REVIEW ARTICLE

blood advances

Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

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Fitness assessment in patients with acute myeloid leukemia (AML) is critical to deliver the right therapy to the right patient. Although several scoring systems are available to aid in determining fitness, the absence of validation studies has resulted in the lack of universally accepted assessment procedures. This limitation, combined with the increasing availability of novel agents expanding the spectrum of less-intensive options, has introduced additional complexity to the fitness assessment process. In this evolving context, fitness should reflect eligibility for a specific treatment among the several available, rather than a generic binary classification of eligibility for intensive chemotherapy. Moreover, the growing emphasis on patient-centered care, further highlights the importance of integrating quality of life, patient preferences, patient self-reported physical and social functioning status, social support, and early integration of palliative care into the assessment framework. A modern interpretation of fitness assessment should incorporate a comprehensive evaluation that extends beyond traditional clinical and biological disease characteristics. Thus, fitness assessment in patients with AML represents only 1 piece of a larger puzzle, encompassing the patient's overall capacity to sustain and benefit from a specific therapeutic program.

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Introduction

Numerous factors predict short- and long-term outcomes in patients with acute myeloid leukemia (AML).[1] With many new therapeutic options becoming available, these factors could serve to assess the risks and benefits of a specific therapeutic intervention for each individual patient. However, considering the diversity of patients, including variations in disease-related characteristics, biological factors, personal circumstances, and preferences, no single clinical or biological parameter provides sufficient information for this purpose.[2] Thus, several models integrating various parameter combinations have been developed for daily clinical practice.[3-6] The application of these models is referred to as a fitness assessment, because it aims to select which of the currently available treatments would better "fit" each patient's unique clinical context.[7] Although a precise, comprehensive fitness assessment is widely recognized as a critical step of care, there is still no consensus on its exact definition or which specific parameters should be included.[8] To help address this, an international panel of experts convened on behalf of the European LeukemiaNet (ELN), focused on relevant aspects of fitness in patients with AML, aiming to (1) provide tools for a general definition of fitness/unfitness, and (2) identify and categorize individual factors that contribute to this definition.

Methods

Thirty-one hematologists were convened based on their qualifications and track record in the clinical management of AML, in geriatrics and quality-of-life (QoL) assessment. Furthermore, several members had previously contributed to guidelines on fitness definition and geriatric assessment in AML. Moreover, patients' representatives from the Acute Leukemia Advocated Network (ALAN) provided additional insights and contribution based on their evidence-based advocacy work. After a comprehensive review of recent literature covering the last 25 years, a set of 21 statements was developed. Literature research was primarily conducted by the steering committee (A.V., R.P., L.M., D.d.L., G.O., and F.E.), although all authors contributed to this task. The statements covered 5 main aspects: general definitions (n = 5); fitness components (n = 4); influence of fitness and disease genetics on treatment choice (n = 4); timing for fitness/genetic determination (n = 4); expected impact on QoL; and available social support (n = 4). Based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, each statement was assigned an evidence level (level of evidence [LoE]) and a recommendation grade (grade of recommendation [GoR]).[9] Subsequently, a 2-rounds Delphi poll was conducted to determine the level of agreement on the statements.[10,11] Participants rated their level of agreement on a Likert scale of 1 (completely disagree) to 5 (completely agree). Consensus on each statement was defined as ≥70% agreement (ratings of 4 or 5) or disagreement (ratings of 1 or 2). After the first round of voting, 3 statements (5, 12, and 20) did not reach a consensus and were adjusted after discussion by the steering committee. The resulting statistics were presented in the final discussion with the participants. Despite adjustments after round 1, 2 statements (12 and 21) still did not reach a consensus (supplemental Materials). Statistics and figures were computed using R version 4.2.1.[12]

General definitions (statements 1-5)

Fitness refers to a comprehensive evaluation of age, performance status, comorbidities, and functional capacity (LoE, I; GoR, A). Age as a single parameter is a significant prognostic factor[13]; however, it also serves as a surrogate for comorbidities, functional limitations, and frailty (Table 1). Age significantly affected outcomes in patients with poor performance status (PS) but had only a minor effect on outcomes of older patients with excellent PS.[14] Analysis of the Swedish Acute Leukemia Registry showed that older patients with good PS had low early death rates, whereas those with poor PS had increased early mortality across all ages.[15] Poor PS has been associated with increased 30-day and 8-week mortality, lower rates of complete remission (CR), and shorter overall survival (OS).[16,17] Comorbidities should be assessed in patients with AML to help define overall fitness for a specific treatment. They are also an independent predictor of CR.[6,18,19] Comprehensive comorbidity indices, such as the Charlson Comorbidity Index and the Hematopoietic Cell Transplantation (HCT)–specific comorbidity index (HCT-CI), determine organ dysfunction and predict early death rates after induction chemotherapy or transplant in AML.[5,19,20] The Società Italiana di Ematologia/Società Italiana di Ematologia Sperimentale/Gruppo Italiano Trapianto Midollo Osseo consensus criteria defined fitness for intensive chemotherapy (IC) or non-IC by associating the presence of a set of geriatric and comorbidity parameters with a specific treatment choice.[3] A large retrospective analysis of patients treated with IC confirmed that these criteria had excellent accuracy in predicting 28- and 100-day mortality.[21] The AML composite model (which incorporates HCT-CI, cytogenetic risk, and age) also accurately predict early and late mortality in patients with AML treated with IC.[22] Because aging and age-induced frailty are not solely the result of comorbidities, a comprehensive geriatric assessment (CGA) that examines multiple factors (comorbidities, physical function and cognition, depression or geriatric syndromes, malnutrition, polypharmacy, and social isolation) has been shown to

Table 1. General definitions

Statement	Recommendations: general definitions	LoE	GoR	LoA
1	Fitness refers to a comprehensive evaluation of age, performance status, comorbidities, and functional capacity.	I	A	96%
2	Different fitness levels correspond to different treatment intensities. Accordingly, patients should be considered "fit for" a specific treatment strategy.	IV	A	92%
3	Eligibility for intensive chemotherapy does not necessarily entail eligibility for allo-SCT.	IV	B	84%
4	Ineligibility for intensive treatment does not exclude eligibility for allo-SCT after achieving CR following nonintensive treatment.	IV	B	81%
5	For mitigating disease-related symptoms, antileukemic therapy should be considered even with unattainable curative intent.	IV	C	88%

LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation; SCT, stem cell transplantation; CR complete remission.

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predict IC side effects and OS.[6,23,24] AML CGA can detect physical and cognitive abnormalities even in patients considered fit by standard oncological evaluation.[6,25] The feasibility of CGA has also been demonstrated in multicenter trials of patients treated with hypomethylating agents (HMAs).[25,26]

PANEL RECOMMENDATION: Several parameters, including age, PS, comorbidities, and a CGA, concur to influence a patient's ability to tolerate AML-directed therapies. Therefore, a comprehensive, patient-centered evaluation of these factors should be conducted before initiating any therapeutic program.

Different fitness levels correspond to different treatment intensities. Accordingly, patients should be considered "fit for" a specific treatment strategy (LoE, IV; GoR, A). Current treatments for patients with AML are divided into intensive and low intensity. IC options include cytarabine and anthracycline (7+3) with or without the combination of other agents, (gemtuzumab ozogamicin, midostaurin, or targeted agents) or CPX-351.[27] Low-intensity therapies include HMAs, venetoclax (VEN) combined with HMAs, or low-dose cytarabine (LDAC), glasdegib combined with LDAC, ivosidenib or enasidenib single agents or combined with azacytidine, and single agents gentuzumab ozogamicin or gilteritinib.[27,28] Pretreatment cytogenetics and mutational profiles are important independent predictors of treatment effectiveness. Poor-risk karyotypic abnormalities and mutational profiles, as defined by the ELN genetic risk stratification guidelines,[29] are more prevalent in older patients and may confer resistance to chemotherapy. In high-risk patients, IC regimens such as 7+3 are associated with low CR rates and poor OS.[30] Other disease features, such as AML evolving from an antecedent myeloid neoplasm or therapy-related AML, also significantly influence outcomes.[31] Thus, besides clinical fitness, biological characteristics should be considered in the decision-making process (Table 1).[32]

PANEL RECOMMENDATION: The diverse intensities of available treatments emphasize the necessity of recognizing additional fitness levels extending beyond the conventional categories of "fit," "unfit," and "frail." Therefore, patients should be considered "eligible" for a specific treatment strategy based on clinical fitness and biological factors, with a clear explanation of the treatment approach and the provision of alternative options.

Eligibility for IC does not necessarily entail eligibility for allo-SCT (LoE, IV; GoR, B). Allogeneic stem cell transplant (allo-SCT) is an important step in achieving a curative outcome for patients with AML, yet its potential benefits must be weighed against the risk of transplant-related mortality (TRM). Age and, more importantly, PS and CGA predict outcomes in patients undergoing allo-SCT[33] and are commonly assessed to determine their suitability for the procedure.[34,35] Because no absolute upper age limit exists to define allo-SCT eligibility/ineligibility,[29] dedicated tools including HCT-CI, are currently available to predict outcomes.[35,36] For patients aged ≥70 years, a geriatric assessment before allo-SCT may support a judicious selection of those who are most likely to benefit from the procedure.[37] However, patients considered fit for both IC and allo-SCT at diagnosis may experience health deterioration during the treatment and become ineligible for allo-SCT. Conversely, some patients may improve during treatment after achieving a response, becoming eligible for allo-SCT (Table 1).

PANEL RECOMMENDATION: Because a patient's fitness status can change during treatment, it should be reassessed before each treatment phase, including before allo-SCT.

Ineligibility for intensive treatment does not exclude eligibility for allo-SCT after achieving CR after non-intensive treatment (LoE, IV; GoR, B). Allo-SCT significantly reduces relapse risk compared with chemotherapy alone and represents an important option for fit patients with AML.[38] Currently, allo-SCT indication is decided based on disease risk.[29,39] However, the high morbidity and mortality rates associated with allo-SCT remain a major drawback.[40] Accordingly, patients in good general condition and with an acceptable estimated TRM are considered suitable candidates for allo-SCT.[41] Based on this, only patients receiving standard induction and consolidation chemotherapy are usually considered for transplant. However, allo-SCT has shown promising results in patients achieving CR after less-intensive therapies, with 40% to 55% of them remaining in CR and alive 1 year after transplant.[42-44] Although nonintensive approaches cannot yet be considered the standard of care, they may serve as a "bridge to transplant" for selected subgroups of patients, reducing treatment-related toxicities (Table 1).[44]

PANEL RECOMMENDATION: Ineligibility for IC does not necessarily exclude eligibility for allo-SCT in patients achieving CR, after nonintensive treatment.

For mitigating disease-related symptoms, antileukemic therapy should be considered even with unattainable curative intent (LoE, IV; GoR, C). Antileukemic treatment is the straightforward approach to reducing symptoms, prolonging life, and maintaining patients' QoL, particularly compared with supportive care only. In the AML-001 study, azacitidine (AZA) improved survival over best supportive care (BSC) alone, even among patients who were preselected for BSC. The median OS was 5.8 with AZA vs 3.7 months with BSC. Moreover, no QoL deterioration was observed in either groups during treatment.[45] The addition of VEN to HMA or LDAC significantly prolonged survival and preserved QoL, thereby further underlining the correlation between active treatment, response, prognosis, and improved QoL.[46] Data from the Swedish registry and the US American SEER database showed that any cytoreductive treatment was associated with lower early death rates and longer survival.[15,47] These results implicate that any antileukemic treatment is preferable to no treatment, with the potential side effects outweighed by the benefits of extended survival and maintained QoL (Table 1).

PANEL RECOMMENDATION: Antileukemic therapy should be considered for mitigating disease-related symptoms, even if a curative intent is unattainable. Decisions regarding symptom management should be informed by patient preferences and QoL objectives, ensuring they align with individual values and expectations. Real-life data collection and activation of dedicated registries should be implemented to better investigate the impact of this strategy on clinical practice and patients' lives.

Components of fitness (statements 6-9)

Age, as a single parameter, should not be considered for the definition of fitness (LoE, II; GoR, C). Advanced age is a predominant determinant in assessing patients' fitness and suitability

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Table 2. Components of fitness

Statement	Recommendations: components of fitness	LoE	GoR	LoA
6	Age, as a single parameter, should not be considered for the definition of fitness.	II	C	92%
7	For patients aged >75 years, eligibility for IC should be evaluated carefully.	III	B	96%
8	PS plays a crucial role in the definition of fitness.	II	A	92%
9	Patient's self-reported physical and social functioning as well QoL before illness onset, should be considered as an important parameter when evaluating fitness.	II	B	92%

LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation; IC, intensive chemotherapy; PS, performance status; QoL, quality of life.

for IC[48,49] and is linked to an increased likelihood of comorbidities, resulting in low CR rates and shorter OS.[50-53] However, as life expectancy increases within the general population, many older individuals reach advanced age in a better overall health.[54] Consequently, chronological age does not inherently reflect biological age.[4] Indeed, early TRM rates in physically fit older patients are comparable to younger ones and are potentially even better than those observed in younger patients with multiple comorbidities (Table 2).[13]

PANEL RECOMMENDATION: Although fitness for IC declines with aging, age as a single parameter should not be considered as the sole criterion to define patients' fitness, Overall health status, physiological reserve, QoL, and life expectancy are additional components to examine.

For patients aged >75 years, eligibility for IC should be evaluated carefully (LoE, III; GoR, B). Concerns regarding administration of IC to very old yet fit patients have been reinforced by recent changes in AML treatment.[55,56] Novel less-intensive therapies have significantly improved response rates and OS in patients ineligible for IC.[42,57-61] Particularly, less-intensive VEN-based approaches have demonstrated promising efficacy and better tolerability in older patients, and those considered at high risk for TRM.[62-64] A trial by the European Organization for Research and Treatment of Cancer and Gruppo Italiano Malattie Maligne dell'Adulto (EORTC-GIMEMA 1301) randomized fit patients aged >60 years between 10-day decitabine and IC and demonstrated comparable survival rates and improved QoL in decitabine-treated patients.[44] Randomized trials are needed to determine whether the addition of VEN will increase responses without elevating toxicity, thereby enhancing the benefit of VEN-based regimens over IC (Table 2).[65-69]

PANEL RECOMMENDATION: Given that only a small proportion of patients aged >75 years can benefit from IC and considering the lack of clinical trials focusing exclusively on intensively treated patients in this age group, careful evaluation of eligibility for IC is needed for patients aged >75 years. It is crucial to also consider the patient's QoL expectations, psychosocial circumstances, and willingness to undergo IC.

Performance status plays a crucial role in the definition of fitness (LoE, II; GoR, A). A correlation was observed between PS and the risk of complications in adults undergoing IC.[4,15,17,18,70] Patients with a good Eastern Cooperative Oncology Group PS have comparable early mortality rates across all age groups when treated with IC.[13] In contrast, in patients with PS score of ≥3, the probability of early death substantially increases with age.[13] Older patients with poor PS have a high likelihood of early mortality, irrespective of treatment intensity. Nevertheless, a subset of these patients achieves long-term survival, indicating that selected individuals may potentially benefit from IC.[15,71] Conversely, physiologic reserve capacity varies considerably within the geriatric population. Even patients with a favorable PS may show significant variations and impediments in cognitive, emotional, and physical well-being, potentially affecting outcomes (Table 2).[23,72]

PANEL RECOMMENDATION: PS should be determined during treatment planning. Nevertheless, considering its subjective nature and limited sensitivity, a geriatric assessment is particularly useful for patients with a PS score of >2 to inform decision about treatment intensity. For patients with a PS score of >3, the decision between active treatment and supportive therapy alone should be made on a case-by-case basis.

Patient's self-reported physical and social functioning as well as QoL before illness onset, should be considered an important parameter when evaluating fitness (LoE, II; GoR, B). Several studies showed that patient-reported physical functioning is significantly associated with OS.[73-76] This prognostic value remains regardless of whether physical functioning is assessed by patients or physicians.[77] Combining physician-assessed and patient-reported scores may represent a valid approach to enhancing prognostic accuracy, as physical functioning scales alone do not fully capture the spectrum of functional abilities in older patients. More detailed self-reported questionnaires may assess a patient's ability to perform basic activities of daily living needed for independence at home or instrumental activities of daily living required for community independence.[23,77,78] Findings from ALAN underscore key factors, such as age, sex, and socioeconomic status, that clinicians should consider when developing support strategies.[79] Additionally, the role of social functioning in relation to patient QoL must be incorporated into these considerations (Table 2).

PANEL RECOMMENDATION: Although retrospective self-evaluation may provide biased results, patient-reported physical and social functioning before AML onset should be considered appropriately.

Influence of fitness and disease genetics on treatment choice (statements 10-13)

Treatment decisions should rely on patient- (fitness) and disease-related (genetic) features as well as patients' preferences (LoE, I; GoR, A). Patients with unfavorable genetic risk have lower remission rates and shorter OS after standard IC compared with those with more favorable profiles.[80-85] Retrospective analyses indicated that less-intensive, HMA-based

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Table 3. Influence of fitness and disease genetics on treatment choice

Statement	Recommendations: influence of fitness and disease genetics (sic) on treatment choice	LoE	GoR	LoA
10	Treatment decision should rely on patient- (fitness) and disease-related (genetic) features as well as patient preferences.	I	A	100%
11	Patients unfit for active therapy should be tested for mutations that could be susceptible to targeted monotherapy before being considered for supportive therapy alone.	IV	C	88%
12	Adverse genetic/cytogenetic profiles are not a contraindication to IC, in older, fit patients.	IV	B	69%
13	Psychiatric comorbidities that may interfere with patient compliance to therapies should be carefully evaluated before treatment initiation.	V	C	100%

LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation; IC, intensive chemotherapy.

treatments are at least equally effective and better tolerated than IC in patients with adverse-risk AML.[86-89] In a relatively small, propensity-matched cohort of patients with AML treated with IC or VEN-AZA, age of >65 years, ELN adverse risk, and a RUNX1 mutation favored VEN-AZA for OS, whereas IC was superior in patients with ELN intermediate-risk disease.[63] In real-world data, early mortality and OS were not significantly different between patients treated with CPX-351 or VEN-AZA. Similarly, no survival benefit with any treatment was observed in patients with adverse-risk AML. Conversely, CPX-351 treatment was associated with higher rates of documented infections, neutropenic fever, and longer inpatient hospital stays compared with VEN-AZA (Table 3).[90]

PANEL RECOMMENDATION: Treatment decisions should be always individualized and made in partnership with patients after careful consideration of all patient- and disease-related characteristics that may affect efficacy or tolerability of any therapeutic intervention.

Patients unfit for active therapy should be tested for mutations that could be susceptible to targeted monotherapy before being considered for supportive therapy alone (LoE, IV; GoR, C). Survival in patients unable to tolerate any active therapy is very poor.[47,91,92] Ivosidenib and enasidenib are paradigmatic examples of effective targeted therapies that can offer advantages over supportive therapy.[93,94] Results from a phase 1 study indicate that ivosidenib monotherapy showed CR/CR with partial hematological recovery rates of 42.5% in patients with newly diagnosed isocitrate dehydrogenase-1 (IDH1)-mutated AML who were considered too frail to tolerate HMA-based treatment. Responses were durable with a median OS of 12.6 months.[95] In 39 patients who are frail with newly diagnosed IDH2-mutated AML who received enasidenib monotherapy, the CR/CR with incomplete count recovery rate, ORR, and median OS were 21%, 31%, and 11.3 months, respectively.[94] These outcomes are superior to those reported for BSC alone in noncomparative studies.[96] Other oral, targeted, small-molecule inhibitors (eg, menin inhibitors, SYK inhibitors, etc) are currently available in clinical trials and may offer future options for patients with AML who are frail (Table 3).

PANEL RECOMMENDATION: Patients for whom supportive therapy seems the only option should be tested for actionable mutations.

Adverse genetic/cytogenetic profiles are not a contraindication to IC, in older fit patients (LoE IV; GoR B; consensus not reached). The negative impact of adverse genetic/cytogenetic profiles on chemosensitivity has been extensively reported.[97] Considering disease-related factors can potentially alter the traditional paradigms and clinical fitness algorithms.[7] The EORTC-GIMEMA randomized trial investigating 10-day decitabine vs 7+ 3 regimen demonstrated a CR/CR with incomplete count recovery rate of 44% and 43% with decitabine and 7+3, respectively. However, in patients within the ELN 2017 adverse-risk category, the OS was poor, particularly in those with Tp5 mutations, consistent with other studies.[44] Randomized studies are investigating whether standard cytotoxic chemotherapy, such as 7 + 3 or CPX-351–based regimens, vs lower-intensity VEN combinations should be preferred for older, fit patients who are candidates for allo-SCT. This approach, followed by a prompt bridging to allo-SCT, may lead to durable response with improved OS/disease-free survival.[65,68] In this highly heterogeneous group of patients with adverse genetic and cytogenetic profile,[29] the differential impact of IC and nonintensive strategies remains controversial. The impact of new agents and combinations, within adverse subgroups, exemplifies the current complexity of treatment decision-making (Table 3).[98]

PANEL RECOMMENDATION: Although an agreement was not reached, 67% of the panelists concurred that no clear contraindications exist to treating adverse risk, older, fit patients with adverse-risk profiles using IC. The lack of consensus on this issue stems from unsatisfactory results when treating patients with adverse risk with either intensive or nonintensive approaches. The authors agree on the necessity to implement treatment strategies for this patient population.

Psychiatric comorbidities that may interfere with patient compliance to therapies should be carefully evaluated before treatment initiation (LoE, V; GoR, C). Mental disorders and overall cognitive status may significantly affect therapy compliance and lead to prolonged hospitalizations. Along with physical function and comorbidities, geriatric scales also explore domains such as cognition, depression, and overall psychological function.[6,99] Cognitive function evaluation through CGA may uncover undiagnosed cognitive impairments that could increase the risk of complications during and after intensive treatment.[78] However, few studies have addressed the impact of mental disorders, including cognitive deterioration, on clinical outcomes in patients treated non-intensively (Table 3).

PANEL RECOMMENDATION: Psychiatric comorbidities and cognitive disorders should be carefully assessed to inform therapeutic decisions, as they may affect patient compliance with therapy and increase the risk of complications. Involving specialists, such as psychiatrists or psychologists, for targeted support may be beneficial.

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Table 4. Timing for fitness/genetic determination

Statement	Recommendations: timing for fitness/genetic determination	LoE	GoR	LoA
14	Because the time to treatment start does not seem to affect short- and long-term outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy.	IV	B	96%
15	Fitness level attribution should be performed after appropriate supportive therapy when general condition impairments are suspected to be due to disease burden rather than preexisting conditions.	IV	B	81%
16	Fitness improvement/worsening should be assessed dynamically throughout therapy in responding and nonresponding patients to modulate treatment intensity as appropriate.	IV	B	100%
17	Biological reassessment should be performed at disease relapse to assist the choice of salvage therapy.	I	A	100%

LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation.

Timing for fitness/genetic determination (statements 14-17)

Because the time-to-treatment start does not seem to affect short- and long-term patient outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy (LoE, IV; GoR, B). Whether the time from AML diagnosis to treatment affect the short- and long-term outcome has been addressed in recent years.[100-102] Such an impact appears negligible in patients with stable disease. Therefore, waiting a short period to better characterize leukemia, manage concurrent and transient medical conditions, and then design adapted treatments seem feasible with low risk for the patient (Table 4).

PANEL RECOMMENDATION: A comprehensive approach that considers both patient- and disease-related factors is recommended. Because diagnostic workup may require time, patients with clinically stable disease may wait up to 3 weeks[100-102] from diagnosis to treatment. Patients should be informed that the time spent on comprehensive assessments is critical for tailoring the most effective treatment plan.

Fitness level attribution should be performed after appropriate supportive therapy when general condition impairments are suspected to be due to disease burden rather than preexisting conditions (LoE, IV; GoR, B). AML presentation often involves significant deterioration in the patient's general condition.[100] Therefore, it should be carefully evaluated whether the general condition is affected by the underlying AML or reflects the patient's usual health status (Table 4).[103] Supportive therapy should be initiated at AML presentation to revert disease-induced conditions that hamper accurate fitness assessment,[102] potentially leading to overtreatment or undertreatment.[7] A more objective measure of fitness status could be provided by CGA, because such methodology is only moderately affected by disease burden (Table 5).

PANEL RECOMMENDATION: If poor general condition may be attributed to disease burden rather than preexisting conditions, fitness level should be reassessed after adequate supportive therapy.

Fitness improvement or worsening should be addressed dynamically throughout therapy in both responding and nonresponding patients to modulate treatment intensity as appropriate (LoE, IV; GoR, B). Just as a patient's clinical fitness may improve after supportive therapy at disease presentation, additional changes may also occur during or after treatment.[104] In some cases, IC can worsen the patient's general condition, requiring deintensification of the subsequent therapeutic strategy.[105-108] Conversely, patients initially considered ineligible for IC may improve after nonintensive approaches.[109] Therefore, dynamically reevaluating fitness status is critical to recalibrate treatment intensity according to the patient's actual clinical conditions (Table 4).[43]

PANEL RECOMMENDATION: Fitness modifications should be assessed dynamically throughout therapy to modulate treatment intensity as appropriate. Patients and caregivers should be kept informed about how fitness changes may affect treatment adjustments, ensuring they understand the rationale behind modifications in therapy intensity.

Biological reassessment should be performed at disease relapse to assist the choice of salvage therapy (LoE, I; GoR, A). Genetic/cytogenetic profiling is essential at baseline to define disease risk and is also recommended in relapsing/refractory AML to intercept clonal transformations.[110-112] Identifying new, emerging molecular mutations is crucial to personalize salvage therapy.[113] This is the case of FLT3 mutations, that can be acquired in up to 25% of relapsing cases.[110] Indeed, novel targeted agents, such as FLT3-inhibitors, have been effective as salvage therapy, offering lower toxicity than IC.[106] This approach may benefit patients who, once in remission, become candidates for allo-SCT.[114,115] From this perspective, molecular retesting represents a fundamental step, providing therapeutic alternatives for patients who were historically considered only for BSC (Table 4).

PANEL RECOMMENDATION: Biological reassessment should be performed at disease relapse to assist the choice of salvage therapy.

QoL and social support (statements 18-21)

Social support should be offered to all patients regardless of treatment intensity and throughout the entire therapeutic process (LoE, III; GoR, C). A meta-analysis found a relationship between perceived social support, social network, and marital status with OS in patients with cancer, including those with leukemias/lymphoma.[116] Perceived social support had a stronger association with reduced mortality in patients with leukemia/lymphoma than in those with other cancers.[116] Patients with AML living alone were less likely to receive IC or undergo postremission allo-SCT, potentially leading to worse outcomes.[117] An ALAN study demonstrates that living alone, younger age, and being

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Table 5. Available tools for comprehensive geriatric assessment

Tool	Aim	Number of items	Completion time	Score range	Interpretation	Level of priority
Activities of daily living	Measuring functional basic activity of daily living in older patients	6	5-10 min	0-6	Higher score corresponds to higher level of functional activity	***
Instrumental activities of daily living	Measuring elaborate functional activities in older patients	8	5-10 min	0-8 (women) 0-5 (men)	Higher score corresponds to higher level of functional activity	**
MMSE	Evaluating cognitive function in clinical practice patients	30	5-10 min	0-30	MMSE score ≤23 is indicative of cognitive impairment	***
Geriatric depression scale	Rating depression in older individuals	15	5 min	0-15	0-4: normal 5-8: mild depression 9-11: moderate depression 12-15: severe depression	***
Mini nutritional assessment	Evaluating nutritional status	30	10-15 min	0-30	24-30: normal nutritional status 17-23.5: risk for malnutrition <17: malnourished patient	**
Time to get up and go	Evaluating gait and balance	1	<5 min	1-5	>3: patient at risk of falling	*
ACE-27	Evaluating comorbidity index in patients with cancer	27	>20 min	None, mild, moderate, and severe	In the cases in which ≥2 moderate ailments occur in different organ systems or disease groupings, the overall comorbidity score is designated as severe	*

This table summarizes the available tools that can be adopted to perform a comprehensive geriatric assessment in patients with AML. Based on evidence from AML studies,[6,24,25,35,37] we defined different levels of priority (***, high level of priority; **, intermediate level of priority; and *, low level of priority).

MMSE, mini mental state examination; ACE-27, adult comorbidity evaluation-27.

female are associated with higher rates of nonadherence to treatment. Proactive strategies should be implemented before treatment initiation to address all these factors.[79] In a study of hospitalized patients with hematologic malignancies, limited social support was independently associated with a shorter OS and a higher likelihood of death or readmission within 90 days of hospital discharge (Table 6).[118]

PANEL RECOMMENDATION: Social support provided through a multidisciplinary approach involving professionals beyond physicians should be offered to all patients from the beginning of therapy.

In the absence of a caregiver, patients' social support should be intensified when considering any therapeutic intervention (LoE, IV; GoR, D). Most patients with AML are older and often lack caregivers.[119] When caregivers are present, they may experience high levels of burden.[120] Therefore, alleviating distress and enhancing their skills and service capabilities should be considered.[121] Accordingly, increasing social support may be a decisive component in managing patients with AML (Table 6).

PANEL RECOMMENDATION: Although social support is not a component of fitness, it may affect the success of a therapeutic program. Accordingly, patients' social support should be intensified when considering any therapeutic interventions, especially in the absence of caregivers.

Treatment selection should consider the impact of any given therapy on patients' QoL and preferences (LoE, IV; GoR, D). QoL is an end point nowadays incorporated in AML trials to determine the value of novel drugs.[46] Systematic QoL data collection in cancer care is associated with several benefits, including improved symptom control, better patient-physician communication, and higher satisfaction with care.[122,123] Although not specifically in the AML setting, previous trials showed that monitoring patient-reported symptoms is associated with longer survival than traditional follow-up care.[124-126] Investigating QoL indicators provides independent prognostic information beyond PS or other clinical and genetic tests, a finding replicated across several cancer populations, including those with hematologic malignancies.[127-130] The independent prognostic value of QoL data was also observed in patients with high-risk myelodysplastic syndromes and AML,[131,132] further emphasizing its importance in these patients. Findings from one ALAN study revealed that demographic factors most strongly associated with poorer QoL include younger age, female sex, and lower income (Table 6).[79]

PANEL RECOMMENDATION: Although there is insufficient evidence to consider QoL as a measure of fitness, any antileukemic treatment significantly affects patients' QoL. Therefore, the extent of such an impact should be considered and discussed with patients when making therapeutic decisions and monitored throughout treatment.

Integration of early palliative care (EPC) during diagnosis should be considered standard of care to improve QoL and patients' care in those receiving IC (LoE, II; GoR, B; consensus not reached). EPC refers to the integration of palliative care into active disease treatment within 8 weeks of cancer diagnosis.[133] EPC includes communication with patients, symptom management, social coping support, regular follow-up visits addressing physical and psychological symptoms, as well as setting realistic treatment goals and facilitating patient choices about care planning.[134] In patients with advanced non–small-cell lung cancer,[135] EPC resulted in longer OS than standard care, along with significant improvements in QoL, mood, and survival advantages.[136]

A Cochrane systematic review and meta-analysis published in 2017 confirmed the value of EPC in reducing symptom intensity

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Table 6. QoL and social support

Statement	Recommendations: QoL and social support	LoE	GoR	LoA
18	Social support should be offered to all patients regardless of treatment intensity and throughout the entire therapeutic process.	III	C	100%
19	In the absence of a caregiver, patients' social support should be intensified when considering any therapeutic intervention.	IV	D	96%
20	Treatment selection should consider the impact of any given therapy on patients' QoL and preferences.	IV	D	85%
21	Integration of early palliative care during diagnosis should be considered standard of care to improve the QoL and patients' care in those receiving IC.	II	B	65%

LoA, level of agreement; LoE, level of evidence; GoR, grade of recommendation; QoL, quality of life; IC, intensive chemotherapy.

and improving QoL vs standard cancer care.[134,137-141] Similar benefits were observed in patients with AML. EPC is particularly valuable for patients with AML because they are burdened by several physical and psychological symptoms and have several unmet palliative care needs.[142] In a trial enrolling 160 patients with high-risk AML receiving IC, those receiving EPC reported significantly better QoL, along with reduced depression, anxiety, and posttraumatic stress disorder symptoms at both early (week 2) and late (week 24) time points compared with those receiving standard care. The study concluded that EPC should become standard of care for patients with AML.[143] In a retrospective study, EPC was associated with high frequency of quality palliative care indicators and low rates of treatment aggressiveness at the end of life.[144] However, consensus was not reached because of factors including the novelty of the topic in AML setting and the experts' focus on prioritizing life-saving interventions. Future studies should explore this crucial aspect further (Table 6).

PANEL RECOMMENDATION: Although not reaching a consensus, 67% of the panelists agreed that EPC should be standard of care, even for patients receiving IC, to improve QoL, and treatment outcome. EPC should be integrated at diagnosis, tailored to the patient's goals, preferences, and expectations, with a focus on symptom management and psychosocial support.

Conclusion

Given the current therapeutic options, fitness assessment in patients with AML is becoming increasingly complex yet essential. The growing knowledge of AML genetics, alongside the development of novel targeted agents, has complicated the process. The continuous discovery of new gene mutations, which can serve as therapeutic targets, has challenged old-fashioned, dualistic, "yes or no" approach (fit or unfit for IC) and introduced a spectrum of intermediate situations in which almost any patient with AML could be considered for active treatment. Moreover, in recent years, QoL assessments and patient-reported outcomes have gained prominence, providing a more comprehensive understanding of the patients' experience and perspective. The present recommendations represent an effort to collate and harmonize all these evolving factors. Similar studies have recently dissected this topic[145] but they mainly focused on "clinical- and biological-oriented" therapeutic programs. This work also contemplates a broad range of "patient-centered" aspects, thus extending the concept of fitness to include the patients' reported perception of their well-being and preferences. Clear communication of these fitness levels to patients, using nontechnical language, is essential to support informed decision-making. Future research should deepen the involvement of patients' and caregivers' representatives. By doing so, we may gain valuable insights into the definition of fitness in the AML setting. Physicians' awareness of patients' and caregivers' expectations and goals can contribute to a more informed and accurate treatment selection, ensuring that it is a shared decision.

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Authorship

Contribution: A.V. and G.O. conceptualized and designed the study; R.P. and L.M. performed literature research; L.L.N. and J.T. organized the meetings and analyzed the Delphi polls; A.V., R.P., L.M., C. Röllig, A.W., D.d.L., F.E., and A.C. were responsible for section assembly and manuscript writing; G.O., S.N., and C.G.M. revised the manuscript; and all authors were responsible for final approval of the manuscript.

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