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ACUTE MYELOID LEUKEMIAS (H ERBA, SECTION EDITOR)

Health-Related Quality of Life and Treatment of Older Adults with Acute Myeloid Leukemia: a Young International Society of Geriatric Oncology Review Paper

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Abstract

Purpose of Review The treatment landscape for older patients with acute myeloid leukemia (AML) is evolving. Many treatments have comparable efficacy making their impact on quality of life (QoL) an important differentiating factor. In this review, we discuss QoL in older adults with AML, focusing on therapeutic and observational trials that have incorporated QoL assessments.

Recent Findings Health-related quality of life (HRQoL) is a multi-dimensional concept incorporating physical, mental, emotional, and social functioning domains. HRQoL components overlap with components of geriatric assessment, a multidisciplinary diagnostic process that identifies underlying vulnerabilities of older adults and guides subsequent management strategies. HRQoL questionnaires may be general, cancer-specific, leukemia-specific, or symptom-focused. Therapeutic and observational cohort studies suggest HRQoL improves, or at least remains stable, during intensive and lower-intensity therapies. Nonetheless, HRQoL is not routinely incorporated in AML therapeutic trials.

Summary HRQoL assessments can inform both decision-making and management for older adults with AML.

Keywords Acute myeloid leukemia · Quality of life · Geriatric assessment · Therapeutic trials · Intensive therapies · Lower intensity therapies

Introduction

In 2019, an estimated 21,250 new cases of acute myeloid leukemia (AML) will be diagnosed in the USA [1]. AML is a cancer of older adults: 25.1% of new cases occur in those aged 65–74 years, 22.7% in those 75–84 years, and 11.0% in those aged ≥ 85 years [1].

Since the 1970s, intensive chemotherapy had been the standard treatment for older adults who are sufficiently fit to receive treatment. Outpatient therapies, such as hypomethylating agents, have been increasingly used since the late 2000s, after multiple studies demonstrated their advantages over best supportive care (BSC) [2–4]. In the last 5 years, the treatment landscape of AML has evolved rapidly, with an explosion of options including the

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isocitrate dehydrogenase (IDH) inhibitors (enasidenib and ivosidenib), FLT-3 inhibitors (midostaurin and gil teritinib), Hedgehog inhibitor (glasdegib), BCL-2 inhibitor (venetoclax), and others (gemtuzumab, CPX-351).

Many of these treatments have comparable efficacy, which makes their impact on quality of life (QoL) an important factor in choosing among them. In addition, without hematopoietic stem cell transplantation (HSCT), these treatments rarely cure the disease. While advances in the procedures and techniques of HSCT have occurred in recent years, many older adults, especially those aged > 75 years, are still largely excluded due to high transplant-related morbidity and mortality [5, 6•]. Therefore, it is crucial to balance QoL and length of life, as many older adults value the former over the latter [7••, 8••]. Older adults are also more likely to accept treatments if they think they can physically and cognitively tolerate them (8). In this review, we discuss QoL in older adults with AML, tools to assess QoL, therapeutic and observational trials that incorporated QoL assessment, and supportive care interventions that improve QoL.

Health-Related QoL

The term QoL is used to evaluate the general well-being of individuals. Health-related quality of life (HRQoL) is a multidimensional concept that includes a variety of domains related to physical, mental, emotional, and social functioning (Fig. 1) [9]. Each dimension by itself or in combination with others may be affected by AML or its treatment, which can in turn affect overall QoL. An example of these interactions is the interconnection between fatigue and sleep disturbances. Almost all older patients with AML experience fatigue, a common physical symptom which can occur before, during, or after treatment [10]. Fatigue may lead to daytime sleepiness which in turn leads to insomnia at night. This creates a vicious cycle which can be hard to break, ultimately affecting mental, emotional, and social functioning [11–14].

Many dimensions that are assessed as part of HRQoL questionnaires are important components of a geriatric assessment (GA) (Table 1). A GA is a multidisciplinary diagnostic process that identifies underlying vulnerabilities of older adults and guides subsequent management strategies [49••]. A GA assesses domains such as physical function, psychological health, cognition, comorbidity, nutrition, medications, and social support. Many of the geriatric assessment domains are related to HRQoL. For example, functional decline and loss of independence are associated with reduced HRQoL in the general geriatric population [50, 51]. Nonetheless, GA captures additional facets of the patient's experience [49••]. The more nuanced approach of GA sets it apart from many HRQoL questions which often equate impaired physical function with impaired HRQoL [17], which may not necessarily be the case (i.e., an older patient with long-standing mobility issues who has adapted to the impairment with good HRQoL).

Benefits of HRQoL Assessments

With many treatment options now available for older patients with AML, HRQoL can help with treatment decision-making. Components of HRQoL have also been shown to predict outcomes. Several studies have shown that domains and items within the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-30) predicted intensive care unit (ICU) admission, remission status, and survival among older patients with AML [43, 52, 53]. Similarly, geriatric domains such as physical function and cognition are also predictive of survival [54, 55]. In addition, HRQoL and GA may identify supportive care needs [56] and improve communication and patient satisfaction [57, 58••]. Finally, studies have suggested that discordance in patients' and physicians' expectation of outcomes and prognoses is common [59], suggesting a considerable degree of misconception in prognostic understanding of AML. HRQoL may be associated with this misconception, and therefore, assessing HRQoL may help with prognostic discussions [60•].

Tools for HRQoL Assessments

Various tools are available to assess HRQoL. Broadly, they can be categorized into general HRQoL questionnaires, cancer-specific HRQoL questionnaires, leukemia-specific questionnaires, and symptom-focused questionnaires, each with different advantages and disadvantages. Table 1 lists several commonly used tools.

General and Cancer-Specific HRQoL Questionnaires

General HRQoL questionnaires include general health-related items which do not focus on cancer or AML. The advantage of utilizing general HRQoL questionnaires is the generalizability, which allows comparisons of HRQoL across studies, especially between cancer and non-cancer cohorts. Some of the more commonly used questionnaires are the European Quality of Life-5 Dimensions (EQ-5D) [15] questionnaire, the Short Form Health Survey-36 (SF-36) [17–19], and the Short Form Health Survey-12 (SF-12) [61]. Cancer-specific HRQoL questionnaires assess overall patient experience during the course of their cancer and its treatment. These include the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) [21] and the Functional Assessment of Cancer Therapy-General (FACT-G) [24].

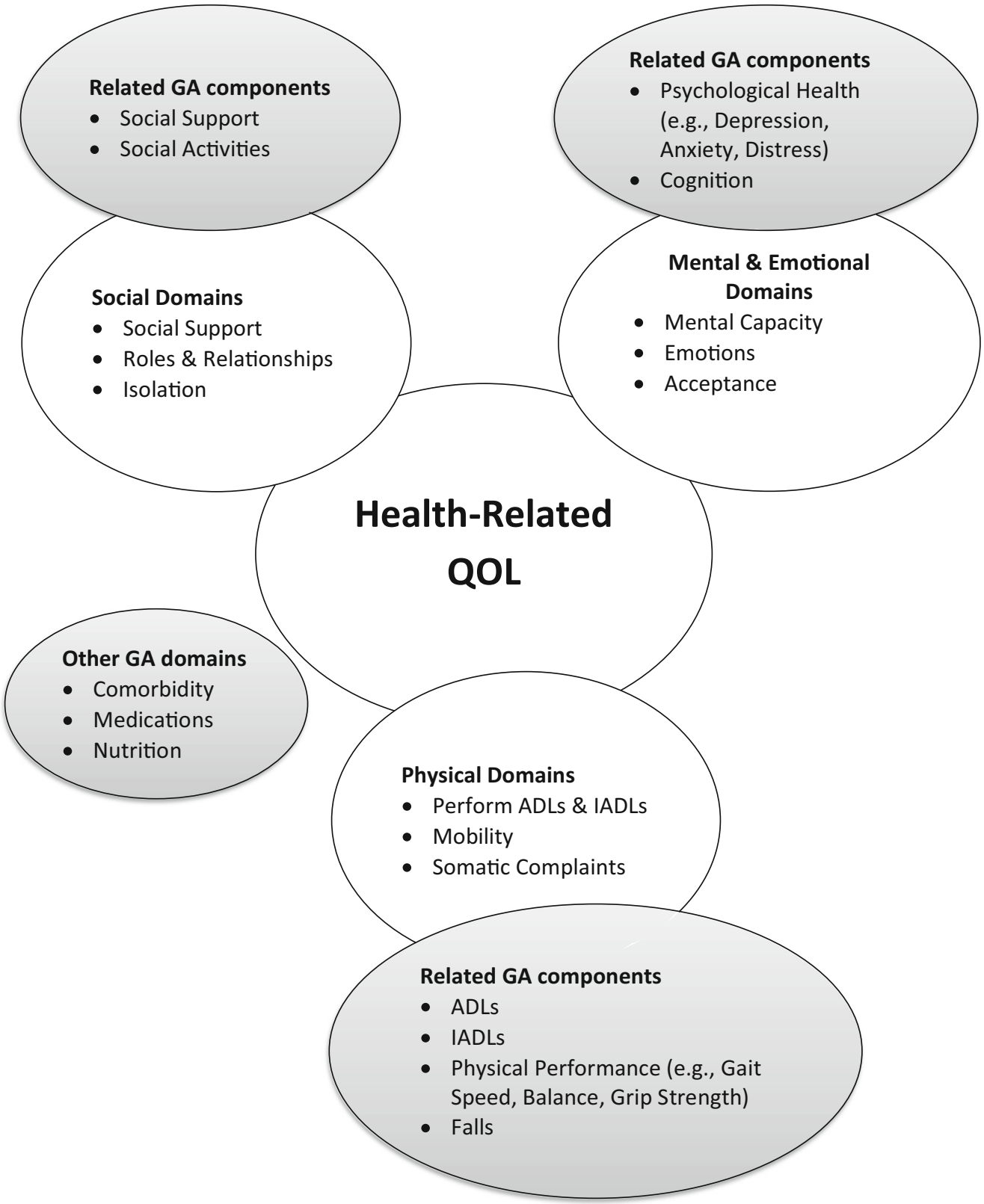

Fig. 1 Health-related quality of life and geriatric assessment components. Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; GA, geriatric assessment

Table 1 Various health-related quality of life questionnaires

Reference	Assessment tools	Description	Strengths	Weakness	Overlap with geriatric assessment
General HRQoL questionnaires					
[15]	EQ-5D-3L/5L (European Quality of Life 5 Dimensions 3 levels/5 levels)	5 questions: on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and VAS scoring of general well-being. Descriptive questions are available in 3 (EQ-5D-3 L) or 5 (EQ-5D-5 L) severity levels	Short administration time	- Difficulties with completing the VAS in older adults [16] - Insomnia not assessed	Contain many questions on ADL/IADL
[17–19]	SF 36, ver 2.0 (Short Form Health Survey-36)	36 questions: generates 8-scale profile of functional health and well-being scores in addition to psychometrically based physical and mental health summary measures and a preference-based health utility index. Short versions are available (e.g., SF12)	Monitoring of outcomes (treatment, cost-effectiveness), not specific to cancer population	Validity for older adults and patients with disabilities is questioned [17, 20]	Some overlapping questions with ADL/IADL
Cancer-specific HRQoL questionnaires					
[21]	EORTC QLQ-C30, ver 3.0 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30)	9 multi-item scale: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale	Most commonly used in oncology clinical trials	- Validity for older adults and patients with disabilities is questioned - Insomnia not addressed	- Some overlapping questions with ADL/IADL - Includes mobility questions
[22]	EORTC QLQ-ELD14 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Elderly-14 items)	14-item scale for patients with cancer aged ≥ 70. Complements the EORTC QLQ-C30, with additional items specific to older adults: 5 scales (mobility, worries about others, future worries, maintaining purpose and burden of illness) and 2 single items (joint stiffness and family support)	Specific to older adults with cancer	Insomnia not addressed	- Some overlapping questions with ADL/IADL - Includes mobility questions
[23]	FACT, ver 4.0 (Functional Assessment of Cancer Therapy)	27-item scale: 4 domains (physical, social/family, emotional, and functional well-being). Multiple indices exist for cancer-, symptom-, and treatment-specific assessment (see below regarding AML and associated symptoms). A shorter 7-item scale is available	Targeted assessments with specific indices, high repeatability	-Ability to work is included as an item -Validated in older adults [24]	No overlap with ADL/IADL
[25]	FLIC (Functional Living Index-Cancer)	22 items: 6 categories including psychosocial state, sociability, somatic sensation, and physical well-being. Format: visual	Reproducible	Procedural difficulties with administration [26]	Some overlap with ADL/IADL

Table 1 (continued)

Reference	Assessment tools	Description	Strengths	Weakness	Overlap with geriatric assessment
		analog scale. An abbreviated version (Quick-FLIC) is available			
[27]	ECOG (Eastern Cooperative Oncology Group) Score	Scores from 0 to 5. Assesses performance status.	Easy to use at pre- and during treatment	Not a comprehensive assessment	Subject to bias and limitations; poor sensitivity at the lower end of the scale [28]
[29]	KPS (Karnofsky Performance Status)	Scores from 0 to 100. Assesses performance status and patient's likelihood of surviving therapy	More focused assessment of functional status	Not a comprehensive assessment	Subject to bias and limitations; poor sensitivity at the lower end of the scale [28]
[30]	SQLI (Spitzer quality of life index)	5-item QoL index: assesses activity, daily living, health support of family and friends, and outlook. A single-item tool (Spitzer Uni-scale) is available	Assesses risks and benefits of treatments/palliative care needs	Mostly used in patients with brain tumor	Significant overlap with ADL/IADL [31]
[32]	RSCL (Rotterdam Symptom Checklist)	39-item: 4 domains (physical distress, psychological distress, activity level, overall valuation of life). Assesses symptoms over the last week	Assesses psychological well-being in the clinical research setting	Difficulty completing questionnaire in patients with advanced disease [33]	Some overlapping questions with ADL/IADL
[34]	SDS (Symptom Distress Scale)	Revised version with 13 items. Assesses 11 symptoms and level of associated distress as well as the frequency of nausea and pain	Assesses trends with treatment	Focuses on symptom assessment	No overlap with ADL/IADL
[35]	QoL CS (Quality of Life Cancer Survivors Scale)	4 domains: psychological, physical, social, and spiritual well-being on a 0–10 scale	Post treatment (≥ 5 years) follow-up assessments, can assess treatment success and sequelae	Use is restricted to post-treatment assessment	No overlap with ADL/IADL
Leukemia-specific questionnaires					
[36–38]	FACT-Leu (Functional Assessment of Cancer Therapy-Leukemia)	Composed of FACT-G and 17 additional leukemia-specific items (Likert scale)	Time to completion 5–15 min. Cross-culturally relevant (scale construction based on international input) Contains items on infertility and sexual functioning	Validated in 100 patients with acute and chronic leukemia, a minority of patients received treatment	No overlap with ADL/IADL
[39–41]	FACT-BMT (Functional Assessment of Cancer Therapy-Bone Marrow Transplantation)	Composed of FACT-G and 12 additional BMT-specific items (Likert scale)	Reliable and valid	–	No overlap with ADL/IADL
[42]	EORTC QLQ-LEU (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–Leukemia)	9 multi-item scale: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and	Assesses long-term sequelae of leukemia treatment (specifically chronic graft-vs-host disease and infection susceptibility)	Used alongside EORTC QLQ –C30 (i.e., extra step)	No overlap with ADL/IADL (although EORTC QLQ-C30 has some overlap, see above) [42]

Table 1 (continued)

Reference	Assessment tools	Description	Strengths	Weakness	Overlap with geriatric assessment
		a global health and QoL scale			
[43]	QOL-E	MDS-specific QoL instrument consisting of a 29-item questionnaire with: 2 general perception of well-being, 4 physical well-being, 3 functional well-being, 4 social well-being, 2 sexual well-being, 7 related to fatigue and 7 disease-specific items (QOL-MDSS)	Contains items on sexual well-being	Not validated in AML	Some overlap with ADL/IADL (physical well-being component of the scale)
Symptom-specific questionnaires					
[44]	FACT-N (Functional Assessment of Cancer Therapy-Neutropenia)	Symptom-specific questions for patients with neutropenia (19 additional items specific to periods of neutropenia)	Snapshot assessment for periods of neutropenia Validated in older adults	Not suitable for long-term assessment of QoL—not validated for patients with leukemia	Minimal/no overlap with ADL/IADL
[45, 46]	FACT-Th6/FACT-Th11 (Functional Assessment of Cancer Therapy-Thrombocytopenia 6/11)	Symptom-specific questions for patients with thrombocytopenia (6 additional questions specific to thrombocytopenia)		Not validated in AML (only in idiopathic thrombocytopenic purpura)–not suitable for long-term assessment of symptom burden	No overlap with ADL/IADL
[47]	FACT-An (Functional Assessment of Cancer Therapy-Anemia)	Symptom-specific questions for patients with anemia/fatigue		Not suitable for long-term assessment of QoL and symptom burden	No overlap with ADL/IADL
[48]	MDASI-MDS/AML (MD Anderson Symptom Inventory for acute myeloid leukemia/-myelodysplastic syndrome)	Composed of 13 symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness/tingling) and 6 interference items (general activity, mood, work, relations with others, walking, enjoyment of life) from MDASI core set and 4 items specific to AML/MDS: feeling of malaise, diarrhea, muscle weakness, and skin problems	Easy to use, comprehensive assessment of symptoms, good reliability	Limited to symptoms being assessed	Minimal overlap with ADLs (general activity)

ADL, activities of daily living; *HRQoL*, health-related quality of life; *IADL*, instrumental activities of daily living; *QoL*, quality of life; *VAS*, visual analog scale

Leukemia-Specific HRQoL and Symptom-Focused Questionnaires

AML generally has rapid onset and may lead to a sudden change in daily functioning, akin to trauma or acute neurological disorders. This temporal pattern is distinct from many advanced solid tumors where declines in daily functioning can occur relatively slowly. Therefore, leukemia-specific HRQoL questionnaires may better capture the particular experience of patients with AML. Available tools include the

EORTC QLQ-Leukemia Module (EORTC QLQ-Leu) [42], the EORTC QLQ-Leukemia/Bone Marrow Transplantation Module (EORTC QLQ-LEU-BMT) [39–41], and the FACT-Leukemia (FACT-Leu) [36–38]. In addition, there are several symptom-specific questionnaires relevant to specific complications of AML such as neutropenia (e.g., FACT-N) [44], thrombocytopenia (e.g., FACT-Th) [45, 46], and anemia (e.g., FACT-An) [47]. The MD Anderson Symptom Inventory for AML (MDASI-AML) [48] provides a comprehensive assessment of symptoms related to AML.

Beyond Quantitative Assessments of HRQoL

Qualitative assessment provides an in-depth understanding of patient experiences that may not otherwise be captured through the use of standardized questionnaires. Occasionally, discrepancies in quantitative and qualitative assessments may arise [62]. Qualitative assessment is typically performed via semi-structured interviews with open-ended questions. Given the nature of the data, comparisons across studies are challenging, and therefore, qualitative data are not used as endpoints in clinical trials.

Hospital admissions, lengths of stay, and intensive care admissions may also influence QoL [63], although they are not directly incorporated into HRQoL scores. For example, low-intensity treatment with azacitidine compared with conventional care regimens (CCR; consist of BSC, induction IC, and low-dose cytarabine (LDAC)) has been associated with shorter LOS [64].

Trials and Studies that Incorporated HRQoL Assessment

HRQoL may be affected in patients with AML at various points in the course of the disease and its treatment. HRQoL has been assessed in studies ranging from phase III randomized trials to observational cohort studies for patients with AML as well as myelodysplastic syndrome (MDS), receiving both induction and non-intensive therapies. We provide a summary of relevant studies which highlight data specific to older adults, broadly divided into those conducted during treatment and those conducted post-remission.

During Treatment

Intensive Therapies

HRQoL has been assessed in prospective longitudinal studies in patients receiving intensive induction chemotherapy (IC). Mohamedali and colleagues examined HRQoL and physical function in patients with newly diagnosed AML throughout induction and consolidation chemotherapy [65]. HRQoL was assessed using EORTC QLQ-C30, FACT-Fatigue, and a global single-item fatigue measure. Physical function was assessed by testing grip strength, timed chair stand, and 2-min walk test. While the majority (63%) of patients were < 60 years, both older and younger patients had reported significant symptom burden at the time of diagnosis. Over time, HRQoL was generally similar in both older and younger age groups. However, compared with younger patients, older patients had more declines/less recovery of measures of physical function. They were also less likely to receive all cycles of consolidation chemotherapy. While there may be selection and survivorship biases, there was a high completion rate of HRQoL measures in the setting of a longitudinal study.

Alibhai and colleagues studied HRQoL among 237 older and younger patients with newly diagnosed AML who underwent IC [66]. HRQoL was assessed in all patients using EORTC QLQ-C30 and FACT-Fatigue before IC and over the subsequent 12 months, which included post-remission therapy. For older adults, Instrumental Activities of Daily Living (IADL) were also assessed over the same period. In all patients, global HRQoL and fatigue improved significantly over time. IADL also improved in older adults.

In a prospective observational study, Klepin and colleagues performed a geriatric assessment in 49 older patients with AML undergoing IC [67••]. Impairment in physical function (based on the Short Physical Performance Battery, IADL, Activities of Daily Living, and mobility) was present in 34 to 62% of patients, which increased to 59 to 82% after induction therapy. Cognitive impairment and depression were present in 22% and 36%, respectively. Unlike physical function, fewer patients had cognitive impairment and depression after induction therapy, 19% and 26%, respectively.

The studies above indicate that some older adults may tolerate IC and have stable or even improving HRQoL during treatment. However, they may experience declines in physical function, which may or may not recover to baseline. It is also important to consider that the impact of therapies on various domains considered in QOL assessments may differ, highlighting the importance of considering both global QOL measures, which may improve largely due to improve symptoms, and domain-specific measures such as physical, cognitive, and emotional well-being. Available evidence suggests older adults may be more likely to experience declines in physical function. These data can be used both for informed treatment choices as well as in active supportive care management.

Lower Intensity Therapies

In a phase III study, Lubbert et al. evaluated survival outcomes for older patients with intermediate- and high-risk MDS

(mean age, 70 years; also included those with blasts 20–30%) who were randomized to either decitabine (every 8 h for 3 days on a 6-week schedule) versus BSC [68]. HRQoL was a secondary outcome and assessed using EORTC QLQ-C30. The study identified an improvement in progression-free survival but not overall survival among patients receiving decitabine. Patients randomized to decitabine experienced improved fatigue and physical functioning (trend for improvement in most QoL scales), but no change in dyspnea. However, there were 60% missing data in HRQoL outcomes.

Kornblith and colleagues assessed the impact of azacitidine versus BSC on HRQoL in patients with MDS (also included those with blasts 20–30%) through an open-label phase III randomized controlled trial, Cancer and Leukemia Group B (CALGB) 9221 [69]. HRQoL and psychological state were assessed using the EORTC QLQ-C30 and Mental Health Index (MHI) respectively, at baseline and throughout treatment. The study included 191 patients with MDS (mean age, 67.5 years). Patients receiving azacitidine demonstrated significant improvements in fatigue, dyspnea, and physical function scores on the EORTC QLQ-C30 and psychological well-being scores on the MHI, even when controlling for differences in red blood cell transfusions. Notably, a large subset of patients with disease progression crossed over to azacitidine and experienced significant improvement in HRQoL after cross over.

In a phase II b study, Sekeres and colleagues randomized newly diagnosed older patients with AML (median age, 70 years) to either low-dose cytarabine alone or low-dose cytarabine in combination with lintuzumab, a monoclonal CD33 antibody [70]. The addition of lintuzumab was not associated with survival benefit or change in HRQoL, measured using FACT-Leu.

The aforementioned studies suggest that azacitidine and decitabine may improve HRQoL in older patients with AML, at least for those with low blast counts, in addition to the survival benefits seen in phase III studies.

Intensive Therapies Vs. Lower Intensity Therapies

In an international randomized phase III open-label study, Dombret and colleagues compared the efficacy and safety of azacitidine to CCR in newly diagnosed AML patients ≥ 65 years [4]. Of 488 patients enrolled, 291 were evaluable for HRQoL (157 received azacitidine, 134 received CCR). EORTC QLQ-C30 was used to assess HRQoL on day 1 of cycle 1 and every other cycle thereafter throughout treatment in a subset of patients. This large study identified an improvement in OS among patients receiving azacitidine compared with patients receiving CCR. Both cohorts demonstrated improvement in HRQoL over time. With a decreasing number of evaluable patients, particularly among the CCR group (reasons were not provided), generalizability may be limited. Further, as the CCR group included both intensive and non-intensive therapies, HRQoL findings may have differed among these two different treatment approaches. Nonetheless, this study demonstrated the feasibility of incorporating HRQoL assessments in phase III studies.

Older patients with AML have poor overall outcomes and high treatment-related mortality, which may partially explain why BSC is used more frequently in this age group [71]. Sekeres and colleagues conducted a prospective longitudinal study of older patients with AML and advanced MDS to examine HRQoL and decision-making considerations when choosing between IC and non-intensive chemotherapy/BSC [59]. Patients were assessed at diagnosis and periodically thereafter over 1 year with instruments that included the SF-12, an abbreviated SF-36, FACT-G, FACT-Anemia (FACT-An), and a shortened version of the Geriatric Depression Scale (GDS). Baseline HRQoL scores were similar in patients receiving IC and non-intensive chemotherapy, although the former group was younger (median age 66 vs. 76). While HRQoL scores initially decreased in the IC group, scores recovered by week 6 to levels not different from the non-intensive chemotherapy group. Baseline HRQoL score was not associated with treatment choice. Most importantly, 97% of older patients reported that HRQoL was more important to them than length of life.

El-Jawahri and colleagues conducted an observational study of 100 adults aged 60 and older with newly diagnosed AML and compared HRQoL and mood between those receiving intensive ($N = 50$) versus less intensive ($N = 50$) therapies [72••]. Assessments using FACT-Leu and Hospital Anxiety and Depressio n Scale (HADS) were obtained at baseline, 2, 4, 8, 12, and 24 weeks. HRQoL and anxiety improved while depressive symptoms did not change. Trajectories of HRQoL and mood were similar regardless of treatment intensity.

In a multi-center prospective observational study, Oliva and colleagues evaluated the impact of HRQoL alongside disease and treatment factors on overall survival in older patients with AML [43]. HRQoL was assessed through self-administered EORTC QLQ-C30 v.2 and QOL-E v.2 questionnaires. Treatment was physician's choice and broadly classified into intensive (aimed at achieving a complete remission) or palliative. Among the 113 patients with de novo AML (mean age 72 years), nearly 60% received palliative therapies; these patients were more likely to be older and have more comorbid illnesses. There was no correlation between baseline HRQoL scores and treatment allocation. Self-assessed HRQoL scores correlated with prognosis, whereas physician-assessed ECOG scores did not correlate with prognosis or patients' self-perceived HRQoL. HRQoL was predictive of survival in patients aged > 70 years receiving palliative treatment.

Overall, studies comparing HRQoL between IC and lower intensive therapies are limited. The above studies suggest that

HRQoL may initially worsen with IC, but may improve to the levels of lower intensive therapies.

Post-Remission HRQoL Assessments

Limited longitudinal data are available on HRQoL in older adults who have achieved remission, due in part to the poor overall survival of patients with AML and the heterogeneity of post-remission care. Cheng and colleagues completed a cross-sectional study of younger AML patients ($N = 18$, age range 18–65 years) who had achieved remission after induction chemotherapy. Nearly all patients felt HRQoL was relevant to their disease. Patients cited concerns about the survivorship phase of care, including future testing, recurrence, and development of second malignancy [73•]. Leunis and colleagues performed a single-center cross-sectional study of patients treated on the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) studies ($N = 103$) and compared HRQoL among long-term AML survivors with the general population by extrapolating data from published studies [74]. Using the EQ-5D and QLQ-C30, they found that AML survivors experienced more fatigue, pain, appetite loss, and financial difficulties compared with the general population. Prior allogeneic stem cell transplantation and absence of social support were associated with poorer HRQoL after treatment. These studies, while limited by single-center cross-sectional design, highlight the importance of incorporating HRQoL measures in the survivorship phase of care for AML patients.

Supportive Care and Behavioral Interventions

Older patients with AML spend 28% of their time in the hospital and 14% of their time attending clinic appointments [75]. In addition, almost one-third are admitted to ICU during their initial diagnosis [76•], and many have high symptom burden [77]. Although one goal of AML treatment is to improve HRQoL, this may not be achieved due to treatment-related side effects which may negatively impact HRQoL. Therefore, it is important to consider supportive care and behavioral interventions to maintain or improve HRQoL by preventing the development of, or by treating these side effects. Palliative care services may improve patient understanding of goals and prognosis [78], address symptoms, and improve HRQoL [79]. While not limited to AML, a randomized controlled trial of adults with hematologic malignancies undergoing HSCT who received inpatient palliative care services reported a smaller decrease in HRQoL and less increase in symptom burden and depression compared with those who did not receive palliative care. In addition, those who received palliative care services had lower anxiety levels [80••].

Some examples of behavioral and psychosocial interventions include exercise and cognitive behavior therapy (CBT). Exercise has the potential to improve cardiorespiratory fitness, muscle strength, physical function, and HRQoL in older patients with AML [81–83]. While data on CBT in AML are limited, it has been shown to improve HRQoL in other cancer types [84]. The risks of these behavioral interventions are minimal and therefore should be highly encouraged.

Gaps and Barriers of HRQoL Integration in AML Trials

Several gaps exist in studies of HRQoL among older adults with AML. Therapeutic trials generally lack HRQoL data. For example, HRQoL data were not included in any of the AML trials that led to drug approvals by the FDA, even though these agents were primarily evaluated in older adults or patients deemed unfit to receive intensive chemotherapy. There is also insufficient inclusion of HRQoL data in studies of HSCT. Given the morbidity associated with HSCT, HRQoL data may guide patient and physician decision for transplant. HRQoL is related to geriatric assessment as well hospitalizations, ICU admissions, and lengths of stay. As such, these measures should be incorporated when assessing QoL in older adults.

Barriers that prevent the integration of HRQoL measures in AML trials include understanding the optimal time points for QOL assessment both throughout treatment as well as after treatment completion, since symptoms may persist for months after treatment, particularly if disease progresses. Assessing QOL in larger multicenter studies requires multiple resources including financial support and healthcare provider time and effort. Single center studies, particularly in academic institutions, diminish generalizability to community practices, a population that is inadequately represented in clinical research. We propose that HRQoL measures be routinely assessed during large phase III studies, as secondary outcomes at least, to determine the effects of treatment regimens on HRQoL. This has been done in pediatric cooperative group studies in Hodgkin lymphoma [85] and is being planned for an upcoming phase III trial that spans all ages, pediatric to older patients, with Hodgkin lymphoma (NCT03907488). If two similarly effective therapies are compared, HRQoL may be studied as a primary outcome. In the AML17 trial for patients with acute promyelocytic leukemia, the primary outcomes were HRQoL, assessed using EORTC QLQ-C30 and the Hospital Anxiety and Depression Scale [86]. International efforts are underway to support standarding collection of QoL data, which can further support study design and directly meet the needs of patients and providers [87].

Conclusions

Many older adults prioritize QoL over survival or at least value QoL as much as survival. With an evolving treatment landscape for older patients with AML and many therapies with similar efficacy, data on HRQoL (including GA) are important for treatment decision-making. Validated tools are available for measuring HRQoL in AML trials, but these tools are not routinely incorporated in therapeutic trials. Future studies should assess HRQoL as part of large phase 3 therapeutic trials, either as primary or secondary outcomes.

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Compliance with Ethical Standards

Conflict of Interest Dr. Neuendorff declares travel support from Jazz Pharmaceuticals and advisory work for Janssen outside of the submitted work. Dr. Loh services as a consultant to Pfizer and Seattle Genetics. Dr. Kumar, Dr. Klepin, and Dr. Abdallah declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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