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Personalizing therapy for older adults with acute myeloid leukemia: Role of geriatric assessment and genetic profiling

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ABSTRACT

Acute myeloid leukemia (AML) presents therapeutic challenges in older adults because of high-risk leukemia biology conferring chemoresistance, and poor functional status resulting in increased therapy-related toxicities. Recent FDA approval of 8 new drugs for AML has increased therapeutic armamentarium and also provides effective low-intensity treatment options. Rational therapy selection strategies that consider individual's risk of therapy-related toxicities and probability of disease control can maximize benefits of available treatments. Studies have demonstrated that fitness level, measured by geriatric assessment can predict therapy-related toxicities, whereas cytogenetic and mutation results correlate with the probability of responses to standard chemotherapy. We are approaching an era when we move from "one size fits all" approach to personalized therapy selection based on geriatric assessment, genetic and molecular profiling.

Introduction

The therapeutic landscape of acute myeloid leukemia (AML) has changed with the recent discoveries of novel and targeted therapies. The FDA approval of 8 new AML drugs in a two-year time is unprecedented and is the result of decades of work in leukemia biology and therapeutics. The availability of multiple therapies requires us to develop rational therapy selection strategies to maximize the benefit of therapies and minimize the risk of toxicities for an individual patient. This review will focus on selection of an upfront chemotherapy option for older adults aged ≥60 years with AML, other than acute promyelocytic leukemia.

The fundamental challenges in selecting a therapy option for an older adult include difficulty in predicting the risk of chemotherapy-related toxicities and identifying the probability of achieving remission and long-term disease control [1]. Older adults often have multiple comorbidities and poor functional status that increases the risk of toxicities [2]. AML in older adults is frequently associated with high-risk genetic and molecular features and chemotherapy resistance [3,4]. Thus, older adults face a double threat of higher toxicity and lower efficacy. These issues may be overcome, to some extent, with the incorporation of geriatric assessment, and genetic and molecular features of AML in selecting therapy. Therapy selection should also consider patient's preferences and goals of care [5]. For fit older adults, goals of care may include achievement of complete remission, consolidation with allogeneic stem cell transplant and long-term survival. For older adults with poor functional or cognitive status, goals of care may include reduction in therapy-related toxicities, improvement in quality of life, disease control and extension of survival to the extent possible.

Therapy options for initial management of AML

Available therapy options for AML may be divided into intensive or low-intensity chemotherapy. Intensive chemotherapy options include cytarabine and anthracycline ("7 + 3") with or without gemtuzumab or midostaurin, or CPX-351 (liposomal preparation of cytarabine and daunorubicin in fixed 5:1 M ratio) (Table 1). Low-intensity chemotherapy options include hypomethylating agent (HMA) such as azacitidine or decitabine, venetoclax in combination with HMA or low-dose cytarabine (LDAC), glasdegib in combination with LDAC, or single-agent gemtuzumab ozogamicin. Other off-label options in use include single-agent ivosidenib (IDH1 inhibitor) or enasidenib (IDH2 inhibitor), or HMA in combination with targeted or novel agents such as FLT3 inhibitors, or IDH 1 or IDH2 inhibitors. Additional promising therapies not currently approved but undergoing phase III trials for upfront use are listed in Table 2.

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Table 1
Landmark trials of newly approved agents for management of acute myeloid leukemia.

Study drugs/arms	Study population	Phase, N	CR, CRi or CRp	OS	Comments
Intensive therapy options for upfront use					
7 + 3 with vs. without gemtuzumab ozogamicin [34]	50–70 years with *de-novo* AML	Phase 3, n = 280	81% vs. 75%, p = 0.2	53% vs. 42% at 2 years, p = 0.04*	Higher EFS benefit for good- and intermediate-risk AML
7 + 3 with vs. without midostaurin [38]	< 60 years old with FLT3 ITD or TKD mutation	Phase 3, n = 717	59% vs. 54% CR, p = 0.1	51% vs. 44% at 4 years, p = 0.009	Similar benefit across FLT3 subtypes, data reflect outcomes in younger adults
CPX-351 vs. 7 + 3 [25]	60–75 years with secondary or therapy-related AML, or AML MRC	Phase 3, n = 309	48% vs. 33%, p = 0.02	31% vs. 12% at 2 years, p = 0.003	No CR/CRi or OS benefit in patients with prior HMA exposure (subset analysis)†
Low-intensity therapy options for upfront use					
Venetoclax and hypomethylating agent [77]	Mostly ≥ 75 years or comorbidities precluding intensive induction	Phase 1b, n = 145	67%	17 months; 46% at 2 years	60% response rate in high-risk AML, 71% in IDH1/2 mutated AML
Venetoclax and LDAC [87,88]	Mostly ≥ 75 years or comorbidities precluding intensive induction	Phase 1/2, n = 82	42% (54% CR/CRi and 32% MRD response for those treated with 600 mg venetoclax)	10 months median, 27% at 2 years	30% response rate in TP53 mutated AML, 72% in IDH1/2 mutated AML, 44% in FLT3 mutated AML
Glasdegib and LDAC vs. LDAC [80]	≥75 years or comorbidities precluding intensive induction	Randomized phase 2, n = 132 (16 MDS patients)	24% vs. 5% CR/CRi	8 vs. 5 months, p = 0.002	OS 4 vs. 2 months in poor-risk patients
Gemtuzumab ozogamicin vs. BSC including hydroxyurea [79]	≥61 years and unfit for intensive induction	Phase 3, n = 237	27% with gemtuzumab	24% vs. 10% at 1 year, p = 0.005	24% of patients ≥ 81 years‡
Newly approved agents for relapsed or refractory AML					
Ivosidenib [52]	≥18 years (median 68 years) with IDH1 mutation (39% with secondary or therapy related AML; 31% with poor-risk AML)	Phase 1, n = 258	30%	9 months, median OS	Lower response rate with higher co-mutational burden, with receptor tyrosine kinase pathway mutations, multiple lines of therapies¶
Enasidenib [53]	≥18 years (median 67 years) with IDH2 mutation (27% with AML MRC, 33% with poor-risk AML)	Phase 1/2, n = 239	27%	9 months, median OS	Lower response rate with higher co-mutational burden, with RAS pathway mutations¶
Gilteritinib [43,44]	≥18 years (41% ≥65 years) with FLT3 mutation	Phase III trial, interim analysis of 138 patients	21%	Not available	No CR/CRi in 12 FLT3 TKD mutated patients

AML acute myeloid leukemia, BSC best supportive care, CR complete remission, CRi CR with incomplete count recovery, CRp CR with incomplete platelet recovery, EFS event-free survival, HMA hypomethylating agent, LDAC low-dose cytarabine, MRC myelodysplasia-related changes, N number of patients in the trial, OS overall survival.

* Addition of gemtuzumab improved event-free survival (41% vs. 17% at 2 years), primary endpoint of the study including among subgroups of patients with NPM1 mutated AML and FLT3 ITD mutated AML. OS benefit not seen in subgroup analysis except for FLT3 ITD mutated patients.

† For FLT3 mutated patients, CPX-351, compared to 7 + 3, resulted in a higher CR/CRi rate (68% vs. 27%) without statistically significant increase in OS (median OS, 10 vs. 5 months).

‡ The OS benefit with GO was consistent across most subgroups, and was especially apparent in patients with high CD33 expression status, in those with favorable/intermediate cytogenetic risk profile, and in women.

¶ Variant allele frequency of IDH1 or IDH2 mutation does not affect responses. Also, single co-occurring mutation does not affect responses. Both ivosidenib and enasidenib can achieve molecular remission in a subset of patients who achieve CR.

Table 2
Preliminary results of agents undergoing phase III trial for upfront management of acute myeloid leukemia in older adults unfit for intensive chemotherapy.

Study drugs/arms	Phase, N	Response rate	Median OS	Ongoing phase III trial
Guadecitabine, (2 different doses) [57]	Randomized phase 2, n = 107	53% CR/CRi, no difference among high-risk AML or sAML	10 months, no difference among high-risk AML or sAML	Guadecitabine vs. treatment choice (NCT02920008)
Ten-day decitabine [50]	Phase 2, n = 53	64% CR/CRi (74–75% CR/CRi among sAML or tAML and high-risk AML)*	55 weeks	10-day decitabine vs. 7 + 3 (NCT02172872)
Pracinostat and azacitidine [56]	Phase 2, n = 50	52% CR/CRi/MLFS	62% at 1-year, median OS 13 months in high-risk AML	Azacitidine with or without pracinostat (NCT03151408)
Pevonedistat and azacitidine [55]	Phase 1b, n = 64	50% CR/CRi/PR, no difference in de novo vs sAML, and int vs high risk AML; 80% CR/PR in TP53 mutated AML (n = 5)	7 months	Azacitidine with or without pevonedistat in low-blast AML, CMML, high-risk MDS (NCT03268954)
Glasdegib with LDAC, decitabine or 7 + 3 [89]	Phase 1b, n = 52 including 7 MDS	CR/CRi 9%, 29% and 54%	4, 11 and 35 months	Azacitidine or 7 + 3, with or without glasdegib (NCT03416179)
Ivosidenib or enasidenib and azacitidine [84] in IDH mutated†	Phase 1b/2, n = 17 (ongoing)	53% CR/CRi/PR	NA	Azacitidine with or without ivosidenib (NCT03173248)
Azacitidine and nivolumab [90]‡	Phase 2, n = 10 (ongoing)	55% CR/CRp	NA	4-arm phase II/III trial, azacitidine alone, with nivolumab or midostaurin, or decitabine and cytarabine (NCT03092674)
Uproleselan (GMI-1271) and 7 + 3¶ [54]	Part of a phase 2 trial, n = 25	72% CR/CRi, 69% among sAML	52% at 1 year; median OS of 10 months for sAML	7 + 3 with or without uproleselan (phase II/III trial, NCT03701308)

AML acute myeloid leukemia, CMML chronic myelomonocytic leukemia, CR complete remission, CRi CR with incomplete count recovery, CRp CR with incomplete platelet recovery, MDS myelodysplastic syndrome, MLFS morphologic leukemia-free state, N number of patients in the trial, NA not available, OS overall survival, PR partial remission, sAML secondary AML, tAML therapy-related AML

* Another study [51] also demonstrated a high response rate among patients with AML and myelodysplastic syndrome with high-risk cytogenetic (67%) and TP53 mutation (100%) with 10-day decitabine.

† An ongoing phase 1 trial of single-agent ivosidenib in newly diagnosed IDH1 mutated AML patients demonstrated a CR/CR with incomplete hematological recovery (CRh) of 41% among 34 patients treated with a dose of 500 mg daily [91]. Early results of a phase 1b/II sub-study from the BEAT AML Master Trial demonstrated a CR/CRi rate of 43% with enasidenib monotherapy in 23 older adults with newly diagnosed AML [92]. Another phase 1 trial of ivosidenib or enasidenib in combination with intensive chemotherapy in IDH mutated AML (n = 134) demonstrated high rates of CR/CRi/CRp among de novo and sAML patients treated with ivosidenib (93% and 46%) and enasidenib (73% and 63%). MRD negative rates were 89% and 58% for IDH1 and IDH2 mutated patients, respectively [93].

‡ Nivolumab in combination with idarubicin and intermediate-dose cytarabine in newly diagnosed AML or high-risk MDS patients aged 18–65 years resulted in a CR/CRi of 77%, MRD negativity rate of 53% and median OS of 18 months (versus 13 months in historical cohort, p = 0.2) [94].

¶ No grade 3/4 mucositis was seen with uproleselan and 7 + 3.

Geriatric assessment: Predicting chemotherapy tolerance

Geriatric assessment examines multiple health domains including comorbidities, physical function, cognition, presence of depression or geriatric syndromes (e.g. falls, delirium, urinary or stool incontinence), malnutrition, polypharmacy and social isolation [6–8]. Studies in patients with various solid and hematological malignancies have demonstrated that geriatric assessment can predict chemotherapy-related toxicities and overall survival (OS) [6,9,10]. Serious treatment-related toxicities can worsen physical function, cognition and quality of life of older adults, and increase early mortality and hence, attempts should be made to avoid toxicities. A phase III randomized multicenter trial in advanced non–small-cell lung cancer demonstrated a reduction in toxicity with geriatric assessment-guided therapy selection compared to treatments based on age and performance status [11]. Identification of specific health impairments can also allow opportunities to tailor supportive care interventions such as physical therapy, nutritional support, or treatment of depression or geriatric syndromes to improve functional status [7,12]. Based on these reasons, the International Society of Geriatric Oncology [8], American Society of Clinical Oncology [7], National Comprehensive Cancer Network guidelines [13] and Cancer and Aging Research Group [14] recommend integrating geriatric assessment for therapeutic decision-making and supportive care planning.

Klepin et al., and other groups have demonstrated the feasibility of geriatric assessment before initiation of treatment in AML [15], and its ability to uncover physical and cognitive [16] impairments even among patients considered fit by standard oncological evaluation [15,17]. Feasibility of geriatric assessment has also been demonstrated in multicenter trials of patients treated with HMA [17,18] or intensive chemotherapy (for example, in trials conducted through the Alliance in Clinical Trials in Oncology). Geriatric assessment can predict the risk of chemotherapy-related toxicities and OS in AML [2]. Three domains of geriatric assessment, cognition, physical function and comorbidity burden may be particularly important [2,19,20]. Impaired cognition (hazard ratio, HR 2.5, 95% confidence interval, CI 1.2–5.5) and impaired physical function measured by short physical performance battery (HR 2.2, 95% CI 1.1–4.6) were associated with a higher risk of mortality among older adults treated with intensive chemotherapy [2]. A hematopoietic cell transplant comorbidity index (HCT CI) predicted a higher risk of mortality in 1100 newly diagnosed adults with AML, aged 20–89 years (median 60 years), who were predominantly treated with intensive chemotherapy. The probability of one-year OS decreased with increasing score on HCT CI (70–74% for a score of 0–2, and 30–50% for a score of ≥ 3) [21]. Taken together, these studies indicate that older adults who are physically fit and do not have cognitive impairment or high comorbidity burden (e.g. a score of ≥ 3 on HCT CI) can tolerate intensive chemotherapy. Conversely, unfit patients are likely to have significant toxicities from intensive chemotherapy, poor quality of life, and poor OS. Hence, geriatric assessment should include measures of cognition (mini-mental state exam, or Montreal Cognitive Assessment, MOCA), physical function (instrumental activities of daily living, IADL or short physical performance battery, SPPB) and comorbidities (HCT CI) at the least. Further details regarding comprehensive geriatric assessment and screening tests for frailty assessment, care models and supportive care management are described in recent reviews [6,7].

While various components of geriatric assessment are prognostic, prospective trials using geriatric assessment-guided treatments have not been published yet. Key trials that have resulted in approval of drugs provide information on study participants' age, performance status and comorbidities but not detailed geriatric assessment. This fact indicates that future trials in older patients should utilize and report the results of geriatric assessment. The limitation of other definitions to identify older patients unfit for intensive chemotherapy is highlighted by the European Leukemia Net (ELN) recommendations that indicate, "firm criteria to consider older patients unfit for intensive induction therapy cannot be provided." Both the ELN [22] and National Comprehensive Cancer Network (NCCN) guidelines [23] recommend taking into consideration poor performance status, significant comorbidities and adverse cytogenetics or molecular mutations to decide against intensive chemotherapy. The NCCN guidelines [23] highlight that "comprehensive geriatric assessments are complementary to assessment of comorbid conditions and are emerging as better predictive tools of functional status."

Genetic and molecular profiling: Predicting efficacy

Multiple large studies demonstrate the prognostic value of cytogenetic risk categories in AML including in older adults specifically [4,24]. Patients with high-risk AML are less likely to obtain benefit from intensive chemotherapy such as 7 + 3. For instance, in the phase III randomized trial assessing the role of dose-escalation of anthracycline as a part of 7 + 3 in older adults, the probability of complete remission (CR) rate (82% vs. 60–65% vs. 34–56%) and two-year OS (60% vs. 31–34% vs. 4–19%) significantly differed between good-, intermediate- and high-risk AML [24]. Older adults with secondary AML or treatment-related AML are less likely to benefit from intensive chemotherapy; the CR and two-year OS rates with 7 + 3 were 40% and 12% respectively in a recent phase III trial comparing 7 + 3 versus CPX-351 [25].

The presence of high-risk mutations such as TP53, SRSF2, ASXL1 or secondary-type mutations confers lower benefit from intensive chemotherapy [3,26,27]. The presence of secondary-type mutations such as SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, or STAG2 identifies a group of *de novo* AML in older adult that behaves like a secondary AML. Approximately half of patients with these mutations do not achieve a CR after intensive chemotherapy [3]. The presence of ASXL1 or SRSF2 mutations and particularly concurrent presence of both mutations are associated with poor prognosis [26]. Overall, the presence of either high-risk cytogenetic or high-risk mutations confers chemotherapy resistance. In such high-risk patients, the use of intensive therapy is associated with low rates of CR and poor OS. For these reasons, the NCCN guidelines [23] recommend to use karyotype and several molecular markers for risk stratification and to guide therapy. The ELN guidelines [22] recommend that the results from cytogenetics be obtained preferably within 5 to 7 days, and NPM1 and FLT3 mutational screening within 48 to 72 h. This may require the use of circulating blasts for genetic testing or quickly performing a bone marrow aspirate and biopsy.

Clinico-genetic risk stratification and therapy selection

Multidisciplinary team approach and development of geriatric leukemia program are important aspects of caring older adults with AML [1]. Early integration of geriatricians, palliative care specialists, physical therapists, social workers, and other specialists can identify health impairments, optimize functional status and management of complex comorbidities, develop supportive care interventions throughout the course of treatment, and provide useful insights regarding patients' goals of care. Palliative care is significantly underutilized and early integration of palliative care should be a goal [28]. Collaboration with genetic and molecular laboratories should be established to expedite the results of genetic and molecular analyses. Such results should be made available as early as 5–7 days of specimen collection and should guide therapy selection. Awaiting the results of genetic and molecular test for a few days before initiating therapy is not associated with worsening of outcomes in stable older adults with AML [29]. While waiting for genetic and molecular results, patients who are unfit, or have multiple comorbidities, fevers, organ dysfunction or other concerns may need to be admitted in the hospital for close monitoring and treatment of leukemic complications. The BEAT AML trial has established the feasibility of rapid precision medicine approach in older adults with newly diagnosed AML. This trial opened with 3 arms but currently has 11 treatment arms with 7 novel agents, which are

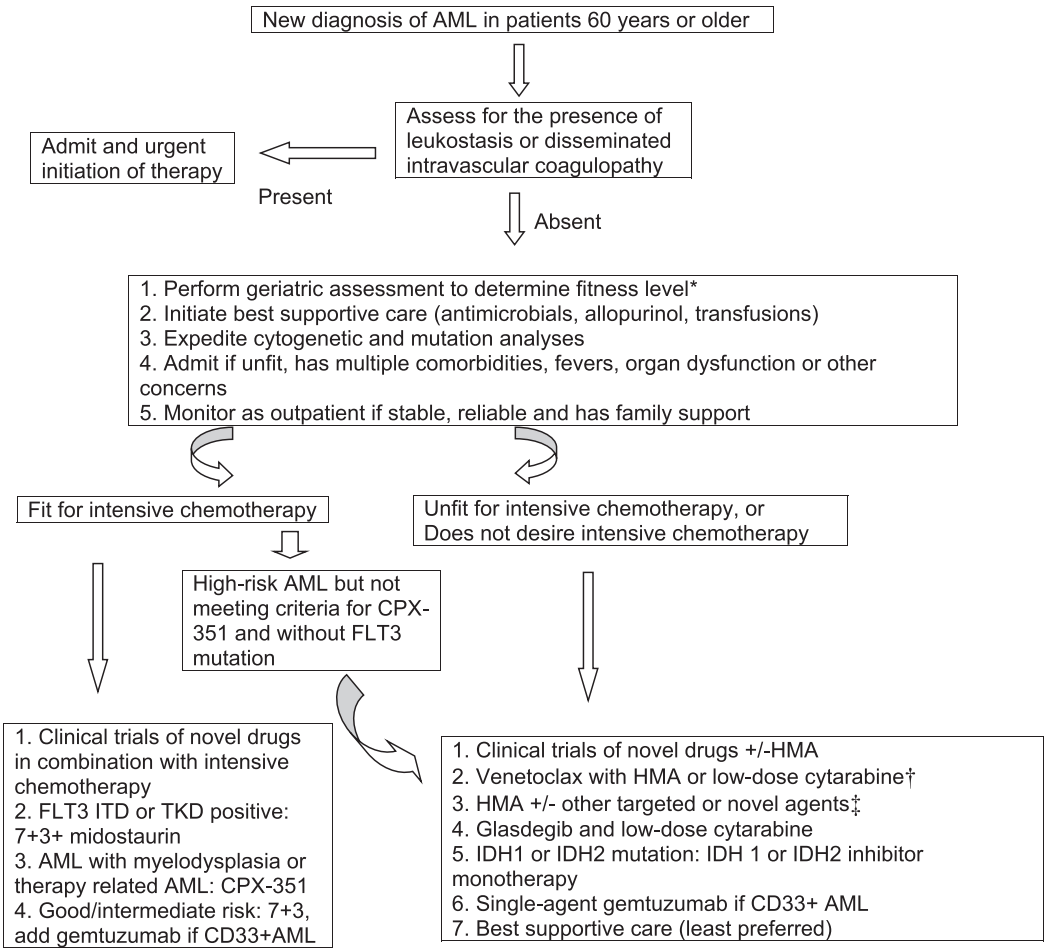

Fig. 1. Selection of therapy for older adults with newly diagnosed acute myeloid leukemia (AML), other than acute promyelocytic leukemia. HMA indicate hypomethylating agent. *Older adults who have poor physical function measured by instrumental activities of daily living or short physical performance battery, cognitive impairment (e.g. Montreal Cognitive Assessment of < 25) or high comorbidity burden (e.g. a score of ≥3 on hematopoietic cell transplant comorbidity index) may be considered unfit or poor candidate for intensive chemotherapy. †Venetoclax in combination with hypomethylating agent, given its high efficacy, may be the preferred low-intensity option for patients who can tolerate the combination. ‡Other novel and targeted agents in current use include ivosidenib (IDH1 mutated AML), enasidenib (IDH2 mutated AML), gemtuzumab ozogamicin (CD33 + AML) or FLT3 inhibitors.

assigned based on cytogenetic and molecular characteristics of AML. The initial report of this trial demonstrated that 210 out of 268 patients received treatment assignment, about 95% of whom received assignment within 7 days. Early death and disease progression are uncommon outside of MLL rearranged AML, promising efficacy has been observed in one phase 2 sub-study (enasidenib +/- HMA: 43% CR or CR with incomplete count recovery, CRi rate), and three additional studies have completed phase 1b dose escalation for combined novel agent + HMA therapy [30].

Selection of specific chemotherapy regimen requires consideration of patient's fitness level, measured preferably by geriatric assessment, cytogenetic and molecular features of AML, and patients' preferences including a possibility of financial toxicities (Fig. 1). Patients who have high-risk cytogenetic features or mutations are less likely to achieve CR and long-term disease control with intensive chemotherapy. Unfit patients with poor functional status, or multiple comorbidities are at a higher risk of significant toxicities, frequent hospitalization, decline in functional status [31] and quality of life [32], and higher early mortality [33]. For these reasons, outside of clinical trials of novel therapies in combination with standard induction, intensive chemotherapy may be limited to fit patients with good- or intermediate-risk AML or patients meeting indication for CPX-351, who desire long-term disease control and accept a risk of significant toxicities. At the University of Nebraska Medical Center, we are investigating the feasibility and role of genetic results and geriatric assessment-guided therapy selection in older adults with AML (NCT03226418). In our trial, patients with significant physical or cognitive impairment (measured by ADL, IADL, SPPB and MOCA) or HCT CI of ≥3 (≥5 in therapy-related AML, to allow the use of CPX-351) do not receive intensive chemotherapy. Additionally, patients' preferences of desired level of disease control, acceptability of toxicities of specific treatment, characteristics and burden of treatment (e.g. inpatient versus outpatient administration) can guide therapy selection [5].

Treatment of AML in fit older adults

Good or intermediate risk AML: Fit older adults with good-risk AML treated with standard 7 + 3 achieve a high complete remission rate (up to 82%) and OS (60% at 2 years) [24]. Among good-risk AML, intensive chemotherapy may be able to control disease for a long time without the use of allogeneic hematopoietic cell transplant (HCT). The probability of CR (60–65%) and OS (31–34% at 2 years) is generally considered acceptable among patients with intermediate-risk AML as well [24]. Intensive chemotherapy can achieve remission faster, may achieve minimal residual disease negative status and allow use of HCT in patients with intermediate-risk AML. As more effective treatment

options are approved, and longer follow-up data are available with newer treatments, the use of intensive chemotherapy for intermediate-risk AML may decline in the future. Conversely, the use of geriatric assessment may allow selection of older adults who have lower risk of toxicities and early mortality, thus reducing harm with intensive chemotherapy.

The addition of fractionated doses of gemtuzumab ozogamicin to 7 + 3 increases event-free survival (EFS) (41% vs. 17% at 2 years), particularly among good- and intermediate-risk AML [34], hence is recommended for good- and intermediate-risk CD33 + AML. A phase 3 trial in NPM1-mutated AML demonstrated that the addition of gemtuzumab ozogamicin to intensive chemotherapy (idarubicin, cytarabine, etoposide and arsenic trioxide) increased induction-related mortality (7% vs 3%, p = 0.02), and decreased risk of relapse (p = 0.02) but did not affect event-free survival. This trial utilized etoposide and arsenic trioxide in addition to idarubicin and cytarabine, and induction therapy consisted of two cycles of intensive chemotherapy [35]. Such differences may explain the discrepancy in the results of this trial.

In patients with intermediate-risk AML, who are planned for HCT, concern exists that the use of gemtuzumab ozogamicin may increase the risk of veno-occlusive disease. Hence, an interval of 2–3 months has been suggested between the last dose of gemtuzumab ozogamicin and HCT [36,37]. This may mean use of gemtuzumab ozogamicin with induction only. A recent analysis of the ALFA-0701 trial demonstrated similar post-transplant survival among patients who did (n = 32) versus did not (n = 53) receive gemtuzumab ozogamicin before HCT. Of 85 patients in the study, 3 patients in the gemtuzumab ozogamicin arm and 2 in the control arm (both of whom received gemtuzumab ozogamicin as follow-up therapy) developed veno-occlusive disease [37].

FLT3 ITD or TKD mutated AML: The addition of midostaurin to 7 + 3 increases OS among FLT3 ITD or TKD mutated AML among adults younger than 60 years (4-year OS 51% vs. 44%) [38]. A phase II trial has demonstrated safety of midostaurin in combination with intensive chemotherapy in adults up to the age of 70 years (34% ≥60 years) [39]. Hence, fit older adults may receive midostaurin in combination with 7 + 3 for FLT3 mutated AML. Although posaconazole reduces risk of fungal infection over fluconazole and improves survival in AML [40], drug interaction exists between midostaurin and posaconazole (strong CYP3A4 inhibitor). Isavuconazole is a moderate CYP3A4 inhibitor and may be a safer alternative [41]. Nonetheless, co-administration of midostaurin with strong CYP3A4 inhibitors, without midostaurin dose adjustment, resulted in shorter time to toxicities but no increase in midostaurin-related toxicities. Additionally, increase in dose intensity was associated with improvement in remission and survival [42]. Close monitoring of QTc interval while on midostaurin is also important in older adults, who frequently have cardiac diseases and are on other drugs (e.g. ondansetron and fluoroquinolones) that can prolong QTc interval.

For FLT3 mutated patients, CPX-351 resulted in higher response rate than the standard 7 + 3 (68% vs. 27%, p = 0.01) [25] but a combination of CPX-351 and FLT3 inhibitor has not been studied yet. The addition of gemtuzumab ozogamicin to 7 + 3 increases EFS in FLT3 ITD mutated patients [34]; however, a combination of 7 + 3 to midostaurin is generally preferred over combination with gemtuzumab ozogamicin in such patients. Currently, a combination of both midostaurin and gemtuzumab to 7 + 3 cannot be recommended because of lack of safety data.

Newer FLT3 inhibitors have shown promising results and are undergoing further evaluation in phase III trials. Gilteritinib was recently approved for relapsed/refractory AML based on response rate on an interim analysis of a phase III trial [43,44]. Preliminary results of an ongoing study in newly diagnosed AML also demonstrate high response rate with gilteritinib in combination with 7 + 3 (90–100% CR/CRi) [45]. A phase 1 trial of quizartinib in combination with 7 + 3 resulted in a CR/CRi/complete recovery with incomplete platelet recovery (CRp) rate of 74% among newly diagnosed AML patients with or without FLT3 mutation [46]. Quizartinib improved OS (27% vs. 20% at 1 year) over standard salvage chemotherapy in a phase III trial [47], and is expected to be approved in the near future for relapsed/refractory AML. A preliminary result of study using crenolanib in combination with 7 + 3 also indicated an improvement in 18-month OS (50–100% vs. 20–40% for historical control) among newly diagnosed patients with concurrent FLT3 and other driver mutation such as RUNX1, WT1 and NPM1 with DNMT3A [48]. Multiple phase III trials are ongoing among patients with newly diagnosed FLT3-mutated AML. These studies will compare crenolanib versus midostaurin in combination with 7 + 3 in younger patients (18–60 years) (NCT03258931), quizartinib versus placebo in combination with standard chemotherapy in adults up to the age of 75 years (NCT02668653) and gilteritinib versus placebo maintenance post-remission after induction and consolidation therapy (NCT02927262) or after HCT (NCT02997202). The results of these trials will provide further evidence to select specific chemoregimen for FLT3 mutated AML.

Secondary or therapy-related AML: The use of CPX-351, compared to standard 7 + 3, improves CR/CRi (48% vs. 33%), and two-year OS (31% vs. 12%) among older adults with secondary AML, AML with myelodysplasia and therapy-related AML (AML with a history of myeloproliferative disorder other than chronic myelomonocytic leukemia was excluded). Although early mortality rates were lower, and the rate of HCT was higher with CPX-351, statistical significance could not be reached. For those patients, who underwent HCT, the post-transplant mortality was significantly lower with CPX-351 in an exploratory analysis; however, the overall risk of grade ≥3 toxicities is otherwise similar to 7 + 3 [25]. For fit older adults, who are agreeable to intensive chemotherapy followed by HCT, CPX-351 is preferred treatment given the availability of phase III data. Whether CPX-351 is superior to low-intensity chemotherapy is a matter of debate [49]. Several newer treatments including ten-day decitabine,[50,51] venetoclax and HMA [52], ivosidenib [52], enasidenib [53] and newer agents such as uproleselan (GMI-1271) and 7 + 3 [54], pevonedistat and azacitidine [55], pracinostat and azacitidine [56] or guadecitabine [57] have shown promising results in patients with high-risk AML including those with secondary AML, therapy-related AML, TP53 mutated AML or AML with myelodysplasia-related changes. Preliminary results of a phase 1b trial with venetoclax in combination with intensive chemotherapy (5-day cytarabine and 2-day idarubicin) in induction treatment naïve older adults demonstrated a CR/CRi of 95% in de novo AML, 42% in secondary/therapy-related AML, 46% in AML with high-risk cytogenetic and 33% in TP53 mutated AML [58]. As further data emerge, the role of these newer treatments in these high-risk diseases may be better established.

Other high-risk AML: Older adults with high-risk AML, even if fit and eligible for intensive chemotherapy, have a low likelihood of achieving CR (56% for high-risk genetic, 34% for monosomal karyotype) and low two-year OS (19% for high-risk genetic, 4% for monosomal karyotype) when treated with 7 + 3 [24]. The addition of gemtuzumab does not improve outcomes in these patients [34,59,60]. A phase III randomized trial demonstrated that azacitidine results in similar or higher OS (10 vs. 6 months) compared to conventional care regimens (intensive chemotherapy, low-dose cytarabine or best supportive care) or intensive chemotherapy specifically (subgroup analysis) in older adults in general. Patients with high-risk cytogenetics and AML with myelodysplasia-related changes favored azacitidine [61]. Another phase 3 trial compared azacitidine to a combination of fludarabine and cytarabine following granulocyte-colony stimulating factor (G-CSF) priming. Preliminary results demonstrated similar CR rates (21% vs. 27%), and a non-significant trend towards lower MRD-negativity rate (15% vs. 26%, p = 0.28) with azacitidine, compared to intensive therapy [62]. Welch et al. [51] demonstrated a high response rate among patients with AML and myelodysplastic syndrome with high-risk cytogenetic (67%) and TP53 mutation (100%), when treated with 10-day decitabine, hence 10-

day decitabine has been used by many oncologists particularly for patients with TP53 mutation. A randomized phase II trial, however, failed to demonstrate an improvement in CR/CRi/CRp (40% vs. 43%) with 10-day versus 5-day decitabine. One-year OS was 25% for both groups, and median OS did not differ for TP-53 mutated AML based on the duration of decitabine [63]. A phase III trial aims to compare the results of 10-day decitabine versus 7 + 3 followed by HCT among older adults with AML (NCT02172872). In an exploratory analysis, the combination of venetoclax and HMA resulted in CR/CRi rate of 52–56% among patients with high-risk AML [52]. Interim analysis of another trial of venetoclax and 10-day decitabine demonstrated high CR/CRi and MRD rates in newly diagnosed AML (92% and 52%) and secondary AML (71% and 40%) [64]. Taken together, in older adults with high-risk AML, low intensity options such as HMA in combination with venetoclax are preferred over standard intensive chemotherapy regimens. Over time, as novel therapies are integrated to standard intensive chemotherapy, the treatment paradigm may shift.

Treatment of AML in unfit older adults

Unfit patients are often excluded from many clinical trials, especially those that use intensive chemotherapy, hence high-quality data for this specific population remain sparse. This frequently limits our understanding of how to optimally manage such patients and calls for large prospective trials for this specific group of patients. Until such trial results are available, questions include how to identify unfit patients, whether to select intensive or low-intensity chemotherapy and what specific regimen to use? Age and performance status by themselves can predict early mortality to some extent [33]. Several prognostic tools [65–67] (discussed elsewhere [68]) have been developed to predict probability of early mortality. As discussed previously, we prefer the use of geriatric assessment to identify prognostically important health impairments and to develop supportive care interventions. Unfit patients are generally ineligible for and unlikely to benefit from intensive chemotherapy [61,69], have higher risk of early mortality [33] and are at a higher risk of decline in functional status [31], and quality of life after intensive chemotherapy [32]. Unfit patients should be enrolled in clinical trials when possible or treated with low-intensity options. An argument may possibly be made to consider intensive chemotherapy for good-risk AML (e.g. core-binding factor or NPM1 mutated AML without other high-risk features) in older adults who are judged to likely tolerate intensive chemotherapy to fair extent despite other health impairments.

A few multicenter [70] or population-based studies [71] have indicated an improvement in survival or quality of life with the use of intensive chemotherapy; however, these studies were retrospective, the control arm received less effective chemotherapy, and a large retrospective study [72] does not support this findings. For example, in the Swedish AML Registry study [71], the control arm received therapy such as hydroxyurea, supportive care or LDAC, all less effective than HMA or HMA in combination with newer treatments. Additionally, intensive chemotherapy is rarely used in community centers (< 1% in one large study of the US community oncology practices [73]), and many older adults do not even receive chemotherapy at all. For example, in a large National Cancer Database study, one-third of adults aged 71–80 did not receive chemotherapy during the years 2003–2011 [74]. As discussed above, the randomized trials [61,75] have demonstrated HMA to be as effective as conventional care regimens including intensive chemotherapy.

For the aforementioned reasons, HMA such as azacitidine or decitabine (for 5 or 10 days) [51,61,69,76] were considered as preferred agents until recently for many unfit older adults outside of clinical trials. Azacitidine alone results in a response rate of 28% (CR/CRi) and a median OS of 10 months [61]. Ten-day decitabine has been shown by some groups to increase the complete remission rate to approximately 40–50% and median OS of approximately 1 year [50,51]; however, a randomized phase II trial did not confirm a benefit of 10-day over 5-day decitabine [63]. The integration of novel drugs to HMA can improve response rates and OS, which further argues against the use of intensive chemotherapy in such patients. With the recent approval of venetoclax, a combination of HMA with venetoclax [52] represents a good option for this patient population. The combination of venetoclax to HMA increases the overall response rate (CR, CRi or partial remission) to 63% [52,77] or higher [78]. Remission can be durable and associated with MRD negative status in some cases [78]. However, venetoclax is associated with myelosuppression and risk of serious infections. Venetoclax requires significant dose reduction when combined with posaconazole; a dose of 50–100 mg has been used [52]. Although the trials leading to approval of venetoclax and HMA required an age of ≥75 years or significant comorbidities, all enrolled patients had Eastern Cooperative Oncology Group (ECOG) PS of 0–2, hence the combination should be cautiously used in patients with poor physical function [77].

In adults in their 70 s or 80 s, single-agent gemtuzumab ozogamicin improves response rate (27% CR/CRi) and OS (median OS 5 months) over best supportive care. Gemtuzumab ozogamicin is generally well tolerated, and remission can be achieved after one cycle, faster than the results achieved with HMA. Hence, for patients who do not want to present to hospital for frequent administration of HMA, gemtuzumab ozogamicin is a good option [79]. Glasdegib and LDAC [80] is another option at centers that prefer the use of LDAC. For patients, who are not candidates for any of the aforementioned therapies or do not desire chemotherapy, best supportive care with or without hydroxyurea may be reasonable.

FLT3 mutated AML in unfit patients: FLT3 inhibitors have been studied in combination with HMA. In 27 older patients with FLT3 ITD mutated AML, the combination of sorafenib and azacitidine resulted in an overall response rate of 78% and median OS of 8.3 months [81]. A preliminary result of a phase 2/3 trial comparing gilteritinib with or without azacitidine versus azacitidine alone (NCT02752035) demonstrate a CR/CRi rate of 67% with gilteritinib in combination with azacitidine [82]. Thus, HMA in combination with a FLT3 inhibitor represent reasonable options for unfit patients. Although a relatively high response rate was seen in FLT3 mutated patients who received venetoclax and HMA combination, the number of patients is small to establish the role of combination for this specific patient population [52]. The trials using ivosidenib [83] and enasidenib [53] had only small number of patients with FLT3 mutated AML to conclude about their role in patients with both FLT3 and IDH1 or 2 mutations.

IDH1 or IDH2 mutated AML in unfit patients: Off-label use of single-agent ivosidenib [83] and enasidenib [53] may be reasonable frontline therapy in older patients given oral route of administration and overall good safety profile, and are among options suggested by the 2018 National Comprehensive Cancer Network AML guidelines [23]. Differentiation syndrome, leukocytosis with transient increase in circulating blasts and QT prolongation are important side effects of IDH1 and IDH2 inhibitor that need close monitoring and early intervention. Unlike with the use of all trans retinoic acid, differentiation syndrome with IDH 1/2 inhibitors may be delayed, is less predictable and may occur without leukocytosis [83]. Although ivosidenib has interactions with posaconazole, the concurrent use of posaconazole was allowed in the ivosidenib trial [83]. The combination of ivosidenib to azacitidine has also shown a response rate (CR, CRi or partial remission) of 54% in 11 patients with IDH1 mutated AML in an ongoing phase III trial [84]. Although the risk of grade 3–4 toxicities were higher than single-agent ivosidenib, overall the combination of ivosidenib and HMA is well tolerated, and the risk of differentiation syndrome appears to be lower than single agent on preliminary analysis. Preliminary results also showed a high response rate of 59% (CR/CRi) in 17 IDH1 or IDH2 mutated AML with the use of venetoclax and HMA [52], thus showing a promise of this combination for IDH1 or IDH2 mutated patients.

Conclusion and future perspectives

Studies and interventions are required to overcome barriers to optimize the benefits of available treatments. Such barriers include low utilization of chemotherapy [74] and allogeneic hematopoietic cell transplantation (only 5.5% adults aged 61–75 years with intermediate and high-risk AML received transplant) [85]. Allogeneic hematopoietic cell transplantation is an important modality to achieve long-term disease control in select patients [86]. HLA typing and pre-transplant evaluation should be expedited in potentially transplant-eligible patients. With the approval of effective low-intensity treatment, multiple stakeholders should collaborate to improve the receipt of chemotherapy. Other barriers include high out-of-pocket expenses and societal cost of newer therapies, difficulties in timely accessing oral chemotherapy, and lack of familiarity of providers who do not treat AML on a routine basis in managing toxicities of newer therapies.

Many trials conducted in the past do not provide enough information on the impact of treatment on functional status such as ability to perform IADL and functional independence, which are of interest to older patients. A greater understanding of patients' preferences and values can be crucial in selecting a therapy that meets patients' goal of care [5]. Data on rates of minimal residual disease clearance, and impact of co-occurring mutations on achievement of remission are important but not readily available for some therapies. We are still awaiting final read out of some of the clinical trials and long-term follow up data of newer treatments. Data from many of the ongoing phase III trials will provide crucial information and point out differences between various treatments, thus further guiding therapy selection. We expect multiple combinatorial trials of approved agents and approval of newer agents in the future, which will continue to change the therapeutic landscape of treatment of AML. While selecting and sequencing therapies may present some challenges to providers, the availability of multiple options for a fatal disease such as AML is certainly a great problem to have.

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Conflict of interest

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