Review

Latest Insights and Progress in the Clinical Management of Elderly Patients with Acute Myeloid Leukemia: From Genetic Advancements to Targeted Treatments

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Latest Insights and Progress in the Clinical Management of Elderly Patients with Acute Myeloid Leukemia: From Genetic Advancements to Targeted Treatments

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Abstract: Acute myeloid leukemias (AMLs) are heterogeneous hematologic cancers that occur prevalently in older patients as the result of a complex pathobiology. The clinical outcomes of older patients with AML, often unsuitable for intensive chemotherapy and allogeneic stem cell transplantation, are generally disappointing. However, recent advances in understanding molecular pathogenesis and other biological mechanisms recognized in AML development and progression have changed the treatment approach, especially for this particularly vulnerable category of patients. Indeed, non-intensive biologically tailored approaches, such as combining venetoclax with hypomethylating agents, have changed the therapeutic paradigm in this field. Moreover, other promising compounds and treatment strategies are currently under advanced clinical development. This article delves into the latest biological understanding and therapeutic advances in the clinical management of older AML patients into new conceptual frameworks that progressively transform the clinical practice in this challenging setting.

Keywords: genomic profiling; targeted therapies; hypomethylating agents; venetoclax-based combinations; intensive chemotherapy; transplantation clinical trials; supportive care; quality of life

1. Introduction

Acute myeloid leukemias (AMLs) are blood cancers due to the uncontrolled proliferation of myeloid blasts infiltrating the bone marrow (BM), the peripheral blood (PB), and other organs or tissues [1]. AMLs are genetically diverse and heterogeneous age-related diseases [2], presenting the affected older patients with peculiar biological and molecular features differing from those recorded in younger individuals [2,3]. Of note, the incidence of AMLs prevails in the former population, with a median age of 68 years at diagnosis [4]. Clinical outcomes are very dismal in this setting, with a disappointing overall survival (OS) of about 10% [4]. However, this finding refers to traditional treatment approaches, relying on intensive chemotherapy (ICT) regimens followed by allogeneic stem cell transplantation (SCT), for which most older patients are unsuitable due to the accompanying comorbidity burden, personal vulnerability, and socioenvironmental frailties. However, recent insights into disease pathobiology have provided a better understanding of genomic underpinnings and other important underlying biological mechanisms involved in AML development, clonal expansion, and progression [2]. This increased knowledge of AML genomics (chromosomal abnormalities and molecular mutations) [6] has led to the prominent role of molecular characterization in prognosis and treatment decisions [1,4]. In addition, advances in genomic understanding have prompted the development of updated classification systems (Tables 1 and 2)

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[9,10], such as the fifth update to the WHO Classification of Haematolymphoid Tumors (WHO-5) [9] and the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemia [10], reaffirming the importance of genetic alterations as critically diagnostic qualifiers with a prognostic impact [9–12] beyond the blast counts.

Table 1. WHO-5 [9] and ICC [10] classifications of AMLs and their comparison.

Blast threshold	WHO-5	ICC	Blast threshold
20%	AMLs with DGA	APL with t (15;17) (q24.1; q21.2)/PML: RARA. APL with others RARA rearrangement	10%
	APL with PML: RARA fusion gene.		
	AML with RUNX1:RUNX1T1 fusion gene.	AML with t (8/21) (q22; q22.1) / RUNX1:RUNX1T1 fusion gene.	
	AML with CBFB: MYH11 fusion gene.	AML with inv (16) (p13.1; q22) or t (16;16) (p13.1; q22)/CBFB: MYH11.	
	AML with KMT2A rearrangements.	AML with t (9;11) (p21.3; q23.3)/ MLLT3:KTM2A or other KMT2A rearrangements.	
	AML with DEK: NUP214 fusion gene.	AML with t (6;9) (p22.3; q34.1)/ DEK: NUP214.	
	AML with MECOM rearrangements	AML with inv (3) (q21.3q;26.2) or t (3;3) (q21.3; q26.2)/GATA: MECOM (EV1) or other MECOM rearrangements	
	AML with other rare translocations (NUP98; RBM15; MRTF1, DEK: NUP214)		
20%	AML with BCR: ABL1 fusion gene	AML with t (9;22) (q34.1; q11.2) / BCR: ABL1	20%
No cut-off.	AML with NPM1 mutation.		10%
20%	AML with CEPA mutation.	AML with bZIP CEBPA in-frame mutation.	20%
	Not classified	AML with TP53 mutation.	20%
20%	AML with MDS-related genetic abnormalities	AML with MDS-related genetic abnormalities (ASXL1; BCOR, EZH2; RUNX1; SF3B1; SRSF2; STAG2; U2AF1, ZRSR2). AML with MDS-related cytogenetic alterations.	20%
20%	AMLs defined by differentiation Table 2	AML NOS	20%
	Myeloid sarcoma		

WHO-5: 5th update to the WHO Classification of Haematolymphoid Tumours; ICC: International Consensus Classification of Myeloid Neoplasms and Acute Leukaemia's; DGA; defining genetic abnormalities, APL: acute promyelocytic leukemia; PML: Promyelocytic Leukemia gene; RARA: Retinoic Acid Receptor Alpha gene; AML: acute myeloid leukemia; RUNX1: runt-related transcription factor 1; RUNX1T1: runt-related transcription factor 1; translocated to, 1 (cyclin D-related); CBFB: core binding factor beta; MYH11: Myosin Heavy Chain 11; KMT2A: (Lysine methyltransferase 2A; MLLT3: Myeloid/Lymphoid or Mixed-Lineage Leukemia Translocated To Chromosome 3 Protein; DEK: DEK Proto-Oncogene; NUP214: nucleoporin 214; MECOM: myelodysplasia syndrome 1 (MDS1) and ecotropic viral integration site 1 (EVI1) complex locus; GATA2: GATA Binding Protein 2; NUP98: nucleoporin 98, RBM15: RNA binding motif protein 15; MRTF1; myocardin-related transcription factor 1; BCR: breakpoint cluster region protein; ABL:Abelson murine leukemia viral oncogene homolog 1 : NPM1: nucleophosmin 1;CEPA;CCAAT enhancer binding protein alpha; bZIP: basic leucine zipper region;TP53:tumor Protein P53;MDS: myelodysplastic syndromes; ASXL1:additional sex comb-like 1 ; BCOR:

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Back central optic radius ; EZH2: Enhancer of zeste homolog 2; SF3B1: splicing factor 3b subunit 1; SRSF2: serine and arginine rich splicing factor 2; U2AF1: U2 small nuclear RNA auxiliary factor 1; ZRSR2: zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2; NOS; not otherwise specified.

Table 2. WHO-5: AML classification by differentiation features and diagnostic markers [9].

AML subtype	Diagnostic criteria
AML with minimal differentiation.	Cytochemistry: MPO and SBB negative blasts (<3%).
	MFC: expression of myeloid antigens (two or more), such as CD13, CD33, and CD117.
AML without maturation.	Morphology: <10% maturing myeloid progenitors of the BM nucleated cells.
	Cytochemistry: ≥ 3% blasts positive for MPO or SBB and negative for NSE.
	MFC: expression of myeloid antigens (two or more), such as MPO, CD13, CD33, and CD117.
AML with maturation.	Morphology: >10% maturing myeloid progenitors and < 20% of the monocytic lineage cells of the BM nucleated cells.
	Cytochemistry: ≥ 3% blasts positive for MPO or SBB.
	MFC: expression of myeloid antigens (two or more), such as MPO, CD13, CD33, and CD117.
Acute basophilic leukemia.	Morphology: blasts and mature/immature basophils.
	Cytochemistry. Basophils: metachromasia on toluidine blue staining. Blasts: negative for MPO, SBB, and NSA.
	MFC: negative CD117 (to exclude mast cell leukemia).
Acute myelomonocytic leukemia.	Morphology: ≥ 20% monocytes or their precursors and ≥ 20% maturing granulocytic cells.
	Cytochemistry and/or MFC: < 3% of MPO-positive blasts.
Acute monocytic leukemia.	Morphology: ≥ 80% of monocytes and/or their precursors (monoblasts and/or promonocytes); ≤ 20% of maturing granulocytic cells.
	MFC/cytochemistry: expression of monocytic antigens (two or more), such as CD11c, CD14, CD36, and CD64, on blasts and promonocytes or their NSE positivity.
Acute erythroid leukemia.	Morphology: erythroid predominance in the BM (> 80% of BM cellularity); > 30% of immature erythroid (proerythroblasts).
Acute megakaryoblastic leukemia.	MFC: expression of one or more of platelet GP: CD41(GP IIb), CD61 (GP IIIa), or CD42b (GP Ib).

AML: acute myeloid leukemia; MPO: myeloperoxidase; SBB: Sudan Black; MFC: multiparameter flow cytometry; BM: bone marrow; NSE: nonspecific esterase; GP: glycoproteins. Taken and adapted from [9].

Furthermore, after four decades of using ICT, targeted treatments for apoptotic regulators, epigenetic or micro-environmental pathways, and immune-system modulators are now available or in clinical development for AML [1,4]. Therefore, many older patients with AML can be treated with new therapeutic options and strategies, allowing for achieving complete remission (CR) or extended OS or, in selected cases, proceeding with allogeneic SCT [1,4]. The availability of molecular techniques [6,7] and tailored therapies [12–14], as well as the recent applications of machine learning (ML) [15–19] with their transformative impact and potential in the diagnosis, prognosis, and clinical

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management of AML, make these diseases a fascinating setting for both clinical research and daily clinical practice. Hence, we review the most recent advances in biological understanding and therapeutic approaches in AML, focusing on older patients.

2. Search Strategy and Selection Criteria

References for this updated review were identified through PubMed searches using multiple search terms related to several aspects of the biology, diagnosis, prognostication, and clinical management of older individuals with AML, considering only studies published in English until June 2024. With some exceptions, only papers published over the last three years have summarized the most recent developments as up-to-date as possible.

3. Disease Overview and AML Pathophysiology

AML are blood cancers involving rapid growth and accumulation of abnormal myeloid cells in the BM, PB, and extramedullary sites [1]. The consequent BM failure causes cytopenia and related clinical features, such as anemia, increased infection susceptibility, and bleeding tendencies. About the onset and the previous patient's clinical history, AML can arise as primary (newly diagnosed, ND-AML), therapy-related (t-AML), and secondary (s-AML) categories [1,4,20]. In most cases, AML in older patients emerges alongside previous hematologic malignancies [20,21], such as myeloproliferative disorders (MPNs) [20], myelodysplastic neoplasms (MDS) [22] and potentially predisposing and long-lasting premalignant conditions, such as clonal hematopoiesis (CH), which is prevalent in individuals over 70 [23]. AMLs arise from BM from leukemia stem cells (LCSs) [24], deriving by the malignant transformation of hematopoietic stem cells (HCSs) by acquired genetic mutations [2], resulting in altered cell self-renewal mechanisms, uncontrolled proliferation, and impaired apoptosis [25] of the leukemic clone. Therefore, accumulating acquired somatic mutations, interfering with the normal development of immature HSCs, drives the leukemic process. In this regard, CH-related genes (*ASXL1, TET2, SRSF2*, and *DNMT3A*) are most frequently mutated in AML older patients [2,23]. In most cases, they can be considered the first hit on the path to malignant transformation and appear to be a relatively early event in leukemogenesis. In contrast, other genomic abnormalities, including mutations in *FLT3, NRAS, and RUNX1* [2,26], tend to be acquired later during leukemia development. Acquired genetic mutations that characterize AMLs can be categorized into several pathways [2,26]. Indeed, activating mutations involving genes that sustain cell proliferation and survival, such as *FLT3, NRAS, KRAS, and c-KIT*, lead to the uncontrolled growth of immortalized LSCs. In addition, mutations in genes related to DNA repair (e.g., *TP53*) [27,28], cohesin complex (e.g., RAD21), and spliceosome machinery (e.g., *SF3B1, SRSF2, U2AF1*, and *ZRSR2*) can contribute to leukemogenesis and disease progression [2]. Furthermore, other mutations, such as transcription factors (e.g., *CEBPA* and *RUNX1*) and epigenetic regulators (e.g., *TET2, IDH1/2, DNMT3A, ASXL1*, and *EZH2*) affect genes involved in hematopoietic differentiation [2]. Again, mutations in genes encoding epigenetic modifiers, such as histone modification and DNA methylation, play a critical role in the pathogenesis of AML, leading to aberrant epigenetic patterns, altered gene expression profiles, and the arrest of the HCSs differentiation [2,26]. In s-AML, the most common driver mutation in patients with prior MPNs is *JAK2 V617F*, accounting for 98% of polycythemia vera and 55–60% of essential thrombocythemia and myelofibrosis cases [20]. In contrast, in MDS, the most frequent mutations affect members of the spliceosome, such as *SF3B1, SRSF2, U2AF1*, and *ZRSR2*, as well as genes involved in DNA methylation and chromatin remodeling, such as *TET2, DNMT3A, IDH1/2*, and *ASXL1* [22]. Before progressing to s-AML, patients acquire mutations in other genes, particularly in spliceosome members, such as *SF3B1*, called "short-term" mutations that lead to rapid malignant transformation. In contrast, mutations in genes such as *TP53* and *ATM* are "long-term" as they develop over many years, but they also indicate a poor prognosis upon transformation [2,20]. Mutational profile separated two s-AML groups: those with *FLT3, PTPN11, WT1, IDH1, NPM1, IDH2*, and *NRAS* mutations, conferring a low-risk of progressive disease, whereas the presence of other gene mutations, such as *TP53, GATA2, KRAS, RUNX1, STAG2, ASXL1, ZRSR2*, and *TET2*, are predictive of a high risk of leukemic evolution [20].In addition, several

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non-genomic facilitating factors of leukemic pathways [2], such as the epigenetic state [2], immunological alterations, cytokine release dysregulations [29–32], and oxidative stress [33], can impair the physiological state of HSCs. Indeed, an altered inflamed and immunosuppressive BM microenvironment [30–32] can support LSCs survival and proliferation. In addition, dysregulated interactions of LSCc with stromal cells and altered cytokine signaling lead to disease progression and therapy resistance [30]. In addition, leukemic cells often show genotype-specific metabolic changes, which lead to alterations in epigenetic and functional factors, ultimately resulting in the upregulation or facilitation of oncogenic pathways [34,35]. Furthermore, different types of AML exhibit diverse and highly adaptable energy metabolism, which may have therapeutic implications [36]. In addition, profiling bioactive molecules such as sphingolipids represents a predictive tool for AML. These molecules have differential activities in regulating cell proliferation, differentiation, apoptosis, and immune cell activation and have implications in AML pathogenesis and therapeutic resistance, thus potentially exerting a significant value for understanding and treating AML [37]. Transcriptomic, proteomic, and phosphoproteomic data are valuable for understanding the underlying pathophysiology of AML beyond mutations, allowing these biological findings for the identification of four proteogenomic subtypes and the detection of specific drug response patterns [38]. Furthermore, an emerging understanding of the role of tumoral angiogenesis and the impact of endothelial cell subsets in shaping BM niches have been reported [39]. Moreover, it is relevant to note that AML cells can use different strategies to avoid ferroptosis cell death, controlled by three main cellular processes: iron metabolism, oxidative stress, and lipid metabolism [40]. Additionally, transcription factors, such as *HOXA9*, are overexpressed in approximately 70% of AML cases with poor prognosis, increased chemoresistance, and higher relapse rates [41]. Lastly, genetic polymorphisms in DNA excision repair systems are essential in maintaining genomic integrity and stability [42]. Therefore, the pathogenesis of AML involves a complex interplay of genetic mutations, epigenetic alterations, and disrupted cellular signaling pathways that induce the transformation of normal HSCs into LSCs with clonal and uncontrolled self-renewal properties, thus driving the disease progression [2]. Understanding the molecular mechanisms underlying AML pathogenesis [2] is essential for developing targeted therapies (Table 3) [43–50] for specific biological targets [43]. Notably, changes in *BCL-2* protein expression can promote cell survival or trigger apoptosis. *BCL-2*, a member of this protein family, is located in the cytoplasm and controls apoptosis by capturing proapoptotic proteins. Thus, it prevents mitochondrial membrane permeabilization and cytochrome C release, which activates apoptosomes [51]. *BCL-2* is crucial for the survival and growth of leukemic cells. Specific compounds, such as venetoclax [43,51,52], can target its abnormal activity. However, the most significant genetic changes observed in approximately 30% of AML cases involve mutations in the FMS-like tyrosine kinase 3 (*FLT-3*) gene [53,55]. These mutations are found in CD34+ HSCs and regulate the early stages of blood cell formation. *FLT-3* belongs to a group of receptors known as class III receptor tyrosine kinases, which also include *PDGFR* and *c-KIT*. When a specific molecule binds to *FLT-3* at the cell membrane, it forms pairs, activating the cytoplasmic tyrosine kinase domain (*TKD*), which, in turn, leads to signaling through various pathways such as *PIK3A*, *RAS*, and *MAPK/ERK*. The two main types of *FLT3* mutations are internal tandem duplications (*ITD*) and *TKD* point mutations. Both mutations result in continuous activation of the *FLT-3* receptor and uncontrolled growth of LSCs. At the AML onset, patients with *FLT-3* mutations present with increased blasts in BM and PB and higher white blood cell counts. In addition, patients with these mutations also tend to have shorter progression-free survival (PFS) and OS. In particular, *FLT-3 ITD* mutations significantly affect the complexity of disease biology and prognosis [53–55]. Other genetic abnormalities are potential targets for specific drugs [43,44,56,57]. For example, mutations in the active sites of isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*, reported at frequencies of 6–16% and 8–19% for *IDH1* and *IDH2* are significant in AML [43,44,56]. These enzymes convert isocitrate to α-ketoglutarate, producing nicotinamide adenine dinucleotide phosphate (NADH). Therefore, these gene mutations reduce the conversion of isocitrate to α-ketoglutarate and decrease NADPH-dependent conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG). In turn, the accumulation of 2-HG in cells competitively inhibits α-ketoglutarate-dependent processes, affecting cytosine 5-

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hydroxymethylation of DNA and leading to hypermethylation patterns in *IDH*-mutant LCSs [43,57]. Furthermore, high levels of 2-HG inhibit cytochrome C oxidase, making cells more susceptible to apoptosis when *BCL-2* is inhibited [58]. For AMLs characterized by mutations in specific genes such as lysine methyltransferase 2a (*KMT2A*, also known as *MLL1*) [59] and nucleophosmin (*NPM1*) [60,61], new compounds have been developed, such as Menin inhibitors [62–66] which are in clinical investigations. *KMT2A*, located on chromosome 11q23, is a DNA-binding protein essential for regular cellular growth. The interaction with some proteins, such as Menin, which regulates gene expression through histone methylation, influences its DNA binding. Abnormalities in the *KMT2A* gene occur in 70–80% of cases of infant leukemia. They are rare in older AML patients [43,59] but are common in those with t-AML [20,59], particularly if they have received topoisomerase II inhibitors. *NPM1* is a nuclear chaperone protein that exerts several cellular functions, including ribosomal synthesis, stress response, and genomic stability [61,62]. In adult AML, *NPM1* is one of the most commonly mutated genes, occurring in 20–30% of cases [43,61,62]. The *NPM1* gene encodes a multifunctional protein prevalently located in the nucleoli and shuttles between the nuclear and cytoplasmic compartments. Importantly, *NPM1*-mutated AML cells exhibit abnormal cytoplasmic localization of mutant *NPM1c* due to the loss of a nucleolar localization signal and gain of a nuclear export signal (NES) at the C-terminus. This NES interacts with the nucleus cell exporter Exportin-1 (*XPO1*), causing accumulation of the *NPM1* mutant in the cytoplasm [60,61]. The overexpression of the HOX gene [40], similar to *KMT2A* rearranged AML, guides the *NPM-1* mutated AML development. Notably, overlapping features between t-*NPM1* and de novo *NPM1* AMLs suggest they can represent a single disease entity [67]. Generally, *NPM1* mutations indicate a favorable prognosis without other genetic alterations, and the growth of *NPM1*-mutated AML is responsive to Menin inhibitors [62–66]. Additionally, nucleoporin 98 (*NUP98*) [67], a gene located on chromosome 11p15, is involved in nuclear membrane transport and acts as a transcription factor in the nucleoplasm. In approximately 1–2% of adult AML patients, *NUP98* fuses with one of over 30 different partners, contributing to the development of leukemia. *NUP98* fusions are usually associated with poor prognosis and may lead to resistance to chemotherapy [66]. Like *MLL* fusion and *NPM1* mutations, *NUP98* fusion proteins bind to chromatin near *HOX* genes, causing their overexpression through various mechanisms, including altered DNA methylation and acetylation. The binding of these fusion genes to chromatin depends on both *MLL* and Menin. In preclinical studies, leukemic cells with *NUP98* fusions responded to Menin inhibition [62–66]. Again, the AML cell surface expresses some target proteins [68], such as CD123 [69,70], CD33, CD37, and CD47 [71]. Notably, CD123 is a primary diagnostic marker of a rare and aggressive hematodermic neoplasm, such as blastic plasmacytoid dendritic cell neoplasm (BPDCN) [69,70] which was included among AML in updated WHO-5 [10] and new ICC [11]. Again, the smoothened transmembrane protein mediates Hedgehog signaling [72] and represents a therapeutic target for an available therapeutic compound [68]. Thus, advances in genomic profiling and molecular characterization have enabled the development of innovative treatment approaches for patients with AML, particularly older and frail individuals unsuitable for ICT and allogeneic SCT [13,14].

Table 3. Current targeted therapies in AML involving older patients [43–50].

Therapeutic mechanisms and biological targets		Therapeutic agent	Indications
Antiapoptotic by inhibition of BCL2 overexpression		Venetovlax	ND AML in patients > 75 years old or with comorbidities in combination with HMA or LODAC
FLT3	FLT-3 ITD FLT-3 TKD	Midostaurin, Quizartinib	Frontline, in combination with ICT
		Gilteritinib	R/R setting
		Sorafenib	Maintenance following consolidation

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IDH1	IDH1	Ivosidenib	ND AML in patients > 75 years old or with comorbidities; R/R setting
		Olutasidenib	R/R setting
IDH2	IDH2	Enasidenib	R/R setting
Inhibition of Hedgehog pathway		Glasdegib	Adults older than 75 years who have comorbidities.
ICT with liposomal compounds in s-AML and t-AML		CPX-351	As induction ICT for ND s-AML and t-AML
Anti-CD33 monoclonal antibodies		GO	During induction, ICT for CD33-positive AML or as a single agent in the R/R setting.
Targeting CD123 membrane receptor, Cell death via disruption of intracellular protein synthesis by CD123 binding and internalization of the drug.		Tagraxofusp (anti-CD123 conjugate with toxin).	Treatment of BPDCN

AML: acute myeloid leukemia; ND: newly diagnosed; HMA; hypomethylating agents; LODAC: low dose of cytarabine; BCL2: B-Cell Lymphoma 2; FLT3; fms related receptor tyrosine kinase 3; ITD: internal tandem duplications; TKD tyrosine kinase domain mutation; ICT: intensive chemotherapy; R/R: relapse/refractory; IDH1: isocitrate dehydrogenase (IDH)-1 mutation; IDH-2 mutation; S-AML: secondary AML; t-AML: therapy-related AML; CPX-351: liposomal encapsulation of cytarabine and daunorubicin at a fixed 5:1 synergistic molar ratio; GO: gentuzumab ozogamicin; BPDCN: blastic plasmocytoid dendritic neoplasms.

4. Diagnosis and Classification of AML

AMLs are fast-developing blood cancers that require quick and accurate diagnosis even to early identify high-risk leukemic subtypes, such as acute promyelocytic leukemia (APL) [73], and severe clinical features, such as hyperleukocytosis and coagulopathies, representing eventually medical emergencies [74]. Therefore, early diagnosis is crucial for guiding initial treatment and preventing early mortality, in particular for older patients, owing to their physical frailty and the frequent concomitance of significantly impacting comorbidities. Although rarely occurring in older patients and outside the scope of this article, APL should be considered in older patients because of its potentially devastating clinical presentation of an otherwise highly curable disease if diagnosed early and correctly treated [73]. Appropriately diagnosing AML [13,14], other than recognizing blast cells and their dysmorphological features, requires a combination of several analyses, such as multiparameter flow cytometry (MPFC) tests [13,75], cytogenetic, and molecular studies [6–8]. Regarding MPFC, the application of an extensive panel including precursor markers, such as CD34, CD117, and HLA-DR, as well as those of myeloid (Cytoplasmic MPO, CD33, CD13), monocytic (CD14, CD36, CD64, CD4, CD38, and CD11c), erythroid (CD235a, CD71, and CD36), and megakaryocytic (CD41, CD61, and CD36) differentiations can ensure the optimal immunophenotypic characterization of leukemic cells [13,75]. In addition, deep learning support can provide remarkable added value and further improvements in the MPFC setting [76].

Moreover, pre-treatment genomic DNA should be screened by polymerase chain reaction (PCR) methods for the mutation status of *FLT3-ITD, CEBPA*, and *NPM1* [13]. In addition, NGS panels can detect the mutation status of genes recurrently altered mutated in AML [8,13] for diagnostic, prognostic, and therapeutic purposes. In real-life scenarios, fit young, adult, and very selected older patients who are able candidates for ICT and allogeneic SCT receive this ideally comprehensive work-up. In contrast, most older patients with AML unsuitable for ICT and considered for lower intensive treatments have yet to routinely undergo a thorough investigational work-up other than the minimal basic tests for AML diagnosis. However, the ever-increasing availability of targeted agents and low-intensity but highly effective treatments in this often-neglected category of patients make appropriate

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molecular diagnostics even in this setting. Notably (Tables 1 and 2), new WHO-5 [9] and ICC [10] classifications take into account integrated clinical, morphologic, and immunophenotypic parameters along with molecular and genetic findings. Therefore, accurate diagnosis, precise classification, and adequate risk stratification of AML patients should achieved by integrating clinical history, patient fitness, morphology, cytogenetic results, and NGS of DNA and RNA to detect eventually targetable genetic abnormalities. Consequently, NGS and MFCM tests will likely increase significantly over the next few years to accommodate these new classification schemes and provide precise treatments, especially for older patients. However, most older patients can benefit considerably from tailored agents to biological and molecular targets, requiring these innovative treatment approaches, the appropriate diagnostic evaluation, and the regular monitoring of treatment responses [79–83].

5. Prognosis, Risk Assessment, and Monitoring of AML

The accurate estimation of prognosis for AML is complex and depends on patient-related factors, AML manifestations at diagnosis, and disease genetics [83]. While NGS platforms have enhanced our understanding of AML biology, performing these tests is rare in older patients. Moreover, traditional prognostic factors identified in patients treated with ICT are becoming less reliable as new effective treatments become available. Currently, the most commonly used consensus risk stratification guidelines for AML are those from the European LeukemiaNet (ELN) [13] and the National Comprehensive Cancer Network (NCCN) [14]. Real-life data, including the reported analysis of 624 ND AML patients from 1998 to 2014 [84] and, also in older patients, deep learning technologies [19], have validated The ELN genetic risk stratification [13]. However, these guidelines derive from cytogenetic and molecular features diagnosed in patients submitted to ICT. Therefore, they present some limitations, particularly for patients with age-related frailty and comorbidities [85]. As the trend towards using lower intensive treatments for most elderly patients continues, the existing risk stratification guidelines and recommendations for post-remission therapies are limited to a few selected ND AML older patients [83]. However, MRD detection is not a routine practice in older patients with AML due to age-related factors, disease features, and available treatment options. Despite this, MRD detection can be a valuable guide for potential applications of personalized medicine in the setting of lower-intensive treatments [81,82]. Therefore, the prognosis for an individual patient relies on both clinical features and the leukemic blasts' immunophenotypic and cytogenetic/molecular characteristics. Patient age, comorbid conditions, and prior history also contribute to clinical manifestations and treatment. Adverse risk factors are more common in older adults with AML, leading to a generally inferior prognosis compared to younger patients. While curative therapy for AML has traditionally relied on ICT and allogeneic SCT, these measures are associated with potentially severe complications in older AML patients. Therefore, risk stratification systems are essential in older patients with AML candidates to receive lower-intensity treatments by tailored agents and new effective combinations, facilitating new possibilities in this challenging setting [83].

6. Clinical Management

The AML outcome in older patients depends on age, overall health, and fitness status. Managing AML in older patients is difficult due to decreased functional abilities and individual fitness [5,46,85–87]. As a result, most older patients with AML are not suitable for ICT, are more likely to have genetic features with negative prognostic impact as well as may be resistant to treatments. In the last two decades, several efforts have provided appropriate tools to determine which patients are fit or unfit for ICT or non-ICT in clinical practice [83,86,87]. However, recent progress in understanding the genetic factors affecting AML outcomes has expanded treatment options for older patients, including targeted and lower-intensity therapies (Tale 3) [45–50] in both frontline and relapsed/refractory (R/R) settings [88,89]. In particular, combining HMAs, mainly azacytidine, with venetoclax is the current standard of care for AML patients unfit for ICT [51,88–91]. The availability and approval of this innovative treatment have led to significant changes in current clinical practice for which a recent Italian retrospective survey suggested modifications to the "Ferrara criteria" to accommodate the use

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of venetoclax/HMA, used in other than one-third of AML patients, compared to 2008-2016 [92]. In contrast, a reduction of ICT from 40% to 18% and HMA alone from 19% to 13%, respectively, was recorded [92]. Although the "Ferrara criteria" have been validated in this setting by a retrospective study [87], proposals for updating the treatment-specific fitness criteria in the context of venetoclax/HMA, due to the unique toxicity profile of this treatment combination, inducing prolonged neutropenia and increased risk of infections. In particular, an age limit of 80-85, a cardiac function > 40%, the absence of certain lung conditions, and an adequate caregiver should be essential to update fitness criteria for patients to evaluate for venetoclax/HMA combination treatment [92]. Therefore, the following paragraphs will discuss the management of ND and R/R older AML patients by currently available therapies but mainly focus on novel treatment options arising from the latest advances in our biological understanding of AML (Table 3) [43–50].

7. Intensive Chemotherapy and Allogeneic SCT

The primary induction treatment for AML is ICT, which traditionally involves combining cytarabine and daunorubicin (7+3 regimen) [4,13,14,47] and already represents the standard of care also in older patients who are able candidates for this therapeutic option based on individual fitness evaluation [85,86,92]. However, most older patients with AML are unsuitable for ICT because of advanced age, coexisting health issues, and social concerns. Indeed, ICT for AML may result in lower OS and high mortality rates in older patients, particularly those over 75 years old [45–47]. Adding gemtuzumab-ozogamicin, an antibody-drug conjugate targeting CD33 [93], to traditional ICT has expanded treatment options. However, the survival benefit appears limited to patients with favorable-risk *CBF* AML [93–95]. In addition, a new treatment option, such as CPX-351, has been introduced to address ICT-related challenges in older patients with AML [96]. This therapeutic combination is a dual-drug liposomal encapsulation exerting its antileukemic action by maintaining a synergistic molar ratio of cytarabine to daunorubicin of 5:1 within the liposome while in circulation [96]. Overall, CPX-351 showed promising benefits among older patients with s-AML or t-AML, resulting in higher response rates and significant improvements in OS and event-free survival (EFS) compared to the standard 7 + 3 regimen [96] with a favorable safety profile mainly related to decreased incidence of mucositis and others off-target side effect [96].

Interestingly, in responsive patients fit for allogeneic SCT, CPX-351 is a feasible bridging measure [96]. Notably, low-intensity therapy, such as HMA/venetoclax [88–91,97,98] and molecularly tailored treatments [54,56,99], have been proven reliable bridges to allogeneic SCT. However, due to the frailty of older patients with comorbidities as well as socioenvironmental factors, the decision to undergo a transplant must be carefully considered by evaluating the treatment-related morbidity associated with allogenic SCT [1,4.88,92]. Furthermore, treatment decisions based on chronologic age alone have been the most common barrier to referring older patients for consideration of allogeneic SCT; concerning this finding, the risk that a significant proportion of older individuals with AML could benefit from allogeneic SCT does not. Therefore, this represents an unmet need, considering that patients who undergo transplants have significantly longer OS than those potentially eligible but did not undergo transplants. However, advancements in lower intensity and less toxic treatments bridging to allogeneic SCT [88], a better understanding of transplant complications, the increased utilization of unrelated donors, and the development of less intense conditioning strategies have improved transplant outcomes and survival rates over time [88,100] also for older AML patients.

8. Novel Therapies for Older Patients with AML

Therapeutic options and approaches for older AML patients (Table 3) have significantly expanded in recent years [13,14,43–50], paralleling innovative diagnostic technologies [6–8] and advances in our understanding of the complex biological mechanisms [2] underlying these aggressive blood cancers [1]. Before 2017, older AML patients who were considered fit were typically treated with standard ICT chemotherapy, while unfit patients aged 75 years and older received a hypomethylating agent (HMA) as a single agent [45–50,101]. However, the approval of new therapeutic combinations incorporating venetoclax [51,88–92], which induces apoptosis in AML cells

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by *BCL-2* inhibition, has changed this treatment landscape. The phase 3 VIALE-A trial included 431 patients 75 years older or with significant comorbidities. Patients were randomly assigned to receive the azacytidine-venetoclax combination or azacytidine alone [102]. Combining azacytidine/venetoclax resulted in a higher composite CR rate of 66% and OS of 14.7 months compared to 28% and 9.7 months for those treated with azacytidine alone [102]. Moreover, the durable efficacy and the maintained safety of venetoclax-azacytidine were confirmed at 43.2 months of median follow-up, with the reported OS of 14.7 months by this combination compared to 9.6 months by azacytidine alone [90]. A recently published meta-analysis of nine studies, including 1232 patients, confirmed a significantly higher composite CR rate and longer OS in older patients with ND AML treated with azacytidine/venetoclax compared to those who have received azacytidine monotherapy [91]. The former group of patients presented more severe neutropenia and gastrointestinal toxicity in comparison to those treated with azacytidine alone [90,91]. Of note, this treatment combination allowed for long-term efficacy in the challenging setting of extramedullary AML [103]. Therefore, for older patients with AML, the combination of venetoclax-azacytidine has portrayed remarkable changes in the therapeutic paradigm, becoming this treatment regimen currently recognized as the established standard of care frontline regimen in this setting [1,4,13,14]. Another therapeutic target is the overactive Hedgehog pathway in AML cells [72]. Glasdegib, an inhibitor of the Hedgehog pathway that targets the Smoothened protein [72], gained its approval in association with low-dose cytarabine (LDAC) in ND AML patients over 75 years old who are not eligible for ICT due to age or significant health issues [104]. In a controlled study involving 132 AML patients, 88 received the combination treatment of glasdegib and LDAC, while 44 received LDAC alone. Compared to LDAC alone, glasdegib with LDAC led to a significantly longer OS and a higher CR rate (8.8 vs. 4.9 months and 17% vs. 1%, respectively) [104]. Other than these therapeutic options relying on dysregulated biological activities, different treatment modalities have been developed based on recognizing somatic mutations druggable by specific targeted agents [13,14,89]. With this regard, the approval of *IDH1* inhibitors for patients with *IDH1*-mutated ND AML unsuitable for ICT and those with R/R disease [56–58,105] allows targeted therapy in this setting. In particular, ivosidenib in combination with azacytidine gained approval for ND *IDH1*-mutated AML patients aged 75 and above or those with comorbidities following the results of the phase III AGILE trial [105], which included 146 patients randomly assigned to receive azacytidine plus ivosidenib or azacytidine alone. Compared to the azacytidine monotherapy arm, the study demonstrated a longer EFS and OS (24 vs. 7.9 months) in patients treated with azacytidine and ivosidenib [105]. In addition, ivosidenib/venetoclax combination, in a clinical trial [106], was administered as a therapeutic combination alone or in triplet with azacytidine in *IDH1*-mutated MDS, ND, and R/R AML with promising results [106]. Indeed, 63% of treated AML patients achieved MRD negativity. Of note, the 24-month OS duration rates were 50% and 67% in R/R and ND AML, respectively. In addition, *IDH2* inhibitors, such as enasidenib [107], have also been used as monotherapy, allowing for a composite CR of 46%, and in association with azacytidine in patients with suboptimal response with a further composite CR rate of 41% [107]. In R/R AML harboring mutant *IDH1*, another *IDH* inhibitor, such as olutasidenib, was approved based on a recently published multicenter clinical trial [108], which evaluated this agent alone or in combination with azacytidine. In this study, olutasidenib allowed for a CR rate of 32%. The median OS for patients with R/R AML was 8.7 months with monotherapy and 12.1 months with combination therapy [108]. Olutasidenib was well tolerated and induced durable responses in older patients with R/R *IDH1*-mutated AML. Therefore, despite the challenges of treating older AML patients who had already failed prior therapy, the results suggest that they can benefit from olutasidenib, providing the rationale for further studies on the therapeutic role of this agent in R/R *IDH1*-mutated AML. Another group of therapeutic agents (Table 3) [43–50] currently having a significant role in targeted therapy for older AML patients is *FLT3* (53-55) inhibitors, particularly concerning the R/R setting. Indeed, mutations in *FLT3* at diagnosis remained at the disease recurrence and, interestingly, were often acquired, eventually along with other abnormalities, such as *TP53, KIT, RUNX1*, and *WT1*, at relapse [26,56,109]. Therefore, it is of utmost importance to test for the presence of the *FLT3* mutation in relapsed older AML patients, including those who no

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longer respond to venetoclax/azacytidine combination therapy. Indeed, acquiring the *FLT3* mutation during the clonal evolution that characterizes leukemic relapse would make these patients suitable candidates for treatment with the *FLT3* inhibitor gilteritib [110–113], an oral, selectively effective *FLT3* inhibitor with single-agent activity in R/R *FLT3*-mutated AML [111]. In such a setting, gilteritib showed a good safety and tolerability profile [112,113], allowing its use even in fragile or otherwise compromised patients. Therefore, for eligible older patients with R/R AML, harboring *FLT3* mutations, gilteritinib represents the most critical current salvage option. In many cases, it may be the only rescue approach for those experiencing a relapse after venetoclax-containing therapy [110]. On the other hand, the effective role of venetoclax-based salvage therapeutic combination in patients with R/R AML previously treated with *FLT3* or *IDH1/2* inhibitors has been reported [114]. Gilteritinib received approval for patients with R/R *FLT3*-mutated AML based on the results of the ADMIRAL trial [111], which included 371 patients randomized to receive this agent alone (247 patients) or salvage ICT (124 patients). In the gilteritinib arm, the reported OS (9.3 months) was significantly longer than that (5.6 months) recorded in ICT patients [107]. An updated analysis [112] confirmed the survival benefits of gilteritinib compared to ICT, other than its stable safety profile and its role of bridging to allogenic SCT in many responsive patients [112]. Notably, other classes of agents have expanded the AML therapeutic armamentarium or are in clinical development in this setting. The drug tagraxofusp, which targets CD123, was approved for treating BPDCN [115,116] based on the results of a single-arm study on 13 treatment-naïve patients, where the drug showed a high CR rate of up to 54% [115]. Since the approval, research has focused on managing side effects, combining therapies to improve outcomes in suitable patients, and developing dosing and combination strategies to reduce toxicities while maintaining effectiveness, especially in older patients. Successful targeting of CD123 in BPDCN has also spurred research into other CD123-positive blood cancers, particularly AML, and to promote the development of new agents targeting CD123 [69,70,116]. Hence, the approved agents for older AML patients, listed in Table 3, represent significant progress in this field. Clinical trials are exploring their combined use in various therapeutic combinations, such as double or triple combinations, to improve further the management of challenging patients [117–119]. However, AML remains a diagnosis with uncertain outcomes and often unsatisfactory results, particularly for older patients. Numerous trials have investigated targeted therapies, including revumenib, a menin inhibitor, in patients with *KMT2A* or *NUP98* rearrangements or *NPM1* mutations [43,62–66]. Additionally, specific immunotherapy approaches, such as CAR-T cell therapy [120], and agents like macrolimab [71], an anti-CD47 monoclonal antibody, and bispecific antibodies [116,121], are being studied as potential treatments for AML. Again, some innovative studies are ongoing, exploring other therapeutic targets, such as those linked to already poorly understood metabolic [122] and inflammatory [123] aspects of AML. Despite limitations and difficulties in the ongoing research, developing these novel and awaited therapies may also offer hope for therapeutic possibilities in very challenging situations such as *TP53*-mutated AML [27,28,43,124,125] or those with MLL rearrangements [43,62,66].

9. Conclusions

AML is a complex and diverse disease, as shown by the expanded genetic and cytogenetic qualifiers in the updated WHO and ICC classification systems [8,10]. While outcomes have improved through novel therapies [43,45,57], a better understanding of toxicities, and advances in allogeneic SCT [88], the long-term OS remains poor, especially for older patients [5,45,47,50]. With this regard, it is essential to assess the patient's fitness [83,85–87] and to stay updated on the latest treatments [92]. Moreover, a critical step is performing diagnostic tests that allow the detection of baseline mutations and monitoring changes at relapse. In addition, MRD assessment can help predict relapse and guide treatment decisions [78,79]. When determining the best treatment, it is crucial to consider the patient's age, overall health, and quality of life [126]. Additionally, integrating physical therapy and nutrition services is essential for comprehensive care. Advances in precision medicine [42–49,113] and new treatment options have improved outcomes for older AML patients. In conclusion,

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personalized care [127] is critical in managing these patients, reducing the impact of the side effects of novel treatments, and, finally, improving outcomes.

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