPN AML is linked with a poorer prognosis [72]. TP53, SRSF2, and TET2 mutations have been seen to be associated with a poor overall survival rate in secondary AML arising from MPN [73, 74].

Therapy-related acute myeloid leukemia (t-AML)

Therapy-related AML in most events emerges after cytotoxic chemotherapy following treatment of other malignancies, including lymphoma, breast cancer, multiple myeloma, ovarian cancer, and testicular cancer, or may also begin after autoimmune disorders due to the mutagenic treatment agents [30-33, 36, 75, 76]. Two common types of t-AML have previously been recognized. One type is seen after therapy with alkylating agents (e.g., cyclophosphamide, melphalan, etc.) and presents typically as therapy-related myelodysplasia with deletions or loss of chr 5 or 7. Alkylating agents begin cell necrosis by crosslinking in DNA, followed by mutations and chromosomal rearrangements [63, 77-79, 95]. The other type is seen after therapy with topoisomerase II inhibitors (e.g., doxorubicin, etoposide, etc.) and characteristically manifests as overt t-AML with repeated balanced chromosome abnormalities. The leukemogenic mechanism of topoisomerase II inhibitors depends on their involvement with DNA re-ligation and chromosomal damage. Topoisomerase II inhibitors prevent the DNA resealing step and inducing double-strand breaks [80]. Chromosomal abnormalities generally correlated with topoisomerase II inhibitors are balanced translocations, most

Table 1. Genetic pathways involved in pathogenesis of therapy related acute myeloid leukemia

Pathways	Type of therapy for primary malignancy	Primary abnormality	Secondary abnormality	Ref.
I	Alkylating agent	del 7q/loss of chr. 7	t(3;21), Mutation in RAS gene	[85, 86]
II	Alkylating agent	del 5q/loss of chr. 5 can be associated with a chr. 7 aberration	Mutation of TP53 gene, trisomy 8	[87, 88]
III	Epipodophyllotoxin	Balanced translocation of chr. 11q23	TP53 gene mutation	[89-91]
IV	Topoisomerase II Inhibitors	t(8;16), t(8;21) and inv(16)	Additional aberrations	[93]
V	Topoisomerase II Inhibitors	PML-RAR α fusion	Mutation in FLT3 gene	[94]
VI	Topoisomerase II Inhibitors	Fusion of NUP98 & HOXChr. (11p15q22)	Absent	[95, 96]
VII	Not associated with any specific therapy	Normal karyotype	FLT3, NPM1 and MLL gene	[85, 97]
VIII	Not associated with any specific therapy	Other aberrations	-	[98]

usually including MLL (e.g., KMT2A) at 11q23 and RUNX1 at 21q22 [47, 48, 81, 82]. Novel investigation intimates that these 2 common types of t-AML can now be subdivided into 8 genetic pathways with diverse etiology and different biologic characteristics, as shown in (Table 1).

Pathway I

This pathway is delineated by the loss of chromosome 7 or monosomy 7 or other chromosomal abnormalities in chromosome 7 [83-85]. These aberrations further cause secondary abnormalities such as balanced t(3; 21) [85]. This pathway is closely correlated to therapy with alkylating agents for treating any primary malignancy. It is also characterized by mutations of the rat sarcoma (RAS) pathway, which leads to aberrant proliferation of myeloid hematopoietic stem cells through activation of the signal transduction pathway [86].

Pathway II

This pathway is characterized by the loss of the long arm of chromosome 5 or monosomy 5 [87]. This may also; in addition, be associated with chromosomal aberrations in chromosome 7. Further, secondary aberrations such as mutation of TP53, trisomy 8 can occur [88]. These result in impaired differentiation and enhanced expression of cell cycle regulatory proteins due to the loss of the tumor suppressor gene [89]. This pathway is closely linked to therapy with alkylating agents for treating any primary malignancy.

Pathway III

This pathway is characterized by balanced translocation of chromosome 11q23 [89]. This

aberration further causes secondary abnormalities like mutations of the TP53 gene. This pathway is firmly associated with therapy with epipodophyllotoxin for treating any primary malignancy. This mutation is most commonly seen in infants [90, 91]. Patients with this mutation usually achieve a complete remission following intense antileukemic treatment, but the prognosis is terrible due to multiple relapses [91, 92].

Pathway IV

This pathway is characterized by balanced translocation, including t(8;16), t(8;21), and inv(16). They are usually associated with many additional aberrations. This pathway is closely linked with therapy with topoisomerase II inhibitors for treating any primary malignancy [93]. Patients in this pathway display an excellent response to intensive antileukemic chemotherapy.

Pathway V

This pathway is characterized by chimeric rearrangement between the PML and the RAR α genes. This aberration further causes secondary anomalies like mutations of the FLT3 gene. This pathway is closely correlated to therapy with topoisomerase II inhibitors for treating any primary malignancy. Patients with this pathway usually respond favorably to intense antileukemic chemotherapy when used with retinoic acid [94].

Pathway VI

This pathway is characterized by the Fusion of NUP98 and HOX-Chr.11p15q22. This pathway is closely associated with therapy with topoi-

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somerase II inhibitors for treating any primary malignancy [95, 96].

Pathway VII

This pathway is associated with normal karyotype and associated with various mutations like FLT3 and NPM1 mutations [85, 97].

Pathway VIII

This pathway is uncharacteristic. They may represent incidentally identified cases of dn-AML [98].

Therapy-related acute myeloid leukemia (t-AML) following chemotherapy and radiation

In 5-10% of cases, patients present with therapy-related AML (t-AML) due to antecedent cytotoxic therapeutics or radiation treatment for a previous malignant or non-malignant disorder [99]. Since radiation therapy is typically administered along with chemotherapy as a part of multi-modality treatment, comparable to alkylating agents, radiation therapy induces double-stranded DNA breaks [66]. Consequently, most incidents of t-AML affect the proliferation of a myeloid clone with genetic variability influenced by previous chemotherapy and radiation. Chemotherapy may build an environment that allows proto-leukemia cells to harbor mutations and develop uncontrolled proliferation from local niche cells [100-102].

Mutational landscape of secondary and therapy related acute myeloid leukemia

The pathophysiology of s-AML and t-AML and its progression involve multiple genetic aberrations. The development of myeloid malignancies is triggered by somatic mutations resulting in the clonal extension and maturational arrest of HSCs. Advanced genome-wide and targeted analyses by microarrays and next-generation sequencing (NGS) have distinguished novel mutations of prognostic and therapeutic importance responsible for the development of AML. In 2008, AML was the first disease for which the entire cancer genome was sequenced. The genetic heterogeneity in AML is vast and includes structural chromosomal aberrations as well as point mutations. Conventional cytogenetics, somatic point mutations, and smaller copy number alterations plays a critical role in

the pathogenesis of disease. Various unfavorable mutations were present in patients with s-AML that promote clonal development and disease progression [6, 10, 103-111]. The number of driver mutations in s-AML resulting from an AHD is more when compared to t-AML [112]. AML displays a lower number of coding mutations per exome at the molecular level compared to other cancers. The mutational landscape in s-AML and t-AML can be classified according to various functional categories, and the genes involved in each of the categories are: Epigenetic regulation (TET2, DNMT3A, IDH1/IDH2, EZH2, ASXL1), RNA spliceosome machinery regulators (SRSF2, SF3B1, U2AF1), Transcription regulator (TP53, RUNX1) and Signaling pathway regulators (FLT3) correlate to a mechanistic role in leukemogenesis [6, 113-116]. These mutation groups correlate with clinical outcomes, underlying disease progression, and predict responses to therapy. There is a substantial overlap in the genomic landscape of the s-AML resulting from an AHD-like precursor MDS, MPN, and t-AML [10]. But, on the other hand, several specific mutations can also prove to be possible therapeutic targets [31, 32]. Hence, the molecular landscape in secondary and therapy-related AML has significant involvement in prognostication, therapeutic response, and different molecular therapeutic targeting.

Targeting mutations in epigenetic regulator genes (TET2, DNMT3A, IDH1, IDH2, EZH2, ASXL1)

The epigenetic modifications lead to a change in the gene expression without actually changing the DNA sequence. Abnormal methylation of DNA, histone modifications, and RNA-mediated silencing lead to dysregulation of gene expression promotes the pathogenesis of myeloid malignancies [117, 118]. In cancer, DNA hypermethylation probably leads to chromosomal instability & promoter hypermethylation has been correlated with silencing of tumor suppressor genes [119]. Genome-wide DNA methylation profiling in AML has displayed different patterns in various genetic subgroups that can categorize AML into prognostic groups [119-121]. In AMLs, epigenetic mutations, chromosomal aberrations, and somatic mutations are closely associated. Abnormal DNA methylation is a crucial mechanism to

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alter epigenetic regulations in secondary and therapy-related AML [11]. Commonly mutated genes related to this pathway include TET2, DNMT3A, IDH1 & IDH2, EZH2, and ASXL1.

TET2 mutations: The TET gene produces TET1, TET2, and TET3 dioxygenase proteins. TET2 is located on chromosome 4q24. TET1/2, which catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine (5-hmc), likely influences the epigenetic regulation of transcription factors and thereby has a crucial function in the maintenance of hematopoietic stem cell (HSC) homeostasis [122-124]. Moreover, TET2 mutations involve frameshift, nonsense, and missense mutations seen in a diversity of myeloid neoplasms, including s-AML, MDS, and MPNs [43, 123, 125-127]. A higher incidence of TET2 mutations is observed in patients with s-AML (24%-32%), but these mutations occur at a lower frequency of about 20%-25% in MDS [128-131]. TET2 mutations confer a higher survival in MDS but a poorer survival in the case of AML and chronic myelomonocytic leukemia (CMML) [132-134]. Moreover, TET2 mutations may predict a more beneficial response to HMAs in patients carrying these mutations [42, 110, 124].

DNMT3A Mutations: The de novo methyltransferase 3 alpha (*DNMT3A*) belongs to the DNA methyltransferases family, which has other members, including DNMT1 and DNMT3B, which play an essential role to catalyze DNA methylation by transfer of methyl groups to specific cytosine residues of CpG islands [135-137]. They are involved in differentiation, proliferation, and apoptosis [138]. Aberrant methylation of CpG island promoters of tumor suppressor genes is an important pathogenetic mechanism for the development of many malignant tumors and suggests that DNMTs play a significant role in oncogenesis. DNMT3A mutations are associated with age, white blood cell (WBC) count, cytogenetics, prognosis, and patient's response to chemotherapy [148]. DNMT3A is essential in normal hematopoietic stem cell differentiation and self-renewal and is highly expressed in lymphocytes [139]. DNMT3A mutations are present in 30%-35% of AML patients with normal karyotype and in approximately 10% of MDS patients [140, 144, 145]. The majority of *DNMT3A* missense mutations were found in hematological cancers

at amino acid residue R882 near the carboxyl terminus of the DNMT3A protein [5,140-143]. *DNMT3A* R882H the mutation seems to predict a worse prognosis, has a lower overall survival (OS) rate and has higher leukemic transformation [146, 147].

IDH1 AND IDH2 mutations: Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) belong to the family of epigenetic modifiers that transform isocitrate to α -ketoglutarate (α -KG) [144, 145]. Missense mutations of IDH1/2 associated with blood tumors frequently occur at specific arginine residues R132 in IDH1 and R140 or R172 in IDH2 [149]. These mutations generate D-2-hydroxyglutarate (2-HG), which is structurally similar to α -KG in that it can bind in place of α -KG and inhibits its function [150]. As a result, the overproduction of D-2-HG inhibits the α -ketoglutarate-dependent dioxygenase enzymes JumonjiC (JmjC), TET2, and cytochrome C oxidase (COX), leading to DNA hypermethylation and can block cell differentiation. These enzymes intervene with cellular metabolism, and this epigenetic regulation promotes oncogenesis [144-146, 151]. In myeloid malignancies, IDH1/2 mutations can be observed in patients with cytogenetically normal AML, MDS, and MPN [144, 152]. IDH1 mutations at residues R132 are found in 6%-16% of dn-AML and are associated with inferior OS rate [153, 154]. Patients with *IDH2* R172K mutation have an inferior prognosis, a higher relapse rate, a lower complete remission rate, and bad OS [155, 156]. IDH2 mutations are seen in 4% to 12% of MDS cases and are often present together with ASXL1, SRSF2, and DNMT3A mutations and prognosticate lower OS, particularly those at codon 172 [153, 157-160]. Additionally, some investigations propose that *IDH1* and *IDH2* mutations contribute to the progression from MDS or MPN to AML through reactive oxygen species (ROS) accumulation and DNA damage influencing the activation of HIF-1 [161-163]. IDH1/2-mutated myeloid malignancies are likely targetable by obstructing mutant enzymatic activity and their metabolic pathways [164].

EZH2 mutations: Mutations in the enhancer of zeste homolog 2 (*EZH2*) gene is linked with hematologic malignancies. EZH2, a histone-lysine N-methyltransferase enzyme, is responsible for the addition of methyl groups to a high-

ly conserved histone H3 at lysine 27 (H3K27) that regulates stem cell differentiation and maturation by epigenetic modifications in the genes linked with transcriptional repression [165]. EZH2 mutations have been associated with many hematopoietic malignancies, most commonly in myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) [166, 167]. EZH2 mutations are observed in 6%-12% of patients with MDS, and these mutations correlate with a lower survival rate. EZH2 mutations usually co-exist with TET2 mutations, linked with a higher risk of developing secondary AML [145].

ASXL1 mutations: Additional sex comb-like 1 (ASXL1) gene is one of the most commonly mutated genes in a variety of myeloid malignancies, including in CMML (43%), MDS (20%), MPN (10%), and AML (20%) [174, 175]. The ASXL1 protein is implicated in epigenetic modulation and transcription by interaction with polycomb repressive complex PRC2 and different transcriptional activators or repressors [168-171]. ASXL1 gene is present on chromosome region 20q11.21, and it controls histone modification by interacting with the PRC2. PRC2, along with ASXL1 methylates histone protein (H3K27), is a crucial regulator in malignant myeloid diseases and hematopoiesis [172, 173]. ASXL1 deprivation is linked with hematopoietic alteration and enhanced self-renewal [145]. Simultaneously, the mutated ASXL1 indicates a poor prognosis for AML and MDS patients, resulting in an inferior OS rate linked to a higher risk of secondary AML [176, 177].

Targeting mutations in the RNA spliceosome machinery genes (SRSF2, SF3B1, U2AF1)

RNA spliceosome machinery genes code for the spliceosome components, including small nuclear RNAs (sn-RNA) and proteins that catalyze the process of splicing by which mature RNA is developed from pre-mRNA through intron replacement and exon splicing. Components of pre-mRNA splicing machinery are generally mutated in myeloid malignancies, including SRSF2, SF3B1, and U2AF1 [94, 178].

SRSF2 mutations: The Serine/Arginine-rich Splicing Factor 2 (SRSF2) gene is positioned on chromosome 17q25.1 and encodes pre-mRNA, which is required for spliceosome assembly, and alternative splicing [160, 178]. SRSF2

mutations may lead to disease progression in patients with MDS [179]. SRSF2 mutations are observed in 11%-15% of patients with MDS, it has been seen that SRSF2 mutations generally co-exist with RUNX1, ASXL1, IDH1, and IDH2 mutations. In CMML, SRSF2 mutation is seen in nearly 28-47% of cases, closely associated with TET2 mutations [110, 178]. SRSF2 mutations are linked with more inferior OS and an enhanced risk for AML progression [178, 180, 181].

SF3B1 mutations: The Splicing Factor 3B Subunit 1 (SF3B1) gene (chromosome 2q33.1) encodes the splicing factor 3B crucial for forming a ribonucleoprotein complex known as U2 snRNP [182]. Clonal and in vitro investigations of human leukemia cells have revealed that SF3B1 mutations initiate events that occur in rare lymphoid-myeloid hematopoietic stem cells (HSCs) [183,184]. SF3B1 mutations have been observed in 6%-18% of patients with MDS [185]. SF3B1 mutations are linked with cytopenias, thrombocytosis, and lower blasts percentage in MDS-Ring Sideroblast (RS) or MDS/MPN-RS. SF3B1 mutation is an indicator of good prognosis and prolonged survival [186].

U2AF1 mutations: The U2-complex auxiliary factor 1 (U2AF1) gene, located on chromosome 21q22.3, encodes the U2 spliceosome that promotes dinucleotide recognition in pre-mRNA introns. Repetitive mutations in U2AF1 at codon Q157 and S34 have been observed in 11% of cases with MDS and approximately 4% of patients with AML [178, 187]. U2AF1 mutations affect the generation of neomorphic phenotypes by changing splicing patterns for multiple RNA downstream genes. U2AF1 modifications seem to affect erythroid progenitors' division and consequently alter the differentiation of leukocytes [188]. The prognostic impact of U2AF1 mutations remains with a lower remission rate and poorer survival linked to an increased risk of AML transformation [178].

Targeting mutations in transcriptional regulatory genes (TP53, RUNX1)

Transcriptional regulatory genes are usually involved in leukemic progression across secondary and therapy-related AML includes TP53, RUNX1.

TP53 mutation: Tumor protein 53 (TP53) is a tumor suppressor gene found on chromo-

some 17p13.1. TP53 controls apoptosis, senescence, cell cycle arrest, and DNA repair [189]. More than 70% of patients have been seen to harbor TP53 mutations in t-AML cases [12, 190, 191]. TP53 gene mutation may benefit the malignant clone that expedites the development of a malignant tumor [192, 193]. The vast majority of TP53 mutations arise in two mutational hot spots: residues R273 and R248 encode the DNA-binding domain [192, 194]. TP53 mutations are linked with a high risk of leukemic transformation, resistance to chemotherapy, inferior OS, and DFS [110, 192, 194].

RUNX1 mutations: Runt-related transcription factor 1 (RUNX1), also known as acute myeloid leukemia 1 protein (AML1) or core-binding factor subunit alpha-2 (CBFA2) found on chromosome 21q22.12, is a crucial regulator of myeloid differentiation that strongly drives leukemic transformation [195]. Co-expression of RUNX1 and ASXL1 mutations contribute to leukemic change by preventing myeloid stem cells' differentiation and improving self-renewal activity by transcriptional activation of hypoxia-inducible factor 1 (HIF1- α) [198, 199]. RUNX1 mutations are observed in 24% of patients with secondary AML and independently confer inferior prognosis [110, 196, 197].

Targeting mutations in activated signaling pathway

Tyrosine kinase and RAS pathways have been seen to get affected in s-AML [119]. FLT3 is the most commonly mutated gene associated with this pathway [204].

FLT3 mutation: Fms-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase highly expressed in hematopoietic stem cells [200-203]. The activation of the FLT3-mediated signaling accelerates PI3K/AKT and RAS/MAPK pathways, which leads to an uncontrolled proliferation of the hematopoietic stem cells (HSCs). FLT3 ITD mutation, which is observed in about 30% of AML cases, is linked with higher relapse rates and poorer survival [200, 204].

Treatment strategies and novel therapeutics approach in secondary and therapy related AML

Secondary AML is a complex disease with high incidence and mortality. The standard of care

for the treatment of s-AML and t-AML has remained consistent for decades. Hence, novel treatment strategies are needed to combat s-AML [29]. The therapeutic armamentarium of AML has progressively evolved in the past several years due to recent advancements in sequencing technologies and experimentation methodologies that improve our knowledge insight of the functioning of multiple genomic abnormalities. These genomic abnormalities play an impactful role in the pathogenesis of s-AML and t-AML as well as on mechanisms facilitating resistance to conventional therapies [205, 206]. With plenty of novel therapeutic modalities available, the patient's treatment will depend on a specific combination of the personalized genomics. s-AML has generally been treated with intense chemotherapy 7 + 3 regimens, comprised of 7 days consecutive intravenous cytarabine infusions and 3-day anthracycline infusions (i.e., daunorubicin or idarubicin) is considered a standard of care for induction which significantly diminishing the leukemia burden in patients. Complete remission (CR) varies between 30 to 60%, and overall survival (OS) is nearly nine months for cases with s-AML treated when treated with standard 7 + 3 induction chemotherapy with cytarabine and an anthracycline [30, 207-209]. Usually, older patients diagnosed with s-AML are treated with low-dose cytarabine (LDAC) or treatment with a hypomethylating agent (HMA) such as 5-azacitidine, which can influence remission and increase OS [210-212]. Despite the effectiveness of chemotherapy regimens, the prognosis of patients with sAML remains poor, particularly for older patients. Allogeneic hematopoietic stem cell transplant (allo-HSCT) is a potential therapeutic treatment and possibly offers the most promising long-term remission in s-AML [213, 214]. Due to the absence of sustained response to traditional induction chemotherapy, patients with s-AML who attain CR, belonging to intermediate or adverse risk groups, will be referred for allo-HSCT [215]. In preclinical investigations, several novel agents in combination with conventional chemotherapeutic medications have been conferred to overcome drug resistance in AML [216-218]. A few pathway-specific agents and chemotherapy with a new drug delivery system being approved by the US FDA to treat AML, including CPX-351, venetoclax, gemtuzumab ozogamicin (GO), glasdegib, and various agents targeting FLT3 or IDH such as midostaurin, gilteritinib,

enasidenib, ivosidenib. A few of these new drugs have been on trial s-AML cases. A p-glycoprotein expression is responsible for poor outcomes with anthracycline-based regimens in patients with s-AML [219]. CPX351 therapy with a cytarabine and daunorubicin liposomal formulation has been considered to enhanced overall survival (OS) in s-AML and overcome resistance mechanisms such as p-glycoprotein efflux [220, 221]. CPX-351, a dual-drug liposomal co-encapsulation of cytarabine and daunorubicin, has been approved to treat patients diagnosed with s-AML and t-AML. A nanoliposomal carrier of the drug improves intracellular uptake of the drug [222-224]. In contrast with the traditional 7 + 3 regimen, CPX-351 medication was linked with significantly increased OS, EFS, CR in newly diagnosed s-AML patients [225, 226]. Regimens with high-dose cytarabine (HiDAC) have shown an added advantage in cases with s-AML [227]. AML cells typically depend on anti-apoptotic Bcl-2. Bcl-2 is usually overexpressed in AML and associated with cell survival, chemoresistance, and lower OS in AML patients [228]. BCL-2 inhibitor Venetoclax, combined with hypomethylating agents such as azacitidine, decitabine exhibit promising alternative therapeutic medications for high-risks s-AMLs that may be preferred in older patients who cannot tolerate the intense and likely critically unfavorable consequences of intensive chemotherapy [229, 230]. HMA exerts anti-tumor outcomes primarily through an epigenetic alteration to facilitate tumor suppressor genes re-expression [231-236]. Therefore, venetoclax, a small-molecule inhibitor of Bcl-2, mainly targets AML cells, leading to cell death [237, 238]. CD33 antigen is a transmembrane receptor, and blasts express myeloid differentiation marker in most cases with AML. Using the benefit of the particular expression of CD33 by blasts, Gemtuzumab ozogamicin (GO) was developed as a conjugate of an anti-CD33 antibody. After binding to the antigen on the surface of leukemic blasts, the antibody is internalized and binds to DNA leading to double-strand break and cell death [239]. In a randomized phase III trial, GO in combination with daunorubicin and cytarabine has improved EFS, OS, and RFS in s-AML cases [240-244]. The hedgehog pathway performs a crucial function in developing leukemic stem cells and procuring a drug-resistant phenotype in AML. Glasdegib (Daurismo™, Pfizer) drug

acts by repressing the hedgehog pathway in leukemic stem cells. In phase 2 multicenter randomized investigation, the combination of glasdegib with low dose cytarabine (LDAC) increased OS. It attained a higher CR rate than LDAC alone in newly diagnosed AML patients who were unfit for intense chemotherapy [245]. This led to its approval by US FDA in 2018 as a treatment for adults with newly diagnosed AML [246, 247]. Various drugs that can repress FLT3 kinases have been tested in AML. In April 2017, the US FDA approved Midostaurin, a small-molecule inhibitor of FMS-like tyrosine kinase 3 (FLT3), which works by inhibiting multiple receptor tyrosine kinases. In a randomized phase 3 trial, midostaurin was administered in addition to conventional chemotherapy extended OS, and EFS was significantly higher than placebo. Due to its survival advantage, the US FDA has approved its usage in combination with cytarabine and daunorubicin chemotherapy to treat AML patients with FLT3- mutation-positive [248, 249]. Gilteritinib is a profoundly effective inhibitor approved by the FDA in 2018 for relapsed AML patients with FLT3-mutation. This drug as a monotherapy conclusively enhanced survival in relapsed FLT3-mutated AML patients contrasted with conventional chemotherapy [250, 251]. Ivosidenib and enasidenib were approved by the FDA in 2018 for treatment of relapsed AML with IDH mutation, which raises myeloid differentiation and decreases blast counts by repressing IDH1 and IDH2 mutant, respectively. Enasidenib has been shown to target the IDH2 mutation selectively and gave an overall response rate (ORR) of 40.3% with survival advantages [252, 253]. On the other hand, Ivosidenib inhibited the IDH1 mutant enzyme and showed an ORR of 42% and CR of 22% in relapsed AML patients [254]. The possible advantage of emerging therapies such as chimeric antigen receptor T cells therapy targeting surface marker of AML, e.g., CD33, CD123, and FLT3, or agents targeting different pathways such as DNA repair, epigenetic modification, TP53 pathway assessed in patients with s-AML in future clinical trials [255]. MHC differentially expresses multiple leukemia-associated antigens on tumor cells. In clinical investigations, they have been examined to be used as a vaccine or dendritic cell-based therapy [256]. Immune checkpoint inhibitors are also of great interest and need to be investi-

gated, especially in s-AML treatment [257]. While the genomic complexity and the interaction of the various complex molecular aberrations in AML pose an immense challenge in specific risk stratification and targeted therapeutics [258, 259]. Several novel agents, such as immune checkpoint inhibitors, monoclonal or bispecific antibodies, have been developed as a new therapy for AML [260, 261]. The availability of various personalised inhibitors gives a better option of treatment to the patients. The genomic signature, age, co-morbid conditions and affordability are some of the major driving factors for the treatment of choice. The maintenance of balance between the toxicity and the therapeutic effects has always been a critical phenomenon. The prior exposure to chemotherapy and the illhealth created due to toxicity also plays a major role for the therapy selection in s-AML and t-AML.

Conclusion

The treatment of secondary and therapy-related acute myeloid leukemia remains one of the most formidable challenges in oncology today. Transformative molecular technologies have led to a more in-depth insight into the molecular and genomic landscape of driver mutations has unraveled the subclonal lineage of secondary acute myeloid leukemia. A better understanding of the molecular and genomic landscape of secondary and therapy-related AML will undoubtedly be the key to improved prognostication and monitoring. These advances have also paved the way for developing novel targeted and personalized therapeutics for individuals harboring the specific genetic signature. These advances also provide a rationale for drug development and repurposing the available drugs in combination with current treatment options.

Disclosure of conflict of interest

None.

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