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Chapter

Management of Newly Diagnosed Acute Myeloid Leukemia in Older Adults

Gopila Gupta and Vikas Garg

Abstract

With an increase in the incidence of acute myeloid leukemia with age, there is a worsening in organ function and the patient’s ability to tolerate intensive therapies. To deliver the best possible care to this vulnerable group and maintain a good quality of life in patients, physicians need to individualize management to minimize adverse effects while still not compromising the prospects of the cure for fit individuals. In this chapter, we will discuss the tools for assessment in older adults and patients and disease-related parameters to be considered for appropriate classification into the fit, unfit, or frail categories. We will also discuss the treatment as per global fitness status, including novel agents, that have recently become available for older acute myeloid leukemia patients.

Keywords: AML, acute myeloid leukemia, older adults, elderly, management

1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematological malignancy resulting from the uncontrolled proliferation of myeloid precursor cells. Older patients are most at risk for developing AML because its incidence rises with age. The definition of older adults in AML is imprecise, with a cutoff of 60–65 years of age considered in various studies. Outcomes in these patients are poor with 5-year survival rates of less than 15%. Multiple factors are attributed to poor outcomes, including declining performance status, associated comorbidities, higher prevalence of poor risk cytogenetics and molecular aberrations, antecedent hematologic disorders, and drug resistance phenotype. In this chapter, we will focus on the management of newly diagnosed AML in older adults.

2. Epidemiology

AML is the most common hematological malignancy among adults and constitutes around 1% of all malignancies. The incidence of AML increases with advancing age, with a median age at presentation is 68 years and males have slightly higher predilection over females [1–3]. It is more predominant among whites compared to non-white races [4].
Although it is idiopathic in most cases, some patients have known risk factors. Risk factors for the development of AML include exposure to ionizing radiation, chemical exposure (viz. benzene, pesticides), genetic predisposition, and chemotherapeutic drugs (alkylating agents and topoisomerase inhibitors) [5, 6]. Germline mutations in the DDX41 gene have a known association with hematological malignancies in the elderly [7]. AML can also be preceded by myelodysplasia (MDS), myeloproliferative neoplasms (MPN), aplastic anemia (AA), clonal hematopoiesis of indeterminate potential (CHIP), or clonal cytopenia of unknown significance (CCUS) [8, 9].

3. How to define elderly AML

Even though there is no universal consensus, the majority of studies and guidelines classify “elderly AML” or “older adults with AML” as those above the age of 60 years. The National Comprehensive Cancer Network (NCCN), as well as the European Society of Medical Oncology (ESMO) treatment guidelines, have adopted 60 years as a cutoff, while the American Society of Hematology (ASH) has also included 55—60 years in elderly AML [10–12]. Most landmark trials have included patients ≥65 years in their inclusion criteria. While chronological age is an important parameter, other factors, including function status, comorbidities and organ function, must be considered before categorizing as elderly AML [13, 14].

3.1 Prognosis

Although the 5-year survival of patients with AML has significantly improved from 20% in 2000 to around 35% in 2020, survival in patients aged >65 years remains dismal. According to the Surveillance, Epidemiology, and End Results (SEER) database 5-year relative survival in patients aged <50 years, 50–64 years, and ≥ 65 years are 62.2, 36.6, and 9.4%, respectively. Outcomes are even worse in patients aged >75 years with 5-year relative survival of 3.2% [15]. Poor outcomes in elderly patients are attributable to various host, disease, and treatment-related factors (Table 1). Elderly patients are more prone to adverse effects due to poor performance status (PS), multiple comorbidities, organ dysfunction, impaired cognition, and poor bone marrow reserves compared to younger ones. As a result, these patients are unfit for intensive chemotherapy, which is considered the standard of care in younger individuals. Additionally, they are more often associated with poor risk features, such as high total leucocyte count (TLC), low platelets, and adverse cytogenetic and molecular features. There is a higher likelihood of antecedent hematological disorders and therapy-related AML in the elderly population. Furthermore, there is inherent chemoresistance due to the increased expression of multidrug-resistance 1 (MDR-1) transporter protein in the cell membranes which facilitates drug efflux [16–19].

3.2 Clinical manifestations

AML can cause constitutional symptoms, symptoms due to bone marrow suppression or organ infiltration. Patients with anemia present with generalized weakness, dyspnea on exertion, and progressive pallor. Bleeding manifestations may result due to thrombocytopenia or coagulopathy. Patients are prone to infections due to a reduction in normal leukocytes. Rarely, hyperleukocytosis may cause leukostasis,
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leading to blurred vision, respiratory symptoms, or seizures. (20) Extramedullary involvement, more common with monocytic variant can present as gum hypertrophy, leukemia cutis, or central nervous system (CNS) infiltration. Hepatosplenomegaly and lymphadenopathy are observed in minority (<10%). Bone pains can occur due to the expansion of the medullary cavity by growing leukemia cells [21–23].

3.3 Pathogenesis

Elderly patients with AML have a distinct genetic landscape compared with the younger population. The favorable prognostic molecular mutations, such as NPM-1 and CEBPA, are uncommon in elderly AML [24]. Interestingly, FLT3-ITD mutation, which has an adverse prognosis is found in up to one-third of younger patients but only 15–18% in >65 years. Mutations in spliceosomes, epigenetic mutations, and those in DNA repair pathways, such as DNMT3A, SRSF2, IDH1/2, RUNX1, TET2, ASXL1, TP53, and BCOR, are more common in the elderly conferring a poor prognosis and leading to chemo-resistance and inferior survivals [25, 26].

Myeloproliferative neoplasms (MPN), aplastic anemia (AA), and premalignant conditions (Table 2), such as clonal hematopoiesis of indeterminate potential (CHIP), clonal cytopenia of unknown significance (CCUS), and myelodysplastic syndrome (MDS), are associated with a higher risk of developing AML. Mutations in DNA methylation genes, such as TET2, ASXL1, DNMT3A, and histone modifiers, such as ASXL-1 and EZH2, keep accumulating in hematopoietic stem cells and increase the risk of developing AML [27, 28]. The risk of progression to AML in patients with CHIP is 1–2% per year. CHIP is also associated with a high risk of atherosclerosis and cardiovascular events in the elderly [9, 29].

With the increasing number of cancer survivors, the incidence of therapy-related myeloid neoplasms (t-MN) is also rising and is estimated to be around 10–15% [30].Approximately, three-fourth t-MN occurs after alkylating agents and radiation exposure, and has a latency period of 5–6 years after initial exposure. These are often preceded by myelodysplasia and harbor complex karyotype and TP 53 mutation. Whereas, t-MN following exposure to topoisomerase II inhibitors has a shorter latency of 2–3 years, associated with abnormalities in KMT2A (11q23.3) and RUNX1 (21q22.1)

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Disease factors</th>
<th>Treatment-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declining performance status.</td>
<td>Higher prevalence of poor risk cytogenetic/molecular features, such as complex cytogenetics and TP53 mutation.</td>
<td>Higher expression of proteins that cause drug efflux.</td>
</tr>
<tr>
<td>Comorbidities and poor organ function.</td>
<td>High prevalence of leukocytosis and thrombocytopenia.</td>
<td>Poor tolerance to therapy.</td>
</tr>
<tr>
<td>Poor nutritional status.</td>
<td>Higher risk of t-AML.</td>
<td>Polypharmacy and drug interactions.</td>
</tr>
<tr>
<td>Impaired cognition</td>
<td>Gene mutations suggestive of antecedent myelodysplastic syndromes and AML-MRC (SRSF2, SF3B1, U2AF1, ZRSR2, BCOR, EZH2, ASXL1, STAG2).</td>
<td></td>
</tr>
</tbody>
</table>

AML—Acute myeloid leukemia, t-AML—Therapy-related acute myeloid leukemia.

Table 1. Factors associated with poor outcomes in “elderly AML” [16–20].
genes and are usually not preceded by myelodysplasia [31]. According to the European Leukemia Net (ELN), 2022 classification the term therapy-related acute myeloid leukaemia (t-AML) is no longer a separate disease entity and is classified according to molecular profiling [32]. Most of these cases present in older adults and are often associated with adverse risk molecular and cytogenetic abnormalities and have inferior survival.

### 3.4 Diagnosis

Diagnostic evaluation in a patient with suspected hematological malignancy begins with a complete blood count (CBC) and a peripheral smear examination. A bone marrow examination is required for accurate morphological evaluation, immunophenotyping, cytogenetics, and molecular analysis. It aids in confirming the diagnosis, classification, and prognostication. Immunophenotyping provides further information on classification and can be utilized for measurable residual disease (MRD) assessment. Cytogenetic analysis (G banding and FISH analysis) and molecular testing for NPM, CEBPA, and FLT3 (TKD and ITD) with polymerase chain reaction (PCR) are required for prognostication.

In the era of precision medicine, next-generation sequencing (NGS) has become an important part of initial workup as it helps in better risk stratification and therapeutic management. International consensus classification (ICC) has recently published a revision of the World Health Organization (WHO) classification of AML ([Table 3](#)). It is a more genetically defined classification that includes new genetic entities and excluded therapy-related AML (t-AML) as a separate class [33]. Risk stratification is important for prognostication as well as to decide consolidation post-remission. ELN has risk-stratified AML based on morphological, cytogenetic, fluorescent in situ hybridization (FISH), molecular testing, and NGS ([Table 4](#)) [34].

<table>
<thead>
<tr>
<th>Entity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic cytopenia of undetermined significance (ICUS).</td>
<td>Persistent cytopenia (≥ 6 months), with no somatic mutations, clonal cytogenetic abnormality, or no or mild marrow dysplasia (&lt;10%).</td>
</tr>
<tr>
<td>Idiopathic dysplasia of undetermined significance (IDUS).</td>
<td>Marrow dysplasia in ≥10% of any one or more cell lines, with no somatic mutations, clonal cytogenetic abnormality, or cytopenia.</td>
</tr>
<tr>
<td>Clonal hematopoiesis of indeterminate potential (CHIP).</td>
<td>One or more myelodysplasia-related somatic mutations with variant allele frequency &gt; 2% or clonal karyotypic abnormality in ≥2 metaphases, no cytopenia, or no or mild marrow dysplasia (&lt;10%).</td>
</tr>
<tr>
<td>Clonal cytopenia of unknown significance (CCUS).</td>
<td>One or more myelodysplasia-related somatic mutations with variant allele frequency &gt; 2% or clonal karyotypic abnormality in ≥2 metaphases, with cytopenia (≥ 4 months), but no or mild marrow dysplasia (&lt;10%).</td>
</tr>
</tbody>
</table>

Table 2. Premalignant conditions associated with myeloid neoplasms.
prior respiratory disorders). Serum creatinine, uric acid, potassium, calcium, and phosphate are important to rule out tumor lysis syndrome (TLS). A comprehensive infection workup should be performed in the presence of fever or suspicion of infection. Lumbar puncture and brain magnetic resonance imaging (MRI) are reserved
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3.5 Pretreatment assessment

Pretreatment assessment of the patient with a diagnosis of AML includes evaluation of performance status, physical functioning, and comorbidities. Eastern Cooperative Oncology Group performance status (ECOG-PS) helps in assessing general well-being and poor ECOG-PS has been associated with poor outcomes in multiple studies [35–37]. The functional assessment measured by activities of daily living (ADL) and instrumental activities of daily living (IADL) complement ECOG-PS in assessing functioning in elderly patients [38]. In addition, physical assessment using a short physical performance battery (SPPB) has been shown to predict hospitalizations and mortality among the elderly [39, 40].

Comorbidities also play a role in predicting survival and toxicity with treatment. Large population-based studies have shown that approximately half of the elderly patients with AML have at least one preexisting comorbidity, while one-fourth have ≥2 comorbidities. The Charlson comorbidity index (CCI) and the hematopoietic cell transplantation comorbidity index (HCT-CI) are commonly used in hematological malignancies [41]. HCT-CI was initially used for predicting non-relapse mortality in HSCT patients, but recent studies show that it can also predict early death and overall survival (OS) in AML > 60 years after receiving induction therapy [42].

Apart from chronological age, performance status, functional status, and comorbidities, other variables, such as cognition, nutritional status, social support, and

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Table 4. European leukemia net (ELN) 2022 risk stratification of acute myeloid leukemia (AML) [34].

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Intermediate</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;21)(q22;q22.1)/RUNX1::RUNX1T1</td>
<td>Mutated NPM1 with FLT3-ITD</td>
<td>t(6;9)(p23;q34.1)/DEK::NUP214</td>
</tr>
<tr>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 Mutated NPM1 without FLT3-ITD</td>
<td>Wild-type NPM1 with FLT3-ITD</td>
<td>t(v;11q23.3)/KMT2A-rearranged</td>
</tr>
<tr>
<td>bZIP in-frame mutated CEBPA</td>
<td>t(9;11)(p21.3;q23.3)/MLLT3::KMT2A</td>
<td>t(9;22)(q34.1;q12)/BCR::ABL1</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic and/or molecular abnormalities not classified as favorable or adverse</td>
<td>t(8;16)(p11;p33)/KAT6A::CREBBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(3q26.2;q12)/MECOM(EVI2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(q26.2;q2)/MECOM(EVI2)-rearranged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−5 or del(5q); −7; −17/abn (17p)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complex karyotype, monosomal karyotype</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutated ASXL1, BCOR, EZH2, RUNXI, SF3B, SRSF2, STAG2, U2AF1, or ZRSR2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutated TP53</td>
</tr>
</tbody>
</table>

for patients with suspected neurological involvement due to AML. Human leukocyte antigen (HLA) typing may be considered in a patient with the potential for hematopoietic stem cell transplant (HSCT).

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polypharmacy, also play a key role in treatment decisions. Cognitive impairment is more frequent among the elderly and is associated with a higher risk of complications during AML treatment. A modified mini-mental scale (3MS) can be used for brief bedside cognitive assessment and includes assessing various domains of cognition (attention, concentration, orientation, memory, language, constructional praxis, fluency, and abstract thinking) [43].

Many geriatric assessment (GA) scores have been developed considering the above-mentioned domains of patient health. Comprehensive geriatric assessment (CGA) is a multidimensional approach to assess elderly patients and includes functional status, cognition, mental status, comorbidities, social status, and medications. However, it is tedious and may not be feasible for routine clinical use [44]. Lately, screening questionnaire, such as G8 screening tool, for frailty assessment has been devised for use in busy oncology clinics to help identify patients who need geriatric assessment [45]. Multiple tools are also available to categorize elderly patients into those fit for intensive chemotherapy versus those who are not, but the majority of these have been studied in solid tumors [17]. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score can be used in elderly patients with solid tumors as well as hematological malignancies to predict treatment toxicity [46].

Although we have multiple tools, these have not been integrated into clinical practice due to their complexity, paucity of time and manpower required to perform these tests, and lack of uniformity in implementation and interpretation. In general, a score of more than 1 on CCI or HCT-CI, 3-MS score < 77, SPPB <9, and ECOG PS > 2 would predict a higher risk of treatment-related morbidity and mortality with intensive chemotherapy. Patients may be broadly classified into fit, vulnerable, and frail using these variables (Table 5). However, the treating physician should base the management on their judgment as these have not been clinically validated [43].

<table>
<thead>
<tr>
<th>Fitness category</th>
<th>Parameters</th>
</tr>
</thead>
</table>
| **Fit**          | ECOG PS 0–2  
CCI ≤ 1, HCT-CI ≤ 1  
3-MS score > 77  
SPPB >9  
No impairment in ADL/IADL |
| **Unfit/vulnerable** | ECOG PS 2  
CCI < 2, HCT-CI < 2  
3MS score < 77  
SPPB <9  
Mild impairment in ADL/IADL |
| **Frail**        | ECOG PS ≥ 3  
CCI >2, HCT-CI > 2  
3MS score < 77  
SPPB <9  
Impaired ADL/IADL |

3-MS—Modified mini-mental scale, ADL—Activities of daily living, AML Acute myeloid leukemia, CCI—Charlson comorbidity index, IADL—Instrumental activities of daily living, ECOG-PS—Eastern Cooperative Oncology Group performance status, HCT-CI—Hematopoietic cell transplantation comorbidity index, and SPPB—Short physical performance battery.

Table 5.  
Suggested categorization of “elderly AML” patients.
4. Management

4.1 Management of newly diagnosed AML

Management of AML is based on the patient’s age, performance status, comorbidities, and geriatric assessment. It includes either intensive therapies (daunorubicin + cytarabine, 3 + 7), less intensive therapies, such as low-dose cytarabine (LDAC), hypomethylating agents (HMA), or best supportive care. Intensive chemotherapy is considered the standard of care for fit adults with AML, while less intensive therapies are preferred for others [10, 11]. Therefore, it is important to carefully assess patients before initiating any therapy.

Recently, the management of elderly patients (Table 6) has transformed with the introduction of targeted therapies (venetoclax and ivosidenib) in combination with HMA markedly improving the responses and survival. Many new targeted therapy approvals in the past 5 years have also modified the landscape of managing older adults with AML. With knowledge of patient physiology and disease biology, we can now better personalize the treatment and tailor it to the individual patient's needs. We will discuss the management according to the fitness of the patients as discussed in the pretreatment assessment.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Fit*</th>
<th>Unfit</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>• 3 + 7 chemotherapy +/- GO • FLT3 mutated: 3 + 7 + midostaurin • t-AML, AML-MRC: CPX-351 • Complex karyotype/monosomal karyotype/ Tp 53- HMA+ Venetoclax</td>
<td>• HMA+ Venetoclax • LDAC+ Venetoclax • LDAC+ Gladegeib • IDH-1 mutated: ivosidenib+ azacytidine • IDH-2 mutated: enasidenib+ azacytidine</td>
<td>• Clinical trials • Best supportive care (BSC) and transfusion support • LDAC • HMA monotherapy</td>
</tr>
<tr>
<td>Consolidation</td>
<td>• HiDAC +/- midostaurin or GO* • Allogenic HSCT**</td>
<td>Same as induction • Allogenic HSCT** in selected cases</td>
<td>Same as induction</td>
</tr>
</tbody>
</table>


*Adverse risk.

#Maintenance therapy with oral azacytidine (onureg) or sorafenib (in FLT3 mutated cases).

Table 6. Summary of management of newly diagnosed AML in older adults.

5. Patients fit for intensive chemotherapy

5.1 Induction therapy

The goal of therapy in these patients is to achieve swift remission with minimizing treatment-related mortality or morbidity. 3+ 7 chemotherapy has been a gold
standard with cytarabine (100–200 mg/m2/day daily infusion for days 1 to 7) combined with either daunorubicin (60 mg/m2/day for days 1 to 3) or idarubicin (12 mg/m2/day for day 1 to 3) since almost five decades [47]. Many modifications have been suggested like the addition of 6-thioguanine, dose intensification of daunorubicin to 90 mg/m2, or increasing cytarabine infusion to 10 days but none of them offered any survival benefit [48, 49]. As a result, 3 + 7 chemotherapy remained the standard of care until two seminal studies from the last decade, RATIFY and ALFA-0701, showed improved responses and survivals when 3 + 7 chemotherapy was combined with FLT3 inhibitor midostaurin (in FLT3 positive cases) or anti-CD 33 monoclonal antibody gemtuzumab ozogamicin (GO), respectively [50, 51]. In elderly patients with secondary AML (t-AML or AML MRC) CPX-351 (Vyxeos) is preferred as it has shown improved survival with lesser toxicity compared to the standard 3 + 7 regimen [52]. Response evaluation is based on residual blast percentage on bone marrow examination and recovery of peripheral blood counts (Table 7) [34].

5.2 Consolidation therapy

Consolidation therapy post-achieving remission is based on baseline cytogenetic/molecular risk stratification (Table 4) [34]. Favorable-risk patients have good long-term outcomes with high-dose cytarabine (HiDAC). However, optimal dose, schedule, and number of cycles are a topic of debate [53–56]. The addition of midostaurin (in FLT3-mutated cases) and GO with consolidation chemotherapy should be considered.

For patients with high risk, allogenic HSCT is preferred due to suboptimal outcomes with chemotherapy alone. It is important to consider the risk of transplant-related mortality (TRM) and expected benefits before proceeding to HSCT. The decision should be made after carefully assessing the risk of TRM based on age,
comorbidities, donor source, and conditioning regimen [57]. Myeloablative conditioning (MAC) improves relapse-free survival (RFS) but is associated with higher TRM. Reduced-intensity conditioning (RIC) regimens may not confer similar benefits as they depend mainly on the graft versus leukemia (GVL) effect but have lower TRM [58]. Recent data suggest that RIC transplant confers a survival benefit compared to chemotherapy in elderly AML patients with intermediate or poor risk cytogenetics (5-year OS 37 vs. 20%, HR-0.67, p < 0.001) [59].

Consolidation therapy for patients with intermediate-risk disease has been debated due to the lack of clear survival benefits and risks of TRM with HSCT. Young fit patients without comorbidities may derive greater benefit from HSCT due to lower TRM, while elderly patients with known comorbidities are at risk of increased TRM. However, with advancements in conditioning regimens (NMA and RIC) and greater experience with alternate donor sources (haploidentical, matched unrelated donor and cord blood) more patients are considered eligible for HSCT [60–62]. Maintenance therapy with oral azacytidine (Onureg) has demonstrated a survival benefit in patients who achieved remission but are unable to tolerate an intensive consolidation regimen or are unfit for transplant [63].

5.3 Patients unfit for intensive chemotherapy

The goal of therapy in these patients is to achieve a durable response and maintain it by continuing the therapy until relapse or intolerable side effects. Conventionally, LDAC (20 mg/m² per day as a subcutaneous injection for 10 consecutive days every 28 days) and HMAs (azacytidine 75 mg/m² daily for 7 days every 28 days or decitabine 20 mg/m² daily for 5 days every 28 days) were the mainstay of therapy for elderly AML unfit for intensive chemotherapy. These therapies have low response rates (CR rates ranging from 10 to 30%) and a median OS of fewer than 12 months [14, 64].

With a better understanding of disease biology, a new class of drugs promoting apoptosis in cancer cells has been introduced. The intrinsic pathway of apoptosis is regulated by the B-cell lymphoma 2 (BCL-2) family of proapoptotic and antiapoptotic proteins. Proapoptotic proteins, such as BAX, BIM, and BAK [share BCL-2 homology 3 (BH3) domain], promote apoptosis by triggering mitochondrial outer membrane permeabilization (MOMP). B-cell lymphoma 2 (BCL-2) protein is a key regulator of the apoptotic pathway in mitochondria, which helps in the survival of myeloid blasts by sequestering proapoptotic BAX [65]. Venetoclax is a selective oral BCL-2 inhibitor that acts by binding to the BH-3 binding groove of BCL-2 and displaces BH-3 proteins, such as BAX and BIM, to induce apoptosis. Thus, it is also called the BH-3 mimetic drug. In the VIALE-A study in newly diagnosed AML ≥ 75 years or preexisting comorbidities, the combination of venetoclax with azacytidine demonstrated complete response (CR) rates of 36.7% and CR + CR with incomplete hematological recovery (CRi) rate of 66.4%. Median OS was significantly better than azacytidine and placebo, 14.7 months vs. 9.6 months (HR: 0.66, 95% CI 0.52–0.85, p-value <0.001). Venetoclax was administered as a ramp-up schedule in the first cycle, starting at 100 mg on day 1, 200 mg on days 2–3 and 400 mg, thereafter oral once daily for a total 28 days cycle [66]. Similarly, in the VIALE-C study, newly diagnosed AML ≥ 75 years or preexisting comorbidities were randomized to venetoclax plus LDAC or LDAC alone. CR + CRi was observed in 48% in combination versus 13% in LDAC alone. At primary analysis, the median OS was better 7.2 months vs. 4.1 months (HR 0.70; 95% CI 0.52–1.07; p-value 0.11) but not statistically significant [67]. Magrolizumab, an anti-CD47 antibody that blocks the “do not eat me signal” on
macrophages, has demonstrated good efficacy in old or unfit treatment naïve as well as relapsed/refractory AML. In a phase 2 study, the combination of magrolizumab, azacytidine, and venetoclax demonstrated CR rates in 86% of newly diagnosed AML patients (82% adverse risk and 47% TP53 mutated) [68].

Somatic mutations in isocitrate dehydrogenase genes IDH-1 and IDH-2 may be detected in up to 10 and 12% of patients with AML. It leads to the generation of D-2-hydroxyglutarate, which disrupts cellular metabolism and epigenetic control resulting in carcinogenesis [69]. Targeted therapy with oral IDH-1 inhibitor drug, ivosidenib either alone or in combination with HMA has been recently approved in elderly AML ≥ 75 years who are ineligible for intensive chemotherapy. In patients with de-novo or secondary AML with IDH-1 mutation ineligible for intensive chemotherapy, ivosidenib 500 mg oral daily achieved CR in 30.3% and CR + CR with partial hematologic recovery (CRh) in 42.4% [70]. A combination of ivosidenib with azacytidine was compared with azacytidine alone in phase 3 AGILE study in newly diagnosed IDH1-mutated AML ineligible for intensive chemotherapy, improved median OS (24 vs. 79 months, HR 0.44, 95% CI 0.27–0.73, p-value = 0.001), CR (47 vs. 15%) was observed with the combination [71]. Enasidenib, an oral IDH-2 inhibitor has also been tried in newly diagnosed IDH-2 mutated AML. Overall responses were seen in only 30% with CR in 18%. Similarly, a combination of enasidenib with azacytidine has been tested in newly diagnosed IDH-2 mutated AML in phase Ib/II trial. Responses were observed in 74% in combination compared to 36% with azacytidine alone [72].

Combination of LDAC with oral hedgehog inhibitor glasdegib has also shown improved OS (8.8 months vs. 4.9 months, HR 0.52, 80% CI 0.39–0.67, p-value 0.0004) in AML and high-risk MDS unfit for intensive chemotherapy compared with LDAC alone [73].

Currently, a combination of venetoclax with azacytidine is considered the standard of care for elderly patients with newly diagnosed AML unfit for intensive therapy. In patients, ≥ 75 years with IDH-1 mutation combination of ivosidenib with azacytidine is also approved. However, if these newer molecules cannot be accessed due to cost or availability, HMA remains the treatment of choice for these patients.

6. Frail patients

Management of frail elderly AML patients should aim at symptomatic relief and improving the quality of life. Patients with hyperleukocytosis may be given cytoreductive therapy with hydroxyurea. Supportive care includes blood transfusions and prophylactic anti-microbials. Based on physician discretion LDAC or HMA may be started. Single-agent targeted therapy, such as IDH or FLT-3 inhibitors, may demonstrate some benefit.
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