SPECIAL SERIES: CARING FOR OLDER ADULTS WITH CANCER

Advances in Management for Older Adults With Hematologic Malignancies

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INTRODUCTION

Hematologic malignancies (HMs) represent a varied set of diseases ranging from indolent to aggressive that are increasingly common in the growing older adult population. Representation of older adults in clinical trials remains low, particularly among those over 75 years old. As treatment options expand, questions remain regarding fitness for therapies, sequencing of therapies, management for vulnerable or frail patients, and strategies to optimize functional independence and quality of life (QOL). This review provides updates on new therapies for common HMs with an emphasis on older adult–specific evidence and the evolving role of a geriatric assessment (GA) in informing therapy selection and management.

MULTIPLE MYELOMA

Multiple myeloma (MM) is a disease of aging (median age at diagnosis 69 years). MM is not considered more biologically aggressive with aging, but older age is associated with advanced-stage disease.[1,2] The therapeutic landscape is increasingly complex with combinations of drug classes including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), alkylating agents, corticosteroids, monoclonal antibodies (mABs), targeted agents, and cellular therapy (autologous hematopoietic cell transplantation [autoHCT], allogeneic hematopoietic cell transplantation [HCT], and chimeric antigen receptor T-cell therapy [CAR-T]). In the past 5 years, the US Food and Drug Administration has approved seven new therapies for MM. This dynamic field complicates treatment decisions for older adults as it pertains to treatment selection, expected toxicities, and therapy sequencing. Importantly, undertreatment of older adults with MM (≥ 65) is evident; recent large registries report that 38%-49% of patients with MM do not receive antimyeloma therapy.[3,4] With MM treatment, 5-year myeloma-specific survival is improving (ages 66-79) from 26% during 1973-1979, to 32% during 1980-1999, to 41% from 2000-2009 ($P < .05$).[5] Survival among younger adults (< 50) approaches 68%, whereas survival is inferior and unchanged for octogenarians.[5]

For newly diagnosed MM (NDMM), treatment strategies are framed as transplant eligible versus ineligible. A growing body of literature, however, recognizes that health status, and therefore eligibility, fluctuates.[6] MM guidelines recommend frontline autoHCT as the standard of care (SOC) for eligible patients.[7,8] AutoHCT with high-dose melphalan remains the cornerstone of therapy for MM, although randomized controlled trials evaluating tolerance of transplant are limited by upper age restrictions, centered around age 65.[9] Long-term data from the IFM-2009 trial reported improved progression-free survival (PFS) with lenalidomide, bortezomib, and dexamethasone (RVD) before and after autoHCT compared with RVD alone for patients ≤ 65 years, 47.3 months vs 35.0 months respectively ($P < .001$).[10] After 8 years, the median overall survival (OS) was not reached with no difference in OS rate by treatment arms.

Nontransplant strategies for older adults with NDMM include doublets, triplets, and quadruplet induction regimens based on patient fitness, disease biology (eg, cytogenetics), and shared decision making. The FIRST trial evaluated lenalidomide-dexamethasone continuously (Rd) versus 18 cycles (Rd18) versus melphalan-prednisone-thalidomide; PFS was superior with Rd, and OS was significantly improved in both Rd treatment arms; older age was an adverse risk factor.[11] Prospective observational data evaluating real-world treatment in the United States reported that RVD is the most common induction strategy,[12] based on the SWOG S0777 study where RVD resulted in superior PFS and OS in comparison with Rd with acceptable toxicity profiles.[13] Triplet therapy in the MAIA trial evaluated continuous daratumumab (D)-Rd versus Rd and demonstrated improved PFS and overall response rate (ORR) with D-Rd, with more leukopenia and pneumonia in daratumumab-exposed patients.[14] Other triplet induction strategies such as carfilzomib, lenalidomide, and dexamethasone in transplant-ineligible patients have not improved PFS compared with RVD and had higher rates of grade 3-5 treatment-related cardiac, pulmonary, and renal toxicity ($P \leq .0001$).[15] Quadruplet therapy in the ALCYONE study yielded OS advantages of daratumumab, bortezomib, melphalan, and prednisone followed by daratumumab maintenance, in comparison with bortezomib, melphalan, and prednisone, with a 40%

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CONTEXT

Key Objective

How do advances in therapeutics and geriatric assessment (GA) strategies inform personalized management for older adults with hematologic malignancies?

Knowledge Generated

Novel therapeutics, targeted therapies, and maintenance strategies are improving outcomes for older adults including those who have functional impairments and competing comorbid conditions. GA and frailty measures are predictive of treatment tolerance and outcomes across various hematologic malignancies.

Relevance

Integration of GA measures into practice can inform shared treatment decisions and guide management of identified vulnerabilities to enhance therapeutic benefit and quality of life.

reduction in the risk of death.[16] For transplant-eligible high-risk patients, daratumumab and RVD (D-RVD) is gaining traction given high ORR of D-RVD versus RVD (odds ratio = 8.75 [95% CI, 1.08 to 71.01], $P = .016$).[17] Studies reporting D-carfilzomib, lenalidomide, and dexamethasone efficacy and tolerability peri-autoHCT are forthcoming.[18]

Treatment for Relapsed or Refractory MM (RR MM) is complex, combining novel therapies (PIs and IMiDs) with next-generation agents (mABs, targeted) or with the use of cellular therapy. Relapsed therapies are crafted based on several factors including disease biology; tempo of disease relapse; tolerance, toxicity, and type of prior therapy; underlying health status; and shared decision making.[19] Studies evaluating symptom trajectories show improved symptom burden and health-related QOL post-diagnosis with therapy that worsens again at time of relapse. Exploring tolerability of next-generation therapies is imperative. In one example evaluating idecabtagene vicleucel, B-cell maturation antigen–directed CAR-T cell for triple-class RRMM (refractory to IMiDs, PI, and mABs), 35% of patients were ≥ 65 years and the response or duration rates and PFS were similar for older adults versus younger adults with QOL improvement nine months post-infusion.[20]

Objectively characterizing health status at each MM treatment decision point (diagnosis, transplant, and relapse) can right size therapy. GA metrics are well-characterized to identify vulnerability and have prognostic significance in MM. GA tools have been evaluated in NDMM before AutoHCT[21] and in large registries.[22] Several MM-specific geriatric tools are available to estimate treatment tolerance, each with limitations, but are better estimates of health status than age or comorbidities alone (Table 1). Well-established tools include the International Myeloma Working Group Frailty Score, Revised-Myeloma Comorbidity Index, and the Geriatric Assessment in Hematology scoring system.[23-28] Robust characterization of health using GA, longitudinal functional assessment, and nonage-based clinical trials can improve morbidity and mortality for older adults with MM.

DIFFUSE LARGE B-CELL LYMPHOMA IN OLDER ADULTS

The most frequent non-Hodgkin lymphoma subtype among older adults is diffuse large B-cell lymphoma (DLBCL) (median age at diagnosis of 66 years). Management of older adults with DLBCL requires a multidisciplinary approach, where frailty, cognition, malnutrition, comorbidities, polypharmacy, social isolation, and depression are commonly seen. GA remains the gold standard to classify patients into frailty phenotypes. To simplify the GA, the Fondazione Italiana Linfomi consortium proposed the use of age, activities of daily living (ADLs), instrumental activities of daily living (IADLs), and the Cumulative Illness Rating Scale for Geriatrics to classify patients as fit, unfit, or frail.[29,30] The International Society of Geriatric Oncology also published a position paper about the impact of prognosis, comorbidities, GA, and supportive care in selecting a best approach for older adults with DLBCL.[31] Further considerations at initial assessment should include infection risk, growth factor support as a primary prophylaxis, the role of bone protection, and prephase therapy (eg, steroids and vincristine) in older patients with impaired performance status (PS) driven primarily by disease burden, which has been indirectly shown to reduce treatment-related mortality.[32]

Trials that are not older adult–specific largely exclude octogenarians. The evidence base is predominantly limited to phase II trials and retrospective series (Table 2). The choice of dose intensity in anthracycline-fit older patients represents a trade-off between the risk of treatment-related toxicity and the risk of insufficient dosing resulting in inadequate efficacy. This is of relevance in this group of patients who have historically had few effective options at relapse or progression.

In 2011, Peyrade et al[32] provided the first prospective phase II evidence to show that anthracycline-based immunochemotherapy provided curative potential in octogenarians with DLBCL. Over the last decade, the use of anthracycline-based immunochemotherapy has become

TABLE 1. Studies Highlighting the Use of Geriatric Metrics in Multiple Myeloma

Study	Sample (N, eligibility)	Median Age, years (range)	Geriatric Metrics Used to Estimate Fitness and/or Outcomes	Outcomes		Other Considerations
				PFS (median)	OS (median)	
IMWG: Frailty Score Calculator[25]	NDMM 65+ or transplant ineligible N = 869	74 (70-78)	ADL, IADL, age, and comorbidities	3-year PFS Fit: 48% Intermediate: 41% HR = 1.18, $P = .211$ Frail: 33% HR = 1.68, $P < .001$	3-year OS Fit: 84% Intermediate: 76% HR = 1.61, $P = .042$ Frail: 57% HR = 3.57, $P < .001$	Predictive of treatment toxicities and drug discontinuation. 50 of 260 patients classified as frail by age alone
GAH[24]	ND HM (includes MM); 65+ N = 363	76 (71-81)	ADL, comorbidities, nutrition, mental status, SPPB, subjective health status, polypharmacy, and mood	Not noted	Not noted	Limitations in GAH in predicting treatment tolerability
Revised-Myeloma Comorbidity Index[26]	NDMM transplant eligible and ineligible N = 801	63 (21-93)	PS (KPS), age, comorbidities, renal eGFR, lung dysfunction, frailty score, and cytogenetics	Fit: 4.1 years Intermediate: 1.9 years Frail: 0.9 years	Fit: 10.1 years Intermediate: 4.4 years Frail: 1.2 years	Comparisons to IMWG, HCT-CI, and CCI
Frailty Assessment pre-AutoHCT[21]	MM pre-autoHCT N = 108	59.5 (36-75)	PS (KPS), ADL, IADL, nutrition, cognition, hospital anxiety and depression scale, SPPB, handgrip, and brief fatigue inventory	Not noted	EFS (relapse or death) associated with weight loss HR = 3.13, $P = .03$	Transplant LOS: 16 days (12-36); shorter LOS correlated with higher SPPB
Simplified Frailty Scale[27]	NDMM 65+ or < 65 and ineligible for ASCT N = 1,623	Nonfrail: 70 (40-80) Frail: 77 (44-92)	PS (ECOG), age, and comorbidities (CCI)	Frail: 19.4 months Nonfrail: 24 months HR = 1.36, $P < .005$	Frail: 42.1 months Nonfrail: 70.1 months HR = 1.86, $P < .0001$	ORR Frail: 72% Nonfrail: 79% $P = .0002$
Frailty Index[22]	MM 65+ N = 3,807	75 (65-96)	31 deficits (morbidity, functional status, cognition, mood, sensory loss, and geriatric domains)	Not noted	Nonfrail: 38.4 months Prefrail: 27.1 months Mildly frail: 15.6 months Mod frail: 8.4 months Severely frail: 9.5 months Log-rank test $P < .0001$	US Veterans Registry
mGA[28]	MM 65+ N = 165	72 (65-85)	ADL, IADL, age, and comorbidities	Not noted	Not noted	19.4% grade 3 or higher heme toxicities; 38.9% patients had dose modifications; 18% had early therapy cessation

Abbreviations: ADL, activity of daily living; autoHCT, autologous hematopoietic cell transplantation; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; eGFR, estimated globular filtration rate; GAH, Geriatric Assessment in Hematology; HCT-CI, hematopoietic cell transplantation comorbidity index; HM, hematologic malignancies; HR, hazard ratio; IADL, instrumental activity of daily living; IMWG, International Myeloma Working Group; KPS, Karnofsky performance status; LOS, length of stay; mGA, modified geriatric assessment; MM, multiple myeloma; Mod, moderate; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; SPPB, short physical performance battery.

more widespread. The regimen named mini rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone (adriamycin [25 mg/m^2], cyclophosphamide [400 mg/m^2], and vincristine [1 mg capped dose]) resulted in a 2-year OS of 59% with a survival plateau. Similar outcomes were seen when ofatumumab was investigated in place of rituximab and in the phase III SENIOR trial,[33] where the 2-year PFS of R-miniCHOP arm (subcutaneous rituximab)

TABLE 2. Recent Clinical Trials That Included Older Adults With Diffuse Large Cell Lymphoma

Regimen or Study Design	Sample (N, eligibility)	Median Age, years (range, if available)	Outcomes	Toxicity	Other Considerations
R-mini-CHOP Phase II, multicenter, single-arm, open-label[32]	N = 150 Newly diagnosed DLBCL Over 80 years	83 years (80-95)	Median OS: 29 months 2-year OS: 59% (49%-67%) Median PFS: 21 months 2-year PFS: 47% (38%-56%)	Grade ≥ 3 neutropenia in 59 patients: grade 3 febrile neutropenia in 11 patients	IADL was assessed in all patients OS was only affected by a serum albumin concentration of 35 g/L or less
Subcutaneous R-mini-CHOP *v* subcutaneous R-mini-CHOP plus lenalidomide Phase III, multicenter, open-label[34]	N = 249 Newly diagnosed DLBCL Over 80 years	83 years (80-96)	2-year OS was 66% in R-mini-CHOP *v* 65.7% in R2-mini-CHOP	Grade ≥ 3 AEs occurred in 53% of patients with R-mini-CHOP *v* 81% of patients with R2-mini-CHOP	55% of the patients were classified as non-Germinal Center subtype Baseline, G8, IADL, MNA, and CIRS-G data were collected
Ofatumumab plus reduced-dose CHOP Phase II, multicenter, single-arm, open-label[33]	N = 120 Patients older than 80 years Untreated histologically proven CD20-positive DLBCL Ann Arbor stage I-IV	83 years (80-95)	2-year OS: 64.7% 2-year PFS: 57.2%	Grade ≥ 3 neutropenia was reported in 21%, thrombopenia in 2%, anemia in 6%, and 1 episode of febrile neutropenia	Patients received a prophase with one vincristine 1 mg total dose 1 week before cycle 1 (days 1-7) and oral prednisone 60 mg total dose for 4 days, 1 week before cycle 1 15% of patients had RBC transfusions, and 3% had platelet transfusion IADL, Buzby nutritional index, and CCI was explored
Obinutuzumab—mini-CHOP Phase II, multicenter, single-arm, open-label[35]	N = 34 Newly diagnosed DLBCL Patients older than 65 years Defined as unfit according to a simplified GA	82 years (68-89)	CR: 42% 2-year OS: 68% 2-year PFS: 49%	Grade ≥ 3 neutropenia was reported in 26%	Simplified GA (age, ADL, IADL, and CIRS-G)

Abbreviations: ADL, activity of daily living; AE, adverse event; CCI, Charlson Comorbidity Index; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CR, complete response; DLBCL, diffuse large B-cell lymphoma; G8, Geriatric Eight Questionnaire; GA, geriatric assessment; IADL, instrumental activity of daily living; MNA, Mini-Nutritional Assessment; OS, overall survival; PFS, progression-free survival; R, rituximab.

was 67%.[34] In a phase II multicenter trial to investigate miniCHOP plus obinutuzumab in older patients with DLBCL (≥ 65), prospectively defined as unfit according to a simplified comprehensive GA, the 2-year PFS and OS were not improved when compared with historical data obtained with R-miniCHOP in this group of patients.[35] When analyzing intended dose intensity (IDI), IDI lower than 80% is associated with worse outcomes in patients 70-80 years old, whereas survival in those ≥ 80 years was similar independent of IDI.[36] Similar results were reported in patients ≥ 80 years in the large Danish registry.[37] R-mini-CHOP is a reasonable strategy and serves as the backbone of control and experimental arms for patients ≥ 80 years.

Several options exist for patients with a cardiac impairment who are not candidates for anthracycline-based treatment. Prospective phase II data support the use of gemcitabine-based regimens (R-GCVP and R-Gem-Ox).[38] Sixty-two patients received R-CVP plus gemcitabine as an anthracycline substitute. The 2-year PFS was 49.8%, and the 2-year OS was 55.8%. Fifteen cardiac events were documented including three deaths. R-Gem-Ox-14 (rituximab, gemcitabine, and oxaliplatin) was recently assessed in 61 patients (median age 75 years).[39] The 3-year PFS was 49% with survival equivalent in those older than 80 years. Taken together, these data suggest that gemcitabine-based chemoimmunotherapy provides durable DLBCL control in approximately 50% and is well-tolerated including in those with cardiac comorbidities. Another strategy is the use of liposomal formulation of adriamycin. Fifty patients with cardiac comorbidities have been evaluated using this novel formulation in the R-COMP regimen.[40] The three-year PFS was 38%, and the 3-year OS was 50% in a similar population to those receiving R-GCVP. R-bendamustine has been studied in small trials, but outcomes are generally disappointing, with a median progression-free survival of 10 months.[41]

In patients classified as unfit for curative-intent treatment after a GA, QOL and symptom control would be the main goal of therapy. A large population-based series found that in patients > 85 years, OS was equivalent when CVP with or without R or CEOP with or without R was compared with rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone/R-CHOEP (RCHOP plus etoposide).[37] In the Italian study, no benefit was seen in the poor prognosis group, where palliation would be the best strategy.[29] Rituximab monotherapy, steroids, or no drug treatment may be entirely appropriate in the extremely frail or those wishing to avoid treatment-related adverse effects.

For RR DLBCL, recent advances have seen the advent of novel antibody-drug conjugates, anti-CD19 mABs, and anti-CD19–directed CAR-T therapy. Briefly, the conjugated anti-CD79b mAB polatuzumab vedotin has shown promising efficacy in combination with bendamustine-rituximab within a randomized phase II trial and is a licensed option in appropriately selected patients.[42] The novel anti-CD19–directed mAB tafasitamab in combination with lenalidomide is very active, albeit in a low-risk cohort, not including primary refractory patients.[43] Trials are actively investigating CAR-T, autoHCT, and immunochemotherapy in cohorts defined by fitness status.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) have one of the highest median ages at diagnosis, over 70 years. Accordingly, patients with these syndromes are often frail, and clinicians may fear doing more harm than good, especially in the context of lower-risk disease. As frailty and comorbidities frequently limit the goals of MDS treatment to improving function and/or QOL rather than cure, investigators have long recognized that assessing these measures is critical.

One of the advantages of the hypomethylating agent (HMA) azacitidine—the first drug approved for MDS in 2004—was that it was better tolerated than intensive chemotherapy or HCT. In the QOL analysis (n = 191; mean age 67.5),[44] patients treated with azacitidine experienced less fatigue and dyspnea, and better physical functioning compared with those in the supportive care arm. Similar QOL benefits were eventually published for decitabine.[45] Although neither analysis measured frailty per se, improved physical functioning and decreased symptoms likely translate to reduction in markers of frailty.

More recently, data regarding the specific impact of frailty in MDS have come to light through analyses of the MDS-CAN Canadian registry. The investigators evaluated frailty using the Rockwood Clinical Frailty Scale (N = 445; median age 71).[46] Frailty enhanced Revised International Prognostic Scoring System prognostication, was independently associated with survival, and improved risk stratification more than simply factoring in comorbidity: 30% versus 5%.[47] Independent contributions of frailty and comorbidity to outcomes were confirmed in a subsequent analysis of patients with MDS in Japan (N = 118; median age 73).[48]

The Canadian group developed a 42-item MDS-specific frailty index based on deficits in physical function, laboratory values, comorbidity, IADLs, QOL, and PS, which improves upon existing models of disease risk.[49] They eventually parsed these down to 15 items,[50] which are offered in an online calculator[51] combining MDS risk score with metrics such as lactate dehydrogenase, 4-m gait speed, and ability to prepare meals.

Given the early publication of QOL benefits of HMAs, subsequent analyses revealing how frailty affects survival, and emerging data from the National Heart, Lung, and Blood Institute/National Cancer Institute MDS Natural History Study (N = 253; mean age 72), suggesting that frail patients have significantly worse QOL,[52] studies of newer agents in MDS should rigorously incorporate one or both domains in their design and analyses. It is thus disheartening that the analyses used for approval of the two newest agents—luspatercept for anemia in lower-risk MDS with ring sideroblasts (MEDALIST; N = 229, median age 71)[53] and oral cedazuridine/decitabine for intermediate- and higher-risk MDS (eg, ASTX727-01-B; N = 80, median age 69-72)[54]—do not specifically reference frailty or QOL data. For cedazuridine/decitabine, although oral medication is presumed to be easier to tolerate for patients with cancer, this may not be the case for the frail, for patients who have trouble adhering to prescribed regimens, or for whom regular course-correcting check-ins during infusion visits may be beneficial.[55,56]

Finally, given the success of venetoclax plus HMA therapy for newly diagnosed acute myeloid leukemia (AML) in older adults, including those with comorbidities precluding traditional induction, there has been intense interest in this combination for frail adults with MDS. In the AML trial that served as the basis for full venetoclax approval, VIALE-A,[57] frailty was accounted for in the eligibility criteria, but not as an outcome. For the MDS trials of venetoclax combinations, there are few age- or frailty-related entry criteria, but some worry that dual treatments can make QOL or function worse.

These concerns may not be substantiated. For example, M15-531, a phase Ib, dose-escalation study of venetoclax plus azacitidine for higher-risk MDS (N = 78, median age 70)[58] included the European Organization for Research and Treatment of Cancer QOL Questionnaire (QLQ-C30). In preliminary analyses, improvements in dyspnea, fatigue, and global QOL were observed and physical functioning was maintained throughout treatment. Moreover, an ongoing phase III study of the combination (NCT04401748) has as a secondary outcome time to deterioration of physical functioning measured by changes in the QLQC30's physical functioning domain. While not ideal, this is a reasonable proxy for increasing frailty and should

help MDS clinicians characterize the impact that the combination is likely to have on function. Hopefully, future studies will also incorporate one of the many enhanced functional measures shown to be valid for this patient population.

ACUTE MYELOID LEUKEMIA

Most cases of AML are diagnosed among adults over age 65. Although outcomes are improving, age-related disparity persists with 5-year survival rates $< 10\%$ for those ≥ 65 years. Despite evidence of benefit from therapy,[59] a large proportion of older adults receive no treatment for a new diagnosis of AML.[60]

Both disease- and patient-related factors contribute to poor outcomes. Disease-related factors (ie, unfavorable cytogenetic and molecular abnormalities, multidrug resistance phenotype, and secondary AML) contribute to poor response to conventional chemotherapy. Patient-specific factors (ie, comorbidities and functional limitations) contribute to poor treatment tolerance.[61,62] Treatment tolerance and benefit are highly variable among older adults and inadequately predicted by age alone. PS is a useful proxy to predict toxicity risk; the interaction between older age and poor PS (ie, Eastern Cooperative Oncology Group PS ≥ 3) dramatically increases early mortality risk.[63] By contrast, older adults with adequate PS represent a heterogeneous group for whom treatment toxicity and benefit are less predictable and additional assessments are required.

Evidence supports the benefit of antileukemic therapy for older adults[59] (defined as age ≥ 60 years). Initial treatment considerations for nonacute promyelocytic leukemia AML fall into a framework of intensive therapy, less intensive therapy, or best supportive care (BSC). Randomized studies show a consistent survival benefit for antileukemic therapy versus BSC,[59] suggesting that the BSC alone should be restricted to a shrinking minority of older adults (ie, those with pre-existing frailty, limited non-AML life expectancy, or who express clear preference to avoid therapy in favor of hospice care). When possible, older adults should receive care through or in coordination with specialized leukemia centers.[64]

Therapeutic options have expanded significantly for older adults in recent years. Table 3 summarizes studies supporting new therapies. In general, intensive induction therapy, typically inclusive of anthracycline and cytarabine, is recommended for older adults with minimal comorbidity and good functional status (fit) in the setting of favorable- or intermediate-risk disease. Addition of the multitargeted kinase inhibitor midostaurin for FLT3-mutated AML enhances survival and should be considered for fit older adults despite lack of inclusion on the pivotal trial.[65] The goal of treatment is to achieve remission, followed by postremission therapy to render long-term disease-free survivorship. An important advance is CPX-351, a dual-drug liposomal encapsulation of cytarabine and daunorubicin, which improved survival for older adults (age 60-75 years) with secondary AML (ie, therapy-related, antecedent MDS).[66]

Many older adults may not be considered fit for intensive therapy or may prefer a less intensive approach. The addition of BCL-2 inhibitor venetoclax to HMAs or low-dose cytarabine has ushered in a new SOC option with improved remission rates and OS compared with single-agent therapy.[57,67] Registration trials targeted an unfit population defined largely by comorbidities or age ≥ 75 years. Additional options for older adults use targeted therapies including isocitrate dehydrogenase inhibitors (enasidenib and ivosidenib) and the hedgehog inhibitor (glasdegib).[68-71] The Beat-AML trial showed that a precision medicine approach to initial treatment for older adults is feasible and improves outcomes supporting the benefit of incorporating genomic data into early treatment decisions.[72] Advances in postremission therapy, including HCT and use of oral azacitidine maintenance for those who are not transplant candidates, contribute to meaningful improvements in disease control and survival for older adults.[73]

Similar to other HM, defining fitness for therapies remains a challenge in AML.[74] The decision is often based on provider judgment, chronologic age (≥ 75 years), and comorbid conditions. Algorithms exist to predict treatment response and mortality among older adults treated intensively although most rely on chronologic age as a surrogate for patient characteristics.[75,76] Careful characterization of comorbidity burden (ie, HCT Comorbidity Index) adds predictive utility.[77]

GA is feasible and can further refine fitness for patients with AML.[78] Dependence in ADLs and high comorbidity burden (HCT Comorbidity Index score > 3) predict shorter survival with less intensive therapy and can characterize individuals unfit for intensive therapy.[61] Dependence in IADLs is associated with early discontinuation of HMA therapy.[79] Among patients without low or modest comorbidity who are independent in ADLs, the use of objective physical performance testing (short physical performance battery) and cognition screening can further discriminate those who may be most resilient to intensive therapy.[62] Practical screening tools include the 4-m walk test and the five-word recall.[80,81]

Inclusion of QOL information is critical for optimizing patient-centered care for AML. Observational studies show no clear difference in global QOL between intensive and less intensive treatment.[82] Older adult survivors treated intensively experience improvements in QOL, largely driven by symptom improvement.[78,83] Short-term declines in physical function, however, can be expected, which may affect candidacy for subsequent therapies.[84] A recent analysis demonstrated that lower objectively measured function (short physical performance battery score) and depressive symptoms measured at postremission evaluation were independently associated with worse survival.[85]

TABLE 3. Recent Clinical Trials That Included Older Adults With Acute Myeloid Leukemia

Regimen or Study Design	Sample (N, eligibility)	Median Age, years (range, if available)	Outcomes	Toxicity	Other Considerations
CPX-351 *v* cytarabine plus daunorubicin Phase III RCT, multicenter, open-label[66]	N = 309 Newly diagnosed therapy–related AML, AML with antecedent MDS or CMML, or AML with MDS-related cytogenetic abnormalities 60-75 years	68	CR and CRi: 48% *v* 33% Median OS: 9.6 *v* 6.0 months 34% *v* 25% of patients underwent stem-cell transplant	Grade ≥ 3 AEs (> 30%) that are more common in the intervention arm: febrile neutropenia	36% were 70-75 years 12% had ECOG PS 2 Survival benefit noted in subgroup analysis by age (60-69 *v* 70-75 years)
Venetoclax plus azacitidine *v* azacitidine plus placebo Phase III RCT, multicenter, double-blind[57]	N = 431 Treatment-naive ≥ 65 years Ineligible for intensive chemotherapy (≥ 75 years or ≥ 60-74 years with one of the following: EF ≤ 50%, chronic stable angina, CHF requiring treatment, DLCO ≤ 65%, FEV1 ≤ 65%, creatinine clearance ≥ 30 to < 45 mL/min, and ECOG PS 2-3)	76 (49-91)	CR and CRi: 66% *v* 28% Median duration of CR and CRi: 17.5 *v* 13.4 months Median OS: 14.7 *v* 9.6 months	Grade ≥ 3 AEs (> 30%) that are more common in the intervention arm: cytopenias, infections, and febrile neutropenia	Ineligibility for intensive chemotherapy can be subjective Those ≥ 75 years must have ECOG PS 0-2 60% were ≥ 75 years 44% had ECOG PS 2-3 Survival benefit noted in subgroup analysis by age (≥ 75 *v* < 75 years)
Venetoclax plus LDAC *v* LDAC plus placebo Phase III, RCT, multicenter, double-blind[67]	N = 211 Treatment-naive Ineligible for intensive chemotherapy (≥ 75 years or ≥ 18 with one of the following: ECOG 2-3, EF ≤ 50%, chronic stable angina, CHF requiring treatment, DLCO ≤ 65%, FEV1 ≤ 65%, creatinine clearance ≥ 30 to < 45 mL/min, bilirubin > 1.5 to ≤ 3.0 × ULN, other comorbidity per physician judgment)	76 (36-93)	CR and CRi: 48% *v* 13% (by initiation of cycle 2) Event-free survival: 4.7 *v* 2.0 months Median OS: 7.2 *v* 4.1 months (P = .11)	Grade ≥ 3 AEs (> 30%) that are more common in the intervention arm: cytopenias, febrile neutropenia, and nausea 30-day mortality: 13% *v* 16%	Ineligibility for intensive chemotherapy can be subjective Those ≥ 75 years must have ECOG PS 0-2 58% were ≥ 75 years 49% had ECOG PS 2-3 Benefits noted in subgroup analysis by age (≥ 75 years *v* 18 to < 75 years) Similar improvements in global health status and QOL in both arms Possible greater improvement in fatigue in the intervention arm
Glasdegib plus LDAC *v* LDAC Phase II, RCT, multicenter, open-label[71]	N = 132 Treatment-naïve AML or high-risk MDS ≥ 55 years Ineligible for intensive chemotherapy (≥ 75 years, creatinine > 1.3 mg/dL, EF < 45%, and ECOG PS 2)	76 (58-92)	CR: 17.0% *v* 2.3% Median duration of CR in the intervention arm: 9.9 months Median OS: 8.8 *v* 4.9 months	Grade ≥ 3 AEs (> 30%) that are more common in the intervention arm: anemia, thrombocytopenia, and febrile neutropenia	58% were ≥ 75 years 53% had ECOG PS 2

(continued on following page)

TABLE 3. Recent Clinical Trials That Included Older Adults With Acute Myeloid Leukemia (continued)

Regimen or Study Design	Sample (N, eligibility)	Median Age, years (range, if available)	Outcomes	Toxicity	Other Considerations
Ivosidenib Phase 1 dose-escalation and dose-expansion study[69,70]	N = 258 IDH1-mutated hematologic cancer Four groups: (1) RR AML in second relapse, relapsed after stem-cell transplant, refractory to induction or reinduction, or relapsed within 1 year (N = 126), (2) Untreated AML (N = 25), (3) Other non-AML RR HM, and (4) RR AML not eligible for arm 1 ≥ 18 years ECOG PS 0-2	68 (18-89)	CR and CRh: 30% (42% in untreated AML) Median duration of CR and CRi: 8.2 months Median OS: 8.8 months (12.6 months in untreated AML)	Grade ≥ 3 AEs (> 3%): QTc prolongation and IDH differentiation syndrome 30-day mortality: 7%	22% had ECOG PS 2-3 Untreated AML: 58% were ≥ 75 years (18% had ECOG PS 2-3)
Enasidenib Phase 1 dose-escalation and dose-expansion study[68]	N = 239 IDH2-mutated hematologic cancer Four groups: (1) ≥ 60 years with RR AML, (2) < 60 years with RR AML and no prior stem-cell transplant, (3) ≥ 60 years with untreated AML ineligible for intensive chemotherapy (not reported), and (4) Ineligible for other expansion arms (not reported) ≥ 18 years ECOG PS 0-2	70 (19-100)	RR AML only (N = 176) CR, CRh, and CR with incomplete platelet recovery: 26% Median duration of CR: 8.8 months Median OS: 9.3	Grade ≥ 3 AEs (> 3%): hyperbilirubinemia, IDH differentiation syndrome, anemia, and thrombocytopenia	Ineligibility for intensive chemotherapy not defined 19% had ECOG PS 2
Oral azacitidine (CC-486) *v* placebo Phase III RCT, multicenter, double-blind[73]	N = 472 First remission after intensive chemotherapy ≥ 65 years CR with or without count recovery Not candidates of stem-cell transplant	68 (55-86)	Median OS (from time of random assignment): 24.7 *v* 14.8 months Median relapse-free survival: 10.2 *v* 4.8 months	Grade ≥ 3 AEs (> 30%) that are more common in the intervention arm: neutropenia	8% had ECOG PS 2-3 Survival benefit persists in subgroup analysis by age (≥ 75 *v* < 75 years) No differences in health-related QOL between arms

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; CHF, congestive heart failure; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRh, partial hematologic recovery; CRi, complete remission with incomplete count recovery; DLCO, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Group Performance Status; EF, ejection fraction; FEV1, forced expiratory volume in 1 second; HM, hematologic malignancies; IDH, isocitrate dehydrogenase; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; OS, overall survival; QOL, quality of life; RCT, randomized controlled trial; RR, relapsed or refractory; ULN, upper limit of normal.

These observations support the use of GA at key decision intervals to provide prognostic information and guide supportive care to improve fitness.

Finally, the approach to older adults with acute promyelocytic leukemia differs because of the high response and lower toxicity rates with modern therapies. Older adults regardless of fitness or age may benefit from treatment, the majority of whom can be treated with nonchemotherapy-based regimens.[86]

HCT AND CAR-T FOR OLDER ADULTS

HCT and CAR-T may favorably alter the natural history of high-risk HMs although treatment toxicities remain substantial. Advances in HCT have lifted traditional age limits; in 2018 transplant registry data, patients ≥ 60 years and ≥ 70 years represented 39% and 9% of allogeneic (allo) HCT, respectively, and 55% and 15% of autoHCT, respectively.[87] Recent approvals of CAR-T included 23%-50% of patients ≥ 65 years in seminal studies.[88-91]

Autologous HCT

MM and B-cell non-Hodgkin lymphoma (NHL) constitute the major indications for autoHCT among older patients. The large randomized studies defining autoHCT as SOC for MM consolidation were tested in patients ≤ 65 years old or occasionally up to 70 years.[92] Smaller randomized studies conducted 2 decades ago did not clearly establish a benefit of autografting for older patients with MM; however, meta-analysis of recent comparative studies suggests better survival applying autoHCT.[93] The low transplant-related

mortality (TRM) by day 100 of 1% following autoHCT for MM in those ≥ 70 years reinforces autoHCT as an option for older patients.[94]

Limited data exist on how autoHCT in DLBCL in response affects survival for older patients. TRM rates after autoHCT for NHL are higher than MM,[95] warranting more careful appraisal of HCT candidacy in lymphoma.

Allogeneic HCT

AlloHCT remains one of the most potent therapies against high-risk AML and MDS. Table 4 underscores the outcomes and danger, as registry data show around one-third of patients ≥ 70 years succumb to TRM. The studies also highlight lower TRM employing low-intensity regimens at the cost of higher relapse, particularly for AML.[96,97]

Observational comparative studies offer evidence, albeit of low quality, of a 10%-15% survival benefit of alloHCT for patients with AML ≥ 60 years old.[98,99] In a prospective donor versus no donor design, Nakamura et al[100] presented preliminary data of a 20% improved 3-year survival in patients with high-risk MDS of age 50-75 who were biologically assigned by donor match to alloHCT.

A GA in HCT may facilitate a broader concept of patient resilience and may vary based on the treatment approach; autoHCT with reduced dose melphalan at 140 mg/m^2 may be safely performed with selected patient deficits, whereas alloHCT with an intermediate-intensity regimen necessitates greater resilience. Evidence supports[6] pre-HCT GA uncovering deficits in a large proportion of auto/allo HCTs. Single-center studies have linked various pre-HCT functional measures with inferior outcome, primarily higher TRM after alloHCT and inferior PFS for autoHCT. One multicenter retrospective analysis applying the same panel of functional and cognitive tools found only cognitive impairment by a brief cognitive screen, not function, independently tracked with higher TRM among alloHCT patients ≥ 50 years.[101] Investigators recently described a novel strategy to use GA-guided optimization to better select HCT candidates and further suggested fewer complications, less TRM, and better survival relative to historical controls.[102]

The era of cellular therapy has arrived with US Food and Drug Administration approval of three CAR-T products indicated for RR B-cell NHL in older adults; other approvals may emerge soon including CAR-T for MM. CAR-T therapy can produce deep and durable responses of around 40% in RR aggressive B-NHL; however, cytokine release syndrome and neurologic toxicities mandate careful consideration of candidacy and management after therapy.

Among those enrolled on the pivotal axicabtagene study (RR aggressive B-cell NHL), patients ≥ 65 years achieved similar ORR (92% older patients *v* 81% in patients < 65 years old) and reassuringly no difference in peak CAR-T expansion.[103] Real-world data with axicabtagene likewise demonstrated higher CR at 72% for those patients ≥ 60 years old versus 55% in younger patients.[104] The higher rates of grade 3 neurologic toxicity in the pivotal trial were not observed in the real-world data. Of interest, lisocabtagene maraleucel demonstrated particularly promising activity and safety (minimal grade 3+ neurotoxicity or no grade 3-5 cytokine release syndrome) in a study with 42% of patients with RR aggressive B-NHL ≥ 65 years of age.[90]

Risk stratification by GA or detailed health inventories have only been reported to date in a small number of older

TABLE 4. Outcomes in Series Among Patients 70 Years and Older Undergoing Allogeneic Hematopoietic Cell Transplantation

Author, year	No.	Age Range, years	Disease	Source	Donor	2-Year Outcome		Comment
						OS	TRM	
Sorror, 2011[105]	33	70-75	HM	Single center	Matched[a]	25% (5 years)	31% (5 years)	70+ are subset
Brunner et al,[96] 2013	54	70-76	HM		Matched[a]	39%	5.6%	
Muffly, 2017[106]	1,106; 899 in 2008-2013	70-84	HM	Registry	All donors	39%: 2008-2013	33% in 2008-2013	OS and PFS improving over time but not NRM
Al-Malki, 2018[107]	53	70-76	HM	Single center	Matched[a]	68.9%	17%	
Imus et al,[97] 2019	93	70-78	HM	Single center	Haploidentical	53%	27%	
Ringden, 2019[108]	713	70-79	AML	Registry	Matched	39%	34%	2004-2014
Lachowiez, 2019[109]	22	70-77	AML and MDS	Single center	Matched	Median 2.2 years	NR	

Abbreviations: AML, acute myeloid leukemia; HM, hematologic malignancies; MDS, myelodysplastic syndromes; NR, no response; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; TRM, transplant-related mortality. [a]Matched includes matched related, matched unrelated, and single antigen/allele mismatch unrelated donors.

CAR-T recipients.[110] Special attention to cardiovascular reserve and neurologic function is prudent based on the known toxicity profile. The feasibility and promising outcomes for adults in their seventh and eighth decade have been established for autoHCT, alloHCT, and CAR-T. Prospective studies among older adults to quantify risks and benefits are necessary. GA or other health tools to gauge patient resiliency may guide both candidacy if not strategies to mitigate toxicities.

In conclusion, therapies are expanding for older adults with HM. Personalized care requires careful consideration of disease- and patient-specific characteristics throughout the survivorship continuum. The use of GA can guide treatment selection and inform supportive care to optimize function and QOL. As the evidence supporting the use of GA measures in HMs increases, disease-specific guidelines should incorporate these data to inform evidence-based care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Advances in Management for Older Adults With Hematologic Malignancies

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