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REVIEW

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Prognosis and treatment in acute myeloid leukemia: a comprehensive review

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous disorder that is characterized by clonal expansion of immature "blast cells" in the bone marrow and peripheral circulation, resulting in bone marrow failure and inefficient erythropoiesis. The identification of numerous recurrent genetic mutations such as NPM1, CEBPA, and FLT3-ITD has stratified AML into favorable, intermediate, and adverse-risk groups, respectively, along with a cytogenetic profile that carries a considerably different prognosis among these groups. For post-induction treatment, cytogenetics and genetic mutation testing continue to be vital prognostic tools. Despite advancements, including an increased understanding of biology and new drug targets, the cornerstone of treatment still consists of a combination of cytarabine- and anthracycline-based regimens. The majority of patients eventually relapse and die of the disease, especially the elderly population. This review describes the prognosis of different molecular markers and the major recent advancements in the treatment of AML.

Introduction

Acute myeloid leukemia (AML) is the most prevalent form of acute leukemia that typically affects older people and rises with age. Myeloid cell proliferation and differentiation lead to the accumulation of immature myeloid cells, which in turn causes gene mutations and chromosomal translocations [1]. Multipotential hematopoietic stem cells that have undergone malignant transformation and subsequently acquired many genetic mutations give rise to AML, an extraordinarily complex cancer. Genotoxic chemical exposure or an underlying hematologic condition may have contributed to its development although the exact cause is uncertain. Because leukemia cells are heterogeneous, the leukemic clone may alter from diagnosis to relapse during the disease [2]. Over the past 15 years, the enormous molecular heterogeneity of AML has become more noticeable, despite the genetic heterogeneity being known for more than 30 years [3]. Overall cure rates of younger patients are 35 to 40 percent, compared to older patients (over 60 years old), who were formerly considered incurable, although the prognosis is still dire [4].

Molecular mechanisms of AML

The formation of AML is linked to the accumulation of acquired genetic and epigenetic changes, mostly in hematopoietic stem and progenitor cells (HSPCs). These changes abnormally modify the cellular and molecular states of HSPCs, converting them into leukemia stem cells. It is known that leukemia-stimulating cells (LSCs) are cells that can self-renew, differentiate, and remain in a quiescent state. LSCs are at the top of a hierarchical cellular arrangement resembling normal hematopoiesis, which is evident in many AML patient samples [5]. Recent studies have demonstrated that AML blasts are the cause of normal hemopoiesis abnormalities. In actuality, the number of hemopoietic stem cells (HSCs) appears to be normal or even higher in AML patients. Peripheral blood neutropenia and thrombocytopenia are predicted by the expression of myeloproliferative leukemia, the thrombopoietin scavenging receptor, on AML

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blasts. AML exosome-directed microRNA trafficking to HSCs is also a contributing factor in the systemic loss of hemopoietic function [6].

Criteria used for stratifying AML based on genetic mutations and cytogenetics

A precise prognostic assessment requires an understanding of the intricate relationships between cytogenetic abnormalities and gene mutations, which have been revealed by improvements in the molecular mechanisms underlying AML oncogenesis. Consequently, a more comprehensive approach to risk classification has replaced the hierarchical one that just took into account gene mutations in cytogenetically normal AML.

A wider range of classifications identified by cytogenetic and mutational profiles was further expanded by the International Consensus Classification of AML, which updated the previous revised fourth edition World Health Organization (WHO) classification of AML and introduced new genetic entities and blast thresholds to define AML. Genetic aberrations have a predominant influence on the phenotype and outcome of the disease, so they are given priority when classifying AML disease. Other predisposing factors, such as therapy-related factors, prior myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MPN), and germline predisposition, are appended as qualifiers of the primary diagnosis (WHO Classification 2022) [7].

Cytogenetically, AML has three prognosis groups: the favorable, intermediate, and poor-risk groups. Balanced translocations with a favorable outcome are included in the first group. Both normal karyotype and various karyotypic anomalies are included in the intermediate prognosis category. A complicated aberrant karyotype in the poor-risk group contributes to a poor clinical outcome [8].

Prevalence and its impact on public health

AML, the most common kind of acute leukemia in adults, is diagnosed in about 80% of cases. AML predominantly affects older adults, with a median diagnosis age of 68 years [9]. The USA alone reports around 18,000 new cases a year, with an incidence of 5–6 new cases per 100,000 people for both men and women. Moreover, the incidence is higher in men than in women with a ratio of 5:3. Every year, around 10,000 (55.5%) AML patients die, accounting for almost 2% of all human malignant diseases [10]. The prevalence of AML has been rising in Europe over the past few years, with the UK having the highest incidence in 2017 with 4.05 cases per 100,000 people [11].

In general, the burden of AML increased over the last 28 years, suggesting that additional health resources may be required to address this issue related to the aging of the population. At this point, the majority of AML cases and deaths occurred in developed countries with high socio-demographic index (SDI). In addition, developing nations with middle- or low-middle SDI must act to reduce the rapidly rising burden of AML [12]. There was a substantial correlation found between the SDI and the incidence, death, and disability-adjusted life years (DALY) rates of AML in the older population, and these rates have been rising continuously. Particularly in regions with a high SDI, this had grown to be a major worldwide health concern [13].

French-American-British (FAB) classification

Based on morphology and cytochemical data, the French-American-British (FAB) categorization system represents the first attempt to describe different forms of AML. Since its establishment in 1976, the diagnostic technique has undergone significant evolution and progression, with the definition of eight subtypes ranging from M0 to M7. Along with morphology, immunophenotypic profiles, and clinical aspects, the World Health Organization (WHO) 2008 categorization of AML has also added chromosomal and molecular characteristics. This molecular and cytogenetic inclusion has shown subtypes of various disease outcomes [14].

Acute promyelocytic leukemia (APL) is usually identified by morphology, immunophenotype, and molecular/cytogenetic traits, while monocytic leukemias can be easily identified by morphological and immunophenotypic characteristics alone [15]. Despite recent advances in WHO classification, most developing countries still routinely utilize the FAB classification to classify AML because of the limitations of genetic analysis.

Genetic heterogeneity in acute myeloid leukemia

When compared to most solid tumors, AML has fewer overall genetic alterations and a lower frequency of chromosomal aneuploidy, but it nonetheless has a strikingly heterogeneous genetic profile. For AML patients, the prognosis and response to therapy are determined by the particular driver mutation in various combinations [16]. Both genomic and epigenomic changes include different types of cytogenetic abnormalities and somatic mutations, resulting in a range of morphological, immunophenotypic, cytogenetic, biomolecular, and clinical features [17].

Prognosis/risk stratification of established genetic alterations

Based on the presence or absence of known associations with AML and predicted functional alterations, various gene mutations were categorized into four groups. Class

I mutations involve signal transduction, class II mutations involve hematopoietic transcription factors, class III mutations involve epigenetic regulators, and class IV mutations involve tumor suppressors [18].

Class I mutations

Class I mutations that contribute to increased proliferation and/or survival of leukemic progenitor cells engage signal transduction pathways. Examples of these mutations include those that activate the FLT3-tyrosine kinase receptor or the RAS signaling pathway.

1. FLT3 (Fms-like Tyrosine Kinase 3) FLT3 is a class III receptor tyrosine kinase (RTK) that is crucial for cellular survival, differentiation, and proliferation. One of the most commonly found and clinically difficult groups of AML mutations is FLT3, which comes in two varieties: (1) internal tandem duplications (FLT3/ITD mutations) in the receptor's juxtamembrane domain and (2) point mutations in the tyrosine kinase domain's activation loop (FLT3/TKD mutations) [19].

The FLT3 gene mutations have been identified as important contributors to leukemogenesis among the several genetic changes linked to AML pathogenesis. These mutations cause constitutive activation of the FLT3 signaling, which results in dysregulated proliferation, impaired differentiation, and enhanced survival of leukemic cells. FLT3 mutations cause the equilibrium of hematopoietic cell populations to be disrupted, which promotes the growth of undifferentiated blasts and inhibits the development of normal hematopoietic cells. Furthermore, leukemic cells benefit from FLT3 mutations by blocking apoptosis, a mechanism that leads to programmed cell death. Cell death signals are suppressed when constitutively active FLT3 signaling activates anti-apoptotic pathways such as the PI3K/AKT and RAS/MAPK pathways. As a result, leukemic cells carrying FLT3 mutations exhibit increased resistance to programmed cell death, which prolongs their survival. FLT3-ITD mutations frequently exhibit adverse clinical characteristics, such as elevated leukocyte counts, increased blast percentages, and an increased risk of relapse. Although FLT3-ITD mutations are typically linked to a more severe phenotype, the prognostic significance of TKD mutations in AML is still controversial [20].

Even though both kinds of mutations constitutively activate FLT3, several studies have shown that patients with FLT3/ITD mutations have notably high rates of recurrence. This has prompted the development of tyrosine kinase inhibitors (TKI) that specifically target FLT3. Some of these compounds are still in preclinical development, while others have moved into phase I, II, and III clinical trials despite their promising activity [21]. FLT3 inhibitors have demonstrated encouraging outcomes in various phases, including sunitinib (phase II), lestaurtinib (phase II, III), tandutinib (phase I), quizartinib (phase I, II), sorafenib (phase I, II, III), midostaurin (phase I, II, III), and gilteritinib (phase I, II, III). However, the primary concern still stands regarding the development of resistance [22].

2. KIT Mutations in the KIT receptor tyrosine kinase are thought to be a risk factor that offers crucial prognostic data for adults with core-binding factor (CBF) AML harboring t(8;21) and inv (19). However, the prevalence and prognostic relevance of pediatric CBF AML is still little understood. Multiple prognostic indicators for age, gender, WBC count, c-kit mutations, and cytogenetic abnormalities of chromosome 22 were discovered earlier [23]. Additionally, it was noted that, in contrast to inv(16) AML, where KIT mutations have no discernible impact on prognostic outcomes, overall survival tended to be lower in cases of t(8;21) AML [24]. Thirty percent of inv(16) patients and 20 to 25% of t(8;21) cases have C-KIT mutations. Exons 17 and 8 are the most common locations for c-KIT mutations in CBF AML. While exon 8 encodes the extracellular part of the KIT, exon 17 encodes the activation loop of the kinase domain [25].

3. RAS The RAS pathway, which is most frequently found in NRAS, KRAS, and HRAS genes, is a family of membrane-associated proteins that controls signal transduction. It is the outcome of a ligand binding to a variety of membrane receptors. It has been identified as a crucial element of the proliferative drive in AML [26]. Up to 10–15% of de novo AML cases include activating mutations in the RAS gene, and 10% of AML patients have constitutive activation due to the NRAS mutation. While the HRAS mutation is uncommon in AML patients, the KRAS mutation is found in 5% of AML patients [27]. Although some smaller studies have found worse outcomes, NRAS and KRAS mutations have not been found to significantly affect outcomes in major adult and pediatric research [28].

4. JAK2 Oncogenes like JAK2 V617F can cause leukemia to evolve into a more aggressive subtype by activating the JAK2-STAT5 pathway, which significantly changes myeloid cell proliferation, self-renewal capacity, and apoptotic response. A previous study reported that patients with de novo AML had a low incidence (1%) and a considerably higher relapse rate in JAK2V617F patients with either inv(16) or t(8;21) [29].

5. PTPN11 The nonreceptor tyrosine phosphatase SHP2, which is encoded by PTPN11 on chromosome 12q24, is involved in signal transduction and is essential for the survival and growth of hematopoietic cells. Four to six percent of AML cases have PTPN11 mutations. The PTPN11 mutation is inversely associated with FLT3/

ITD but strongly linked with older age, normal karyotype, FAB M4/M5 subtypes, CD14 expression, and the NPM1 mutation.

It was also observed that patients harboring PTPN11 mutation had lower overall survival than those without, among NPM1-wild patients but not among NPM1-mutated patients [30]. AML patients with PTPN11 mutation have a poor prognosis and unique clinical and molecular features [31].

Class II mutations

Class II mutations that impact the function of transcriptional factors or specific components of the transcriptional co-activation complex cause hematopoietic stem and progenitor cells to self-renew. This results in abnormal acquisition and/or poor differentiation.

1. NPM1 One of the most common somatic abnormalities in AML is NPM1, especially in patients whose cytogenetics is normal. As a possible prognostic genetic marker, it is present in 20–30% of patients and is crucial for early diagnosis, risk assessment, and therapy recommendations. Instead of chromosomal translocations, the NPM1 frameshift mutation affects exon 12 which provides an alternative leukemogenic mechanism to disrupt cell-cycle regulation [32].

They most likely result from replication errors that are triggered by an illegitimate terminal deoxynucleotidyl transferase activity. The majority of NPM1 mutations are 4-bp insertions that frameshift in the last few C-terminal amino acids, resulting in the deletion of W288 and W290 (or W290 alone) and the generation of a new C-terminal NES. The cytoplasmic location of NPM1 mutants requires both modifications. NPM1 mutants have a dominating influence on NPM1wt, leading to its cytoplasmic delocalization through the formation of heterodimers between NPM1 mutant and NPM1wt. Therefore, all NPM1 mutations increase the amount of NPM1 mutants exported, suggesting that cytoplasmic delocalization is essential for leukemogenesis [33]. NPM1 mutations are associated with a favorable outcome and frequently coexist with FLT3 mutations, especially the ITD-type variants. While NPM1 mutations are less common in children, especially those under three years old, they are present in adult AML patients of all ages.

2. CEBPA (enhancer-binding protein α) The transcription factor requires CCAAT enhancer-binding protein alpha (CEBPA) for the normal development of granulocytes and its dysregulation linked to myeloid transformation in hematopoiesis. Patients with AML have dysregulated CEBPA function through a variety of pathways. It was hypothesized that leukemic cells from AML patients may have reduced or nonexistent CEBPA function, given its critical involvement in myeloid formation. Indeed, a growing body of research indicates that certain AML patients have important alterations in CEBPA function at different degrees. Most of the AML-CEBPA cases are sporadic and include somatic CEBPA mutations; nevertheless, 10% of people either inherit or produce de novo germline CEBPA mutations, which increase their risk of developing early-onset AML when somatic CEBPA mutations are acquired [34].

CEBPA mutations, which are observed in 5–14% of AML cases, exhibit favorable clinical outcomes. The majority of CEBPA mutant AML shows two mutations, which typically combine mutations in the N- and C-terminals of the basic leucine zipper (bZIP) gene [35]. The CEBPA mutation was most frequently found in AML patients with the M1 or M2 subtypes and those classified as cytogenetic with intermediate risk. Previous research has indicated that this mutation could be a primary alteration in the development of AML but does not trigger the disease progression [36].

3. RUNX1 The regulation of multiple hematopoietic genes, including those that code for growth factors, surface receptors, signaling molecules, and transcription activators, has led to the identification of RUNX1 as a major contributor to hematopoiesis [37]. Therefore, for distinct hematopoiesis in all lineages, RUNX1-regulated target genes are essential. Poor prognosis and distinct genetic characteristics are associated with RUNX1-mutated AML, which is linked to a complicated mutation cluster [38].

Class III mutations

Class III gene mutations act as epigenetic regulators in acute myeloid leukemia.

1. **DNMT3A** AML patients typically have DNMT3A mutations, which are associated with a poor prognosis; however, it is unknown how stable these mutations are during the disease. The DNMT3A mutation is inversely correlated with CEBPA mutations and strongly linked to higher WBC and platelet counts, older age, normal and intermediate-risk cytogenetics, NPM1, FLT3-ITD, PTPN11, and IDH2 mutations [39]. Patients with DNMT3A mutations are substantially more likely to have mutations in FLT3, NPM1, and IDH1.

2. IDH About 20% of adult patients with AML have recurrent mutations in their isocitrate dehydrogenase (IDH) genes, and these mutations become more common as patients age. In AML, IDH1 mutations are less frequent than IDH2 mutations and rarely do both the mutations co-occur in the same patient. The prognostic impact of IDH1 and IDH2 mutations in AML has remained controversial [40].

3. TET2 Through epigenetic changes, TET2 mutations likely alter the activities and development of

hematopoietic stem cells. Nonetheless, there is ongoing debate over the prognostic significance of the TET2 mutation in AML [41]. An earlier study, which demonstrated that TET2 loss-of-function mutations and IDH mutations are implicated in similar aberrant global hypermethylation, shows that mutations of the two genes may entail a common pathway in leukemogenesis. According to the earlier research, 13.2% of patients had the TET2 mutation, which was strongly associated with older age, increased white blood cell and blast counts, fewer platelets, cytogenetically normal AML, intermediate-risk cytogenetics, isolated trisomy 8, mutations in NPM1, and ASXL1 [42].

4. ASXL1 NPM1 mutations and additional sex comb-like 1 (ASXL1) mutations are mutually exclusive and inversely related to FLT3 internal tandem duplications. ASXL1 mutations confer an adverse prognostic factor and there is a markedly reduced complete response rate [43]. The prevalence of ASXL1 mutations in de novo AML is 6.5%, yet it is still unclear how exactly ASXL1 functions in normal hematopoiesis and how mutant ASXL1 affects the development of hematological malignancies.

5. EZH2 The po**lycomb** group complex's enhancer of zeste homologue 2 (EZH2), histone methyltransferase, is essential to the normal development of hematopoietic stem cells. Interestingly, only a few AML patients have EZH2 mutations. By promoting the development of leukemic cells in mice transplanted with MLL-AF9 altered granulocyte–macrophage progenitors (GMP), loss of EZH2 perturbs the development of AML and raises the possibility that EZH2 is carcinogenic in AML [44]. While EZH2 mutations are uncommon in AML, the pattern of these mutations is linked to a poor prognosis for AML patients undergoing HSCT [45].

Class IV mutations

In acute myeloid leukemia, class IV gene mutations function as tumor suppressors.

1. TP53 TP53 is one of the most frequently mutated genes in human cancers. In de novo AML, the frequency of TP53 mutations is 5–10%. The co-prevalence of complex aberrant karyotypes with TP53 mutations is slightly higher (69–78%) in AML [46]. AML patients with TP53 gene mutations typically have a poor prognosis due to their aggressive disease course and treatment resistance. The majority of TP53 gene mutations are located in exons 5 through 8.

2. WT1 Approximately 10% of AML patients have WT1 mutations. Wilms tumor 1 (WT1) may function as an oncogene since it has been shown to affect cell survival, proliferation, and differentiation; however, hotspots in the four zinc finger domains that comprise exons 7 and 9 indicate that it may also function as a tumor suppressor gene. Therefore, it is unclear how WT1 operates in tandem as a tumor suppressor gene and an oncogene. In AML, WT1 mutations have largely been linked to poor clinical outcomes [47].

Cytogenetics risk group

Cytogenetic analysis is the best predictor of survival and response to induction therapy in AML patients. In most AML patients, acquired clonal chromosomal abnormalities are detectable. AML has been linked to numerous recurrent chromosomal abnormalities to date. These discoveries cleared the path of identification of new genes, which provided an important understanding of normal hematopoiesis and its role in leukemogenesis [48].

Favorable

1. **RUNX1-RUNX1T1** Approximately 15% of AML patients and up to 40% of those classified as M2 subtypes by the FAB system, carry the t(8;21) translocation, which results in the RUNX1-RUNX1T1 fusion transcript. Compared to other forms of AML, t(8;21) AML typically manifests in early adulthood and appears to have a better prognosis. Studies on humans and mice have shown that leukemogenesis involves coordinated secondary processes and cannot be achieved solely by RUNX1-RUNX1T1 [49].

2. CBFB-MYH11 It is widely documented that inv(16) and t(16; 16) cytogenetic abnormalities are present in 5–7% of patients with AML and having aberrant eosinophils. Type A is detected in over 85% of patients, while type D and E fusions occur in 5–10% of patients, respectively [50]. AML with inv(16)/t(16;16) chromosomal abnormalities has a better prognosis; patients tend to live longer and experience longer durations of complete remission.

Acute promyelocytic leukemia (APL), a distinct subtype of AML

APL, which occurs in 5–10% of cases of AML, confers a good prognosis. It is defined by hematopoietic differentiation at distinct stages, leading to the accumulation of leukemic promyelocytes in the bone marrow. A chromosomal translocation of 15;17 results in the fusion transcript PML-RARα, which defines APL. The frequent presence of FLT3, WT1, NRAS, KRAS, ARID1B, and ARID1A genes and the lack of DNMT3A, NPM1, TET2, ASXL1, and IDH1/2 genes in APL are indicators of the existence of somatic mutations. Due to their susceptibility to ATRA- and ATO-based therapy, patients with APL have seen dramatic improvements in their outcomes over the past three decades since the development of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) [51].

Table 1 shows the prognostic significance of different genetic abreactions in AML.

Sensitivity and specificity of existing diagnostic methods for detecting genetic mutations associated with AML

In recent years, the diagnosis and follow-up of patients with AML have entered a new era as a result of significant advancements in our understanding of the disease's pathophysiology and advancements in technology. To diagnose AML, a multidisciplinary approach involving immunophenotyping, cytogenetics, and molecular research is necessary. Next-generation sequencing (NGS) gene panels are utilized to test for any genetic abnormalities that may have diagnostic, prognostic, or therapeutic relevance. Quantitative PCR/RT-PCR and multiparametric flow cytometry are now the most widely used approaches for measurable residual disease (MRD) evaluation in AML monitoring.

Diagnosis and monitoring MRD

While morphological blast count is still a key component of standard AML response criteria, both molecular and multiparametric flow cytometry (MFC) methods provide improved sensitivity and specificity for identifying malignant cells at diagnosis and following treatment.

Flow cytometry

The quickest methods to confirm the diagnosis when acute leukemia is suspected are bone marrow and peripheral blood morphologic and immunophenotypic investigations. The signature of myeloid commitment is myeloperoxidase (MPO) expression; however, it is not always seen. The absence of lineage-assigning antigens along with the presence of at least two additional myeloid-related antigens (such as CD13, CD33, or CD117) characterizes AML with little differentiation. MPO expression is frequently lost in monocytic AML, which is distinguished by certain markers such as CD11c, CD14, CD64, and lysozyme.

Molecular methods

The molecular profile of AML has been analyzed during the past ten years by genomic studies based on next-generation sequencing (NGS), which have revealed novel mutations, copy number variations, and recurring fusion genes. The primary drawback of NGS technology is that batching must be economical, which makes it impractical for the majority of diagnostic labs to report NGS results in less than a week. Therefore, standard PCR-based methods are still employed to screen for relevant markers such as NPM1, FLT3, IDH1/2, and fusion genes that require a quick turnaround time (three to five days). In particular, capillary electrophoresis is recommended for FLT3-ITD detection [52]. While morphological blast count is still a key component of standard AML response criteria, both

Table 1 Prognostic significance of different genetic abreactions in AML

Prognosis/risk stratification	Genetic aberrations	Prognostic significance	References
Class I mutations	FLT3-ITD	Unfavorable	[20]
	FLT3-TKD	Controversial	[20]
	KIT	Unfavorable	[24]
	RAS	Controversial	[26]
	JAK2	Unfavorable	[29]
	PTPN11	Unfavorable	[31]
Class II mutations	NPM1	Favorable	[33]
	CEBPA	Favorable	[35]
	RUNX1	Unfavorable	[38]
Class III mutations	DNMT3A	Unfavorable	[39]
	IDH(1 & 2)	Controversial	[40]
	TET2	Controversial	[41]
	ASXL1	Unfavorable	[43]
	EZH2	Unfavorable	[45]
Class IV mutations	TP53	Unfavorable	[46]
	WT1	Unfavorable	[47]
Cytogenetics risk group	RUNX1-RUNX1T1	Favorable	[49]
	CBFB-MYH11	Favorable	[50]
	PML-RARα	Favorable	[51]

molecular and MFC methods provide improved sensitivity and specificity for identifying malignant cells following treatment. Furthermore, specificity can be impacted by sample viability and sensitivity is directly correlated with the number of processed cells. MRD dependability is also correlated with sample quality.

Real-time quantitative PCR (qPCR)

Because of its ability to precisely and sensitively measure the mutational burden of many genetic abnormalities (10^{-5}–10^{-6}), real-time quantitative PCR (qPCR) was the first molecular tool to be established for MRD leukemia monitoring. The primary limitation of qPCR is its limited applications, even with its excellent sensitivity and specificity.

Digital PCR Droplet digital PCR (ddPCR)

Since each sample is first fractionated and the final analysis is based on thousands of individual measurements, ddPCR can be more accurate than qPCR, especially when it comes to quantifying diseases at very low levels. This allows for the absolute quantification of the amplified target of interest to be obtained without the need for a standard curve. This gives ddPCR the capacity to continuously and highly sensibly monitor patients' MRD.

Next-generation sequencing

The discovery of error-corrected NGS, which boosts sensitivity by using random barcodes or unique molecular identifiers, has made NGS a potentially helpful technique for monitoring MRD in AML. With a limit of detection of at least 10^{-3}, these methodologies enable the identification and elimination of artifacts caused by PCR amplification during library creation, resulting in the accurate and dependable monitoring of genetic targets.

Bone marrow failure and inefficient erythropoiesis in AML patients

AML is a fast-growing myeloid tumor that is identified by the clonal proliferation of primitive hematopoietic stem cells in the bone marrow called blasts. When compared to chronic and indolent leukemias, this expansion causes inadequate erythropoiesis and megakaryopoiesis, which clinically manifests as comparatively rapid bone marrow failure. This results in insufficient formation of red blood cells and platelets. Patients may have recurrent infections, anemia, easy bruising, heavy bleeding, headaches, and bone pain as a result of inefficient erythropoiesis and bone marrow failure. Depending on the severity of anemia, other symptoms like chest tightness, exhaustion, and generalized weakness may also be present. Such symptoms have a fairly quick time course, often lasting a few days to a few weeks [53].

Current treatments for AML

Despite the advancements in treatment over the past three decades, two-thirds of young patients and 90% of elderly patients still die of AML. Only patients with the rare subtype of APL have the best chance of recovering from AML. Recent advancements in medication development, allogeneic hematopoietic cell transplantation, and molecular prognostic markers offer enormous potential for a highly promising future [54]. Ten years ago, patients with newly diagnosed AML were given the "7 + 3 regimen," which consisted of cytarabine (ara-C) at a dose of 100–200 mg/m^2 daily for seven days combined with either daunorubicin (40–60 mg/m^2 for 3 days) or idarubicin (12 mg/m^2 for 3 days) as a continuous infusion for 3 days. The patients responded well to this treatment and were largely invariant. According to guidelines, many older patients are now recommended to get investigational medications at diagnosis since they represent the better potential for new treatments, which were previously considered to target certain abnormalities in AML blast [55].

Established treatments

To achieve complete hematologic remission (CR), eligible patients with AML initially receive induction treatment. Relapse inevitably occurs if treatment is discontinued because MRD frequently exists in CR patients. To eliminate any residual disease and achieve long-lasting remission, consolidation therapy with intense chemotherapy is administered as soon as the patient recovers from induction [1]. Over the past 40 years, the prognosis for this traditional upfront treatment has remained dire, even though many promising agents have advanced to clinical studies. For many years, remission induction regimens—which contain an intense 7-day cytarabine induction with 3 days of anthracycline (7 + 3)—were the standard of care for AML patients followed by consolidation chemotherapy either with or without hematopoietic cell transplantation (HCT). The patient's age and overall health have a significant impact on the therapy dosage. Compared to older patients who are over 60, younger patients undergo the most intense chemotherapy. When treating individuals less than 60 years of age, cytarabine, anthracycline, and cladribine are typically used during the induction phase. Fludarabine and topotecan are the recommended medications for people over 60 and/or with poor health. In contrast to induction therapy, consolidation therapy involves the administration of a single drug at a very high dosage, generally cytarabine, for adult patients. This medication is administered over 5 days and is repeated every four weeks for a total of three or four cycles. The number of treatment cycles is lowered from four to one

or two for elderly and/or sick patients while maintaining a high dosage in these cases [56]. APL treatment in AML usually varies from most other types of treatment. Since the discovery of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), APL in humans has changed from a highly lethal disease to one that is extremely treatable. ATO/ATRA was added to a chemotherapy-free regimen in de novo APL, and this proved to be beneficial. This led to the development of a novel genetically targeted cancer treatment, which is now the conventional first-line treatment for younger adult patients who are not at high risk [57].

Novel agents

Currently, several novel drugs are undergoing advanced research and are categorized into various types according to their mode of action, including small molecule inhibitors, targeted treatments, and cytotoxic agents.

1. Cytotoxic chemotherapy agents

Vosaroxin Vosaroxin is an intercalating drug produced from quinolones that inhibits topoisomerase II, resulting in site-specific damage to DNA. It possesses various advantageous features that may help treat AML. Topoisomerase II inhibitor vosaroxin selectively breaks DNA strands at certain locations, causing G2 arrest and apoptosis in cells. A phase III clinical trial is being conducted to investigate it for AML. Numerous trials have demonstrated vosaroxin's effectiveness in treating AML, especially when combined with intermediate-dose cytarabine [58].

CPX-351 The cytotoxic medications cytarabine and daunorubicin are packaged in liposomes at a 5:1 molar ratio in CPX-351, a liposomal formulation that shields them from metabolism. When compared to the same medications given normally in the animal model, it demonstrated greater efficacy. Additionally, it has been demonstrated that in vitro, the ratio is slightly antagonistic and maximally synergistic [59].

2. FLT3 inhibitors The FDA has not yet approved the majority of FLT3 inhibitors, but some of them are being tested in preclinical and clinical settings to treat patients with FLT3/ITD mutations. Though Rydapt (midostaurin) was approved by the FDA in newly diagnosed adult AML patients in combination with cytarabine and daunorubicin, a combination known as 7 + 3, based on the dosing schedule, followed by cytarabine consolidation. Xospata (gilteritinib) was recently approved by the FDA as a single agent for relapsed or refractory AML.

Several FLT3 small molecule inhibitors have shown conflicting outcomes in clinical trials. Lestaurtinib, tandutinib, sunitinib, and sorafenib are examples of first-generation FLT3 inhibitors that reduce the anti-leukemia effectiveness by decreasing the number of leukemia blasts in the blood and bone marrow and increase toxicity when taken as a single medicine. Clinical trials are being conducted on second-generation FLT3 inhibitors, which include quizartinib and crenolanib. These inhibitors are powerful and selective [60]. Even though FLT3 inhibitors have positive clinical effects, people with FLT3/ITD acquire resistance, which limits the length of the response. New mutations in FLT3 inhibitors arise as a result of this resistance.

3. Isocitrate Dehydrogenase (IDH) Inhibitors Oral inhibitors such as ivosidenib and enasidenib target mutant IDH1 or IDH2, respectively. By inhibiting the conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG), these medications trigger physiological reactions by differentiating malignant cells. These medications have demonstrated encouraging results when used as monotherapy and are linked to strong overall response rates. Both medications are licensed to treat IDH1/2-mutated AML that has relapsed or is resistant, and they are now being investigated in conjunction with conventional induction and consolidation chemotherapies [61].

4. Nuclear Exporter Inhibitors The current combined therapy for AML is hazardous to normal tissues and frequently fails to produce long-term remissions, underscoring the need for new therapeutic approaches. Compounds known as selective inhibitors of nuclear export (SINE) have been identified as a new, powerful, and effective treatment approach against resistance to conventional chemotherapy. Inhibition of the nuclear export protein exportin 1 (XPO1), which facilitates leucine-rich nuclear export signals necessary for RNA transfer, is one attractive cellular pathway with therapeutic potential [62]. More than 200 proteins are transported by XPO1 inhibitors, many of which are tumor suppressors that are essential for controlling the cell cycle like p53, NPM1, and NFκβ. Selinexor, a first-generation SINE, has demonstrated therapeutic efficacy in trials with minor side effects such as anorexia, fatigue, nausea, and myelosuppression. Second-generation SINE KPT-8602 has demonstrated enhanced tolerance in patient-derived rodent models because of its lack of central nervous system penetration [63].

5. Emerging immunological therapies for AML One of the main issues with traditional cancer treatments is their incapacity to eradicate the cancer cells that remain after chemotherapy and exhibit resistance to it. This has led researchers to investigate alternative therapeutic modalities including immune-based therapies or immunotherapies. Immuno- and cell-based treatments for AML were inspired by the expression of CD markers (such as CD13, CD47, and CD123) in AML blasts; these treatments are presently undergoing encouraging clinical trial outcomes. A cytotoxic antibiotic called

gemtuzumab ozogamicin (GO) was previously approved by the FDA for use as a potent and selective humanized anti-CD33 monoclonal antibody conjugated with calicheamicin. However, the drug was later withdrawn due to higher death rates during induction linked to a higher incidence of veno-occlusive disease (VOD). Phase 1 trials did not report any case of VOD using vadastuximab talirine (SGN-CD33A), an anti-CD33 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer to the cysteine residues [64]. The discovery of leukemia-associated antigens has led to the introduction of several immunotherapeutic development strategies, as AML cells can be fully cytotoxically targeted by activating T and NK cells. One of the most promising cytokines to focus on in immunotherapy is interleukin-2. However, its use has been restricted because of the erratic hematological reactions and toxicity linked to high dosages in clinical trials. To address this issue, a cytokine therapy combination, such as combining IL-2 and IL-12, is being tested [65].

6. Mitochondria-targeted therapies Research has indicated that AML cells and stem cells have elevated oxidative phosphorylation activity, which partly reduces reserve capacity in their respiratory chains as compared to normal hematological counterparts. Effective treatment for AML may involve mitochondrial translation, mitochondrial DNA replication, or mitochondrial proteases that target respiratory chain activity or other mitochondrial processes [66]. IDH mutations are linked to altered mitochondrial metabolism in AML patients. This finding also showed that various metabolites are involved in glucose metabolism and were found to have prognostic significance in AML patients who are cytogenetically normal. Mitocans also referred to as mitochondria-targeted anticancer drugs, include thiol redox inhibitors, lipophilic cations, voltage-dependent anion-selective channels, mimics of B cell lymphoma 2 (Bcl-2), drugs that act on mitochondrial DNA, agents that affect the efficiency of the TCA cycle, drugs that target the electron transport chain, etc. These drugs can circumvent certain types of drug resistance by acting on mitochondria. Therefore, mitochondria have become a key target in the development of combinational treatments for the treatment of AML patients.

7. Murine double minute 2 (MDM2) Inhibitors MDM2 has a significant role in suppressing the expression of the p53 tumor suppressor. When MDM2 is inhibited, p53 and its tumor suppressor properties may be lost, leaving normal cells more vulnerable to oncogene-mediated mutations and transformation. In AML, MDM2 inhibition is a potentially effective therapeutic target. The first MDM2 inhibitor to go through clinical testing was RG7112. However, RG7388, also known as idasanutlin, is a second-generation MDM2 inhibitor that was more successful than RG7112 in both in vitro and in vivo experimental models and could produce the anticipated biological effects at much lower concentrations [67].

Treatment for elderly acute myeloid leukemia

Milder treatments are ineffective in treating this aggressive blood malignancy, and older individuals with AML are frequently not healthy enough to withstand the initial conventional chemotherapy regimen. In addition, when choosing traditional cytotoxic induction therapy for elderly patients, considerations such as age, comorbidities, reduced organ function, and performance level are crucial. For patients 75 years of age and older, as well as those with other underlying medical conditions that preclude them from receiving the intensive chemotherapy regimen that is still the standard initial treatment for AML, the Food and Drug Administration (FDA) has approved two medications: venetoclax (Venclexta) and vlasdegib (Daurismo) for these elderly patients.

1. Venetoclax (Venclexta) Venetoclax, a BCL-2 selective inhibitor, has been approved by the FDA. When combined with hypomethylating drugs, this new therapy option for AML seems to be more successful. Additionally, venetoclax was recently approved by the FDA to treat people with newly diagnosed AML who are 75 years of age or older or who have comorbidities that prohibit the use of conventional chemotherapy in conjunction with azacitidine, decitabine, or low-dose cytarabine [68].

2. Glasdegib (Daurismo) An oral, strong, and selective inhibitor of the Hedgehog signaling pathway's activation—which is linked to several cancers—is called Glasdegibs. Glasdegib and low-dose cytarabine (LDAC) have just been approved by the FDA to treat newly diagnosed AML in persons 75 years of age or older with comorbidities that eliminate the need for extensive induction therapy [69].

Potential role of immunotherapy in the treatment of AML and its limitations

Understanding the pathophysiology and chemoresistance of hematological malignancies, the function of immunological checkpoint inhibitors in impeding effective antitumor immune responses, characterizing human tumor antigens, and introducing therapeutic monoclonal antibodies (mAbs) in clinical oncology have given researchers a variety of therapeutic tools to be utilized as a platform for designing rational immunotherapy strategies for AML. Immunotherapy is regarded as a promising approach to managing and curing the disease. It may represent a significant advancement in the management of leukemia, particularly for those patients who are not eligible for intense chemotherapy [70]. Immunotherapies

have attracted interest due to their potential to overcome acquired and primary resistance, which is crucial for patients with relapsed or refractory AML. These treatments mostly consist of adoptive T cell therapy, antibody-based immunotherapies, immune checkpoint inhibitors (ICIs), and cancer vaccines [71].

However, the execution of effective treatment is complicated by the immune escape capabilities of AML blasts in addition to host and disease heterogeneity. The identification of extrinsic and intrinsic resistance mechanisms and the development of counterstrategies are necessary to improve the immunotherapeutic toolbox for AML (Table 2).

Challenges associated with predicting treatment response

Anticipating the treatment response of AML patients is still quite difficult, even with some hopeful achievements. Only a small number of targeted medicines have been discovered for AML because of the extremely complicated patterns of mutations and genetic abnormalities within and between patients. The effectiveness of the AML therapy may be reduced by genetic complexity and may make patient stratification inaccurate. For example, in AML patients with FLT3+, >40% do not respond to midostaurin, but >30% of FLT3-cases may benefit from the same drug. The choice of therapy in clinical practice is frequently subjective, determined by the clinician's experience or intuition due to the intricacy of AML and its possible treatments. These imply that a reliable computational prediction model for each AML patient is still required to achieve a unique treatment response [72].

Impact of age on the prognosis and treatment outcomes of AML

AML, or adult-onset acute leukemia, is the most often diagnosed type of leukemia; elderly populations have an even greater incidence and mortality rate from this disease. Over time, as the global population ages, the prevalence and impact of AML increase. This tendency is particularly noticeable in developed countries. AML is characterized by notable variations in age-based prognoses, disease control strategies, and treatment methods. There is variation among groups in the treatment modalities, rates, and results [73]. The incidence of AML rises with age, with those 65 and beyond having an almost tenfold higher incidence (12.2 vs. 1.3 per 100,000) than those under 65. AML typically results in mortality within a few months of diagnosis if left untreated. Elderly people frequently are unable to tolerate the major side effects of conventional cytotoxic treatment for AML. As a result, the 5-year survival rate for elderly patients is only 2% and has not increased significantly over the last 20 years. The poor performance status of elderly patients, the prevalence of high-risk cytogenetic abnormalities, the common expression of multidrug resistance phenotypes, and the history of hematologic disorders may all contribute to their adverse prognosis [74].

Challenges of treating patients with relapsed or refractory AML

Treating refractory or relapsed AML has been a Sisyphean task for hematologists for decades. Relapse is the most frequent reason for treatment failure. In earlier studies with long-term follow-up and more contemporary series, the 5-year overall survival (OS) for adult patients with AML (non-acute promyelocytic leukemia [non-APL] AML) following disease relapse is only 10%. Moreover, around 20% of patients exhibit primary induction failure. Various prognostic factors impact the outcome of AML patients after relapse, including age, cytogenetics at initial diagnosis, duration of first complete remission, allogeneic stem cell transplant performed during first complete remission, and presence of multiple molecular aberrations.

The only effective treatment available at this time is allogeneic hematopoietic cell transplantation (HCT), with an estimated overall survival (OS) of 15–25% three to 5 years after transplant. However, the recent approval of several novel agents has changed the treatment paradigms for AML which had been in use for nearly fifty years. Reexamining the strategy for treating relapsed or refractory AML is made possible by the current therapeutic landscape [75]. Hopefully, shortly, we will be able to treat patients with relapsed AML more effectively by

Table 2 Different types of immunotherapy

Type of immunotherapy	Examples	References
Adoptive T cell therapies	Chimeric antigen receptor T (CAR-T) cells, TCR-T	[71]
Antibody-based immunotherapies	Monoclonal antibodies, bispecific antibodies, antibody–drug conjugates	
Immune checkpoint inhibitors (ICIs)	CTLA-4 inhibitions, PD-1/PD-L1 inhibitors, nivolumab, pembrolizumab, durvalumab, avelumab	
Cancer vaccine	Peptide vaccines, dendritic cell vaccines	

identifying specific targets and developing techniques to overcome these aberrant processes.

Recent advances in targeted therapies in AML

Many targeted therapies for AML have recently been approved, marking the culmination of fifty years of therapeutic development work on the disease. Nevertheless, there is still a need for molecular therapies that can heal this heterogeneous disease and provide long-term remissions. Previously, a wide range of molecules were developed to address subtypes of AML, primarily in the relapsed and refractory situation. The long-term effectiveness of these small molecule treatments as monotherapies has been undermined by drug resistance. The combination of azacitidine with the small molecule venetoclax has just been introduced, and it has increased response rates and overall survival in older persons with AML when compared to chemotherapy. Nevertheless, this regimen is not curative and is still constrained by cytotoxicity. Therapy that specifically targets AML defects while protecting healthy cells and eradicating leukemia-initiating cells is therefore in high demand [76]. Many potential novel therapeutic agents are being explored in ongoing clinical trials as a result of advances in drug discovery, genomics, and epigenetics (Table 3). To find the most effective way to include these new drugs in the standard clinical therapy of AML, more research will be required. One of the most significant potential therapy options for AML in the future may be epigenetic treatments.

A case study to illustrate the clinical implications of different molecular markers

AML is a highly variable category of hematological malignancies defined by inhibited apoptosis of myeloid hematopoietic stem cells, poor differentiation, and aberrant clonal proliferation. FLT3, NPM1, IDH2, DNMT3A, NRAS, and compound mutations are the most frequently occurring mutations in AML. AML patients with concomitant mutations typically have a poor prognosis, as several clinical trials have shown earlier. Concurrent mutations in DNMT3A, FLT3-TKD, and IDH2 are uncommon, have not been documented in the literature before, and are linked to a dismal prognosis in this patient. China is a big nation where tuberculosis (TB) is prevalent, and many people with leukemia also have concurrent TB.

It is worth investigating how to manage AML patients with active TB, as this is more difficult in the clinical setting. Venetoclax + Azacytidine is a routinely used treatment for AML with FLT3 and IDH2 mutations and is now recommended for patients not suitable for intense chemotherapy. In China, homoharringtonine (HHT), which is more powerful against gene alterations such as FLT3, is a mainstay of combination chemotherapy regimens for AML. The AML patient that followed also had active tuberculosis and mutations in DNMT3A, FLT3-TKD, and IDH2. Under the pretext of active anti-TB treatment, this patient had rapid chemotherapy using the HVA (homeharringtonine + venetoclax + azacytidine) regimen. Additionally, the patient had very great remission, which made a bone marrow transplant possible. Therefore, clinicians should balance the interaction between anti-TB and anti-leukemia medications and be more informed about the diagnosis and course of treatment for this kind of patient as a result of the therapeutic study in this case [77].

Potential side effects and toxicities associated with current treatment regimens

The ability to treat AML in the outpatient setting with novel agents of equal or greater efficacy than 7 + 3 has been transformative for clinicians. However, the recent introduction of myriad targeted therapies for AML has led to new hope but also brought new challenges in managing the disease.Though there is a lot of enthusiasm, the truth is that many patients are still frail and susceptible to side effects from treatment. Each of these agents/drugs

Table 3 Target and mode of action of selective and non-selective drugs in AML

Selective inhibitor	Target	Mode of action	Non-selective inhibitor	Target	Mode of action	References
CD33-Targeted ADCs	CD33 Target	Targeted delivery of toxic drug	Idarubicin	Anthracycline	Cytotoxic	[76]
Flavopiridol	CDK Inhibitor	Cell-cycle arrest and apoptosis	Daunorubicin	Anthracycline	Cytotoxic	
Eltanexor	XPO1 Inhibitor	XPO1 inhibition	Mitoxantrone	Anthracycline	Topoisomerase inhibitor	
Sorafenib	FLT3 Inhibitor	FLT3-ITD inhibition	Guadecitabine	Hypomethylation	DNA Methyltransferase inhibition	
Venetoclax	BCL-2 Inhibitor	Anti-apoptotic Protein inhibition	Cytarabine (CPX351)	Pyrimidine analog	DNA polymerase inhibition	

has a different mode of action and toxicity profile such as hepatotoxicity, nephrotoxicity, embryo-fetal toxicity, neurologic complications, gastrointestinal toxicity, pulmonary toxicity, hematologic toxicity, and immunologic toxicity. It is necessary to comprehend the best ways to manage the side effects of these drugs to translate the outcomes of clinical trials into better outcomes for these people and therefore prolong and preserve quality of life [78].

Limitations of current treatment strategies and potential avenues for improvement

The diagnosis and treatment of AML frequently encounter social, operational, and economic challenges. Patients with AML may encounter obstacles such as financial difficulties during diagnostic testing or delays in diagnosis (Fig. 1). The management of relapsed/refractory disease and allogeneic stem cell transplantation appears to be associated with high economic burden. Delays in starting treatment and the unavailability of newer treatment options in many countries may have significant outcomes during AML management. From straightforward to intricate, there are several options available, including enhancing the infrastructure of healthcare facilities, minimizing the time needed for diagnostic test results, assisting centers in communicating about quick access to certain treatment options like clinical trials and allo-SCT, broadening the scope of treatment covered by health insurance plans, and increasing access to cutting-edge treatment options in underdeveloped countries.

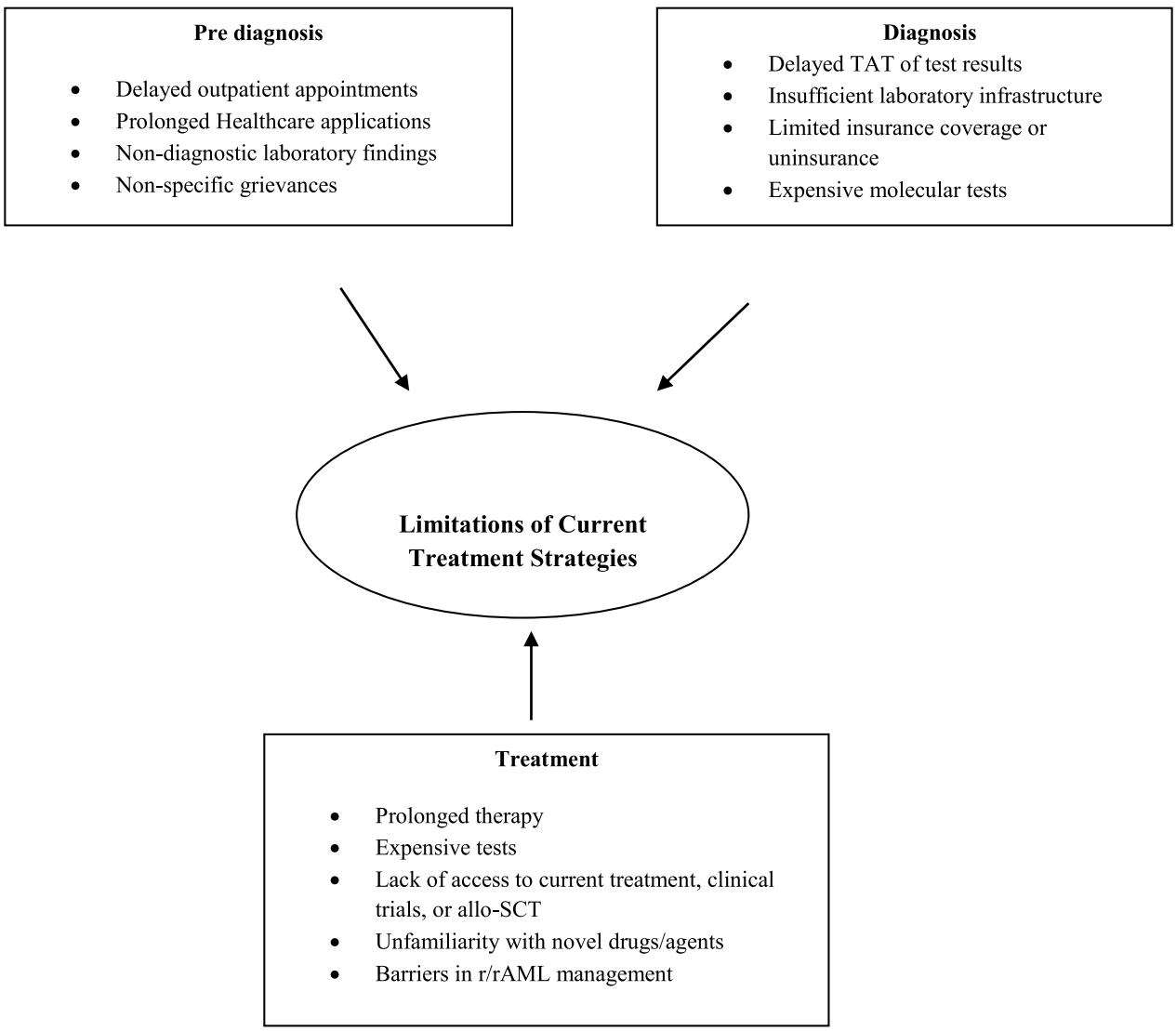

Fig. 1 Limitations of current treatment strategies

Importance of multidisciplinary approaches involving hematologists, geneticists, and other specialists in managing AML

All advancements in managing AML necessitate a multidisciplinary group or network to handle AML patients in a way that provides comprehensive patient care through planning and organization. Hematologists, specialized nurses (oncology nurses; hematology nurses), laboratory specialists (cytogenetics specialists; microbiologists, etc.), physiotherapist, bone marrow transplant specialists, psychologists, clinical pharmacists, social workers are not only expected to provide simple access to specialty care that may be necessary for AML patients, promote effective and comprehensive patient-cantered management, enhance cross-specialty collaboration to further enhance AML understanding and management but also take on more testing for new tests and increased patient and family test volumes, take into account the expediency of TATs in conjunction with clinical processes for evaluation, counseling, and donor clearance services.

Emerging therapies to address the unmet needs in AML treatment

The standard treatment for AML consists of cytarabine and anthracycline regimens followed by consolidation therapy, which may include allogeneic stem cell transplantation to prolong remission. The use of novel and efficient target-directed therapies has significantly increased in recent years. Examples of these therapies include isocitrate dehydrogenase (IDH) and mutant FMS-like tyrosine kinase 3 (FLT3) inhibitors, venetoclax, an inhibitor of B cell lymphoma 2, and glasdegib, an inhibitor of the hedgehog pathway.

Venetoclax showed composite response rates in older patients when combined with a hypomethylating drug or low-dose cytarabine; these rates are comparable to those observed in similar groups with typical induction regimens, but they may have reduced toxicity and early mortality. Early-stage trials have demonstrated encouraging clinical activity for venetoclax doublets combined with inhibitors targeting FLT3 and IDH mutations, based on preclinical findings suggesting synergy between these targeted treatments and venetoclax. Currently under evaluation are triplet regimens comprising the FLT3 or IDH1/2 inhibitor and the hypomethylating agent venetoclax; the TP53-modulating agent APR-246 and magrolimab; inhibitors of myeloid cell leukemia-1; or immune therapies like CD123 antibody–drug conjugates and programmed cell death protein 1 inhibitors. Such triplets are expected to further improve remission rates and, more crucially, remission durations and survival when used in the appropriate patient subsets [79].

Role of supportive care measures in enhancing patient quality of life during and after treatment

AML treatment options are changing for elderly people. Since many treatments are equally effective, how they affect the quality of life (QoL) is a key differentiator. The idea of health-related quality of life (HRQoL) is multidimensional and encompasses domains of physical, mental, emotional, and social functioning. AML or its treatment may have an impact on each domain alone or in combination with others, which may then have an impact on overall QoL. The components of geriatric assessment, a multidisciplinary diagnostic procedure that finds older persons' underlying weaknesses and directs subsequent management options, overlap with those of HRQoL. HRQoL questionnaires might be general, symptom-focused, leukemia-specific, or cancer-specific. Research from both therapeutic and observational cohorts indicates that throughout both intense and lesser- intensity interventions, HRQoL either improves or remains stable. However, HRQoL is not usually included in AML treatment trials [80].

Conclusions

AML is a very complex, heterogeneous, and challenging hematological malignancy as demonstrated by the inclusion of genetic and cytogenetic qualifiers in the updated WHO and ICC classification systems. Despite the advances that have been made in our understanding of the molecular mechanism and prognostic impact of AML gene mutations, the greatest challenge in the treatment of AML needs effective and targeted therapies targeting relapsed disease. Newly developed chemotherapies, targeted cancer therapies, and immunotherapies have all been shown to be clinically effective when used as single agents. However, this is probably just the start of treatment strategies, as more combinations of kinase and proteasome inhibitors, chemotherapy, and epigenetic-targeted therapeutics are being developed to treat various AML subtypes. AML treatment in the future requires the rational combination of these agents, and hence, massive efforts are necessary for precision medicine. When defeating diseases, both patient status and disease should be considered as key factors, and more combinatorial and biomarker-driven early-phase clinical trials should be incorporated. We are entering in a new era of precision oncology, where molecularly informed data will allow us to personalized treatment plans based on the pathobiology of the patient. Future studies should concentrate on AML patients to determine their early needs for palliative care and to find out if providing palliative and supportive care to patients with AML who are receiving standard or novel therapies could improve their quality of life and clinical outcome.

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Declarations

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