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Myelodysplastic Syndromes and Acute Myeloid Leukemia in the Elderly

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Synopsis

Myelodysplastic syndromes and acute myeloid leukemia are hematologic diseases that frequently affect older adults. Treatment is challenging due the morbidity of the disease and toxicity of associated treatments with strategies ranging from best supportive care to hematopoietic stem cell transplantation. Management of older adults with MDS and AML needs to be individualized accounting for both the heterogeneity of disease biology and patient characteristics which can influence life expectancy and treatment tolerance. While treatment options continue to expand for older adults, clinical trials accounting for the heterogeneity of tumor biology and physiologic changes of aging are needed to define optimal standards of care. Incorporating outcomes addressing quality of life, symptoms, maintenance of independence, and health care utilization is necessary to inform patient-centered decision-making. This review highlights key evidence related to management of older adults with MDS and AML and highlights future directions for research.

Keywords

myelodysplasia; acute myeloid leukemia; older; treatment; management; elderly

Myelodysplastic Syndromes (MDS)

MDS constitute a heterogenous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis and peripheral blood cytopenias. MDS can be indolent or rapidly progressive with complications secondary to profound cytopenias and the risk of evolution into AML. MDS also impair quality of life, are associated with high symptom burden[1], and high rates of high health care utilization. Estimated 3-year survival rates are <50% in aggregate[2] although survival can vary widely based on risk stratification. MDS are most commonly diagnosed among older adults (80% among adults ≥ 70 years of age) with approximately 15,000 to 20,000 new cases per year in the United States[3]. Given population aging, these are diseases that will be frequently encountered in geriatric practices.

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Diagnosis and work-up

Diagnosis of MDS relies mainly on peripheral blood and bone marrow findings. The diagnosis should be suspected in individuals presenting with cytopenia. A common presentation is progressive macrocytic anemia followed by pancytopenia in older adults. Classic peripheral blood findings associated with MDS include macrocytosis and hypogranular, hypolobated (dysplastic) neutrophils. A bone marrow biopsy with cytogenetic analysis is required to confirm the diagnosis. Cytogenetic abnormalities (often involving chromosomes 5, 7, 8, 17, or 20) play a critical role in the diagnosis and natural history of MDS.

Risk stratification-disease characteristics

Because of the heterogeneity inherent in diseases classified as MDS several risk stratification schemes have been proposed to inform trial design and treatment decisions. The International Prognostic Scoring System (IPSS) is the most commonly referenced risk stratification schema and was developed to assess risk at the time of diagnosis [4]. The IPSS incorporates specific cytogenetic abnormalities, the percentage of marrow blasts, and the number of hematopoietic lineages involved in the cytopenia. A 5-category revised IPSS (IPSS-R) was developed which further subdivides cytogenetic abnormalities and increased the weight of higher blast percentages [5, 6]. The IPSS-R highlights differences in the natural history of the disease by contrasting survival and time to AML progression (Table 1). In the development cohort, age was a prognostic factor for survival but not for progression to AML, having more impact in lower versus higher risk disease. The IPSS does not account for severity of cytopenia and also for transfusion dependence.

Risk stratification-patient characteristics

Selection of treatment for patients with MDS depends not only on disease characteristics but on assessment of a patient's overall fitness and competing comorbid conditions. Patient characteristics that influence life expectancy and treatment tolerance (e.g. comorbidity, functional status, cognition) vary widely among similarly aged patients. While measurement of these characteristics is not routine in most clinical trials, there is evidence regarding the prevalence and prognostic importance of comorbidity[7-9]. Studies suggest that more than half of older adults diagnosed with MDS have competing comorbid conditions and that comorbidity is associated with shorter survival independent of age or disease risk[7-10]. A study utilizing questions from a baseline quality of life (QOL) questionnaire to predict survival indicated that self-reported physical function (“ease taking a long walk”) was predictive of survival[11]. A prospective study investigating the predictive utility of a geriatric assessment among older adults treated non-intensively for MDS (N=51) and AML (N=69) found that requiring assistance with activities of daily living and high fatigue rating were independently associated with survival[12]. These characteristics and others detected by geriatric assessment may help identify those who are vulnerable to the toxicities of therapies and can inform decisions related to the intensity and chronicity of treatment. Larger prospective studies validating these findings are needed to optimally predict treatment benefit and individualize management.

Treatment

Treatment strategies have been evolving to target patients with higher risk MDS and subgroups defined by specific cytogenetic abnormalities. Current treatment recommendations revolve around a risk-adapted therapeutic approach and will be further refined by addition of patient-specific characteristics (Table 2). In general, treatment goals for lower risk patients are to minimize the morbidity of disease (maximize QOL, minimize symptoms and transfusion dependence); goals for higher risk patients include altering the natural history of the disease.

Supportive care, aimed at controlling symptoms related to cytopenias, is indicated for all patients and remains the primary treatment for lower risk MDS or frail patients. Key components of supportive care are transfusion support and antibiotics for infection. Hematopoietic growth factors (e.g. erythropoietin) are used to minimize transfusion requirements for patients with symptomatic anemia and can improve quality of life[13, 14]. Over time, most patients become transfusion-dependent, increasing the risk of iron overload; iron chelation therapy should be started for those with lower risk MDS, ongoing transfusion dependence and expected survival >1 year.

Patients in the higher risk IPSS categories are more likely to experience complications from cytopenias and to progress to acute leukemia more quickly from diagnosis. Hypomethylating agents which inhibit DNA methyltransferases (azacitidine and decitabine) are the primary treatment for most patients. Randomized studies with azacitidine compared to placebo have shown improvements in survival, QOL, and a longer time to progression to acute leukemia[15-1718]. The survival advantage associated with azacitidine has been demonstrated for adults >75 years of age[19]. Registry data comparing differing treatment schedules among patients ≥ 75 years of age provide additional real-world information on the benefits (40% transfusion independence) and complications (29% cycles delayed, 47% hospitalized for infection) of treatment in this age group[19]. The FDA also approved decitabine for the treatment of higher risk MDS based upon data demonstrating decreased transfusion requirements and symptoms[20].

Challenges for older adults using hypomethylating agents include long term management of myelosuppression which often worsens for several months before response is detectable. The duration of treatment can be challenging both physically and psychologically; the median duration of treatment on clinical trials is at least 6 months and often over 12 months for responders[15, 18].

Additional treatment options exist for patients with the 5q minus syndrome, defined by a deletion of the long arm of chromosome 5 as the sole abnormality. The 5q- syndrome often presents as refractory, severe anemia with a preserved platelet count. It is considered a more favorable subtype of MDS with lower risk of AML progression. Lenalidomide, an oral immunomodulatory drug, decreases transfusion requirements and reverses cytogenetic abnormalities in patients with 5q-syndrome [21, 22]. Myelosuppression is the primary toxicity of lenalidomide often requiring dose reduction or dose delay. Studies suggest treatment with lenalidomide may also benefit patients with low-risk MDS without 5q deletion and it can be considered an option for these patients as well if they are transfusion dependent[23].

To date the only curative therapy for MDS is allogeneic hematopoietic stem cell transplantation (HSCT) which is generally restricted to younger adults with acceptable donors due to treatment-associated morbidity and mortality risk. However, HSCT is increasingly considered for selected adults between ages 60-80 with good functional status and minimal comorbidity with use of reduced-intensity conditioning regimens (RIC). HSCT can result in appreciable survival rates among patients with high risk disease[24] although most older adults in this context are age <70 years. At present, HSCT is reserved for fit patients (good performance status, minimal comorbidity) with higher-risk disease. Specifically, among patients 60-70 years of age, evidence suggests survival may be improved by RIC HSCT for int-2/high IPSS patients (36 versus 28 months) but not for low/int-1 IPSS patients (38 versus 77 months)[24]. Balancing the risk of disease versus treatment is critical and remains an active area of research. As the criteria for "fitness" in the context of stem cell transplantation are further refined with use standardized strategies such as geriatric assessment[25], the real world applicability of transplantation will increase.

Unresolved questions for older adults with MDS

Trials targeting vulnerable and frail patients are needed as are consistent definitions of "fit, vulnerable, and frail" in each treatment setting. In the non-curative setting, the duration and timing of treatment to optimally balance disease control and quality of life is unclear. The role of HSCT for older adults needs to be defined; evidence remains confounded by the lack of randomized controlled trials, inadequate characterization of "fitness" and inconsistent collection of additional patient-centered outcomes (functional independence, health care utilization, quality of life, treatment satisfaction).

Acute Myelogenous Leukemia (AML)

AML refers to a group of clonal hematopoietic disorders characterized by proliferation of immature myeloid cells in the bone marrow. Accumulation of leukemic cells impairs the normal hematopoietic function, resulting in cytopenias with or without leukocytosis. AML is most commonly diagnosed among older adults (median age between 68 and 72 years)[3]. In 2014, the American Cancer Society estimated that 18,860 patients would be diagnosed with AML with the majority (10,460) anticipated to die from the disease[26].

Diagnosis

The diagnosis of AML depends primarily upon detection of leukemic blasts of myeloid lineage (≥20%) in the bone marrow. The World Health Organization classifies AML into four major categories (each with two or more subtypes) utilizing morphologic, immunophenotypic, genetic, and clinical features. The main categories are: 1) AML with recurrent genetic abnormalities; 2) AML with myelodysplasia-related features; 3) therapy-related AML and MDS; and 4) AML not otherwise specified. Genetic and molecular abnormalities highlight the heterogeneity of AML and identify subsets associated with better or worse prognosis. For example, the core binding factor leukemias (inv 16, t(8;21), t(16;16)), and acute promyelocytic leukemia (t(15;17)) are associated with better prognosis. The presence of mutations in *FLT-3* in the setting of a normal karyotype is associated with worse outcomes.

Treatment

If untreated or unresponsive to chemotherapy, AML is rapidly fatal (median survival < 2 months). The major causes of death are infection and hemorrhage related to the disease-associated cytopenias. Increased age is associated with poor outcomes [27](Figure 1). There is no consensus regarding optimal therapy for older adults (often defined by age ≥60 years) with AML[28, 29] in part due to the higher morbidity and mortality rates seen in clinical trials. In the US, less than 40% of older adults receive any therapy for newly diagnosed AML[30]. However, it is clear from both clinical trial and population-based data that chemotherapy can provide a survival benefit over supportive care for selected older adults, even among octagenarians[28, 30-33]. Age is a surrogate measure representing both age-related changes in tumor biology (contributing to treatment resistance) and patient characteristics (contributing to decreased treatment tolerance). Individualized decision-making based on evolving stratification of both tumor biology and patient characteristics will help inform tailoring of treatment and supportive care.

Tumor biology

Age-related differences in tumor biology are a major factor contributing to poor outcomes among older adults. Cytogenetic abnormalities are the most important prognostic factors in AML. Older adults are more likely to have poor-risk karyotypes (–7, 7q-, –5, 5q-, abnormalities of 11q, 17p, Inv3 or complex karyotypes involving ≥ 3 chromosomes) and fewer good-risk karyotypes (i16, t(16;16), t(8;21) or t(15;17)) compared with younger patients [34, 35]. In an analysis of >1000 older adults treated on clinical trials, the proportion with favorable, intermediate and adverse cytogenetics were 7.3, 79.1, and 13.6% respectively associated with 5-year OS rates of 34, 13, and 2% respectively[35]. Molecular mutations and gene deregulation also contribute to prognosis[3637]. Older adults also have higher expression of the multidrug resistance (MDR1) gene[38]. MDR-1 encodes a membrane transporter protein responsible for drug efflux and chemotherapy resistance. Finally, older patients are more likely to have a secondary AML arising from underlying MDS, which is less responsive to standard therapy. The biology of AML in the elderly is complex and contributes directly to poor outcomes with conventional therapies.

Review of elderly-specific clinical trial data

Most clinical trials in AML have enrolled patients aged 60 to 80 years with “good” oncology performance status (Table 4). Median survival in AML has historically been less than 1 year with improvements seen in more recent trials[27, 39]. In general, older adults are less likely to achieve remission (although rates vary from 30-80%), are more likely to relapse, and experience higher 30-day treatment mortality rates (10 to 30%)[27, 39, 40].

Standard induction therapy for AML is combination chemotherapy that includes cytosine arabinoside (ara-C) and an anthracycline administered in the inpatient setting. These drugs yield complete remissions (CRs) in ~ 50% of patients. The poorer prognosis associated with increased age is related to both a higher frequency of induction deaths (treatment-related mortality) and to chemotherapy failure due to residual or resistant leukemia. Evidence suggests that selected older adults can benefit from standard intensive therapy although survival improvement is often measured in months[28, 32]. Attempts to improve durable

response rates in older patients with AML have included dose attenuation, anthracycline substitution, use of growth factors, modulation of multi-drug resistance, and targeting of molecular subsets[39, 41-48]. Improvements have been incremental without a clear practice changing regimen identified. [39, 42].

The role of lower intensity therapies including the DNA hypomethylating agents (eg azacitidine and decitabine) is an area of active investigation[18, 49, 50]. These agents have shown some efficacy for older adults with AML and are increasingly utilized in clinical practice particularly among patients with comorbidity or poor functional status. In many cases, the goal of therapy is disease control or palliation. A recent randomized trial among adults ≥65 years of age with newly diagnosed AML showed a survival advantage for azacitidine compared with conventional care[51]. In this study conventional care included a wide variety of treatment options from intensive induction to supportive care alone. The role of lower intensity regimens remains an active area of investigation. To date none have been shown to be superior to intensive induction as a single comparator in randomized trials; cross study comparisons are challenging..

For patients who achieve remission, the median duration of CR is approximately 1 year; a small percentage (≤15%) may be cured. Patients who achieve remission are considered for post-remission therapy in an attempt to prevent or delay relapse. The exact role and optimal type of post-remission therapy remains poorly defined for older adults. On clinical trials up to 20% of older adults who achieve remission never receive any post-remission therapy possibly related to declines in functional status or acquired comorbid conditions[52]. Strategies that are routinely used for younger patients including high dose Ara-C[53] and stem cell transplantation are associated with increased toxicity among older adults. However, with RIC HSCT regimens, an increasing number of older adults who achieve remission are being referred for allogeneic transplantation in an effort to improve longer- term disease free survival and cure rates[54]. Although feasible in selected older adults[55], it remains unclear if this strategy is superior to non-transplant approaches with respect to survival and QOL.

Treatment recommendations differ for patients with acute promyelocytic leukemia (APL). APL is characterized by a translocation between chromosomes 15 and 17 leading to the fusion of the promyelocytic leukemia (*PML*) gene with the retinoic acid receptor α (*RARα*) gene, resulting in disruption of normal cell differentiation. While uncommon among older adults, this disease has a very high response and cure rate with current therapies that include use of all-*trans* retinoic acid (ATRA) which overcomes the differentiation block. Remission and disease free survival rates approximate 90% and thus patients with APML should be treated aggressively with ATRA and arsenic trioxide. [56].

Risk stratification

Improving outcomes for older adults with AML requires more accurate discrimination between those older patients who are more or less likely to benefit from therapies regardless of chronologic age. There are several prognostic models developed from clinical trial or registry data that can be used to predict outcomes for older adults treated with induction chemotherapy [29, 57-59] (Table 5). Application of these models highlights the heterogeneity of expected treatment outcomes for older adults; estimates of early mortality (16-71%)[29],

remission (12-91%)[57], and 3-year survival (3-40%[58]) vary widely. Each model provides useful information to help individualize a treatment choice for an older patient. These models, however, are weighted towards characterization of tumor biology and primarily rely on chronologic age to predict treatment tolerance. Disease characteristics alone do not fully explain age-related outcome disparity in AML. Even among older adults with favorable disease biology, outcomes are worse than for younger patients[27]. Patient characteristics that are more common with aging such as increased comorbidity, functional and cognitive impairment complicate therapy and contribute to decreased treatment tolerance and benefit. Systematic measurement of patient-specific characteristics can help discriminate between fit, vulnerable, and frail patients for a given treatment.

In studies of older adults, comorbidity burden typically measured with a modified Charlson Comorbidity Index [CCI] or the Hematopoietic Cell Transplantation Comorbidity Index [HCT-CI] is associated with lower remission rates, increased treatment-related mortality and decreased survival[60-62]. For example, among 177 patients ≥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)[61]. Current evidence supports pretreatment comorbidity assessment using the CCI or HCT-CI. The prognostic implications of individual comorbid conditions are not well-studied.

Evidence is strong that functional status also influences treatment tolerance. In oncology practice, functional status is frequently assessed using the Eastern Cooperative Oncology Group (ECOG) Performance Score (0-4 scale, higher scores indicating impaired function) and the Karnofsky Performance Scale (scale 10-100%, higher scores indicating better function).The relationship between ECOG performance status (PS) at diagnosis, age, and 30-day mortality during intensive induction is dramatic. Data from older adults enrolled on induction trials showed similar 30-day mortality (11 to 15%) for patients aged 56-65, 66-75, >75 with excellent performance status (ECOG 0), contrasted with rates of 29%, 47% and 82%, respectively for poor baseline performance status (ECOG 3)[27]. Fit older adults, even those >75 years, may tolerate induction chemotherapy similar to those in middle age but the negative prognostic implications of poor PS increases with chronologic age. While ECOG PS is useful in identifying frail patients (ECOG >2), it is an insensitive and subjective measure of physical function. Further refinement is needed to identify vulnerable older adults. In fact, studies have shown that assessment of self-reported activities of daily living and objectively measured physical performance (testing comprised of walking speed, chair stands, and balance) are predictive of survival after accounting for PS[12, 63, 64].

Pretreatment assessment of older adults needs to take into account the complexity of variables that may differ from patient to patient. Geriatric assessment (GA) is an approach to measure the complexity of patient characteristics present in older populations. Pretreatment GA is feasible in the context of AML and suggests that chronologic age may not be a robust predictor of outcome after accounting for function, comorbidity, and symptoms (Table 5)[12, 65]. In a prospective study of adults ≥60 years of age treated intensively, pre-treatment GA detected significant impairments even among those with “good oncology PS” (ECOG 0-1): cognitive impairment, 24%; depression, 26%; distress, 50%; ADL impairment, 34%;

impaired physical performance, 31%; and comorbidity, 40%[65]. Importantly, the majority of patients (63%) were impaired in more than one measured characteristic. Overall, studies utilizing a GA approach have identified impaired cognition, impaired physical performance, ADL impairment and symptoms (e.g. fatigue, pain) as independent predictors of worse survival[12, 63, 66]. The utility of GA is currently under investigation in multi-site trials.

Treatment recommendations for older adults with AML should be individualized based on tumor biology and patient characteristics. While validation is needed, available evidence can inform practical strategies to differentiate fit, vulnerable and frail patients when considering therapy (Table 6). In general, patients categorized as frail are at high risk for treatment toxicity; risks may outweigh benefits. Clinical trials are needed testing novel therapies in this subgroup. Fit patients are most likely to benefit from curative therapy and strong consideration should be given to offering standard therapies similar to those used for middle aged patients. For fit patients, older age is associated with similar QOL and physical function to younger age during and after intensive induction therapy[67, 68]. Optimal therapy for the large proportion of older adults who fall between these two extremes is unclear. In practice, consideration should be given to enhanced supportive care for vulnerable patients by targeting modifiable risk factors (i.e. early physical therapy for patients with impaired physical performance).

Unanswered questions for older adults with AML

There are many unanswered questions regarding best practices for older adults with AML. Many questions revolve around improved characterization of fitness to optimally predict treatment tolerance in a given setting. The interactions between patient characteristics and tumor biology require further study. Ideally trials targeting biologically defined subtypes of AML within the context of defined patient subgroups (fit, vulnerable, frail) will be needed. Finally, patient-centered outcomes outcomes capturing QOL, symptoms, functional independence, patient preference, and healthcare utilization should be captured to fully inform treatment decisions.

Conclusions

MDS and AML are heterogeneous diseases affecting older adults. Significant advances are being made in understanding the complexity of both tumor biology and patient characteristics that influence outcomes. Optimal treatment decision-making requires a frank discussion regarding risks and benefits of therapy interpreted in the context of individualized assessment and the patient's values and goals of care.

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Key Points

- Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic disorders with a variable natural history.
- Treatment recommendations for MDS are risk adapted and range from supportive care to high intensity therapy.
- Optimal therapy for older patients with acute myeloid leukemia (AML) is unclear.
- Management of older adults with MDS and AML needs to be individualized accounting for both the heterogeneity of disease biology and patient characteristics which can influence life expectancy and treatment tolerance

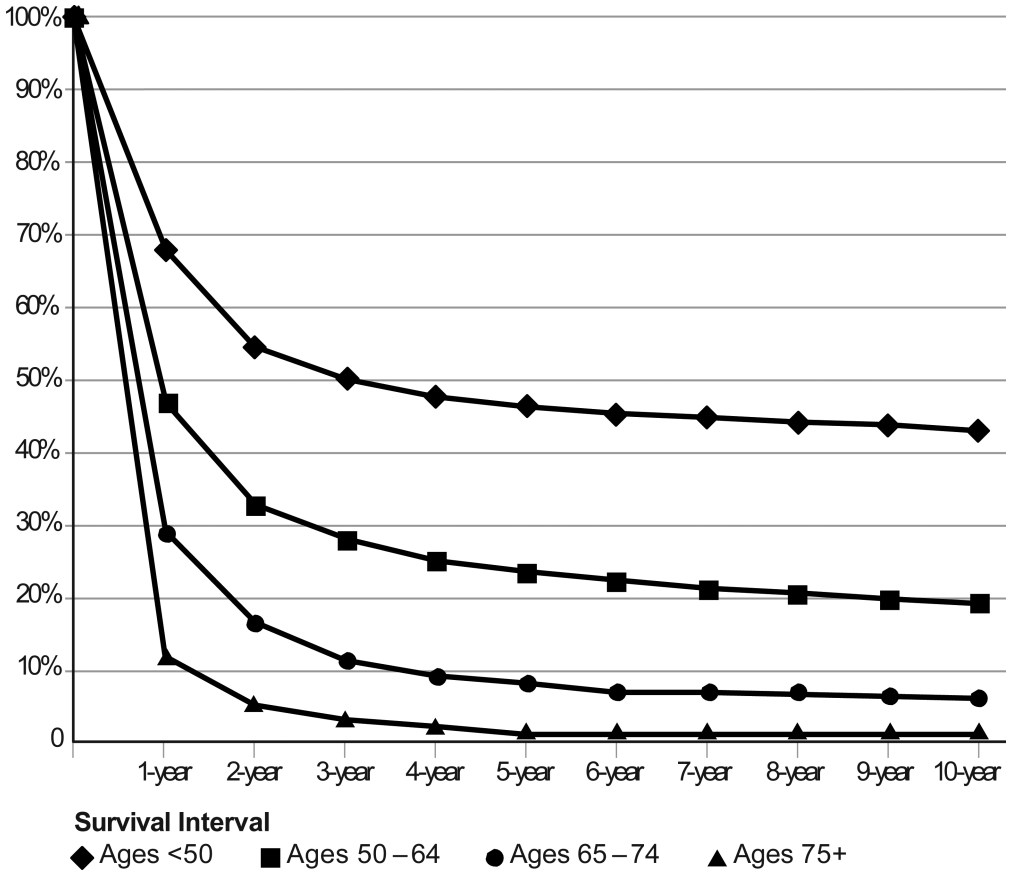

Figure 1.
Relative survival by time and age for Acute Myeloid Leukemia

TABLE 1

Overall survival and risk of AML evolution by revised IPSS score

Risk Group	IPSS-R score	Median overall Survival (years)	Median time to 25 percent AML evolution (years)
Very low	<1.5	8.8	>14.5
Low	<1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

Data from Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65.

Table 2

Treatment options for older adults with MDS based on disease and patient characteristics

Disease Characteristics (Revised IPSS)	Goal of therapy	Patient Characteristics	Treatment Considerations (Comments)
Very low risk, low risk Asymptomatic	Improve QOL	Any	Observation (Evidence is lacking to support QOL or survival advantage with early therapy)
Very Low/low/intermediate Symptomatic			
5q deletion	Improve QOL	Any	Lenalidomide (Understudied in “vulnerable/frail” patients. Dose adjust for impaired creatinine clearance.)
Absence of 5q- with erythropoeitin level <500	Improve QOL	Any	Erythropoeitin+/− GCSF (Discontinue if no response in 8 weeks)
			Consider Lenalidomide (Especially if isolated anemia)
	Improve QOL	Good performance status/minimal comorbidity	Consider hypomethylating agents (Observational data suggests benefit in lower risk MDS)
Intermediate/high/very high	Delay progression Extend life	Any age, good performance status, absence of major comorbidity	Hypomethylating agents (Strongest evidence supports use of 7-day azacitidine regimen)
	Cure	Age 60-75, excellent performance status, absence of major comorbidity	Consider referral for RIC HSCT versus hypomethylating agents. (Comprehensive geriatric assessment may help inform “fitness”, randomized data to support benefits of HCST are lacking)
	Delay progression, Extend life	Poor performance status and/or major comorbidity	Consider hypomethylating agents versus supportive care (Absence of data in frail patients, however given potential to improve survival and QOL would discuss with patient)

Abbreviations: QOL=quality of life; RCT= randomized controlled trial; GCSF=granulocyte colony stimulating factor; HSCT=hematopoietic stem cell transplantation; AML=acute myeloid leukemia; RIC=reduced intensity conditioning

Adapted from Klepin et al. J Clin Oncol 2014 2014 Aug 20;32(24):2541-52.

Table 3

Selected randomized treatment trials for myelodysplastic syndrome (MDS)

Treatment	N	Disease Risk Category	Positive outcomes	Toxicity
Azacitidine [16] 75mg/m^2 SQ × 7days Q 4 weeks vs. supportive care	191	IPSS Int-1/Int-2/High	Improved response rate (23 vs. 5%) Improved time to AML or death (21 vs. 13 months) Decreased AML transformation (15 vs. 38%) Improved QOL (physical function, symptoms, psychological state)	Grade 3-4 myelosuppression (43-58%) Infection (20%)
Azacitidine [15] 75mg/m^2 SQ × 7days Q 4 weeks vs. conventional care (supportive, low-dose cytarabine, intensive chemotherapy)	358	IPSS Int-2 or High	Overall survival (median 24.5 vs. 15 months)	Myelosuppression
Decitabine 15mg/m^2 IV ever 8 hours for 3 days Q 6 weeks vs. supportive care [20]	170	IPSS Intermediate or High	Response rate (17 vs. 0%) Improved QOL (global health, fatigue, dyspnea)	Dose reductions/delays (35%) Grade 4 myelosuppression (>50%)
Lenalidomide 10mg/day days 1-21 vs.5mg/day days 1-28 vs. placebo on 28 day cycle [21]	205	MDS with del5q31 IPSS Low or Int-1 RBC transfusion dependence	RBC transfusion independence for ≥26 weeks (56.1 vs. 42.6 vs. 5.9%) RBC transfusion independence >8 weeks associated with decreased risk of death and AML progression	Myelosuppression in first 2 cycles DVT (5.8%) in 10mg group

Abbreviations: SQ= subcutaneous; Q= every; IV=intravenous; vs.= versus; int=intermediate; FAB= French-American-British; RA= refractory anemia; RARS= refractory anemia with ringed sideroblasts; IPSS= international prognostic scoring system; CMML= chronic myelomonocytic leukemia; RBC= red blood cell; ECOG= Eastern Cooperative Oncology Group; PS=performance status; AML= acute myeloid leuekemia; QOL= quality of life; CR= complete remission; DVT=deep venous thrombosis.

Table 4

Selected randomized trials of induction chemotherapy for older adults with AML

Chemotherapy regimens*	Age range (years)	N	CR (%)	Median OS (months)	P value for OS	Induction death rate (%)	Comments
Intensive versus supportive care							
Ara-C, daunorubicin, vincristine Supportive care [32]	65-85	31	58	5.3	<0.05	9.7	No difference in days hospitalized
		29	0	2.8		N/A	
Type and dose of anthracycline							
Ara-C, daunorubicin 80 mg/m^2	50-70	156	70	No difference	0.16	8	Median OS 17 months forentire study cohort
Ara-C, Idarubacin 12 mg/m^2 ×3days		155	83			3	
Ara-C, Idarubacin 12 mg/m^2 ×4days [47]		157	78			6	
Ara-C, daunorubicin 45mg/m^2 [43]	60-83	411	54	No difference	0.16	11	Benefits suggested among patients aged 60-65
Ara-C, daunorubicin 90mg/m^2		402	64			12	
Dose attenuated induction							
Rubidazone, Ara-C	65-83	46	52	12.8	0.12	31	
Low-dose Ara-C [46]		41	32	8.8		10	
Growth factor support							
Ara-C, daunorubicin [45]	60-80**	195	54	9.4	0.10	16	
Ara-C, daunorubicin,+GM-CSF		193	51	9.4		20	
MDR1 modulation							
Ara-C, daunorubicin, etoposide	60-84	61	46	No difference	0.48	20	
Ara-C, daunorubicin, etoposide, +PSC-833 [41]		59	39			44	
Addition of gemtuzumab ozogamicin							
Ara-C, daunorubicin [39]	50-70	139	75***	11	<0.05	4	
Ara-C, daunorubicin,+gemtuzumab		139	81***	28		6	
Daunorubicin, Ara-C or clofarabine	51-84	556	58	Improved	0.05	9	Improved 3yr survival (25 vs. 20%)
Daunorubicin, Ara-C or clofarabine +gemtuzumab [42]		559	65			8	

Chemotherapy regimens*	Age range (years)	N	CR (%)	Median OS (months)	P value for OS	Induction death rate (%)	Comments
Lower intensity therapy							
Supportive care or low-dose Ara-C	64-91	243	8	5	0.2	8	Poor/intermediate risk cytogenetics only
Decitabine [50]		242	18	8		9	ECOG PS 0-2 with minimal comorbid conditions
Low-dose Ara-C ± ATRA [49]	51-90	103	18	Improved	<0.05	26	No specific “fitness” criteria except comorbidity if <70
Hydroxyurea ± ATRA		99	1			26	
Azacitidine [51]	64-91	241	20	10.4	0.1	7	In adjusted analyses, survival benefit or azacitidine (p=0.03)
Conventional care (supportive, low-dose cytarabine, intensive chemotherapy)		247	22	6.5		10	

Abbreviations: AML= acute myelogenous leukemia; N= number of patients enrolled; CR= complete remission; OS= overall survival; Ara-C= cytarabine; N/A= not applicable; GM-CSF= granulocyte macrophage colony stimulating growth factor, ECOG= Eastern Cooperative Oncology Group; PS= performance status.

*One limitation in translating clinical trial data into best practices is both the lack of consistency in patient populations recruited and in drug doses utilized making comparisons of results between trials challenging.

**4%≥80 years

***rates represent CR with incomplete platelet count recovery

Table 5

Factors associated with survival among older adults receiving chemotherapy for AML

Author (N)	Treatment	Tumor characteristics	Clinical variables	Patient Characteristics	Outcomes
Predictive models developed from treatment trials					
Kantarjian et al. (N=446) [29]	Intensive	Complex karyotype	Creatinine >1.3mg/dl	Age>80 ECOG PS>1	Early mortality (8 week)
Krug et al. (N=1406) [57]	Intensive	Secondary AML or prior hematologic disease Molecular/cytogenetic risk	Body temperature Hemoglobin Platelets LDH Fibrinogen	Age	Early mortality (60 day) Complete remission
Rollig et al. (N=909) [58]	Intensive	Karyotype *NPM1* mutation CD34 expression>10%	White cell count>20/μL LDH>700U/L	Age>65	Survival
Wheatley et al. (N=2208) [59]	Intensive	Cytogenetic risk group Secondary AML	White cell count	Age ECOG PS	Survival
Predictors derived from geriatric assessment studies					
Deschler et al. (N=107) [12]	Non-Intensive (prospective)	Bone marrow blast % Cytogenetic risk group		Impaired ADLs KPS<80 High fatigue score HCT-CI≥3	Survival
Klepin et al. (N=74) [63]	Intensive (prospective)	Cytogenetic risk group Prior MDS	Hemoglobin	Cognitive impairment (3MS<77) Impaired physical performance (SPPB<9)	Survival
Sherman et al.(N=101) [66]	Mixed (retrospective)	Adverse cytogenetics Secondary AML		HCT-CI >1 Difficulty with strenuous activity Pain (more often versus less) ECOG PS>1	Survival

Abbreviations: LDH=lactate dehydrogenase; ECOG=Eastern Cooperative Group; PS=performance status; CR=complete remission; 3MS=modified Mini Mental State Exam; SPPB=Short physical performance battery

Adapted from Klepin et al. J Clin Oncol 2014 2014 Aug 20;32(24):2541-52.

Table 6

Considerations for risk stratification and treatments for older adults with AML

Patient risk category	Characteristics	Treatment Considerations (Clinical trials preferred)
Frail	Poor oncology performance status (ECOG PS score ≥3) Major comorbidity (i.e. HCT CI>2) Impairment in ADLs	High treatment-related mortality (particularly for adults >75 years) Favorable Tumor Biology*: Consider lower intensity therapy (HMAs, low- dose Ara-C). Patients with poor PS (particularly aged 60-75) but without end stage comorbidity may consider intensive treatment if risks/benefits are consistent with goals of care. Intermediate/Unfavorable: Consider best supportive care including palliative care consultation if available versus lower intensity therapy (HMAs, low- dose Ara-C). *Clinical trials targeting frail patients are needed; randomized evidence is lacking.*
Vulnerable	ECOG Performance status score 0-2 Absence of major comorbidity (HCT CI≤2) Presence of: Impairment in IADLs/ self-reported mobility Impaired physical performance (SPPB<9) Impaired cognition (3MS score <77) High symptom burden (fatigue, pain)	Outcomes for this subgroup are poorly defined in clinical trials due to lack of characterization. In non-randomized studies this group is at risk for shorter survival compared to fit patients. Favorable Tumor Biology: Consider intensive therapy. Intermediate/Unfavorable: Consider intensive therapy if risks and benefits are consistent with goals of care versus lower intensity therapies (HMAs, low-dose Ara-C). Consider enhanced supportive care targeting vulnerabilities such as early physical therapy for impaired mobility. *Clinical trials are needed to validate definitions of vulnerability and to test treatment and supportive care strategies to improve outcomes in this group.*
Fit	ECOG performance status score 0-1 Minimal comorbidity (i.e. HCT CI<1) Absence of any above mentioned risk factors	Best evidence suggests fit older adults derive benefit from aggressive therapy. Favorable Tumor Biology: Intensive therapy should be offered. Intermediate/Unfavorable: Consider intensive treatment with possible RIC allogeneic HSCT if risks/benefits consistent with goals of care versus lower intensity therapies (HMAs, low-dose Ara-C). *Future clinical trials should compare investigational therapies to standard intensive treatment among fit older adults.*

Abbreviations: ECOG=Eastern Cooperative Oncology Group; PS= performance status; HCT-CI=Hematopoietic Cell Transplantation Comorbidity Index; ADLs=activities of daily living; TRM=treatment-related mortality; HMA=hypomethylating agent; Ara-C= cytarabine; IADLs=instrumental activities of daily living; SPPB=Short Physical Performance Battery: 3MS=Modified Mini-Mental State Exam; RIC=reduced intensity conditioning; HSCT= hematopoietic stem cell transplant.

Adapted from Klepin et al. J Clin Oncol 2014 2014 Aug 20;32(24):2541-52.

*Favorable Tumor Biology: inv(16), t(16; 16), t(8;21), t(15;17); Intermediate-risk: normal cytogenetics, +8 alone, t(9; 11), other non-defined: Unfavorable: Complex (≥3 clonal abnormalities), −5, 5q-, −7, 7q-, abnormalities of 11q, inv(3), t(3;3), t(6;9). In the normal cytogenetic category, NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation confers better risk versus presence of FLT3-ITD which confers worse risk.