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A precision medicine approach to management of acute myeloid leukemia in older adults

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Abstract

Purpose of the review: Therapy selection in older adults with acute myeloid leukemia (AML) can be challenging due to a higher incidence of high-risk cytogenetic and molecular features conferring chemo resistance and poor functional status leading to increased treatment-related toxicities. The purpose of this review is to highlight the recent advances in precision medicine in AML that have shown promise to improve outcomes of older adults.

Recent findings: The utilization of next generation sequencing to identify and target actionable mutations can influence therapy selection in one-third of patients and can result in higher response rates as well as survival compared to those who do not receive targeted therapy. Oral targeted agents are available for AML with IDH 1, IDH2 or FLT3 mutations. Low-intensity venetoclax-based regimens have shown high rates of responses in AML, particularly among those with NPM1 and IDH2 mutations; responses are often durable and associated with minimal residual disease (MRD) negativity. Multiple studies have demonstrated the prognostic significance of flow cytometric MRD, with potential implications for subsequent therapy.

Summary: Novel approaches for AML risk-stratification, MRD assessment and a precision medicine approach offer significant promise to improve survival and quality of life of older adults.

Keywords

Acute myeloid leukemia; older adults; precision medicine; minimal residual disease; targeted therapy

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Introduction

Survival of older adults above the age of 60 years with acute myeloid leukemia (AML) has largely remained unchanged with only modest improvement in the last few decades, particularly for those with high-risk genetic or molecular features; secondary AML, poor performance status or age greater than 75 years (1). Older adults often have high-risk cytogenetic and molecular features conferring chemo resistance, and poor functional status leading to increased toxicities with intensive chemotherapy(2). These challenges highlight the need for a precision medicine approach based on actionable mutations, predictive biomarkers and functional status of patients.

Genomic landscape of AML

AML is a heterogeneous disease with varying genetic and molecular abnormalities between patients and between sub clones within a patient (3). At least one driver mutation has been reported in 96-99% cases and two or more driver mutations in up to 86% of cases, and these mutations can be grouped into distinct functional categories (3, 4). An analysis of variant allele frequency (VAF) has revealed the existence of at least one subclone in addition to the dominant clone. Clonal evolution may allow an emergence of the subclone as dominant clone following disease progression (5). The spectrum of mutations in older adults differ from that in younger adults (6). Older adults have an average of 3-4 mutations per patient (8, 9). The most commonly mutations involve TET2 (42%), DNMT3A (35%), NPM1 (32%), SRSF2 (25%) and ASXL1 (21%)(9). In one study, eighty-three percent of patients harbored one or more mutations in genes involved in age-associated clonal hematopoiesis (9).

Prognostic implications of karyotypic changes and mutations

The 2017 European LeukemiaNet (ELN) risk stratification incorporates the mutational profile in addition to karyotypic abnormalities and stratifies AML into a three-group classification system: favorable, intermediate, and high. Mutations such as RUNX1, ASXL1 and TP53 mutations are independently associated with poor outcome and identify high-risk AML group (10). A study also demonstrated that the presence of secondary-type mutations identify a group of de novo AML in older adults that behave like secondary AML and confer poor prognosis (11).

The prognostic significance of some of the genetic changes and mutations may differ based on age and co-existing mutations. For instance, the disease-free survival (DFS) was worse among older adults with t(9;11) as compared to those with other abnormalities, whereas the presence of t(9;11) was associated with longer DFS in younger patients(6). Prior studies have suggested that FLT3-ITD and NPM1 mutations have less effect on outcomes of older adults (7, 9). Further, outcomes of NPM1 mutated AML also vary with co-existing mutations. More than half of older adults with NPM1 mutated AML with coexisting ASXL1, SF1, SMC1A or SRSF2 mutations were alive and disease free at 3 years in comparison to 13% of those without(8). Older patients with AML with adverse genetic features like BCOR, RUNX1, FLT3-ITD, TP53, U2AF1 or WT1 mutations, t(9;11), or complex karyotype, had DFS and OS rates of only 2% and 4%, respectively with standard chemotherapy alone (8).

Precision medicine approach to therapy selection

The number of available US Food and Drug Administration (FDA) approved targeted therapies have increased over the last few years, and several other agents are undergoing testing in clinical trials. The feasibility of a personalized approach with the use of multiple targeted therapies in AML was demonstrated by the recent Beat AML master trial where the investigators were able to assign 95% of older adults within 7 days to one of the 11 treatment arms with 7 novel agents based on the cytogenetic and molecular characteristics of AML. The OS was greater for patients enrolled in a targeted therapy arm, compared to those who elected standard therapy (12). In another study, the utilization of next generation sequencing to identify and target actionable mutations influenced therapy selection in one-third of patients with AML. Additionally, patients who did versus did not receive targeted therapy had significantly higher response rates (13).

High-risk karyotypic abnormalities and mutations also correlate with lower remission rates following intensive chemotherapy, hence serve as predictive biomarkers. In a retrospective analysis of NPM1 mutated older patients with AML, the combination of hypomethylating agent (HMA) and venetoclax showed significantly higher complete remission (CR) rates and OS compared to HMA or standard induction chemotherapy (14). Another analysis has shown that the benefit of adding gemtuzumab ozogamicin to chemotherapy in AML is mainly limited to patients with certain mutations including NPM1 mutations, mutations of signaling pathways (FLT3-ITD, FLT3-TKD, NRAS, KRAS) or those involving spliceosome deregulation such as SRSF2.(15)

For many patients, the use of targeted therapies alone or in combination with chemotherapy offer an equally or more effective treatment option compared to cytotoxic chemotherapy alone. The use of single-agent targeted therapy may also be associated with lower toxicities and better quality of life. Some of the targeted therapies are oral drugs that can avoid prolonged hospital stay. IDH inhibitors can also achieve transfusion independence even without achieving remission. The use of targeted therapies based on mutational profile is further discussed in the following sections (Figure 1).

FLT3 mutation

Several agents are available for patients with FLT3 mutated AML. A combination of midostaurin and 7 + 3 chemotherapy in patients with newly diagnosed *FLT3*-mutated AML (aged 18-59 years) improved event free survival and overall survival compared to chemotherapy alone in the phase III RATIFY trial (16). Although this trial excluded older patients, another phase II trial has demonstrated safety of midostaurin in combination with 7+3 chemotherapy in adults up to the age of 70 years with 34% of people enrolled in the trial being ≥ 60 years). In this trial, there was no difference in outcomes between older and younger patients(17).

Several next-generation FLT3 inhibitors with greater specificity and higher potency (such as gilteritinib, crenolanib, and quizartinib), currently under clinical investigations in AML, have also shown promising single-agent antileukemic activity in early clinical trials and are undergoing further evaluation in phase III trials (18). In a phase III ADMIRAL trial(19),

gilteritinib use was associated with significantly longer OS and higher CR rates than salvage chemotherapy. Notably median age in this trial was 62 years, and patients >65 years had comparable benefit to patients <65. This trial led to the approval of gilteritinib for relapsed or refractory FLT3 mutated AML.

In the QuANTUM-R phase III trial, quizartinib improved OS over the standard salvage chemotherapy and benefit was seen across both age groups patients >65 years compared to <65 years (20). The NCRI AML 18 trial is investigating the addition of quizartinib to induction regimen in patients over the age of 60 years with newly diagnosed AML; preliminary results are encouraging (21).

IDH 1 and IDH 2 mutations

The US FDA approved oral ivosidenib (IDH1 inhibitor)(22) and enasidenib (IDH2 inhibitor) (23) for relapsed or refractory AML with IDH1 and IDH2 mutations, respectively. The approvals were based on complete remission with or without count recovery in 20-30% of patients and a median OS of 9 months. A small proportion of patients also had clearance of IDH mutation. More recently, ivosidenib was approved for upfront treatment of IDH1 mutated AML in older adults unfit for intensive chemotherapy. Besides IDH inhibitors, venetoclax has also been shown to produce durable responses in IDH mutated AML in combination with low dose cytarabine (LDAC) (median OS 19.4 months) (24) and with HMA (median OS 24.4 months)(25).

TP53 mutation

TP53 mutation in AML is common in older adults, associated with complex karyotype and confer dismal outcome with a median survival of 4 to 6 months following treatment with standard cytotoxic chemotherapy (26, 27). TP53 mutated AML, compared to TP53 wild type, may have higher rates of responses to 10-day course of decitabine (28) but such responses are not durable and these patients continue to have poor survival(29). Another regimen with promising activity in TP53 mutated AML patients is venetoclax in combination with HMA or LDAC. In a phase 1b trial that evaluated venetoclax in combination with HMA in older adults unfit for intensive chemotherapy, patients with TP53 mutated AML achieved a response rate of 47% although duration of response (median 5.6 months) and OS (median 7.2 months) were still dismal compared to other subgroups (25). In another phase Ib/II trial, venetoclax in combination with LDAC achieved a response rate of around 30% (30). APR-246 is a small molecule that stabilizes mutant P53 protein in its wild type conformation leading to downstream functioning of tumor suppressor pathways. A phase Ib/II study combining APR-246 with azacitidine in patients with TP53 mutated MDS and AML showed a complete remission rate of 80% in AML with deep molecular remissions (31).

Another pathway for inactivation of p53 is degradation after binding to a molecule MDM2. Idasanutlin, a novel, potent and selective small-molecule MDM2 antagonist, thus preserves the tumor suppressor function of p53 by preventing its degradation in patients without any TP53 mutation that can alter p53 functionality(32). Idasanutlin has shown promising overall response rates (~33%) and durable responses (median > 8 months) in combination with

cytarabine in a phase I/Ib trial (33) and this combination is currently being evaluated in a phase III trial. Thus, the absence of TP53 mutation may guide selection of idasanutlin in clinical trials.

NPM1 mutation

Mutations in NPM1 are associated with favorable response to intensive chemotherapy, particularly in younger adults (3). The favorable prognosis of NPM1 mutated AML decreases with increasing age; OS is much better in patients aged 55 to 65 years treated with intensive chemotherapy compared to matched patients aged >65 years (2-year OS 70% vs. 27%)(34). In patients >65 years of age, regimens combining venetoclax with HMA or LDAC have shown good outcomes in a subset analysis of two clinical trials(35); however, the number of patients with NPM1 mutated AML in these trials were small. In a retrospective study, patients treated with HMA and venetoclax had better CR rates and OS compared to HMA alone or intensive chemotherapy alone(14). Larger studies are necessary to confirm these findings.

KIT mutation

Core-binding factor AML generally have favorable prognosis; however, the presence of KIT mutation can worsen the outcome of this subgroup (36). The combination of intensive chemotherapy and dasatinib, a multikinase inhibitor, has shown safety and promising efficacy (37, 38). A recent trial indicated that dasatinib might potentially overcome the poor prognostic effect of KIT mutation (38).

Minimal or measurable residual disease (MRD) monitoring

MRD is a valuable biomarker to investigate response quality and potentially guide post-remission decisions (39). The detection of molecular MRD during complete remission is associated with a significantly higher relapse rate (40). Molecular MRD assessment in older adults faces a few unique challenges. Older adults have a high prevalence of mutation associated with age-related clonal hematopoiesis (DNMT3A, TET2, and ASXL1) (9). Persistence of age-related clonal hematopoiesis mutations may not increase the risk of relapse, hence make the interpretation of MRD using NGS-based technologies challenging in this age group (40). Novel techniques such as targeted single-cell sequencing for MRD have the potential to detect and quantify genotypically different clones in AML patients, thus enabling the investigation of clonal evolution and distinguishing clinically relevant MRD. One small study utilising this technique in 14 AML patients showed that persistence of clones with multiple variants during remission was associated with increased risk of relapse (41). The effect of molecular MRD in outcomes of older adults has been less studied as older adults aged >65 years are often excluded in the landmark studies (40, 42, 43). Older adults are treated more often with low-intensity therapies that differ from intensive chemotherapy in dynamics of response, hence these therapies may not produce deep remission for assessment of MRD (39).

Although there are significant differences in biology and mutational profile of AML in between older and younger adults as well as significant variation in treatment strategies,

serial MRD monitoring by flow cytometry has been shown to identify patients at high risk of relapse even in older adults (44-46). Newer techniques like targeted next-generation sequencing of circulating cell-free DNA have the potential to use peripheral blood for MRD detection. A single-centre study showed that such technique can even identify clinically relevant mutations not detected in the bone marrow, thus can complement MRD assessment using bone marrow source (47). Newer therapies such as venetoclax and HMA can achieve MRD negativity in about a quarter of patients(25). MRD status has potential to inform post-remission therapy. For example, an analysis of MRD data from a phase III trial demonstrated that intensive cytarabine-based consolidation, as compared to clofarabine consolidation, may overcome the negative effect of MRD positivity at the time of CR (46). In a phase II trial, MRD-positive patients with advanced MDS or AML after conventional chemotherapy or allogeneic stem cell transplant received azacitidine maintenance for up to 24 cycles. This strategy delayed relapse in more than half of the cases in this high-risk subset compared to historical data (48). Recent studies have also demonstrated that maintenance therapy with decitabine, azacitidine and particularly oral CC486 can improve outcomes, presumably because of their effect on MRD (49-51). For these reasons, MRD assessment is increasingly captured in clinical trials, where MRD response could also serve as an endpoint for novel therapeutic agents(39).

Future directions

In recent years, older adults with AML are treated based upon cytogenetic and molecular alterations. Increasingly, novel agents are being studied in combination with intensive chemotherapy, in combination with each other as well as with low intensity therapies. The Beat AML trial has established the feasibility of using genetic profiling to assign patients to molecularly defined, subtype-specific therapies without much delay (12). Another trial demonstrated the feasibility of integrating leukemia biology (cytogenetic results) and patient's fitness (measured by geriatric assessment) in selecting intensive versus low-intensity chemotherapy in older adults; preliminary results demonstrated a decrease in early mortality as compared to the historical control (2). The role of mutational testing for MRD assessment continues to evolve in older adults. The implication of molecular MRD depends on the nature of mutations present (52). MRD-directed therapies have the potential to improve patient selection for intensive consolidation including allogeneic stem cell transplant and maintenance strategies using HMA or novel therapies (48, 53). However, many questions remain unanswered. These include identifying role of intensive chemotherapy, how to optimally combine novel therapies for various subsets of patients, development of treatment strategies of fixed duration, design of therapies that can eradicate MRD, and importantly, how to improve long-term survival of older adults.

Conclusion

Older adults present distinct treatment challenges due to the presence of high-risk AML as well as multimorbidity and frailty, thus requiring a careful approach to therapy selection. The outcomes of older adults have not improved significantly with conventional strategies in the last few decades. Novel approaches for AML risk-stratification including mutational profiling and MRD assessment, and a precision medicine approach utilizing molecularly

targeted therapies alone or in combination with chemotherapy can offer promise to improve survival and quality of life.

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Key points

1. Older adults with acute myeloid leukemia (AML) often have high-risk cytogenetic and molecular features conferring chemo resistance, and poor functional status leading to increased treatment intolerance, hence survival of older adults has largely remained unchanged in the last few decades.
2. The spectrum and relevance of mutations in older adults differ from that in younger adults.
3. The utilization of next generation sequencing to identify and target actionable mutations can influence therapy selection as well as improve response rates and survival.
4. Minimal or measurable residual disease detected by flow cytometry or next-generation sequencing can predict the risk of relapse and can have potential to inform subsequent therapy.

Figure 1. Therapy selection based on mutational profile.

AML acute myeloid leukemia, CBF core binding factor.

¹APR-246 has also shown promising results in TP53 mutated AML.

²The addition of gemtuzumab in core binding factor AML in general improves survival.