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Older Patients With Acute Myeloid Leukemia: Treatment Challenges and Future Directions

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Background: Even though acute myeloid leukemia (AML) occurs most commonly in adults ≥60 years, the treatment of AML in older patients remains a significant challenge.

Methods: We reviewed the current literature regarding patient assessment tools, treatment options, and current therapies in clinical trial for patients with AML who are ≥60 years.

Results: Our approach to the older patient with AML is evolving with better understanding of the unique disease epidemiology in this population and the development of tools to assess individual patient functional status, including grading systems for comorbidities, geriatric assessment tools, and measurements of frailty. Almost all older patients will benefit from therapy, whether intensive curative therapy, such as allogeneic stem cell transplant that should be considered whenever possible, or low-intensity therapy that should be offered with concurrent palliative care at diagnosis to improve patient survival and quality of life. To achieve the improved survival demonstrated in younger adults, older patients should also be considered for clinical trial enrollment as more studies are being designed to specifically target this unique patient population.

Conclusion: Older patients with AML are candidates for and benefit from the entire spectrum of AML therapy, including intense chemotherapy, allogeneic stem cell transplant, and clinical trial participation after thorough patient assessment. Older patients with AML would benefit from increased clinical trial enrollment and early inclusion of palliative medicine.

Keywords: *Aged, chemotherapy, leukemia–myeloid–acute, palliative medicine, transplantation–homologous*

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INTRODUCTION

Acute myeloid leukemia (AML) is a cancer predominately of the elderly with a median age of diagnosis at 68 years.[1] AML in older adults (≥60 years for the purpose of general discussion) presents a variety of patient- and disease-related challenges compared to younger populations.[2] Survival after diagnosis has an inverse relationship with age, and standard therapy remains undetermined in older adults.[2] All leukemias as a group are the eighth most common cancers in women and ninth most common cancers in men, with 20,000 diagnoses yearly, and are the fifth most common cause of cancer-related death, with 10,000 deaths in the United States each year.[3] Unlike with younger adults, we have seen little progress in improving overall survival (OS) in older adults that remains approximately (median) 4 months without AML-directed therapy and 7-12 months for intermediate- or high-risk disease treated with therapy that depends on patient- and disease-related factors.[4] With the average life expectancy in industrialized society now approaching 80 years, the need to understand how to approach older patients with AML is growing.[5] In this article, we discuss cytogenetic risk and treatment selection, selecting patients for treatment, and clinical trials for older patients with AML.

CYTOGENETIC RISK AND TREATMENT SELECTION

The epidemiology of AML is different in older adults compared to younger populations. We see an increased incidence of secondary AML after myelodysplastic syndrome (MDS) or other hematologic malignancy, an increased incidence of treatment-related AML after prior chemotherapy or radiation therapy, and an increased risk of MDS and AML after treatment with azathioprine for autoimmune diseases.[6,7] A 2015 study from the Mayo Clinic evaluated epidemiologic exposures associated with AML development and demonstrated that specific disease risk factors may be associated with specific leukemia cytogenetic risk profiles and outcomes after therapy.[8] Exposures such as obesity were associated with intermediate abnormal cytogenetics, and history of statin therapy was associated with increasing complete remission rates after

induction chemotherapy.[8] The Mayo Clinic also demonstrated significant differences in AML risk factors in patients ≥70 years, highlighting epidemiologic differences within the population.[9] Older adults typically have an adverse cytogenetic risk profile, with poor-risk cytogenetics. Older patients with intermediate-risk cytogenetics also have poor outcomes.[10-12] AML cytogenetic and molecular risk categories are listed in the Table.[13]

National registry data from Sweden inform us that all older AML patients should be considered for chemotherapy, and their outcomes are better with intensive chemotherapy rather than palliative or supportive care alone.[14] Therapy for AML is considered intensive by intent to induce first complete remission (CR1).[8] Intensive induction and consolidation chemotherapy may be considered curative for patients with good-risk cytogenetics, including core binding factor AML (t[8;21], inv[16], t[16;16]) without c-KIT mutations; however, core binding factor AML represents only 7%-12% of all patients with AML who are ≥60 years.[10,15] Treatment of good-risk AML compares to the more common need of allogeneic stem cell transplant (ASCT) to potentially achieve a cure in patients with intermediate- or poor-risk cytogenetics and/or adverse molecular mutations (FLT3-ITD, c-KIT) or secondary AML.[16] Traditional intensive chemotherapy for AML remains the 7+3 regimen with either daunorubicin or idarubicin anthracycline agent combined with cytarabine infusion. Induction chemotherapy can achieve a CR1 in 40%-60% of older patients with AML.[14,17-19] Achieving a stringent CR1 without evidence of minimal residual disease (MRD) is an important prognostic factor in patient survival because MRD often indicates the presence of refractory disease or a high risk of relapse and may also impact outcomes after ASCT.[20-22]

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate that the use of ASCT in older patients with AML has increased during the past 15 years (2000-2015).[23] With the development of reduced-intensity conditioning (RIC) regimens that rely on graft vs leukemia effects to eradicate leukemic cells (rather than the myeloablative antileukemic effect of conditioning) and the use of alternative donors (haploidentical and cord blood) when a matched donor is not available, the number of allogeneic transplants in older patients is increasing but still represents a minority of the actual transplant population.[24-26] Patient age alone up to 75 years does not impact survival after RIC ASCT according to the Acute Leukemia Working Committee for the CIBMTR that reported a 2-year posttransplant OS of 35%.[27] This analysis found no significant impact of age on nonrelapse mortality, disease-free survival, or OS, indicating that all older patients with AML should be referred to a bone marrow transplant center early in their diagnosis for appropriate patient assessment.[27] Patients who receive ASCT as indicated for their disease appear to have improved OS compared to patients who receive chemotherapy alone. A Japanese registry study of adults aged 50-70 years in CR1 who received ASCT with a variety of conditioning regimens and alternative donor types showed improved 3-year OS with transplant compared to chemotherapy alone (62% vs 51%, respectively; $P=0.12$), demonstrating no disadvantage and in some high-risk patient populations a clear improvement in survival.[28] Additional studies have demonstrated improved leukemia-free survival after ASCT compared to chemotherapy alone.[29,30] The function of RIC ASCT in older patients with advanced disease or beyond CR1 is uncertain, as response to treatment and OS after ASCT decrease with refractory disease. However, outcomes in refractory or relapsed AML are still better after ASCT (dependent on disease risk categories and patient performance status), highlighting the need to carefully select patients for intense chemotherapy and ASCT.[16,31,32]

SELECTING PATIENTS FOR TREATMENT

A patient's numeric age does not accurately predict benefit from therapy and only relates to years of life, whereas physiologic age appears to influence the older patient's ability to tolerate traditional leukemia-directed treatments. Selecting patients for curative therapy is a multifactorial decision process in which both patient- and disease-related factors must be taken into consideration. These considerations include patient frailty and comorbidities, caregiver availability and social support dynamics, and the increased prevalence of high-risk disease features such as adverse cytogenetics and secondary AML. Patients must be able to tolerate the selected therapy, and treatment should not be futile in settings of highest risk or resistant AML.[11,12,14]

When considering intensive chemotherapy, the patient characteristics that must be considered include functional status, caregiver support, psychosocial issues, and the patient's own goals of care. The Hematopoietic Cell Transplantation-Specific Comorbidity Index score (HCT-CI) predicts nonrelapse mortality and OS after ASCT.[33] The HCT-CI builds upon the Charlson Comorbidity Index but redistributes weights of comorbidities for the AML and MDS patient populations, including mental health, infection, and obesity, and has been validated prospectively.[34] The HCT-CI also predicts early death and OS in patients ≥60 years who are receiving induction 7+3 chemotherapy with idarubicin and cytarabine for AML. Median OS for a score of 0 is 45 weeks, a score of 1-2 equates to a median of 31 weeks, and the median OS for a score of 3 is 19 weeks, demonstrating the importance of careful evaluation and attention to patients' active and past medical history prior to making treatment decisions.[35] Nevertheless, retrospective data suggest a potential advantage for intensive therapy in older adults for all but those with the highest HCT-CI scores.[36,37]

In addition to patient comorbidities, patient frailty may be used to define potential tolerance to intensive therapy. Patient frailty is defined as a syndrome of unintentional weight loss, exhaustion, weakness, decreased walking speed, and decreased physical activity.[38] At least 15% of patients ≥65 years are considered frail.[39] Further expanding on measurements of frailty are comprehensive geriatric assessment tools to predict patient tolerance to chemotherapy and survival after ASCT. The University of Chicago prospectively incorporated a geriatric assessment prior to transplant and found that inclusion of the HCT-CI, frailty measurements, markers of inflammation, and mental health assessments predicted OS after ASCT.[40] Wedding et al reported that performance of daily activities is the most important prognostic factor of survival in older adults.[41] The

Table. Acute Myeloid Leukemia Cytogenetic and Molecular Risk Categories

Prognostic Risk Category[a]	Cytogenetics	Molecular Mutations
Good risk	t(8;21) Inv(16) t(16;16)	Normal cytogenetics with NPM1 mutation or biallelic CEBPA mutation
Intermediate risk	Normal cytogenetics +8 t(9;11) Nondefined cytogenetics	Good risk cytogenetics with c-KIT mutation
Poor risk	≥3 chromosomal abnormalities Monosomal karyotype -5, -5q -7, -7q 11q23 Inv(3), t(3;3) t(6;9) t(9;22)	FLT3-ITD mutation TP53 mutation

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[a]Prognostic risk category predicts rate of remission, risk of relapse, and overall survival.

success of intensive therapy and ASCT is largely determined by patient functional status.

Patients who are not candidates for intensive treatments may still be considered for nonintensive therapy that has a lower incidence of achieving CR1 but has a role in decreasing disease progression and improving patient quality of life. Nonintensive therapy includes the hypomethylating agents azacitidine and decitabine.[42-44] Hypomethylating agents improve OS compared to conventional care regimens such as low-dose cytarabine and/or supportive care alone, although they have not shown an OS benefit in randomized phase 3 clinical trials.[42,44,45]

Referral to palliative medicine and supportive care services should be considered at the time of AML diagnosis for all patients, as palliative medicine services can be offered and administered at the same time as any treatment for AML, including curative induction chemotherapy and ASCT.[46] Palliative care and hospice are both underutilized, even in patients with poor prognosis attributable to high-risk disease, comorbidities, and poor performance status, despite data showing that nearly 85% of older patients with AML are hospitalized within the month before their death.[47] Decreased palliative medicine utilization may be partially related to limitations in blood product transfusion support, a common supportive care need of patients with AML that is not currently covered and provided in hospice treatment and reimbursement models. Nevertheless, early referral to palliative medicine improves both patient and caregiver quality of life and decreases healthcare utilization, including hospital readmissions.[48-52]

CLINICAL TRIALS FOR OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA

Just as palliative care is currently underutilized in older patients with AML, so were agents in clinical trial until recently. Few clinical trial agents were evaluated in the older patient population because of eligibility criteria or the lack of trials designed for this age group.[53] Since 2014, more clinical trials have been designed exclusively for patients ≥60 years.

Challenging the long-time standard induction chemotherapy regimen of 7+3 is CPX-351, a liposomal formulation of cytarabine and daunorubicin.[54] A randomized phase 2 study that enrolled patients ≥60 years with untreated AML demonstrated greater treatment response rates (66.7% vs 51.2%, respectively; P=0.07) and increased survival after ASCT in patients receiving CPX-351 compared to those treated with 7+3 chemotherapy.[55,56] Older patients with high-risk disease and secondary AML were then enrolled in a phase 3 study of CPX-351 vs traditional 7+3 cytarabine/daunorubicin, and the patients treated with CPX-351 achieved the primary endpoint of improved OS (9.56 vs 5.95 months, respectively; P=0.005).[57] With the expectation for Food and Drug Administration (FDA) approval, CPX-351 may become the new standard of care for induction therapy in older patients with AML.[57]

Older patients with AML may also be candidates for targeted therapy for high-risk molecular mutations. Midostaurin is an oral agent targeting the FLT3 mutation that the FDA approved in April 2017 for use during induction and consolidation chemotherapy in newly diagnosed adult patients with AML who harbor any FLT3 mutation.[58] Patients achieving remission may also receive 12 months of single-agent midostaurin maintenance treatment.[58] Of note, the phase 3 RATIFY trial that led to midostaurin approval did not enroll older patients with AML but limited enrollment to patients aged 18-59 years.[59] The full prescribing instructions for midostaurin advise caution in patients ≥65 years, limiting use to patients who are also candidates for induction chemotherapy.[58]

An example of targeted therapy that is in active clinical trial is the isocitrate dehydrogenase enzyme (IDH1 and IDH2) inhibitors. Currently recruiting patients ≥60 years is a phase 3 study of the IDH2 inhibitor AG-221 compared to investigator choice of a conventional care regimen of best supportive care, azacitidine, low-dose cytarabine, or intermediate-dose cytarabine.[60] Many additional novel agents are in clinical trial development, including the CD33 antibody conjugate actinium 225 lintuzumab, an alpha

particle radiation conjugate in early-phase clinical trial enrolling patients ≥60 years.[61-63]

Studies from 2015-2016 suggest ongoing improvement in median survival with intensive therapy in older adults through enhanced patient selection and supportive care. An example is median survival of almost 14 months with standard (7+3 daunorubicin) therapy in the Eastern Cooperative Oncology Group (ECOG) E2906 trial, supporting the use of standard therapy whenever possible.[64] However, low-intensity therapies may achieve similar results in select patients. For example, a 10-day decitabine regimen achieved complete responses in patients with adverse mutation profiles (TP53 mutation) in whom intensive therapy is less effective.[65] Decitabine is being compared directly against intensive therapy in the ongoing European Organization for Research and Treatment of Cancer (EORTC) AML-21 trial. Decitabine is also being studied with azacitidine and, in some cases, low-dose cytarabine as potential backbone regimens to add to novel leukemia-targeted agents to improve remission rates and survival. Other agents in development for older patients with untreated AML include the hypomethylating agent guadecitabine (that is resistant to cytidine deaminase degradation), tosedostat (an aminopeptidase inhibitor), and volasertib (a polo-like kinase inhibitor) that all demonstrated complete remission rates of 30%-40% in early-phase clinical trials.[66-68] Although volasertib has not demonstrated clear-cut improvement in survival in randomized trials, alternate treatment schedules are being considered. Venetoclax, a BCL-2 inhibitor, has shown response rates of 30%-40% in older patients with relapsed or refractory disease and very high response rates in combination with azacitidine in studies conducted at MD Anderson Cancer Center.[69]

Novel approaches to treating AML include research in cellular therapy, including vaccine trials enrolling patients up to 77 years, and novel trial designs such as the Leukemia & Lymphoma Society Beat AML Master Trial and the Southwest Oncology Group (SWOG) S1612 that are being developed to enroll newly diagnosed patients ≥60 years with the aim of matching patients with active therapy in an individualized and efficient manner.[70,71]

Beat AML is an innovative clinical trial that could potentially change the paradigm in older adults with AML by incorporating upfront molecular profiling at the time of diagnosis and assigning patients to novel low-intensity or high-intensity therapies based upon dominant leukemia-associated mutations at diagnosis. This important study will allow more rapid assessment of novel or targeted treatments in defined patient populations and has the potential to significantly advance the evaluation of new therapies in older adults.[71] SWOG is developing a national intergroup rolling phase 2/3 randomized study (S1612) that will test concurrent and consecutive lower intensity novel therapies against standard regimen azacitidine in an expedited fashion, converting any early signal of improved survival rapidly into randomized phase 3 trials. S1612 is expected to open late 2017 and will allow efficient and systematic study of multiple regimens, significantly reducing the time it will take to study the impact of new treatments in older adults.

CONCLUSION

Age alone should not exclude older patients with AML from consideration for intensive chemotherapy, ASCT, or clinical trial participation, and, indeed, we must strongly support clinical trials whenever possible to improve outcomes in this difficult disease. As tools improve to assess patient frailty and functional status, the clinical ability to better select patients for varying degrees of treatment will also improve, enhancing patient outcomes. Early referral to palliative medicine and use of this subspecialty as a supportive care service can improve patient and caregiver quality of life.

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