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Frontline treatment of acute myeloid leukemia in adults

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Abstract

Recent years have highlighted significant progress in understanding the underlying genetic and epigenetic signatures of acute myeloid leukemia(AML). Most importantly, novel chemotherapy and targeted strategies have led to improved outcomes in selected genetic subsets. AML is a remarkably heterogeneous disease, and individualized therapies for disease-specific characteristics (considering patients' age, cytogenetics, and mutations) could yield better outcomes. Compared with the historical 5-to 10-year survival rate of 10%, the survival of patients who undergo modern treatment approaches reaches up to 40–50%, and for specific subsets, the improvements are even more dramatic; for example, in acute promyelocytic leukemia, the use of all-trans retinoic acid and arsenic trioxide improved survival from 30–40% up to 80–90%. Similar progress has been documented in core-binding-factor-AML, with an increase in survival from 30% to 80% upon the use of high-dose cytarabine/fludarabine/granulocyte colony-stimulating factor combination regimens. AML treatment was also recently influenced by the discovery of the superiority of regimens with higher dose Ara-C and nucleoside analogues compared with the "7+3" regimen, with about a 20% improvement in overall survival. Despite these significant differences, most centers continue to use the "7+3" regimen, and greater awareness will improve the outcome. The discovery of targetable molecular abnormalities and recent studies of targeted therapies (gemtuzumab ozagomycin, FLT3 inhibitors, isocitrate dehydrogenase inhibitors, and epigenetic therapies), future use of checkpoint inhibitors and other immune therapies such as chimeric antigen receptor T-cells, and maintenance strategies based on the minimal residual disease evaluation represent novel, exciting clinical leads aimed to improve AML outcomes in the near future.

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Keywords

Acute myeloid leukemia; frontline treatment; high dose Ara-C; nucleoside analogues

1. Definition and history of acute myeloid leukemia

Acute myeloid leukemia (AML) is a genetically heterogeneous, malignant clonal disorder of the hematopoietic system that is characterized by uncontrolled proliferation of immature, abnormal blast cells and impaired production of normal blood cells[1,2].

The first reports of an unknown condition with a “milky blood” were from Scottish physician Peter Cullen (1811), followed by John Hughes Bennett (who named the disease “leucocythemia”) and David Craigie (1845), and French physicians Alfred Francois Donne (1844) and Alfred Velpeau (1825). The disease was named “leukemia” by Rudolph Virchow in 1847, a famous German physician and pathologist[3,4]. In 1964, the long-term survival of AML was less than 5% and currently is reaching 30–40%, and in certain subtypes even twice more[4–6]. Recently, the first whole-genome sequencing of AML was performed at Washington University[7,8].

2. Epidemiology of AML

AML is the most common acute leukemia in adults. The median age at diagnosis of AML is around 70 years (67 in the United States and 72 in Sweden)[9,10]. Approximately 3% of AML cases occur in children age 14 years or younger [9].

In 2015 in the United States, the estimated AML incidence is 20,830 cases (1.3% of all new cancer cases), with an 10,460 deaths in the same year. According to 2010–2012 data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program, around 0.5% of males and females in the United States will be diagnosed with AML at some point during their life. Over the past decade the incidence of AML has been rising on average by 2.2% each year[11].

In adults, AML is more common in males than in females (the male/female ratio is 5/3), and the incidence of AML is slightly higher in whites than in blacks[12]. In a retrospective single-center study, Bierenbaum et al. showed that black patients present with AML at a significantly younger age, and the incidence of AML is higher in black females than in black males[13].

In addition to its clinical, therapeutic, and biological uniqueness, acute promyelocytic leukemia (APL) is a distinct disorder from an epidemiological perspective: it is more common in younger patients (median age 40 years, range 20–59) and in Hispanics, and the incidence is equal in males and females.[14,15]

3. Predisposing factors

Figure 1 lists the major predisposing factors for AML. Among these are genetic factors, environmental factors and lifestyle, drugs, and antecedent blood disorders; of note, there is a

significant association between tobacco smoking and AML. Several studies also reported an increased risk of AML 5–7 years after radiation exposure, 4–8 years after exposure to alkylating agents (commonly associated with chromosome 5 and/or 7 abnormalities), and 1–3 years after topoisomerase II inhibitors (specifically, the French-American-British Cooperative Group [FAB] M4 and M5 subtypes, which are typically is associated with MLL gene rearrangements)[6,16–24]. Previous reports have also suggested a higher risk of APL in electrical workers and in people from industrialized areas, as well as an association with obesity[25,26].

4. Clinical Manifestations of AML

Clinical manifestations of AML are mainly driven by pancytopenia (anemia, leukopenia, and thrombocytopenia) and blast proliferation (some common signs and symptoms of AML are summarized in Table 1)[6,27,28]. At presentation, around 10% of patients have hyperleukocytosis (white blood cell [WBC] count > 100×10^9/L)[6,29,30],[31]. Disseminated intravascular coagulation is quite common in patients with APL; skin involvement (leukemia cutis or myeloid sarcoma) is frequent in acute monocytic or myelomonocytic leukemia[27,32].

For a long time, involvement of the central nervous system (CNS) in patients with AML was considered to be rare; however, recent data from The University of Texas MD Anderson Cancer Center reports that about 20% of newly diagnosed AML patients have CNS infiltration[33]. Continuous headaches, mental and visual changes, sleepiness, palsies, symptoms of CNS bleeding, and spinal column compression can be the clinical manifestations of the CNS involvement, although patients may present with asymptomatic CNS involvement as well[34].

5. Diagnosis, classification, and prognosis

The diagnosis of AML, with a few exceptions, is mainly based on the identification of 20% or more myeloid blasts in the bone marrow and/or peripheral blood. Before 2001, the threshold for AML diagnosis was 30% blasts, which later was reconsidered and set at 20%. The exceptions are cases with the presence of any of these cytogenetic abnormalities: t(8;21)(q22;q22), inv(16)(p12q22) or t(16;16)(p13;q22), t(15;17)(q22;q12); in these cases, AML diagnosis is not correlated with the blast percentage. In some cases, erythroleukemia (FAB M6) also can be an exception owing to the variability in the percentage of erythroblasts in the bone marrow[6,35]. For lineage differentiation, cytochemistry and immunophenotyping are used[36].

From 1977 until 2001, the FAB system, which is based on cytomorphology and cytochemistry, was used to classify AML into eight subgroups (M0–M7)[35,37]. In 2001, a new classification of AML was developed and published with the efforts of the World Health Organization (WHO), European Association for Haemotopathology, and Society for Hematopathology. This system classifies AML taking into account underlying cytogenetic or molecular genetic abnormalities[38], and it was reviewed and updated in 2008 [39,40]. According to the 2008 revised WHO classification, “a myeloid neoplasm with 20% or more

blasts in the [peripheral blood or bone marrow] is considered to be AML when it occurs de novo, evolution to AML when it occurs in the setting of a previously diagnosed myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), or blast transformation in a previously diagnosed MPN…"[39].

5.1. Cytogenetics and molecular genetics

Cytogenetic analysis is an important and mandatory component of AML diagnosis. Many studies have shown that besides being a powerful diagnostic tool, pretreatment cytogenetic and molecular genetic findings are one of the major independent prognostic markers in AML, and they determine chemotherapy response and outcome[30,39,41–44]. Chromosome abnormalities are found at diagnosis in approximately 50–60% of adult patients with AML[41]. The most common abnormalities are t(8;21), inv(16) or t(16;16), t(15;17), trisomy 8, and rearrangements of 11q. Chromosome 5 and/or chromosome 7 changes are quite frequent in therapy-related MDS/AML[1,6,41,45].

Recent molecular studies of leukemic cells in patients with AML and the identification of somatically acquired gene mutations and deregulated gene and microRNA expression have advanced our knowledge of the pathobiology and tremendous heterogeneity of AML[2,41,44,46]. NPM1 and CEBPA gene mutations were included in the WHO 2008 classification as provisional entities[39]. Moreover, besides playing an important prognostic role, many currently known molecular genetic abnormalities are also acting as potential therapeutic targets[1,6,36]. Based on their biologic function, genetic abnormalities can be classified into groups: transcription-factor fusions (PML-RARA, RUNX1, and CEBPA), NPM1 encoding gene, tumor-suppressor genes (TP53 and WT1), genes encoding epigenetic modulation (DNMT3A, TET2, IDH1, and IDH2), activated signaling pathway genes (FLT3, KIT, and KRAS/NRAS), cohesion-complex genes, and spliceosome-complex genes. [2,36,44,47–50]

The whole-genome sequencing of AML revealed even greater heterogeneity of AML, and discovery of previously unknown acquired genetic mutations opened doors for new investigations on target therapies directed to specific cancer-initiating mutations[7],[8]. IDH1 and IDH2 mutations initially were found in brain tumors, where they were associated with favorable outcome[51]. Later studies showed them to be frequent in AML patients with cytogenetically normal karyotype (CN-AML) (10–15%); both IDH1 and IDH2 are associated with older age and confer adverse prognosis in patients with CN-AML[7,8,52–56].

5.2. Prognostic factors

Prognostic factors of AML are categorized into two groups: patient-related factors and AML-related factors. The most important patient-related factor is the age at diagnosis. AML is considered a disease of elderly patients, and increasing age is considered an adverse prognostic factor. However, the comorbidity score is still under investigation, and comorbid conditions might play an important prognostic role as well. Some studies have also suggested that black and Hispanic patients have a higher mortality from AML[10,36,57–59].

Of AML-related factors, high WBC count, prior MDS (secondary AML) and a history of cytotoxic therapy (therapy-related AML) are considered adverse prognostic factors. As previously noted, genetic changes have the strongest prognostic significance. Table 2 shows the comparison of commonly used risk categorization models for AML: Medical Research Council, UK (MRC), European Leukemia Network (ELN), and Southwest Oncology Group, Figure 2 shows a comparison of outcomes of newly diagnosed AML patients based on the MRC and ELN systems [36,42,43,60–63].

Patients with complex karyotype are known to have poor outcomes. The existence of ≥3 (or, in some studies, ≥4 or 5) chromosomal aberrations in the absence of abnormalities listed in the WHO 2008 “AML with recurrent abnormalities” subgroup is considered complex karyotype. Several studies showed that the incidence of adverse cytogenetic abnormalities increases with age[36,41].

About half of AML patients have normal cytogenetic profiles, so for those patients, molecular genetic changes have a crucial role. In CN-AML patients, NPM1 and CEBPA gene mutations are associated with favorable outcome, whereas FLT3-ITD (FMS-like tyrosine kinase 3 - internal tandem duplications) mutations are associated with poor outcome. The outcomes of patients with FLT3 tyrosine kynase domain mutations remain controversial[2,5,7,8,30,36,41–43,48,64–67].

One of the biggest recent discoveries was the identification of the genomic and epigenomic landscapes of adult de novo AML by The Cancer Genome Atlas Research Network, where the authors categorized the disease into 9 categories according to their biologic function. In their analyses, 10 genes were shown to be mutated with more than 5% frequency: FLT3, NPM1, DNMT3a, IDH1, IDH2, TET2, RUNX1, p53, NRAS, CEBPa, and WT1[49,50].

Marcucci and colleagues recently explored the possibility of combining epigenetic and genetic information into a prognostic score for adults with CN-AML. They identified 7 genes (CD34, RHOC, SCRN1, F2RL2, FAM92A1, MIR155HG and VWA8) with promoter DMRs (differentially methylated regions) and expression levels that were correlated with survival, and according the results of the study, patients with fewer of the genes with high expression had better outcomes. The patients, both young and older, with none of the aforementioned genes or with only one gene with high expression had the best survival: the 3-year overall survival (OS) was 80% in younger patients and 42% in older patients[68].

These findings and future studies may pave the road for a new classification and risk stratification of AML[50,69].

6. Treatment of AML

The “7+3” induction regimen (a 7-day continuous intravenous cytarabine infusion and 3 daily doses of daunorubicin) was introduced in 1973[70]. Since that time, most centers still consider the 7+3 regimen the standard of care[5,36,71].

Recent progress in leukemia research showed an advantage with the use of higher dose cytarabine (Ara-C) and nucleoside analogue doublets containing regimens over the standard

7+3; however, the “ideal” treatment regimen is still being debated, and there is no consensus between leukemia experts on the strategy for treating AML in adults[5,72,73].

In this section, we will discuss the treatment of different categories of AML separately.

6.1. Treating AML in young adults (<60 years)

Although there is no universal definition of “young age,” the age range between 18 and 60 years is used to define young adults. Here, we will discuss strategies for treating AML in young and older adult groups individually[5,36,74–77].

Nowadays, one of the burning questions of AML treatment is what kind of regimen to use for the induction: 7+3 or high dose Ara-C (HiDAC) plus a nucleoside analogue. Several studies have proved the benefit of using the latter; however, many other experts have another point of view. This belief also opens the discussion about the other important aspect of treatment—timing of treatment initiation—since it takes time to obtain the results of cytogenetic testing and to identify a few important genetic mutations (NPM1, FLT3-ITD, CEBPA, c-KIT), which are necessary for choosing the best treatment option[71]. Most believe that treatment should be initiated as soon as the diagnosis is established[78], with “treatment” referring to the 7+3 induction regimen. Although, early studies supported beginning treatment as soon as possible in young adults with AML[79], a recent study by Bertoli et al. showed that the time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome (complete remission [CR] or early death rates) regardless of age and WBC count, suggesting the possibility of “waiting for a short period of time for laboratory tests to characterize leukemias better and design adapted therapeutic strategies.” [80]

The main aim of induction therapy is to decrease the quantity of leukemia cells to a cytogenetically undetectable level ($<10^9$ cells)[78]. Studies have proven the importance of residual undetected leukemic cells, which later cause relapse; this is known as minimal residual disease (MRD)[81–85].

In a recent review, Grimwade and Freeman comprehensively described the rationale for using MRD detection toward the individualized care of patients with AML. Current risk classification systems are mainly based on pretreatment characteristics and do not reliably predict individual patients’ outcomes, and there is a significant discrepancy between morphological and flow cytometry-based remission evaluation, which has a great impact on patients’ outcome; these existing problems may give a strong rationale and basis for the use of MRD in disease evaluation in patients with AML[86,87]. The two most frequently used methods to detect MRD are based on multiparameter flow cytometery or real-time quantitative polymerase chain reaction, and both have their own strengths and weaknesses. There is no MRD-based risk stratification system, and MRD detection and reporting methods vary greatly among different institutions, which makes the use of MRD evaluation and MRD-directed therapy more difficult[83,87].

A recent study from the UK National Cancer Research Insititute AML Working Group, where a RT-PCR was used to detect MRD in 346 patients with NPM1-mutated AML,

showed that patients with persistent NPM1-mutated transcripts in blood after 2nd chemotherapy cycle independently have much higher risk of relapse after 3 years of follow-up than those without those transcripts (82% vs 30%)[88]. In another study by Araki and colleagues, where the MRD data from 359 adults with AML who received alloSCT retrospectively were analyzed, MRD-negative remission status was significantly associated with longer survival, both overall and progression-free[89]. Taking into account, the role of MRD in prediction of relapse in AML, some studies recently integrated MRD status before transplantation in prognostic models for allogeneic SCT in AML[90–92].

6.1.1. Conservative approach to treating AML (7+3-based induction)—The 7+3 induction regimen mainly comprises 7 days of continuous intravenous infusion of standard-dose Ara-C (100 or 200 mg/m^2 daily) and 3 days of short infusion or bolus of anthracycline, typically daunorubicin (45–90 mg/m^2 daily) or idarubicin (12 mg/m^2 daily). Table 3 shows several different treatment modifications of the 7+3 regimen[72,93–99].

Ara-C incorporates into the DNA and stops DNA synthesis. Early studies showed that continuous Ara-C infusions were much more effective than single infusions, because they were “covering” at least 2 cell cycles during 5 days[100,101].

Daunorubicin is the most commonly used anthracycline in 7+3 regimens[78]. A study from Japan showed similar remission and survival rates with idarubicin[102]; however, a subsequent meta-analysis done by Wang et al. comparing 10 trials with more than 4,000 AML patients, showed that the CR, event-free survival, and OS rates were significantly higher in the idarubicin arm than in the daunorubicin arm[103].

Both young and older adults had better outcomes with a higher dose of daunorubicin (60 or 90 mg/m^2 vs 45 mg/m^2)[95,98,104]. However, a recent randomized trial from the UK comparing 60 vs 90 mg/m^2 daunorubicin in 1206 adult patients with AML or high-risk MDS, mostly younger than 60 years, did not reveal a benefit in any AML subgroup with the use of 90 mg/m2[105]. With the 7+3 based approach, the CR rate is around 60–80% in young adult patients, with a 5-year OS of 20–40% (median survival, 16–24 months) depending on modifications of the regimen and drug dosages[36,72,93–99,106].

6.1.2. Modern approach to treating AML (HiDAC regimens)—The modern approach mainly takes into consideration the highly heterogeneous nature of AML, trying to individualize the treatment as much as possible and target specific mutations whenever drugs are available[5,71]. This strategy goes veers from the standard 7+3 induction regimen toward modern treatment options. Considering recent developments and the results of different studies, these modern approaches include HiDAC (≥1000 mg/m^2) and nucleoside analogue doublets. To date, Ara-C is the most effective drug against AML, and several studies have demonstrated that purine nucleoside analogues (fludarabine, cladribine, and claforabine) work synergistically with Ara-C and increase its antileukemic potency[5,72,73,97,107–110].

Before starting treatment using this strategy, diagnostic and prognostic factors (i.e. cytogenetics, molecular genetics, etc.) should be refined[5,71,80]. Although, still there is no

consensus about this approach, the results of recent studies are quite promising: the recent UK MRC-15 trial reported around a 20% advantage (66% vs 47%, p<0.001) in 8-year OS with the use of fludarabine containing FLAG (fludarabine, Ara-C, granulocyte colony stimulating factor [G-CSF])-Ida (idarubicin) regimen over 7+3 and 7+3 plus etoposide regimens; quite similar results were reported by a Polish group who added cladribine to the 7+3 regimen (CR rate 64% vs 46%, p<0.001; leukemia-free survival 44% vs 28%, p=0.005) [72,97].

According to recent ELN classification, favorable group includes patients with core binding factor (CBF) leukemias and patients with CN-AML who have NPM1 mutations (without FLT3-ITD) or CEBPA mutations[36]. APL also has a favorable outcome[111,112], but we will discuss it separately.

6.1.2.1. CBF-AML: CBF-AML patients include those with t(8;21)(q22;q22) (leading to the RUNX1-RUNIX1T1 fusion gene) and inv(16) or t(16;16) (CBFB-MYH11 fusion gene) cytogenetic abnormalities. Recent developments have improved the outcome of these patients dramatically; compared with 55% OS in early studies, OS now reaches up to 75–80%[5,30,72,73,113]. After the discovery of the synergism between fludarabine and cytarabine, the FLAG regimen was developed[73,100,114].

In 2008 Borthakur et al. reported a significant benefit of using a HiDAC and fludarabine-based FLAG regimen over idarubicin and Ara-C standard induction: 3 year relapse-free survival (RFS) and OS in the FLAG group were 86% and 80%, respectively, and in the idarubicin-Ara-C group were 57% and 66%, respectively[73]. Later studies also showed the the benefit of adding idarubicin and gemtuzumab ozagomicin (GO) to the FLAG regimen adds on outcome benefit[72,108,115,116]. GO is a combination of cytotoxic antibiotic calicheamicin and humanized monoclonal antibody to CD33 (highly expressed in AML cells), and various studies showed GO to have a potent anti-leukemic effect and provide a significant survival benefit for patients with favorable and intermediate cytogenetics[72,108,115–118].

The presence of c-KIT mutations in CBF-AML and MRD after induction/consolidation was shown to be associated with inferior outcome[5,119–124]. The addition of KIT inhibitors to the chemotherapy has not yet shown clear benefit, and further studies are needed.

6.1.2.2. AML with NPM1 mutation: The NPM1 gene encodes protein nucleophosmin (NPM, also known as nucleolar phosphoprotein B23 or numatrin), and high expression levels of this gene could inactivate the p53/ARF tumor suppressor pathway and promote tumor growth. NPM1 mutations can be found in 25–35% of AML cases[5,6,36,67],[125]. In CN-AML patients, the incidence of NPM1 mutation is >50%, and in FLT3-ITD-positive patients, the incidence of NPM1 mutation is about 60%[65,67]. In the ELN classification system, patients with NPM1 mutations who lack FLT3-ITD mutations are considered to have a favorable outcome, and those who harbor both FLT3-ITD and NPM1 mutations have a poorer outcome; this difference has been shown in many studies[36,65,67,125–128]. For NPM1+/FLT3-ITD- patients, taking into account their favorable features, the treatment

approach at The University of Texas MD Anderson Cancer Center and in several other centers is to offer patients a HiDAC-based induction regimen in clinical studies[5,71].

6.1.2.3. APL: The discovery of the effect of vitamin A derivative all-trans retinoic acid (ATRA) in APL revolutionized the world of leukemia: one of the most fatal diseases transformed to a highly curative one[111,129,130].

APL is a unique subtype of AML that is characterized by t(15;17) abnormalities and PML/RARA fusion transcripts (and variants)[131–134]. Since the discovery of the role of ATRA in APL and the first reports of its combination with chemotherapy, APL patient outcomes have improved dramatically[5,111,130,132,135–138]. Another great achievement was the discovery of arsenic trioxide (ATO) activity in APL[137,139–141]. Subsequent studies explored the combination of ATRA and ATO in standard risk groups, with CR rates reaching up to 95–100% and event-free survival rates exceeding 90%[142]. These findings presented a new standard of treatment for APL, which consists of ATRA plus ATO without chemotherapy in low- and intermediate-risk APL patients[111,142,143]. In the high-risk group (i.e. those who have hyperleukocytosis [WBC count >10.000])[132], clinicians at MD Anderson add GO to the ATRA-ATO regimen, and this strategy showed promising results in multiple studies[5,144–148]. Several European studies also reported the importance of HiDAC during induction and consolidation to reduce the risk of relapse in APL patients with a high or very high WBC count at presentation[149–151].

It also worth mentioning that because of the higher probability of early death caused by disseminated intravascular coagulation in APL, as soon as APL is suspected treatment with ATRA should be started immediately without waiting for the results of genetic testing[132].

6.1.2.4. AML with FLT-3 mutation: FLT3 tyrosine kinase receptor is highly expressed on myeloblasts. It has an important role in normal hematopoiesis and synergizes with other hematopoietic growth factors/interleukins to stimulate the growth of immature myeloid cells and stem cells[152,153].

FLT3 mutations are present in 20–30% of AML patients; FLT3-ITD and FLT3-TKD (tyrosine kinase domain) affecting amino acid D835 are the most common mutations. Several studies have reported inferior outcomes of patients with FLT3-ITD mutated AML compared with FLT3-WT (wild-type). The data on the outcomes of patients with FLT3-TKD mutations are controversial; however, some studies have suggested that they have inferior outcomes compared to FLT3-WT[36,48,65–67,154–159].

Several FLT3-ITD inhibitors (quizaritinib, sorafenib, midostaurin) have shown encouraging results in combination with chemotherapy[5,160–172]. These tyrosine kinase inhibitors competitively inhibit ATP-binding sites on FLT3 kinase domain (KD). Unfortunately, owing to the emergence of resistance, the responses to FLT3 inhibitors are not durable and last just 3–6 months. The resistance is caused either by the gain of ATP binding site point mutations on FLT3 KD (TKD1 mutations in the ATP binding domain and TKD2 mutations involving the activation loop) or several non-mutational mechanisms (upregulation of parallel prosurvival pathways, FLT3 ligand, or FLT3 receptor, other kinase mutations, antiapoptotic

protein activation, and mechanisms related to the tumor microenvironment)[172]. New FLT3-ITD inhibitors such as crenolanib (active against both TKD1 and TKD2 mutations) and ponatinib (in quizartinib-resistant patients) have shown encouraging results[173–175].

Studies also have shown that the allelic ratio of FLT3 mutant and WT genes might have a prognostic significance, assuming that a higher allelic burden confers a poorer outcome. The data on this issue are controversial, and further studies are needed to answer this question[5,159,176–178].

6.1.3. Post-remission therapy—The role of post-remission therapy is to clear leukemia cells that remain after remission induction therapy and that are not detected by conventional methods. Post-remission therapy usually comprises 3 main strategies: intensive chemotherapy (consolidation), prolonged maintenance therapy, and high-dose chemotherapy (conditioning) followed by autologous or allogeneic hematopoietic stem cell transplantation (HSCT). Recent advancements in HSCT and broader use of haploidentical (most patients have a haploidentical match) and cord blood transplants have expanded donor availability and the notion that “everyone has a donor” has become popular among many transplant physicians. Another exciting area for future investigation is cellular therapies, such as allo-transplantation of natural killer cells, which have shown promising results in several clinical trials [1,5,6,36,71,179–181].

The most commonly used consolidation chemotherapy regimen consists of repetitive cycles of HiDAC. For now, Ara-C is considered the most active drug in AML and has dose-response effect. Usually, HiDAC is considered the dose of Ara-C to be ≥1000 mg/m^2. Several studies have investigated the dose of Ara-C from 1000 to 3000 mg/m^2 to be used for consolidation; in terms of outcome, no difference was shown between 1500 and 3000 mg/m^2, but the outcome may have been better with 1500 mg/m^2 than with 1000 mg/m^2 [1,5,6,36,71,72,182,183]. In general, the main aim is to achieve higher outcome rates with less toxic treatment; therefore, different strategies have been suggested and adopted taking into consideration the risk profile of AML[36,71].

In **patients in the favorable group** (CBF-AML, NPM1+/FLT3-ITD-, and CEBPA+) HSCT has not shown any advantage in frontline treatment; therefore, in general, HiDAC-based consolidation is considered (3–4 cycles of cytarabine 1–3 g/m^2 on days 1, 3, and 5) [36,67,69,71,113,184–188].

For **patients with intermediate-risk AML** (ELN intermediate I and II), although many groups still use repetitive cycles of HiDAC, without HSCT, the outcomes are not as good as those in the favorable group; therefore, HSCT is considered the treatment of choice in this subgroup of patients, especially when the risk of transplant-related mortality is low or intermediate[36,69,71,184,186,187]. For patients harboring FLT3-ITD mutations, alloHSCT is preferable, and autoHSCT is used mainly for patients with favorable and intermediate-risk cytogenetics[36,69,71,184,186,187,189,190].

In **patients with adverse-risk AML** who receive cytarabine only or undergo autologous transplantation, 2-year survival is less than 10%; therefore, matched related or matched

unrelated alloHSCT in the first remission is considered the treatment of choice[5,30,36,43,71,186,191–193]. In patients with adverse cytogenetics who undergo matched unrelated alloHSCT in CR1, long-term survival could reach 30%[5,36,69,71,193].

The strategy of performing HSCT in AML patients needs to be assessed while taking into consideration transplant-related mortality, which can vary from >15% up to 50%[194–196]. The outcomes of patients with adverse-risk AML remain poor; therefore, new investigational therapies are emerging[5,36,71].

6.2. Treating AML in older adults (60 years and older)

Treatment of older patients with AML is quite challenging, and older age is independently associated with an inferior outcome. This is mostly due to poor performance status and comorbid conditions, which can increase the rate of treatment-related mortality (TRM). Moreover, increasing age is associated with adverse cytogenetics, which could be the result of treatment-related or secondary AML and could be associated treatment resistance[10,36,57–59,197–199].

However, despite all these features, studies show that for older adult patients “intent to treat” approach is justified over the “supportive care only” approach. For patients younger than 75 years with a good performance status (<2, no comorbid conditions), 7+3-based induction can lead to a CR rate of 50% and TRM of 15% in a favorable risk group, but for the adverse-risk group, the CR rate is less than 30% and OS is less than 5%. For patients with comorbid conditions, dose reductions may be adopted, and for the adverse-risk group, clinical trials or low-dose chemotherapy (mild cytoreductive induction) could be a choice[36,60,71,74,98,199–201].

The results of post-remission therapy are debatable, because most of the studies included fit older adult patients in their cohorts. Some promising results have been shown with nonmyeloablative or reduced intensity conditioning (RIC) allo-HSCT, which is associated with a lower rate of TRM[5,6,10,36,69,71,202].

AML as now understood as an epigenetically regulated disease and further use of epigenetically targeted therapies, in particular hypomethylating agents such as 5-azacytidine and decitabine, has shown to be a promising option for older patients with AML, who are not suitable candidates for intensive therapies. Both drugs showed a survival advantage compared with conventional therapy approaches in older patients with AML[49,203,204]. In a recent phase 1 study, a novel hypomethylating agent, guadecitabine (SGI-110), was well tolerated and clinically and biologically active in both AML and MDS[205]. Vosaroxin, a novel topoisomerase II inhibitor, is another exciting agent that recently showed promising results in combination with decitabine in older patients with AML and high risk MDS[206].

For patients 75 years and older with comorbid conditions and a lower performance status, treatment options are very limited and dismal. Low-dose Ara-C (20 mg 4 times/day subcutaneously for 10 days) has shown slightly superior outcomes than hydroxyurea; however, the treatment-related mortality rate is high in this group of patients. In patients with adverse cytogenetics, low-dose Ara-C has not shown any advantage. Several other

treatments with the addition of novel agents are currently under investigation. The wish of the patient for this subgroup is mostly determining factor for initiating treatment, keeping in mind that patients' expectations of cure are higher than their doctors' expectations s do[5,6,10,36,59,118,207–216].

6.3. New therapies

The increasing heterogeneity of AML and the discovery of previously unknown subtypes with specific mutations have opened doors for new targeted therapies. Figure 3 summarizes potential targets in AML and respective targeted agents that are currently in use or under investigation.

The exciting results of immune therapies, such as checkpoint inhibitors (PD1, PDL1, LAG3) and CAR-T cells, in solid tumors, have influenced their potential implications in hematologic malignancies as well[217,218]. First- and second-generation FLT3-inhibitors (sorafenib, midastaurin, quizartinib, crenolanib, and ASP2215), small-molecule inhibitors of BET and DOT1L histone methyltransferase targeting MLL translocations, SGN-33a and GO targeting CD33 in patients with CBF-AML and APL, IDH1 and IDH2 inhibitors for patients with IDH mutations (AG-120, ABT-199, AG-221), RAS and MEK inhibitors (trametinib and MEK162), and other targets and targeted therapies are currently under investigation, giving hope for better therapies for adult patients with AML[49,160,205,219–221].

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Highlights

- AML is a remarkably heterogeneous disease
- Novel treatment strategies improved outcomes in selected genetic subsets of AML
- Higher dose Ara-C based regimens showed to be superior over “7+3” regimens
- Most centers still use “7+3” regimen and greater awareness will improve the outcome

Summary

Further dissemination of knowledge about the superiority of HiDAC and nucleoside analogue-based induction regimens over the 7+3 regimens, the discovery of targetable molecular abnormalities and recent studies of targeted therapies (GO, FLT3 inhibitors, IDH inhibitors, and epigenetic therapies), future use of checkpoint inhibitors and other immune therapies such as CAR-T cells, and maintenance strategies based on the MRD evaluation represent novel and exciting clinical leads aimed to improve the outcomes of AML in the near future.

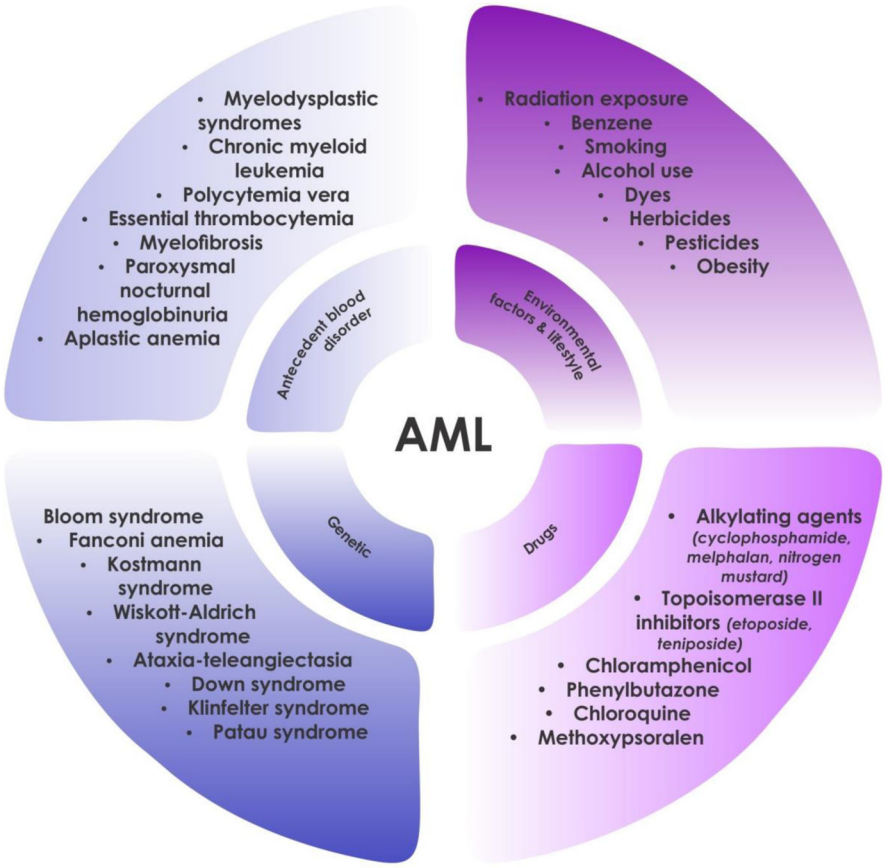

Figure 1.
Predisposing factors of AML

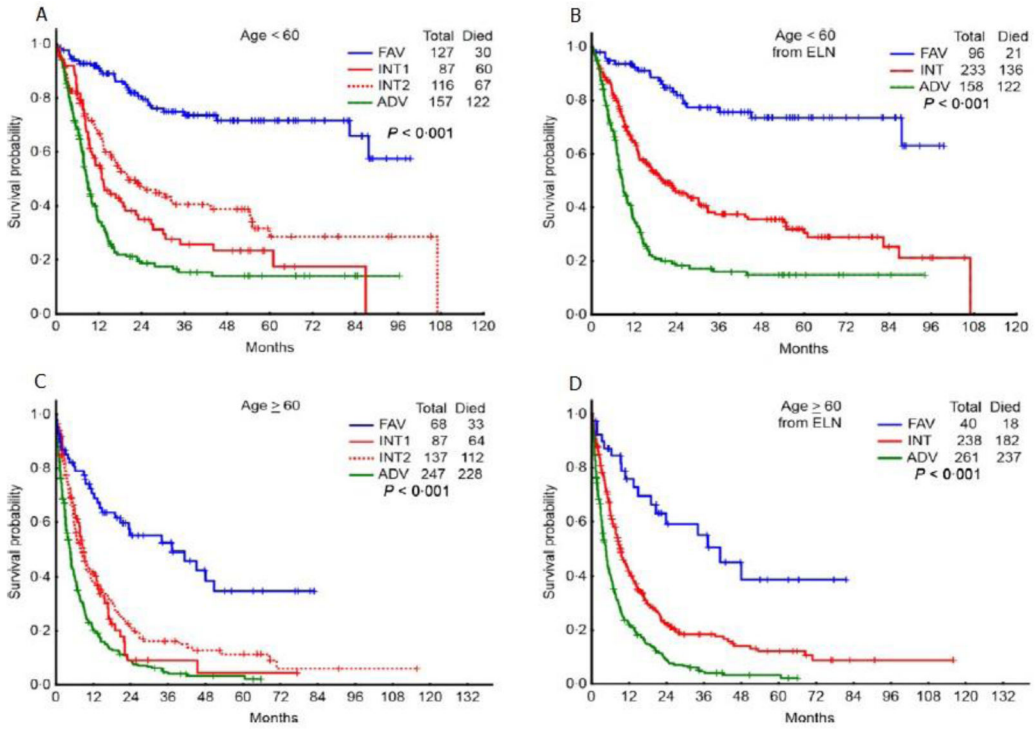

Figure 2. Overall survival of patients classified by the ELN and MRC classification systems

Overall survival of patients <60 years (N=487) classified by the ELN (A) and MRC (B) classification systems. Overall survival of patients ≥60 years (N=539) classified by the ELN (C) and MRC (D) classification systems. FAV, favorable; INT, intermediate; ADV, adverse (adopted from Kadia T, et al. Br J Haematol 2015 Feb 25) [98]

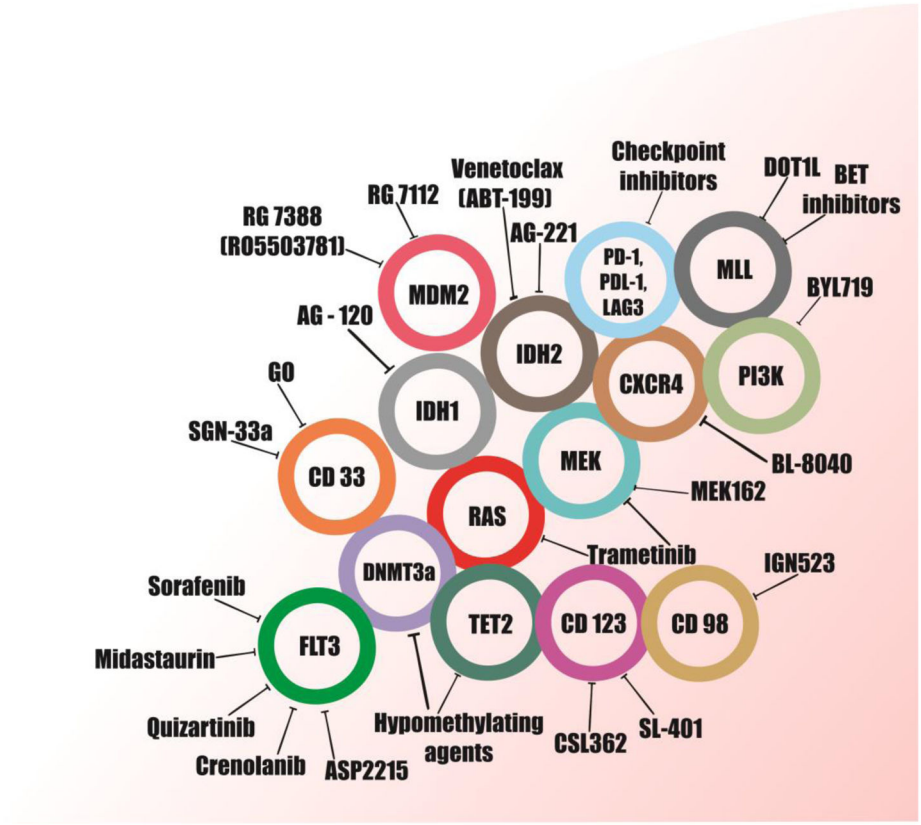

Figure 3. Potential targets and targeted therapies in adults AML

Abbreviations: GO, gemtuzumab ozagomicin; PD1, programmed cell death 1; PDL-1, programmed death-ligand 1; LAG-3, lymphocyte-activation gene 3; IDH (1,2), isocitrate dehydrogenase; MDM2, mouse double minute 2 homolog; MLL, mixed lineage leukemia; CXCR4, C-X-C chemokine receptor type 4; DOT1L, DOT1-like histone H3 methyltransferase; BET, Bromodomain and extraterminal domain family; PI3K, phosphoinositide 3-kinase; MEK, mitogen/extracellular signal-regulated kinase; TET2, Tet methylcytosine dioxygenase 2; FLT3, fms-related tyrosine kinase 3; DNMT3A, DNA (cytosine-5-)-methyltransferase 3 alpha

Table 1

Clinical manifestations of acute myeloid leukemia

Pancytopenia	**Blast proliferation**
Anemia	hepatomegaly
pale	splenomegaly
fatigue	lymphadenopathy
weakness	sternal tenderness
shortness of breath	gingivae, skin, soft tissue, meninges infiltration (M4, M5)
Leukopenia	**Joint involvement**
infection	**CNS involvement**
fever	**Leukostasis**
Thrombocytopenia	dizziness
bruising	blurred vision
bleeding	headaches
Other	confusion
DIC (in APL)	retinal hemorrhage
Acute neurophilic dermatosis (Sweet syndrome)	cranial nerve palses
	altered mental status
	dyspnea
	chest pain
	congestive heart failure
	priapism
	Tumor lysis
	fever
	renal failure

Table 2

Comparison of the Revised MRC, ELN and SWOG Risk Classification Systems of AML

Groups	MRC_{2010}	ELN		SWOG
Favorable	t(15;17)(q22;q21) t(8;21)(q22;q22) inv(16)(p13;q22)/t(16;16)(p13;q22)	t(8;21)(q22;q22)(inv(16)/t(16;16)(p12;q22) NPM1+ and FLT3-ITD-WT (NK) Mutated CEBPA (NK)		t(15;17), t(8;21) inv(16)/t(16;16)/del(16q)
Intermediate	Those cytogenetic abn. not classified as favorable or adverse	Int.1	NPM1+ & FLT3-ITD + (NK) NPM1-WT & FLT3-ITD + (NK) NPM1-WT & FLT3-ITD-WT	Normal +8, +6, −Y, del(12p)
		Int.2	t(9;11)(p22;q23) cytogenetic abn. not classified as favorable or adverse	
Adverse	abn(3q)(excluding t(3;5)(q21~25;q31~35], inv(3)/t(3;3)(q21;q26) add(5q), del(5q), −5, −7, add(7q)/del(7q) t(6;11)(q27;q23), t(10;11)(p11~13;q23), t(11q23) [excl. t(9;11) (p21~22;q23) and t(11;19)(q23;p13)], t(9;22)(q34;q11) −17/abn(17p) complex (≥4 unrelated abnormalities)	Inv(3)/t(3;3)(q21;q23) t(6;9)(p23;q34) t(v;11)(v;23), MLL rearranged −5 or del(5q) −7 Abn(17p) complex (≥3 unrelated abnormalities)		abn(3q) del(5q)/−5, −7/del(7q) t(6;9), t(9;22), 9q, 11q, 20q, 21q 17p complex (≥3 unrelated abnormalities)
Unknown				All other abnormalities

Table 3

Examples of “7+3” induction regimens for AML in adults

Ara-C	Anthracycline	References
100 mg/m^2 days 1–7	**DNR 45 mg/m^2 days 1–3**	J Clin. Oncol. 1992 Jul; 10(7):1103–11
100 mg/m^2 days 1–7	**DNR 50 mg/m^2 days 1–3**	J Clin Oncol. 2013:31(27):3360–8
100 mg/m^2 days 1–7	**DNR 90 mg/m^2 days 1–3**	N Engl J Med. 2009;361:1249–59
200 mg/m^2 days 1–7	**DNR 45 mg/m^2 days 1–3**	N Engl J Med. 2009;361(13):1235–48
200 mg/m^2 days 1–7	**DNR 60 mg/m^2 days 1–3**	Leukemia 2004;18(5):989–97
200 mg/m^2 days 1–7	**DNR 90 mg/m^2 days 1–3**	J Clin Oncol. 1992 Jul;10(7):1103–11
100 mg/m^2 days 1–7	**IDA 12 mg/m^2 days 1–3**	Ann Hematol. 2000;79(10):533–42
100 mg/m^2 days 1–7	**IDA 13 mg/m^2 days 1–3**	Blood 1992;79(2):313–9
100 mg/m^2 days 1–7	**MTZ 12 mg/m^2 days 1–3**	Blood 2003;102:175a (abst.611)