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REVIEW ARTICLE

Acute Myeloid Leukemia and Myelodysplastic Syndromes in Older Adults

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ABSTRACT

Treatment of older adults with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) is challenging because of disease morbidity and associated treatments. Both diseases represent a genetically heterogeneous group of disorders primarily affecting older adults, with treatment strategies ranging from supportive care to hematopoietic stem-cell transplantation. Although selected older adults can benefit from intensive therapies, as a group they experience increased treatment-related morbidity, are more likely to relapse, and have decreased survival. Age-related outcome disparities are attributed to both tumor and patient characteristics, requiring an individualized approach to treatment decision making beyond consideration of chronologic age alone. Selection of therapy for any individual requires consideration of both disease-specific risk factors and estimates of treatment tolerance and life expectancy derived from evaluation of functional status and comorbidity. Although treatment options for older adults are expanding, clinical trials accounting for the heterogeneity of tumor biology and aging are needed to define standard-of-care treatments for both disease groups. In addition, trials should include outcomes addressing quality of life, maintenance of independence, and use of health care services to assist in patient-centered decision making. This review will highlight available evidence in treatment of older adults with AML or MDS and unanswered clinical questions for older adults with these diseases.

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ACUTE MYELOID LEUKEMIA

Median age at diagnosis of acute myeloid leukemia (AML) ranges between 68 and 72 years; approximately one third of newly diagnosed patients are age ≥ 75 years.[1] There is no consensus regarding optimal therapy for older adults (often defined as those age ≥ 60 years).[2,3] Survival is age dependent, with lower rates for older adults (Fig 1).[1] Clinical trial and observational data show that for older adults, chemotherapy can provide a survival advantage over supportive care, even among selected patients age > 80 years.[4-7] However, concerns regarding efficacy and toxicity of therapy have resulted in < 40% of older adults receiving chemotherapy for AML in the United States.[5] Survival has improved over time, although the magnitude of improvement declines with age.[1,5,8,9] Age is a surrogate measure for both changes in tumor biology (conferring treatment resistance) and patient characteristics (decreasing treatment tolerance).[10] Understanding which patients are likely to benefit from aggressive therapies versus low-intensity therapies or supportive care is critical. Individualized decision making based on evolving stratification of tumor and patient characteristics, along with frank discussions with patients, can help inform the tailoring of treatment and supportive care.

Tumor Biology

AML is a different disease in older patients. One reason is the aging of the hematopoietic stem cell (HSC), caused by DNA damage, telomere shortening, and oxidative stress.[11-13] Recipient age has had a dramatic influence on HSC homing and seeding efficiency in murine experiments. Gene expression profiling has revealed that HSC aging is accompanied by the systemic downregulation of genes mediating lymphoid specification and function and upregulation of genes involved in specifying myeloid fate and function.[12,13] A study in 273 older patients with AML demonstrated that leukemic blasts were more likely to be CD34/CD33 positive or CD34/CD33 negative, correlating with poor overall survival (OS).[14]

Cytogenetic abnormalities are the most important prognostic factor in AML. Older patients with AML have more poor-risk karyotypes (eg, −7, 7q−, −5, 5q−; abnormalities of 11q, 17p, and Inv3; and complex karyotypes involving ≥ three chromosomes) and fewer good-risk karyotypes [eg, inv(16), t(16;16), t(8;21), or t(15;17)].[15,16] In an analysis of

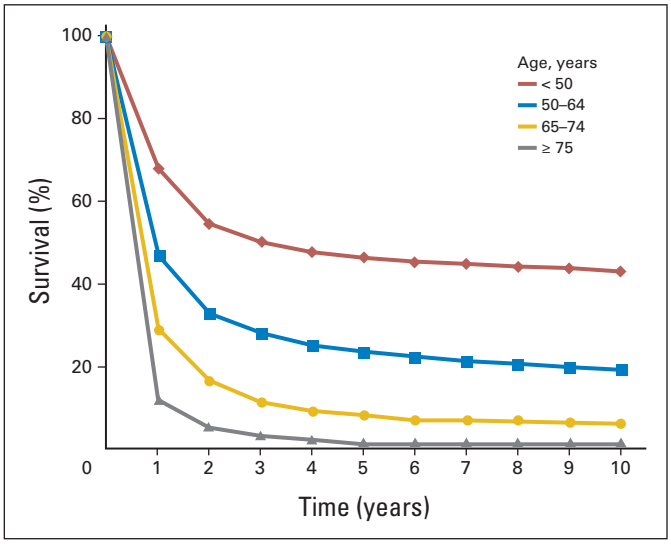

Fig 1. Relative survival by time and age for acute myeloid leukemia based on SEER data.

1,065 older adults treated in clinical trials, the proportions with favorable, intermediate, and adverse cytogenetics were 7.3%, 79.1%, and 13.6%, associated with 5-year OS rates of 34%, 13%, and 2%, respectively.[16] Molecular mutations and gene deregulation also play a role in prognosis. In a comparison of 425 younger and older patients, older patients had a higher probability of RAS, Src, and tumor necrosis factor pathway activation, which may have contributed to their worse survival.[17] In addition, mutations in *FLT3-ITD*, *NPM1*, and *CEPBA* in patients with normal karyotypes affect prognosis. In 99 older *FLT3*-negative patients, presence of the *NPM1* mutation was associated with a higher complete remission (CR) rate (*NPM1* negative, 40.5% *v* *NPM1* positive, 80.0%; $P = .03$) but not with disease-free survival (DFS) or OS. Meanwhile, presence of the *FLT3* mutation was associated with worse OS, regardless of *NPM1* status (*FLT3* positive, 210 *v* *FLT3* negative, 634 days; $P = .03$).[18]

There are several reasons for poor response rates to chemotherapy among older patients. Leukemic blasts from older patients are less likely to undergo apoptosis after treatment[19] and have higher expression of the *MDR1* gene.[20] *MDR1* encodes a membrane transporter protein responsible for drug efflux and resistance and is implicated in apoptosis inhibition.[21] Finally, the bone marrow microenvironment is a dynamic network of growth factors, cytokines, chemokines, and stromal cells that affects AML and patients alike.[22] Thus, the biology of AML in older patients is complex and leads to worse outcomes. Use of evolving risk stratification schema based on genetic and epigenetic data in clinical trials may provide an important advance in individualized treatment.[23,24]

Treatment Trials in Older Patients

Most clinical trials in AML have enrolled patients age 60 to 80 years with adequate performance status (PS; Eastern Cooperative Oncology Group [ECOG] PS 0 to 2). Median survival in clinical trials has historically been < 1 year, with improvements seen in more recent trials.[10] In general, older adults are less likely to achieve CR and remain relapse free, and their 30-day mortality rates range from 10% to 30%.[10,25] In one analysis of trial data (N = 968) using intensive induction, CR rates were 64%, 46%, 39%, and 33% in patients age < 56, 56 to 65, 66 to 75, and ≥ 75 years, respectively. Among those achieving remission, DFS was 21.6, 7.4, 8.3, and 8.9 months, respectively; OS for all participants was 18.8, 9.0, 6.9, and 3.5 months, respectively.[10]

Induction

Standard induction therapy for nonacute promyelocytic AML typically includes cytarabine and an anthracycline administered for 7 and 3 days, respectively (7 + 3). This approach improved survival compared with supportive care (median, 5 *v* 3 months) for adults age ≥ 65 years with no increased time spent hospitalized.[7] Since this landmark trial was published, many subsequent trials have shown only incremental improvements in outcomes. Using different induction regimens to improve the balance between benefit and toxicity has not consistently improved efficacy, safety, health care services use, or quality of life (QOL). Strategies pursued have included dose attenuation,[26] anthracycline substitution,[27-29] addition of sorafenib,[30] growth factors,[28,31] and modulation of multidrug resistance[32] (Table 1).

Improved response rates and survival have been reported in some recent trials. For example, 90 mg/m^2 of daunorubicin improved CR rates compared with 45 mg/m^2 (64% *v* 54%) for older adults receiving 7 + 3,[33] with no significant increased toxicity. Although OS did not improve in the entire cohort, a subset of patients age 60 to 65 years seemed to benefit. No randomized data are available to compare 90- with often-used 60-mg/m^2 dosing. Two studies showed improvements in survival without significant toxicity by adding low-dose gemtuzumab ozogamicin to intensive induction for patients age > 50 years.[34,35] At present, gemtuzumab is currently unavailable in the United States.

Lower-intensity regimens have also been tested.[36-40] Off-label use of DNA hypomethylating agents (eg, azacitidine and decitabine) has increased in recent years.[5] A randomized trial comparing decitabine with treatment choice (supportive care or low-dose cytarabine) for adults age ≥ 65 years with intermediate or poor risk cytogenetics found improved CR rates (18% *v* 8%) favoring decitabine, with nonsignificant improvement in survival.[36] In subset analyses of patients with low–blast count (20% to 30%) AML included in a myelodysplastic syndromes (MDS) trial, azacitidine improved survival compared with conventional care (low-dose cytarabine, best supportive care, or 7 + 3).[40] Low-dose cytarabine improved survival among patients not fit for intensive therapy compared with supportive care alone, although fitness was not defined for patients age > 70 years.[37] The role of lower-intensity regimens is under active investigation; to date, none have been shown to be superior to intensive induction in randomized trials.

Postremission Therapy

Optimal strategies for postremission (consolidation) therapy in older patients with AML are unclear. The average adult harbors an estimated 1×10^9 leukemia cells at the time of remission. A Cancer and Leukemia Group B trial that randomly assigned patients in remission to maintenance or observation was stopped early after 100% of the observation arm relapsed in a median of 4.1 months.[41] In younger adults, high-dose cytarabine consolidation is superior to standard dose; however, this benefit is not seen in patients age > 60 years, as a result of increased toxicity.[42] Intermediate doses of cytarabine (1 to 1.5 gm/m^2) can be safely administered to older patients and have seemed

Table 1. Selected Randomized Trials of Induction Chemotherapy for Older Patients With AML

Chemotherapy Regimen*	Year Published	Age Range (years)	No. of Patients	CR (%)	OS		Induction Death Rate (%)	Comments
					Median (months)	*P*		
Intensive *v* supportive care								
Löwenberg et al[7]	1989	65-85				< .05		No difference in days hospitalized
Cytarabine, daunorubicin, and vincristine			31	58	5.3		9.7	
Supportive care			29	0	2.8		NA	
Type of anthracycline/dose intensification								
Löwenberg et al[27]	1998	61-88				.23		
Cytarabine plus daunomycin			242	38	9.0		6.0	
Cytarabine plus mitoxantrone			247	47	9.7		6.0	
Pautas et al[29]	2010	50-70			No difference	.16		Median OS of 17 months for entire study cohort
Cytarabine plus daunorubicin 80 mg/m^2			156	70			8	
Cytarabine plus idarubacin 12 mg/m^2 × 3 days			155	83			3	
Cytarabine plus idarubacin 12 mg/m^2 × 4 days			157	78			6	
Löwenberg et al[33]	2009	60-83			No difference	.16		OS benefits suggested in patients age 60-65 years
Cytarabine plus daunorubicin 45 mg/m^2			411	54			11	
Cytarabine plus daunorubicin 90 mg/m^2			402	64			12	
Dose-attenuated induction								
Tilly et al[26]	1990	65-83				.12		
Rubidazone plus cytarabine			46	52	12.8		31	
Low-dose cytarabine			41	32	8.8		10	
Growth factor support								
Stone et al[31]	1995	60-80†				.10		
Cytarabine plus daunorubicin			195	54	9.4		16	
Cytarabine, daunorubicin, and GM-CSF			193	51	9.4		20	
MDR1 modulation								
Baer et al[32]	2002	60-84			No difference	.48		
Cytarabine, daunorubicin, and etoposide			61	46			20	
Cytarabine, daunorubicin, etoposide, and PSC-833			59	39			44	
Addition of sorafenib								
Serve et al[30]	2013	61-80			No difference	.88		*FLT3-ITD* positive, 14%
Cytarabine plus daunorubicin 60 mg/m^2			97	60			7	
Cytarabine, daunorubicin 60 mg/m^2, and sorafenib			104	48			17	
Addition of gemtuzumab ozogamicin								
Castaigne et al[34]	2012	50-70				< .05		
Cytarabine plus daunorubicin			139	75‡	11		4	
Cytarabine, daunorubicin, and gemtuzumab			139	81‡	28		6	
Burnett et al[35]	2012	51-84				.05		Improved 3-year survival: 25% *v* 20%
Daunorubicin, cytarabine, or clofarabine			556	58	Improved		9	
Daunorubicin, cytarabine, or clofarabine plus gemtuzumab			559	65			8	
Lower-intensity therapy								
Kantarjian et al[36]	2012	64-91				.2		Poor- or intermediate-risk cytogenetics only; ECOG PS 0-2 with minimal comorbid conditions
Supportive care or low-dose cytarabine			243	8	5		8	
Decitabine			242	18	8		9	

(continued on following page)

Table 1. Selected Randomized Trials of Induction Chemotherapy for Older Patients With AML (continued)

Chemotherapy Regimen*	Year Published	Age Range (years)	No. of Patients	CR (%)	OS		Induction Death Rate (%)	Comments
					Median (months)	*P*		
Burnett et al[37]	2007	51-90				< .05		No specific fitness criteria except comorbidity if age < 70 years
Low-dose cytarabine ± ATRA			103	18	Improved		26	
Hydroxyurea ± ATRA			99	1			26	
Burnett et al[38]	2013	51-90			No difference	.7		
Clofarabine			200	22			18	
Low-dose cytarabine			206	12			13	

Abbreviations: AML, acute myelogenous leukemia; ATRA, all-*trans*-retinoic acid; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating growth factor; NA, not applicable; OS, overall survival; PS, performance status.

*One limitation in translating clinical trial data into best practice is lack of consistency in patient populations recruited and in drug doses used, making comparisons of results between trials challenging. To date, there are no older patient–specific dosing recommendations for many drugs based on physiologic changes of aging beyond adjustments for creatinine clearance when appropriate, cardiac function (ie, anthracyclines), and unacceptable toxicity risk (ie, high-dose cytarabine).

†Age ≥ 80 years, 4%.

‡Rates represent CR with incomplete platelet count recovery.

Table 2. Predictors of Outcome for Older Patients Receiving Induction Chemotherapy for AML

Study	No. of Patients	Treatment	Tumor Characteristics	Clinical Variables	Patient Characteristics	Outcome
Analyses from clinical trials						
Kantarjian et al[3]	446	Intensive	Complex karyotype	Creatinine > 1.3 mg/dL	Age > 80 years; ECOG PS > 1	8-week mortality
Krug et al[48]	1,406	Intensive	Secondary AML/or prior hematologic disease; molecular/cytogenetic risk	Body temperature, hemoglobin, platelets, LDH, fibrinogen	Age	60-day mortality; CR
Röllig et al[49]	909	Intensive	Karyotype; *NPM1*-mutated CD34 expression > 10%	WBC > 20/μL; LDH > 700 U/L	Age > 65 years	Survival
Wheatley et al[50]	2,208	Intensive	Cytogenetic risk group; secondary AML	WBC	Age, ECOG PS	1-year survival
Geriatric assessment						
Deschler et al[51]	107	Nonintensive	Bone marrow blast percentage; cytogenetic risk group		Impaired ADLs; KPS < 80; high fatigue score, HCT-CI ≥ 3	Survival
Klepin et al[52]	74	Intensive	Cytogenetic risk group; prior MDS	Hemoglobin	Cognitive impairment (3MS < 77); impaired physical performance (SPPB < 9)	Survival
Sherman et al[53]	101	Mixed	Adverse cytogenetics; secondary AML		HCT-CI > 1; difficulty with strenuous activity; pain (more often *v* less); ECOG PS > 1	Survival

Abbreviations: 3MS, modified Mini–Mental State Exam; ADL, activity of daily living; AML, acute myeloid leukemia; CR, complete remission; ECOG, Eastern Cooperative Group; HCT-CI, hematopoietic cell transplantation comorbidity index; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; PS, performance status; SPPB, Short Physical Performance Battery.

superior to standard doses in retrospective studies.[43] There is no evidence defining optimal duration or intensity of consolidation, although a clear association between dose-intensity and increased toxicity has been seen.[42,44] Allogeneic HSC transplantation (HSCT) remains a standard approach to improve long-term survival for younger patients with poor-risk AML. Advances in supportive care and use of reduced-intensity conditioning (RIC) regimens have resulted in a trend toward increased use of HSCT in adults age 60 to 70 years.[45] An analysis of > 1,000 patients age 40 to 79 years (11% age ≥ 65 years) who received RIC for AML consolidation or MDS therapy showed no association between age and nonrelapse mortality, relapse, DFS, or OS.[46] Although this therapy may be feasible for selected older adults with good PS and minimal comorbidity, it is unclear if it is superior to conventional approaches for survival and QOL.[47]

A major concern in selecting postremission treatments for older adults is the higher likelihood that patients will no longer be candidates for effective treatments postinduction because of declines in functional status or acquired comorbidities. In trials, up to 20% of older adults who achieve remission do not receive any consolidation therapy.[44] Limitations to delivery of postremission therapy may contribute to age-related outcome disparity.

Individualizing Patient Assessment

Summary of aggregate clinical trial data does not adequately determine which older adults are likely to benefit from specific therapies, given the complexity of tumor and patient characteristics underlying treatment responsiveness and tolerance. Individualized decision making is critical. Prognostic models have been developed from clinical trial data to predict outcomes for older adults (Table 2).[3,48-50] Using algorithms derived from these risk stratification models, estimates of early mortality (16% to 71%[3]), CR (12% to 91%[48]), and 3-year survival (3% to 40%[49]) range widely among older adults treated intensively. Each algorithm provides a useful foundation for improving risk stratification at the time of treatment. However, each model relies on chronologic age as a surrogate for measureable patient-specific factors that vary among individuals of similar age (ie, comorbidity, physical function, cognition, and psychological state). Systematic measurement of patient-specific factors can help discriminate among fit, vulnerable, and frail patients for a given treatment. Although randomized data for comprehensive patient-assessment strategies are lacking, there is supportive evidence available.

Comorbidity is common among patients with AML. In studies of older adults, comorbidity burden (Charlson comorbidity index > 1 and hematopoietic cell transplantation comorbidity index [HCT-CI] > 2) is associated with lower remission rates, increased early mortality, and decreased survival.[51,54-58] For example, among 177 patients age ≥ 60 years who received induction, HCT-CI score was 0 (no major comorbidity) in 22%, 1 to 2 in 30%, and ≥ 3 in 48%, corresponding with early death rates (3%, 11%, and 29%) and OS (45, 31, and 19 weeks, respectively).[51] Current evidence supports pretreatment comorbidity assessment using the Charlson comorbidity index or HCT-CI. The prognostic implications of individual comorbid conditions are not well studied.

It is clear that functional status also influences treatment tolerance. The relationship between ECOG PS at diagnosis, age, and 30-day mortality during intensive induction is dramatic. Trial data show similar 30-day mortality (11% to 15%) for patients age 56 to 65, 66 to 75, and > 75 with ECOG PS 0, contrasted with rates of 29%, 47%, and

82%, respectively, for baseline ECOG PS 3.[10] Fit older adults, even those age > 75 years, may tolerate induction chemotherapy similar to those in middle age, but the negative prognostic implications of poor PS increase with age. Although ECOG scores are useful in identifying frail patients (ECOG PS > 2), physiologic reserve capacity varies widely among older adults with ECOG PS 0 to 2 because of the subjectivity of the scale. Further refinement is needed to identify vulnerable adults. In fact, studies have shown that assessment of self-reported activities of daily living (ADLs) and objectively measured physical performance (testing composed of walking speed, chair stands, and balance) are predictive of survival after accounting for PS.[51,52,59]

Pretreatment assessment of older adults needs to take into account the complexity of variables that may differ from patient to patient. One such method is geriatric assessment (GA). Pretreatment GA is feasible[51,60] and suggests that chronologic age may not be a robust predictor of outcome after accounting for function, comorbidity, and symptoms[53] (Table 2). In a prospective study of adults age > 60 years treated intensively, pretreatment GA detected significant impairments even among those with ECOG PS 0 to 1: cognitive impairment, 24%; depression, 26%; distress, 50%; ADL impairment, 34%; impaired physical performance, 31%; and comorbidity, 40%.[60] Importantly, most patients in the study were impaired in one (92.6%) or more (63%) measured characteristics. The additive effects of multiple impairments may be more important than individual conditions, and the implications likely differ by treatment intensity. GA has identified impaired cognition, impaired physical performance, ADL impairment, and symptoms (eg, fatigue and pain) as independent predictors of worse survival. The utility of GA is currently under investigation in cooperative group treatment trials. Ultimately, understanding specific patient vulnerabilities may help to predict tolerance and response to standard therapies, inform adaptive clinical trial design for specific patient subgroups, and identify targets for intervention to improve treatment tolerance such as exercise for physical impairment.[61,62]

Proposed Approach to Treatment of Older Adults

Treatment recommendations for older adults with AML need to be individualized based on tumor biology and patient characteristics. Although validation is needed, available data can begin to differentiate fit, vulnerable, and frail patients when considering intensive therapy (Table 3). Frail older adults, particularly those age > 75 years, are at high risk for toxicity with therapy.[10] Best evidence suggests frail older adults with unfavorable tumor biology are unlikely to tolerate or benefit from aggressive treatment. In the absence of clinical trials,

Table 3. Proposed Risk Stratification and Treatment Considerations for AML Induction Based on Patient Characteristics

Patient Risk Category	Characteristic	Treatment Considerations*		
		General	Favorable Tumor Biology†	Intermediate or Unfavorable Tumor Biology‡
Frail	ECOG PS ≥ 3; major comorbidity (HCT-CI > 2); impairment in ADLs	High treatment-related mortality (particularly for those age > 75 years); clinical trials targeting frail patients are needed	Consider lower-intensity therapy (HMAs, low-dose cytarabine); patients with poor PS (particularly age 60-75 years) but without end-stage comorbidity may consider intensive treatment if risks and benefits are consistent with goals of care	Consider best supportive care, including palliative care consultation if available, versus lower-intensity therapy (HMAs, low-dose cytarabine)
Vulnerable	ECOG PS 0-2; absence of major comorbidity (HCT-CI ≤ 2); impairment in IADLs; impaired physical performance (SPPB < 9); impaired cognition (3MS < 77); high symptom burden (fatigue, pain)	Outcomes for this subgroup are inadequately defined in clinical trials; in nonrandomized studies, this group has been at risk for shorter survival compared with fit patients; clinical trials are needed to validate definitions of vulnerability and test treatment and supportive care strategies to improve outcomes in this group	Consider intensive therapy	Consider intensive therapy if risks and benefits are consistent with goals of care versus lower-intensity therapies (HMAs, low-dose cytarabine); consider enhanced supportive care targeting vulnerabilities (eg, early physical therapy for impaired mobility)
Fit	ECOG PS 0-1; HCT-CI < 1; absence of risk factors for frail and vulnerable patients	Best evidence suggests fit older adults derive benefit from aggressive therapy; future clinical trials should compare investigational therapies with standard intensive treatment in fit older adults	Intensive therapy should be offered	Consider intensive treatment with possible RIC allogeneic HSCT if risks and benefits are consistent with goals of care versus lower-intensity therapies (HMAs, low-dose cytarabine)

Abbreviations: 3MS, modified Mini–Mental State Exam; ADL, activity of daily living; AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation comorbidity index; HMA, hypomethylating agent; HSCT, hematopoietic stem-cell transplantation; IADL, instrumental activity of daily living; PS, performance status; RIC, reduced-intensity conditioning; SPPB, Short Physical Performance Battery.

*Clinical trials preferred.

†Favorable tumor biology: inv(16), t(16;16), t(8;21), or t(15;17).

‡Intermediate-risk tumor biology: normal cytogenetics, +8 alone, t(9;11), or other nondefined. Unfavorable: complex (≥ three clonal abnormalities), −5, 5q−, −7, 7q−, or abnormalities of 11q, inv(3), t(3;3), or t(6;9). In normal cytogenetic category, *NPM1* mutation in absence of *FLT3-ITD* or isolated biallelic *CEBPA* mutation confers better risk versus presence of *FLT3-ITD*, which confers worse risk.

supportive care or lower-intensity therapy should be pursued. Fit patients are most likely to benefit from curative therapies, and strong consideration should be given to intensive induction regardless of age. Evidence suggests that for fit patients, older age is associated with QOL and physical function similar to those of younger patients during and after intensive chemotherapy.[63] Optimal treatment for the large population of older adults who fall between these two extremes is unclear, and clinical trials are needed. In practice, consideration should be given to enhanced supportive care for vulnerable patients targeting modifiable risk factors (ie, early physical therapy for patients with impaired physical performance). Ultimately, decisions for patients should be determined through patient-centered discussions with frank consideration of best available data interpreted through individualized assessment and patients' values and goals of care.

Future Directions and Unresolved Issues

Although there are more questions than answers when considering best practices for older adults with AML, significant advances are being made in understanding the heterogeneity of both tumor biology and patient characteristics that influence outcomes. Major unanswered questions include: Is intensive therapy better than nonintensive therapy for fit older adults? Can therapy be directed by tumor biology and patient characteristics? What consolidation strategies maximize disease control and QOL? Can trials be designed for vulnerable or frail patients? Answers to these questions will require creative trial design accounting for the following: the role of therapies targeting biologically defined subsets of disease and patients; the interaction between tumor biology and the physiologic changes of aging; and novel outcomes capturing QOL, functional independence, patient-reported outcomes, and health care services use.

MDS

MDS are a heterogeneous group of disorders characterized by ineffective hematopoiesis and cytopenias. MDS can be indolent or progress to bone marrow failure or AML. With an estimated 3-year survival rate of 45%,[64] MDS are associated with significant morbidity, impaired QOL, and high health care services use. Of the estimated 15,000 to 20,000 US patients diagnosed annually, $>$ 80% are age $>$ 70 years.[1] Incidence of MDS will rise as the population ages, making these disorders an important public health concern. Treatment strategies range from supportive care to stem-cell transplantation, requiring a careful analysis of risks to lifespan and QOL versus the risk-benefit ratio of intervention.

Disease Risk Stratification

Several well-validated prognostic schemes are used to classify patients into higher- and lower-risk groups. The most common—the International Prognostic Scoring System (IPSS)—was derived from 816 patients, 75% of whom were age $>$ 60 years. The IPSS incorporates blast percentage, number of cytopenias, and cytogenetics; patients are placed into four risk categories: low, intermediate-1, intermediate-2, and high.[65] These categories have median survivals ranging from 5.7 years (low-risk group) to 0.4 years (high-risk group). Additional factors provide additive prognostic value to the IPSS, including multilineage dysplasia and severe anemia or transfusion dependency. Several of these variables are incorporated into the WHO prognostic scoring system,[66] which divides patients into five risk categories (very low, low, intermediate, high, very high). This system can be used both at diagnosis and after progression. A revised IPSS was developed[67] using data from 7,012 patients (median age, 71 years), which differs by further subdividing cytogenetic abnormalities, better quantifying cytopenias, and increasing the weight of higher blast percentages. It divides patients into five risk categories, from very low to very high, with median survivals from 8.8 (very low) to 0.8 years (very high). Age was a prognostic factor for survival but not for progression to AML and had more impact in lower- versus higher-risk groups. This system has been validated, and its prognostic discrimination seems superior to the IPSS and WHO prognostic scoring system.[68] Importantly, it retains its prognostic ability among patients treated with disease-modifying agents.[68,69]

Patient Risk Stratification

Selection of optimal therapy for older patients with MDS depends on both assessment of patients' overall fitness and disease risk stratification. Unfortunately, optimal evidence-based strategies to define fitness for specific MDS therapies are scarce. Factors that affect life expectancy and treatment tolerance (eg, comorbidity, functional status, cognition, and mood) vary significantly among patients of similar age. We know most about comorbid conditions, which occur in $>$ 50% of patients with MDS.[70,71] Higher comorbidity burden is associated with shortened survival, independent of age and disease risk stratification.[70,71] Specific conditions associated with shortened survival include cardiac disease, hepatic disease, severe pulmonary disease, renal disease, and solid tumors.[70]

GA may be useful to predict both life expectancy and treatment tolerance. A multisite study investigating the predictive utility of pretreatment GA among older adults treated nonintensively for MDS ($n = 51$) or AML ($n = 69$) found that requiring assistance with ADLs, Karnofsky PS $<$ 80%, and high fatigue rating were independently associated with shortened survival after accounting for age and tumor characteristics.[51] These characteristics may also increase vulnerability to toxicity. Issues related to physical and cognitive function and social support may be critical when considering therapies of high intensity, high frequency, or long duration.

Therapy

Treatment recommendations for MDS have evolved to target higher-risk MDS and subgroups defined by cytogenetic abnormalities. An integrated approach using disease and patient risk stratifications, as well as patient preference, is essential to optimize a risk-adapted strategy. Current guidelines recommend classifying patients into relatively low-risk (IPSS low or intermediate-1) and higher-risk groups (IPSS intermediate-2 or high). Treatment goals for lower-risk patients include minimizing disease morbidity (maximizing QOL and independence); goals for higher-risk patients include altering the disease course. Further classification based on patient characteristics is necessary to individualize therapy (Tables 4 and 5).

Supportive Care

Supportive care is essential for all patients. Supportive care includes red-cell and platelet transfusions, antibiotics for infections, growth factors for selected patients, and iron chelation. Patients with symptomatic anemia may benefit from epoetin alfa or longer-acting darbepoetin alfa (response rates approximately 50%).[77] Patients most

Table 4. Selected Randomized Treatment Trials for MDS

Trial	No. of Patients	Disease Characteristics	Patient Characteristics	Positive Outcome	Toxicity
Silverman et al[80]					
Azacitidine 75 mg/m^2 subcutaneously × 7 days every 4 weeks	99	IPSS intermediate-1, intermediate-2, or high	Median age, 68 years (range, 31-92); ECOG PS 0-2; creatinine ≤ 1.5 mg/dL	Response rate, 23% *v* 5%; time to AML or death, 21 *v* 13 months; AML transformation, 15% *v* 38%; improved QOL (physical function, symptoms, psychological state)	Grade 3-4 myelosuppression, 43% to 58%; infection, 20%
Supportive care	92				
Fenaux et al[73]					
Azacitidine 75 mg/m^2 subcutaneously × 7 days every 4 weeks	179	IPSS intermediate-2 or high, 87%	Median age, 69 years (range, 38-88); ECOG PS 0-2	Median OS, 24.5 *v* 15 months;	Myelosuppression
Conventional care (supportive, low-dose cytarabine, intensive chemotherapy)	179				
Kantarjian et al[74]					
Decitabine 15 mg/m^2 IV every 8 hours for 3 days every 6 weeks	89	IPSS intermediate or high	Median age, 70 years (range, 65-76)*; ECOG PS 0-1	Response rate, 17% *v* 0%; improved QOL (global health, fatigue, dyspnea)	Dose reductions or delays, 35%; grade 4 myelosuppression, > 50%
Supportive care	81				
Kantarjian et al[75]					
Decitabine 20 mg/m^2 IV for 5 days	64	FAB MDS or CMML; IPSS intermediate or high	Median age, 65 years; creatinine < 2 mg/dL	CR rate higher with 5-day IV schedule, 39% *v* 21% *v* 24%	Myelosuppression-associated hospitalization, 18%
Decitabine 20 mg/m^2 subcutaneously for 5 days	14				
Decitabine 10 mg/m^2 IV for 10 days every 4 weeks	17				
Fenaux et al[76]					
Lenalidomide 10 mg per day on days 1-21	69	MDS with del5q31; IPSS low or intermediate-1; RBC transfusion dependence	Median age, 69 years (range, 38-86); creatinine < 2 mg/dL	RBC transfusion independence ≥ 26 weeks, 56.1% *v* 42.6% *v* 5.9%; RBC transfusion independence > 8 weeks associated with decreased risk of death and AML progression	Myelosuppression in first two cycles; DVT in 10-mg group, 5.8%
Lenalidomide 5 mg per day on days 1-28	69				
Placebo on 28-day cycle	67				

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; DVT, deep venous thrombosis; ECOG, Eastern Cooperative Oncology Group; FAB, French-American-British; IPSS, International Prognostic Scoring System; IV, intravenous; MDS, myelodysplastic syndromes; PS, performance status; QOL, quality of life.
*Age range for decitabine arm.

likely to respond have low or intermediate-1 IPSS scores, serum erythropoietin level < 200 mU/mL, transfusion requirement < 2 units of red cells per month, and shorter interval between diagnosis and treatment.[78,79] Granulocyte colony-stimulating factor may act synergistically with epoetin.[79,80] Growth factors for symptomatic anemia can improve QOL and decrease transfusions without increased risk of AML progression.[81,82] Improvement in survival is suggested for low-risk patients in nonrandomized studies.[79,80]

Over time, most patients become transfusion dependent, increasing the risk of iron overload, which negatively affects survival. Guidelines recommend iron chelation for patients with lower-risk MDS, ongoing transfusion dependence, and anticipated survival > 1 year.[81]

Hypomethylating Agents

MDS are associated with abnormal methylation of the genome, which worsens with disease progression. Azacitidine and decitabine inhibit DNA methyltransferases and have activity in MDS.[72-74] Only azacitidine (administered at 75 mg/m^2 subcutaneously for 7 days every 28 days) showed a survival benefit in randomized trials of patients with high-risk MDS.[72,73] Treatment of the high-risk group doubled 2-year survival compared with conventional therapy (51% *v* 26%).[73] Treatment with azacitidine also improved fatigue, dyspnea, self-reported physical functioning, and psychological distress, after controlling for the number of transfusions received.[83]

Azacitidine showed a similar survival advantage in patients age > 75 years.[84] Thus, age is not a predictor in a prognostic scoring system derived from patients with high-risk MDS treated with azacitidine.[85] Furthermore, the 24-month survival benefit in a population study of MDS supports the generalizability of benefit outside of clinical trials.[86] A registry study comparing differing azacitidine schedules for patients of all risk groups age ≥ 75 years further illustrates benefits (transfusion independence, 40%) and complications (cycles delayed, 29%; hospitalized for infection, 47%).[87] Decitabine also decreased transfusion requirements and symptoms, although no definitive survival benefit was shown in a randomized trial.[74,75]

Challenges for older adults using hypomethylating agents include the 7-day scheduling for azacitidine, considered optimal based on available evidence but challenging logistically. The primary toxicity

Table 5. Treatment Considerations for Older Patients With MDS Based on Disease and Patient Risk Stratification

Disease Characteristic*	Goal of Therapy	Patient Characteristics	Treatment Considerations	Comments
Very low risk, low risk, or asymptomatic	Improve QOL	Any	Observation	Absence of evidence to support improved QOL or survival with early therapy
Very low risk, low risk, intermediate risk, or symptomatic				
5q− deletion	Improve QOL	Any	Lenolidomide	RCT evidence for decreased transfusion requirements; dose adjust for renal function; tolerance and benefits of lenolidomide understudied in vulnerable and frail patients
Absence of 5q− with erythropoietin level < 500 mU/mL	Improve QOL	Any	Erythropoeitin ± GCSF; consider lenolidomide	Time-limited trial; discontinue if no response in 8 weeks; some data for non-5q disease suggest significant response rate; would consider especially if isolated anemia
		Good performance status and minimal comorbidity	Consider hypomethylating agents	Absence of RCT data for very low– and low-risk patients; observational data suggest potential benefit
Intermediate risk, high risk, and very high risk	Delay progression; extend life	Any age, good performance status, absence of major comorbidity	Hypomethylating agents	RCT evidence supports improvements in survival, progression to AML, symptoms, and QOL; strongest evidence for 7-day azacitidine
	Cure	Age 60-75 years, excellent performance status, absence of major comorbidity	Consider referral for RIC HSCT *v* hypomethylating agents; comprehensive geriatric assessment may help inform fitness	Observational studies support feasibility and potential survival advantage for fit older patients with high-risk disease; RCT data lacking
	Delay progression; extend life	Poor performance status and/or major comorbidity	Consider hypomethylating agents *v* supportive care	Absence of RCT evidence in frail patients; however, given potential for survival advantage and improved QOL, would discuss azacitidine treatment

Abbreviations: AML, acute myeloid leukemia; GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem-cell transplantation; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; QOL, quality of life; RCT, randomized controlled trial; RIC, reduced-intensity conditioning.
*Revised IPSS.

of these agents is myelosuppression, which often worsens before response occurs. Finally, duration of treatment can be challenging; median duration in clinical trials was > 6 months for all patients and > 12 months for responders.[40,73] However, hypomethylating agents can alter the natural history of MDS, and they improve survival and QOL, particularly among patients with good PS and high-risk disease.

Immunomodulatory Agents

In an initial phase II study, lenalidomide used in transfusion-dependent patients at low or intermediate-1 risk with 5q deletion reduced transfusion requirements in 76% of participants, with a median time to response of 4.6 weeks.[88] The primary toxicity was myelosuppression, which required dose adjustment in 84% of participants. A subsequent dose-response placebo-controlled randomized trial in older patients (median age, 69 years) confirmed achievement of transfusion independence (rates of 56%, 43%, and 6% for 10-mg, 5-mg, and placebo groups, respectively), documented cytogenetic responses, and suggested that treatment improved QOL.[76,89] However, dose reductions (52% to 55%) and interruptions (29% to 46%) were common with both doses. Although a 10-mg starting dose seems optimal, 5 mg is also active and may be more appropriate for many older adults, given the need for dose adjustment for mild impairment in renal function (creatinine clearance < 60 mL/minute). Population data from Medicare claims also show reduced transfusion rates consistent with clinical trial data, supporting generalizability.[90] It also has efficacy in patients with low-risk MDS without 5q deletion as well as those with high-risk disease with 5q deletion.[91,92] Lenalidomide can be considered in all patients with transfusion-dependent MDS and 5q deletion as well as older patients with transfusion-dependent low-risk MDS without 5q deletion.

HSCT

Currently, the only curative therapy for MDS is allogeneic HSCT. Transplantation-related mortality increases with age and comorbidities. However, with RIC regimens, HSCT is feasible in selected patients age > 60 years.[46,93,94] When MDS outcomes were analyzed in patients undergoing RIC HSCT (n = 535; age 40 to 78 years), age was not a significant predictor of outcome.[46] The 2-year survival rate for patients age ≥ 65 years (n = 55) was 38%, 57% of whom had high-risk disease. HSCT for selected older patients can result in appreciable survival rates, even for those with high-risk disease. However, most data for older adults in this context refer to patients age < 70 years, with minimal data for those age > 75 years, excluding > half of patients diagnosed with MDS worldwide.

At present, HSCT is reserved for fit patients (good PS and minimal comorbidity) with higher-risk disease. A recent nonrandomized analysis of 514 patients age 60 to 70 years with de novo MDS compared RIC HSCT with nontransplantation strategies and suggested that life expectancy was improved with transplantation in patients at intermediate-2 or high risk according to IPSS (36 *v* 28 months) but not for those at low or intermediate-1 risk (38 *v* 77 months).[95] These findings highlight the critical importance of balancing risks of disease

versus treatment. Referral for transplantation evaluation should be discussed with fit older patients (best evidence for those age 60 to 70 years) with high-risk disease who wish to pursue aggressive, potentially curative therapies. The real-world applicability of transplantation in older adults will depend on refined evidence-based definitions of fitness and collection of outcomes to inform treatment decisions, including QOL, health care services use, and functional independence.

Unresolved Clinical Questions

Despite recent advances in therapy for MDS, many unresolved questions remain concerning optimal treatment of older adults. For example, optimal treatment strategies for patients with impaired functional status and multimorbidity have not been addressed in clinical trials. Trials targeting less fit patients are needed, as are rigorous categorizations of fitness, vulnerability, and frailty for each treatment modality. In the noncurative setting, the optimal duration of therapies to balance disease control, QOL, and functional independence is unclear. The optimal time to begin treatment in lower-risk patients is also unclear. The role of transplantation needs to be further defined; evidence remains confounded by lack of randomized controlled trials, and additional outcomes (eg, functional independence, health care services use, symptoms, and treatment satisfaction) are inconsistently captured to best inform decision making at the time of treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Heidi D. Klepin
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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