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Review Article

Treating acute myelogenous leukemia in patients aged 70 and above: Recommendations from the International Society of Geriatric Oncology (SIOG)

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ABSTRACT

Acute myeloid leukemia (AML) treatment is challenging in older patients. There is a lack of evidence-based recommendations for older patients ≥70, a group largely underrepresented in clinical trials. With new treatment options being available in recent years, recommendations are needed for these patients. As such the International Society of Geriatric Oncology (SIOG) assembled a task force to review the evidence specific to treatment and outcomes in this population of patients ≥70 years. Six questions were selected by the expert panel in domains of (1) baseline assessment, (2) frontline therapy, (3) post-remission therapy, (4) treatment for relapse, (5) targeted therapies, and (6) patient reported outcome/function and enhancing treatment tolerance. Information from current literature was extracted, combining evidence from systematic reviews/meta-analyses, decision models, individual trials targeting these patients, and subgroup data. Accordingly, recommendations were generated using a GRADE approach upon reviewing current evidence by consensus of the whole panel. It is our firm recommendation and hope that direct evidence should be generated for patients aged ≥70 as a distinct group in high need of improvement of their survival outcomes. Such studies should integrate information from a geriatric assessment to optimize external validity and outcomes.

1. Introduction

Acute myeloid leukemia (AML) is a challenging disease to treat, especially in older patients. Options have broadened in the recent years with targeted therapies added to intensive and low-dose chemotherapy choices. While many studies define "older" as 60 years and above, this definition was inherited from a time where allogeneic stem cell transplant was rarely done above the age of 60. Nowadays, many patients with AML in their sixties do undergo hematopoietic stem cell transplant (HCT) and their treatment patterns have become closer to that of younger patients. However, age continues to be the primary barrier for patients in their seventies to undergo HCT [1]. Adults 70 and older continue to represent <10% of patients receiving HCT [1,2].

Furthermore, patients ages 70+ can present with highly variable health and functional status. Deciding on a therapeutic strategy is a multifactorial process in which is crucial to add the patient's

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comprehensive evaluation of physical, emotional, and cognitive health (and not only chronological age) to traditional disease-related factors. Therefore, personalized management is essential for patient outcomes. While there are published AML guidelines for older patients [3–6], these are focused on patients aged ≥60 years with little specific discussion of patients above the age of 70. Therefore, the International Society of Geriatric Oncology (SIOG) assembled a task force to review the evidence specific to treatment and outcomes in this population of patients aged 70 years and above.

2. Methods

SIOG assembled a panel of experts in AML and aging. An initial meeting was scheduled to select key questions of interest for this population. The group members proposed potential questions and six questions were selected by consensus as most critical in patients aged 70 and above with AML:

1) What baseline assessment is needed?
2) What should be used as frontline therapy?
3) What should be used as post-remission with or without transplant therapy?
4) What treatments are available for relapse?
5) What are the available targeted therapies for use in older patients with AML? (defined as therapies designed to target a specific enzyme or mutation)
6) How does AML and its treatment affect patient reported outcomes and function, and what supportive care interventions have been tested to enhance treatment tolerance?

Working groups of four members each were created to review the evidence on each question with instructions to prioritize evidence specific to patients aged 70 and older. Each subgroup conducted an extensive review of the literature, leveraging meta-analyses whenever available. A GRADE approach was used to the rating of the strength of the evidence: Strong (trials focused on this population, systematic review/meta-analysis), moderate (subgroup analyzes of larger studies, decision models, registry studies), or weak (retrospective studies, studies partly including patients age > 70 without subgroup data, heterogeneous data). Strength of recommendation was rated as strong, moderate, or weak by group consensus, based on both the level of evidence and the potential clinical impact. If evidence was indirect, the level of recommendation was qualified as “consensus.” Each subgroup drafted a set of recommendations. The evidence findings were reviewed by the whole panel at regular digital meetings. Iterative rounds of writing and reviewing the assembled findings were held. Once the consensus was obtained about the comprehensiveness of the evidence, a final set of recommendations were assembled and rated with review at digital meetings until consensus was obtained. The prefinal manuscript was sent to two external reviewers and their input and corrections were integrated into the final manuscript.

Each question will be addressed into two sections: “evidence from studies,” then “expert comment and consensus.”

2.1. General Recommendation

As evidence is still limited on many aspects of the treatment of AML in patients aged 70 and older, the panel strongly recommends enrolling older adults with AML in clinical trials as a preferred option.

3. Baseline Assessment (Patient and Disease)

3.1. Evidence from Studies

3.1.1. Patient Assessment

Aging is characterized by great physiological heterogeneity, and chronological age can differ significantly from biological or functional age. Traditional tools used by hematologists and oncologists to assess functional status, such as the Eastern Cooperative Group Performance Status (ECOG-PS), may not be accurately reflecting the health and functional status of older patients [7]. Accumulating evidence supports the need for geriatric assessment (GA) in older patients receiving cancer treatment. GA is a multidimensional tool that incorporates validated instruments to assess health and functional status based on their predictive validity in terms of morbidity, mortality, and treatment tolerance. These instruments include assessments of physical performance, functional status, nutritional status, cognitive status, psychological status, comorbidities, medications, social support, and geriatric syndromes. The GA has proven useful in helping to determine fitness and uncover vulnerabilities, which can guide therapeutic decision and supportive care interventions when it is necessary. Depending on local infrastructure and resources, several models to implement GA exist [8].

A baseline GA is feasible and well accepted by patients and health care professionals in the setting of intensive induction chemotherapy for AML [9]. It is sensitive to changes in functional and mental health and correlates with survival [9,10]. Geriatric problems have a high prevalence in hematologic malignancies [11]. In the AML setting, more specifically, the prevalence of geriatric problems is high, with 63% of patients admitted for induction chemotherapy presenting impairments in two or more domains, and only 7.4% having no impairment [12]. Worse cognitive and objective physical function as well as depressive symptoms are associated with shorter survival in the intensive treatment setting [10,13]. Similarly, worse cognition and reported limitations in physical function are associated with shorter survival in the non-intensive treatment setting [14]. This warrants the need to assess these vulnerabilities to aid medical decision making and guide geriatric interventions.

While GA provides a comprehensive assessment of health status, it can be challenging to implement routine GA in resource limited settings. Screening tools such as the Geriatric 8 (G8) Questionnaire have also demonstrated prognostic utility in hematologic malignancies including AML and can be utilized to identify older adults at higher risk for poor outcomes and guide interventions, including referral for full GA if available, as G8 by itself lacked discriminative power for the outcome of a full GA [15]. Another option in resource limited settings is to screen for specific GA vulnerabilities associated with poor outcomes in AML including self-reported functional dependence (instrumental activities of daily living [IADL] impairment) [16], impaired Short Physical Performance Battery (SPPB) [10,17], or slow gait speed [18].

To assess the impact of comorbidities, the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), initially developed for patients with AML undergoing transplant, was validated for AML one-year overall mortality in patients aged 20 to 89 years old [19]. Specifically, the predictive use of HCT-CI was confirmed in patients ≥60 years undergoing HCT, although data are conflicting [20,21]. No separate validation for adults ≥70 years has been published. To date there is no validated leukemia-specific frailty scale for AML. Although variously defined, frailty is associated with survival [11]; defining its use for treatment choices in AML is work in progress.

Some points require particular attention in older patients with AML. For instance, creatinine clearance should systematically be calculated in every patient, as renal impairment frequently exists above age 70 even in the presence of normal creatinine levels [22]. Renal function impairment is also a key risk factor for tumor lysis syndrome [23]. The effects of drug interactions between chemotherapy and non-oncologic drugs should not be neglected, as the potential of severe side effects can be doubled or even tripled [24]. Many kinase inhibitors are sensitive to p450 interactions. As such, consistent medication review looking to minimize polypharmacy in older adults with AML is warranted throughout treatment. With a 30% prevalence of cognitive impairment at baseline, older patients admitted for AML are at significant risk of delirium. Delirium prevention measures should systematically be

implemented [25]. Likewise, poor nutritional status represents a common problem in patients with AML and is an independent prognostic parameter [26].

3.1.2. Disease Assessment

The advent of several targeted therapies for AML, some of them studied specifically for patients above the age of 75, stress the importance of a standard AML assessment independently of the age of the patient. Several guidelines have been published with recommended assessment panels (National Comprehensive Cancer Network [NCCN] guidelines [4], European LeukemiaNet [ELN] 2022 [5], International Consensus Classification [27], European Society for Medical Oncology [ESMO] [6]).

3.2. Expert Comment and Consensus

- Older patients with AML should undergo a GA in order to best determine their ability to tolerate and benefit from treatment. Validated tools and model summaries can be found for example in the SIOG screening and GA guidelines [28,29]. (**Evidence: Moderate; Recommendation: Strong**)
- In the setting of resource limitations, use of screening tools such as the Geriatric 8 or individual GA measures (such as dependence in IADLs, SPPB, or slow gait speed) provides a strategy to identify higher risk patients to inform clinical care and prompt referrals for full geriatric assessment if available. **(Evidence: Weak; Recommendation: Consensus)**
- Geriatric impairments do not necessarily preclude treatment for AML but should be integrated in decision making. (**Recommendation: Consensus**)
- Just as in younger patients, AML in older patients should be worked up according to general clinical guidelines (e.g., NCCN AML guidelines, ELN 2022 [5]) and patient preferences integrated. Exceptions may be made for patients with major impairments (e.g., severe dementia). (**Evidence: Strong; Recommendation: Strong**)

4. Frontline Therapy

4.1. Evidence from Studies

A large systematic review/meta-analysis including 13,381 patients was published recently [30]. Few studies have been conducted solely in patients 70 and older [30]. Therefore, the data were obtained from either subgroup analyses of larger studies or from cohort studies.

In a decision model among patients aged 70 and older, those with an ECOG PS 2 or more had a higher one-year overall survival (OS) when treated with hypomethylating agents than with intensive chemotherapy [31]. Patients with a Charlson score of $\geq$1 also had a trend into the same direction.

4.1.1. Intensive Chemotherapy

A systematic review/meta-analysis of studies published until December 2016, focusing on data for patients $\geq$70 years, identified a one-year survival of 37% (95% confidence interval [CI] 31–42%) and five-year survival of 8% (6–11%) in a combined cohort of 8525 patients [30].

Few studies published since have targeted this population. A randomized study of liposomal daunorubicin/Ara-C (CPX-351) in patients aged 60 to 75 years with newly diagnosed high-risk or secondary AML showed an improved five-year survival compared to 3 + 7 chemotherapy (18% vs 8%) [32]. One third of patients were aged 70 to 75, and their proportional survival benefit was similar to younger patients. Some prognostic scores might help predict the five-year survival of older patients treated with intensive chemotherapy, such as the European Scoring System (ESS) 70 + [33].

4.1.2. Low-Dose Chemotherapy

The Rejlic et al. systematic review [30] identified 847 patients treated with low-dose regimens (e.g., low-dose Ara-C) and the one-year OS was 11% (6–18%). The three-year OS was 12% (5–21%). No data was available on five-year OS.

4.1.3. Hypomethylating Agents (HMA)

The same systematic review/meta-analysis mentioned above included 496 patients, with a one-year survival of 35% (18–54%). The five-year survival was 3% (1–6%). Another review with pooled data analysis compared the effect of HMAs vs low-dose Ara-C in older unfit patients [34]. Although there was a trend for better results with HMAs, there was significant heterogeneity between studies and the pooled data for both types of treatment provided a median OS of 6.3 months. Complete remission (CR) rate was 15%, and the odds of CR were 1.85 higher in patients <75 vs older [35].

More recently, randomized trials adding venetoclax to hypomethylating agents or low-dose azacitidine in patients not deemed candidates for intensive chemotherapy have yielded an improvement in OS. For example, the DiNardo trial of venetoclax + azacitidine (median age 76yo) had a five-month OS improvement from 9.6 to 14.7 months [36]. The implications for patients eligible for intensive chemotherapy are still being sorted out. More details on venetoclax and other combinations targeting specific mutations are discussed in Section 5.

4.1.4. Best Supportive Care (BSC) (Including Hydroxyurea)

The Reljic study included 3,513 patients and their one-year survival was 17% (13−21). The five-year survival was 1% (0–4). A comparative meta-analysis was not possible in that study due to heterogeneity. Moreover, only one study adjusted for all three factors: cytogenetics, performance status, and comorbidity, although several studies adjusted for one or two of these factors. Therefore, the same group conducted a Markov model analysis based on the systematic review data [31]. The key conclusions were that in patients with ECOG PS of 0–1 and a Charlson score of 0, intensive treatment tended to be preferred by the model, whereas for other patients, HMA-based regimens tended to yield better one-year survival. Hypomethylating agents were clearly superior for patients with ECOG PS 2+ and Charlson score of 1 or more. Best supportive care was a dominated strategy in all models (i.e., one-year survival was shorter with BSC in all models). First line treatment for targetable mutations will be addressed in the Section 5: targeted therapies.

Hence, patients treated with intensive therapy and HMA showed more favourable outcomes than those with low-dose chemotherapy and BSC, with the caveat that these results are overall unadjusted for prognostic variables. This information may be useful for decision analysis models and for the future development of clinical trials focusing on these patients.

4.2. Expert Comment and Consensus

- Leukemia-directed treatment should be offered to older patients with AML above the age of 70 with an expectation of improving one-year survival. (**Evidence: Moderate; Recommendation: Strong**)
- For patients with good functional status and low comorbidity, intensive chemotherapy or HMA -based regimens can be considered. Patients with specific targetable mutations may require a different treatment approach (see Section 5). (**Evidence: Moderate; Recommendation: Strong**)
- Randomized trials directly comparing intensive chemotherapy- and HMA-based regimens should be conducted in fit patients above the age of 70, given similar survival results in a systematic review of published studies. (**Evidence: Moderate; Recommendation: Strong**)
- In patients with ECOG PS 2+ and/or severe comorbidities, HMA-based regimens should be preferred in the absence of a specific

targetable mutation. (**Evidence: Moderate; Recommendation: Moderate**)

- *Comment:* Combinations of HMAs and targeted therapies are rapidly emerging, and physicians should follow updates as they may shift the balance of treatment preferences in the near future.

5. Post-Remission Therapy Including Allogeneic Hematopoietic Stem-cell Transplantation (HCT)

5.1. Non-HCT Consolidation

For patients ≥70 years initially treated with intensive induction chemotherapy, the data are insufficient to delineate an optimal strategy regarding further intensive consolidation chemotherapy, choice of therapy, or number of consolidation cycles (Table 1, post-remission therapy). Importantly, definitive studies are lacking on objective self-reported assessment of patient fitness or resilience. Expert opinion suggests viable pathways based on initial induction regimen and patient fitness for consolidation. Severe neurotoxicity was seen in patients ≥60 years on CALGB 8525 that received consolidation with Ara-C 3 g/m^2 [17]. Therefore, if an Ara-C-based consolidation is chosen, we believe patients should consider appropriate dose-modifications aiming at 500-1500 mg/m^2 to prevent toxicity. Older patients with secondary or therapy-related AML who received CPX-351 as their initial therapy and are candidates for post-remission intensive therapy may continue with CPX-351 in consolidation for up to 2 cycles. However, the benefit of consolidation for CPX-351 was compared to 5 + 2 consolidation, instead of an intermediate-dose-/HIDAC-based regimen in a post-hoc analysis [37]. As such, intermediate dose Ara-C based consolidation and/or hypomethylating agents (HMA-) regimens may be considered as alternatives although randomized validations are lacking [8].

In regards to maintenance therapy, azacitidine in HOVON97 improved disease-free survival [19] vs placebo. The largest trial randomized AML patients ≥55 years to oral azacitidine after induction and

Table 1
Non-HCT-based post-remission therapy after intensive induction chemotherapy in older adults with AML.

Author	Intervention	N	Age range	70+	Data Source	Outcomes	Study Design Comment
Non-intensive consolidation/maintenance strategies							
Wei, 2020 [93]	Oral azacitidine versus placebo	472	55–86	52 pts. ≥ 75+	International, multicenter Phase 3, RCT blinded	**Median OS (mos)*** oral Aza: 24.7 placebo: 14.8 **2-year OS** Age 65+ Oral Aza: 46.7%, Placebo: 33.9% Age 75+ Oral Aza: 51.9%, Placebo: 24.8	Post-consolidation or unable to tolerate intensive cytarabine-based consolidation
Huls, 2019 [94]	Azacitidine versus surveillance	116	60–81	Unknown	HOVON97, phase 3 RCT	**1-year DFS** * Aza: 64% surveillance: 42% **OS equal**	Post 2 cycles IC
Löwenberg, 1998 [95]	LDAC versus surveillance	LDAC: 75 Surveillance: 76	60–88	Unknown	EORTC/HOVON RCT	**3-year DFS*** LDAC: 13% surveillance: 7% **Median OS** LDAC: 62 weeks surveillance: 79 weeks	1st randomization to initial induction; second to post-remission therapy
Intensive consolidation/maintenance strategies							
Kolitz, 2020 [37]	CPX-351 versus 5 + 2, up to 2 cycles	81	60–75	19 pts. (CPX-351) and 12 pts. (5 + 2)	RCT subgroup exploratory analysis	**OS (mos)** CPX-351: 25.43 5 + 2: 8.53	Secondary/high-risk AML. Consolidation based on IC Arm
Prebet, 2009 [96]	IDAC/HiDAC/auto (=IC) versus LDAC	147 patients with CBF AML	60–82	Unknown	French CBF-AML Intergroup: Retrospective study	**LFS (mos)** IC: 26 LDAC: 14 **OS not different t(8;21) median LFS*** (mos) Intensive: NR LDAC: 10	All received intensive anthracycline and cytarabine regimen
Gardin, 2007 [97]	IC: 1 cycle of therapy the same as induction versus ambulatory ("1 + 5") x 6 cycles	Ambulatory: 82 IC: 82	65–85	Unknown	ALFA 9803 RCT	**2- yr OS*** Ambulatory: 56% IC: 37%	
Stone, 2001 [98]	cytarabine versus cytarabine + mitoxantrone	169 in CR1	≥60	Unknown	CALGB 8923 RCT	**DFS (mos)** Cytarabine: 10 Cytarabine+Mito: 9 **OS (mos)** Cytarabine: 18 Cytarabine+mito: 15	Series of cooperative group trials. Some patients received no CT. Subset pursued allogeneic HCT
Mayer, 1994 [99]	Different dosing of cytarabine: 100 mg/m^2 versus 400 mg/m^2 versus 3 g/m^2		16–86	Unknown	CALGB 8525	**4-year DFS** All groups: ≤16%	stopped randomization to high dose cytarabine for ≥60 due to significant neurotoxicity, no separate analysis fpr pts. ≥70 years

Abbreviations: HCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; HMA, hypomethylating agents; 5 + 2, cytarabine 100 mg/m^2/d for 5 days and daunorubicin 60 mg/m^2 on days 1 and 2; IDAC, intermediate-dose cytarabine; HiDAC, high-dose cytarabine; auto, autologous stem-cell transplantation; LDAC, low-dose cytarabine; OS, overall survival; DFS, disease-free survival; LFS, leukemia-free survival.

* Statistically significant.

consolidation is the QUAZAR trial; azacitidine achieved better OS and RFS [20] than placebo. A three-day decitabine regimen, reported in abstract form only from ECOG 2906, had a non-statistically significant trend toward prolonging DFS and OS [38]. A meta-analysis of six HMA maintenance trials among older adults after intensive chemotherapy and consolidation not pursuing HCT quantified an OS benefit for HMA (hazard ratio [HR] = 0.80, 95% CI 0.70 to 0.91) [39]. Marked heterogeneity exists in maintenance studies' populations and is related to hypomethylating agent dose, route, and duration. In summary, for patients who have completed or cannot tolerate intensive consolidation regimens, we consider HMA-based maintenance therapy. Due to the treatment length and potential side effects, patient preferences and goals of care should be integrated in the decision.

5.1.1. *After Initial Non-intensive Therapy*

For patients who are initially treated with non-intensive based regimens and achieve remission, patients should continue with these regimens if they are responding and tolerating the regimens. There is not sufficient evidence to support stopping these therapies at any point after achieving remission without potential increased risk of relapse.

5.2. *HCT Consolidation*

5.2.1. *Evidence from Studies*

No randomized or well-designed donor versus no-donor studies have been published on HCT to consolidate response among older patients with AML.

Multi-institutional studies comparing consolidative allogeneic HCT for AML in first complete remission (CR1) primarily to chemotherapy consolidation are presented in Table 2. The more recent studies suggest improved survival for consolidative allogeneic HCT among patients ≥60 years old with five-year OS after allogenic HCT approximating 30–35% among patients with intermediate and unfavorable cytogenetics [40,41].

5.2.2. *Allogeneic HCT Fitness and Geriatric Assessment*

Although a recent survey among transplant physicians stated that most centers do not provide a dedicated geriatrician/geriatric oncologist service to assess older transplantation candidates, the detection of a high prevalence of impairments by a GA prior to HCT, even among those 50 years or older, has been established [42–45]. Risk-stratification by GA in single institutional studies show functional and/or cognitive impairments with inferior outcomes, usually through higher non-relapse mortality (NRM) [43,44,46,47]. In a multicenter retrospective analysis that reported function and a brief cognitive screen via the Blessed Orientation-Memory-Concentration test, mild cognitive impairment was independently associated with higher rates of one-year NRM [47]. None of the published studies had a significant number of patients ≥70 years [48]. An ongoing prospective multi-institutional study may shed light on the GA variables that optimally risk stratify for NRM among for patients ≥60 years (NCT03992352) (https://clinicaltrials.gov/ct2/show/NCT03992352).

One single institutional study utilized a GA-informed multidisciplinary clinic inclusive of a geriatrician and other team members to address candidacy and bolster patient resiliency before HCT in older patients [49]. Among 85 patients ≥60 years ultimately receiving allogeneic HCT, 16 (18.9%) were ≥ 70 years of age [49]. Relative to a historic cohort undergoing GA without intervention, the authors found shorter length of stay, fewer nursing-home admissions, reduced NRM, and better survival.

5.3. *Expert Comment and Consensus*

- The evidence, albeit of low quality, suggests considering allogeneic HCT in remission for intermediate or unfavorable risk disease, at least up to age 75 years [45]. We recommend assessing HCT eligibility further based on anticipated tolerance to HCT, patient goals, donor availability, and local institutional HCT criteria [50]. A GA may further inform candidacy. (**Evidence: Weak; Recommendation: Consensus)**
- For non-HCT consolidation, we recommend post-remission therapy over no therapy whenever feasible. (**Evidence: Moderate; Recommendation: Moderate**)
- Consolidation after initial induction therapy is reasonable, although individualization may be necessary based on patient fitness for treatment, goals, disease risk, and presence of MRD. (**Evidence: Moderate; Recommendation: Moderate**)
- Maintenance: After intensive chemotherapy, a benefit in survival and relapse-free survival may exist for HMA maintenance. Consideration should be given to HMA-based regimens, either oral or injectable based on local practice, for patients who cannot tolerate further intensive consolidative chemotherapy or have completed their consolidation courses, as improvements in both DFS and OS have been seen. Maintenance should continue as long as there is a continued response, acceptable toxicity, and it is aligned with patient wishes. Likewise, continuous regimens (e.g., HMAs) should be continued beyond CR. (**Evidence: Moderate; Recommendation: Moderate**)
- Data are sparse for patients ≥70 years after CR1 from initial intensive therapy. For non-transplant candidates or when there is a significant

Table 2
Multi-institutional comparative studies of allogeneic HCT or non-HCT to consolidate AML in CR1 in older patients.

Author	N	Age range	70+	Data source	Donor (% matched*)	Outcomes	Study design comment
Ustun, 2019 [40]	Allo: 211 CT: 211	60–75	Allo: 40 (9%) CT: 70 (33%)	Allo: Registry CT: Cooperative trials	66% Matched	5 yr OS Allo: 28.6% CT 13.8	AML CR1 receiving HCT in registry vs consolidation on cooperative group trials.
Versluis, 2015 [41]	Allo: 97 CT: 177 No CT: 177	≥60	Unknown	Cooperative trials	92% Matched	5 yr OS Allo 35% CT 26%, no CT 21%	AML CR1 in series of cooperative group trials. Some patients received no CT. Subset pursued allogeneic HCT
Farag, 2011 [100]	Allo: 94 CT: 96	60–70	Few	Allo: Registry CT: Cooperative trials	All Matched	3 yr OS: allo 32%, CT: 25%	AML CR1 after 4 month in HCT registry vs consolidation on cooperative group trials.
Kurosawa, 2011 [101]	Allo: 152 CT: 884	55–70	Few	Allo and CT: Japanese centers	77% Matched	3 yr OS Allo: 62% CT: 51%	AML CR1 from Japanese centers. Source of data not clear.

AML: acute myeloid leukemia; OS: overall survival; NRM: non-relapse mortality; allo, allogeneic hematopoietic cell transplantation; CT, chemotherapy consolidation; yr, year.

* Matched includes matched related and matched unrelated donors. Other donors may be mismatched related, unrelated, haploidentical or cords.

delay in HCT, we suggest intermediate dose Ara-C following intensive induction or CPX-351 to continue when successfully used for induction, to minimize anthracycline exposure. **(Evidence: Weak/Moderate; Recommendation: Moderate)**

6. Relapse Treatment

Except for a minority of patients who can be transplanted in second (or beyond) CR, relapsed AML remains an incurable disease. After relapse, age is a poor prognostic factor. In the retrospective study of Breems et al. [51] conducted in patients younger than 60, age independently predicted OS. In a retrospective study of the ALFA group on 393 patients >50 (median age 64), age significantly impacted prognosis with a rate of second CR of only 17% and an overall median OS of 5.6 months in patients older than 65 years [52].

The evaluation of patient status is critical for relapsed AML. As compared to the frontline setting, more patients are unfit for intensive chemotherapy, making the clinical management of older patients with relapsed AML challenging. This is due to the number of patients who have developed new or worsened existing comorbidities after an initial intensive therapy.

6.1. Evidence from Studies

Similar to the clinical management of patients with AML at diagnosis, the geriatric status of relapsed patients must be carefully evaluated. Findings are summarized in Table 3.

6.1.1. Patients Eligible for Intensive Salvage

In Sarkozy et al.'s study, 43% of patients were eligible for intensive salvage and only 5% received allogeneic HCT, but this proportion is not described for the sub-group of patients older than 70. In that study, patients treated intensively had better outcomes by propensity score analysis. Similar results were found in the retrospective comparison of intensive therapy versus non-intensive therapy or palliation for older patients with relapsed AML reported by Ferrara et al. [53] A total of 150 patients, with a median age 66 years (61–79), were included in the study. CR was achieved in 36/99 patients (36%) receiving intensive chemotherapy, while no CR was observed in the other group ($p < 0.001$). The median OS durations were five months and three months for intensive chemotherapy and palliation, respectively ($p = 0.01$). Patients managed with palliation required less hospitalization and less supportive therapy as compared to the group receiving intensive chemotherapy.

Table 4 summarizes the results achieved with other regimens in studies that included patients older than age 70. However, none reported specific subgroup data on patients older than 70. For a more detailed overview, see ref.[54]

6.1.2. Patients not Eligible for Intensive Salvage

This group includes patients initially treated intensively who are no longer fit at the time of relapse and patients who were unfit at diagnosis and have failed a frontline low-intensity regimen.

The most widely used low-intensity regimens include low-dose Ara-C (LDAC), a single agent hypomethylating agent, or more recently venetoclax and azacitidine [55]. The detailed results achieved with these therapies are detailed in the review by Vericat et al. [54] No specific study on the outcome of patients older than 70 is currently available. LDAC was associated with CR rate of 44%–49% and an OS of eight months in two small series of older patients in relapse [56,57] With azacitidine monotherapy or in combination with all trans-retinoic acid (ATRA), the CR rates were between 16% and 21%, with OS ranging from 2.9 to 9 months [58–60]. With decitabine, CR/CR with incomplete count recovery (Cri) rate was 19% and the OS was 6.2 months [61].

Two studies evaluated the effects of gemtuzumab ozogamicin (GO) as monotherapy or combined with a low-intensity regimen. A total of 57 patients in first relapse aged 22–80 with 61% >60 years received GO monotherapy [62]. In that study, CR/CRp was 33% and the median OS was 8.4 months. Interestingly, most of the responders received high-dose Ara-C (HIDAC) consolidation, suggesting that these patients were fit for intensive chemotherapy. In another study [63], 52 patients with relapsed/refractory (R/R) AML with a median age of 64.8 years (range 50.2–78.9) received a combination of vorinostat, azacitidine, and GO 3 mg/m^2 on D4 and 8. The overall response rate was 41.9%.

Data currently available on the use of venetoclax and HMAs in patients with R/R AML come mostly from retrospective series including some older patients. DiNardo et al. recently reported on the outcome of 55 patients with a median age of 71 (including 19 patients older than

Table 3
Indications for intensive salvage.

Treatment choice	Intensive salvage	Non-intensive salvage
Criteria -Geriatric assessment -Genetic sub-group -Transplant eligibility	• Fit • >12 months life expectancy • CBF-AML, CEBPa or NPM1 mutations • Favorable/intermediate cytogenetics • Yes	• Unfit • <12 months life expectancy • FLT3-ITD, TP53 mutations • Adverse cytogenetics • No
General considerations	• Prioritize inclusion in clinical trials • Consider applying dose reductions	• Prioritize inclusion in clinical trials
Treatment options	• IDAC monotherapy • GO-containing regimens • Other IDAC-containing regimen (AMSA-Ara-C; MEC; FLAG; CLAG etc.)	• Azacitidine monotherapy or + venetoclax • LDAC monotherapy or + venetoclax • Palliative therapies

CBF-AML: core binding factor acute myeloid leukemia; IDAC: intermediate-dose Ara-C; AMSA, Amsacrine; MEC: Mitoxantrone, etoposide, Ara-C; FLAG: Fludarabine, Ara-C, granulocyte colony-stimulating factor: CLAG, cladribine, Ara-C, granulocyte colony-stimulating factor: LDAC, low-dose Ara-C.

Table 4
Intensive salvage regimens for relapsed/refractory AML.

Study reference	Regimen	Dose-schedule	Age	70+	CR rate
Price 2011 [102]	MEC	ARAC 1 × 5 Mito 8 × 5 VP 100 × 5	55 (21–90)		25%
Kern 1998 [103]	HAM	ARAC 1 or 0.5 × 4 Mito 10 mg/m2x4	50 (18–75)	N./A	43%
Jabbour 2012 [104]	FLAG	FLU 30 × 5 ARAC 0.5/12hX5	62 (19–85)	N/A	19%
Bergua 2016 [105]	FLAG-Ida	FLU 30 × 4 ARAC 2 × 4 IDA 10 × 4	54 (16–76)	N/A	50%
De Astis 2014 [106]	FLAD	FLU 30 × 3 ARAC 2 × 3 DNR 100 × 3	60 (18–77)	N/A	53%
Price 2011 [102]	CLAG	2CdA 5 × 5 ARAC 2 × 5	55 (19–91)	N/A	52%
Faderl 2012 [107]	CLOFA	ARAC 1 g/m2x5 CLO 40 × 5	67 (55–82)	N/A	47%
Ravandi 2018 [108]	Vosaroxin-ARAC	Vosaroxin 70 mg/m2 ARAC: 1.5 × 5	68 (60–78)	N/A	25.8%

AML: acute myeloid leukemia; MEC: Mitoxantrone, etoposide, Ara-C; FLAG: Fludarabine, Ara-C, granulocyte colony-stimulating factor; CLAG: cladribine, Ara-C, granulocyte colony-stimulating factor; CLOFA: Clofarabine, Ara-C; HAM: Ara-C, mitomycin.

70), with R/R AML treated with 10-day decitabine and venetoclax. The rate of CR/CRi was 42% and the median OS was 7.8 months (5·4–13·3) [64]. In another study in 33 patients with a median age of 62 years (range 19–81), CR/Cri was 51% [65]. Stahl et al. [66] recently reported the results of a retrospective study of 86 patients with R/R AML treated with various venetoclax combinations. Approximately 57% of the patients were older than 65. The CR/CRi rate was 24% with higher response rates for azacitidine + venetoclax compared with LDAC + venetoclax (49% vs 15%; $P = 0.008$). Median OS was 6.1 months and was significantly longer with azacitidine + venetoclax. Another retrospective series by Graveno et al. included 77 patients aged 22 to 85 years, median 64, treated with venetoclax and various HMAs. The overall response rate was 68%, with 53% CR/Cri. The median OS was 13.1 months [67]. Piccini et al., in another retrospective cohort of 47 patients treated with venetoclax and HMAs (10% above age 70), reported a CR rate of 55% and an OS of 10.7 months [68]. A propensity score analysis suggests that the combination may compare favorably with intensive salvage regimens, but direct comparisons are lacking [69].

For patients with FLT3 or IDH gene mutations, please see Section 5.

6.2. Expert Comment and Consensus

- Several studies suggest that for the patients who are fit with non-adverse cytogenetics, an intensive salvage should be considered as a bridge to transplant. It is worth noting that these studies are retrospective and that there is no established standard of salvage chemotherapy. The administration of intermediate dose Ara-C (IDAC) alone or in combination with other drugs is consensual (NCCN). (**Evidence: Weak; Recommendation: Weak**)
- The incorporation of GO in the salvage regimens has been shown to be associated with a better outcome in retrospective studies. The benefit seems to be restricted to patients with non-adverse cytogenetics. However, due to the small number of patients older than 70 included in these studies and the potential toxicity, the benefit of GO-containing regimens in this age group remains to be established. (**Evidence: Weak; Recommendation: Weak**)
- The proportion of patients older than 70 who are deemed fit for an intensive salvage is between 10% to 20%. For most patients older than 70, treatment options rely on low-intensity therapies. Based on recent non-comparative studies, the combination of venetoclax and HMAs is recommended. However, best supportive care should also be considered for the oldest and most frail patients, especially for second relapse and beyond. (**Evidence: Weak; Recommendation: Moderate**)

7. Targeted Therapies

7.1. Evidence from Studies

From the current literature, multiple targeted agents are currently being investigated in clinical trials for AML treatment in older patients. The results are summarized in Table 5. However, a number of targeted therapies have not been tested in patients above the age of 70 (e.g., midostaurin). Given the variety of side effect profiles and pharmacokinetic interactions, pre-existing comorbidities and their associated medications may influence the selection of targeted therapies.

7.2. Expert Comments and Consensus

- Gilteritinib, ivosidenib +/− azacitidine, enasidenib, olutasidenib, glasdegib+LDAC, venetoclax + HMA, venetoclax + LDAC all have sufficient data in the ≥70-year-old population to support the currently on-label indications. (**Evidence: Strong; Recommendation: Strong**)
- Midostaurin +7 + 3 induction was not explored in patients 70 year and older, and therefore there is insufficient data to recommend in patients aged 70 and older. (**Evidence: Weak; Recommendation: Moderate**)
- Data support post-transplant maintenance with sorafenib for improvement in relapse-free survival, though this is an off-label indication (**Evidence: Strong; Recommendation: Strong**)
- Quizartinib does not have sufficient data yet to support use in patients 70 years and older and currently is only available in Japan. (**Evidence: Weak; Recommendation: Weak**)
- The incorporation of GO in the salvage regimens has been shown to be associated with a better outcome in retrospective studies. The benefit seems to be restricted to patients with non-adverse cytogenetics. However, due to the small number of patients older than 70 included in these studies, the benefit of GO-containing regimens in this age group remains to be established. (**Evidence: Weak; Recommendation: Weak**)
- GO does not have sufficient data to support use in combination with 7 + 3 induction therapy based on meta-analysis results. (**Recommendation: Consensus**)

8. Quality of Life/ Treatment Tolerability/ Patient-Reported Outcomes

8.1. Evidence from Studies

8.1.1. Quality of Life (QoL)

Health-related quality of life (HRQOL) is an individual's or a group's perceived physical and mental health over time. There are general and cancer-specific QoL instruments. Examples of general QoL instruments include the RAND Medical Outcomes Study 36-Item Health Survey (SF-36) and the Quality of Well-Being scale (QWB). Examples of cancer-specific instruments include the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the Functional Assessment of Cancer Therapy (FACT), and the Cancer Rehabilitation Evaluation System (CARES) and its short form (CARES-SF). Each has been validated and tested in patients with various types of cancer [70]. Specific tools for leukemia include the EORTC-Leukemia Module, EORTC-Leukemia/Bone Marrow Transplant Module, and FACT-Leukemia [71,72]. Patient-reported outcomes (PRO) is a collective name for any information about a patient's health condition that comes directly from the patient without any interference or interpretation from clinical experts. Patient-reported outcome measures (PROMs) are designed to measure the patient experience that cannot be obtained from an observer, but from the patient only, for example, fatigue, symptom severity, impact on daily activities, and HRQOL.

8.1.2. HRQOL & Age

Although HRQOL is relevant for treatment decision making, it is infrequently measured in clinical trials. Of trials that included HRQOL, EORTC QLQ-C30 is the most common measure used [35,73,74]. Functional Assessment of Cancer Therapy (FACT) with or without the leukemia-specific module has also been commonly used in observational studies to characterize HRQOL in the setting of AML therapy. Available evidence suggests that HRQOL is low among older adults diagnosed with AML [4] and that baseline HRQOL measures and components are associated with outcomes (i.e., health care utilization, remission, survival) [75–77].

Limited studies have evaluated differences in HRQOL by age in AML. An observational study showed that older versus younger age was associated with similar HRQOL over time among survivors of intensive induction therapy. Specifically, HRQOL and physical function improved over time independent of age among survivors [76].

8.1.3. HRQOL as a Measure of Treatment Experience

HRQOL measures are sensitive to change during AML treatment

Table 5
Summary of targeted agents for treating AML and data from current literature in the use of targeted agents in older patients.

		Mechanism	Regimen	Data Source	Data in Ages 70+
Perl, 2019 [109]	Gilteritinib Midostaurin	FLT3 inhibitor (ITD and TKD)	*Gilteritinib vs SOC in R/R AML with FLT3 mutated	ADMIRAL Randomized phase 3 study	• 106 vs 49 patients ≥65 years • OS 9.3 mos vs 5.6 mos in total cohort
Stone,2017 [110]			7 + 3 + midostaurin newly diagnosed FLT3 mutated	Single-arm study in FLT3-ITD	• 18–70 years, CR/Cri in 86 patients 61–70 years:77.9% • 2-year OS: 46 (35–59%)
Serve, 2013 [111]	Sorafenib	FLT3 inhibitor (ITD)	7 + 3 + sorafenib vs 7 + 3 + placebo newly diagnosed AML	Randomized phase 3 study	• >60 years irrespective of FLT3 status (median age 68 years); CR rate 48 vs 60%, median OS 13 vs 15 mos (ns)
Uy, 2017 [112]			7 + 3 + sorafenib FLT3 mutated newly diagnosed AML	CALGB 11001: single-arm FLT3 mutated ≥60 years	• Median age 67 years; 20/54 patients >70 years; 17 patients with FLT3-ITD >70 years; median OS 9.7 mos, EFS 2.2 mos
Burchert 2020 [113]			Sorafenib post-transplant maintenance	SORMAIN: randomized, double-blind, placebo controlled study	• Median age 54 (range 18.58–75.58. Improvement in 24-month RFS 85% (sorafenib) vs 53.3% (placebo)
Cortes, 2019 [114]	Quizartinib	FLT3 inhibitor (ITD)	*Quizartinib vs SOC in R/R AML with FLT3 mutation	QUANTUM-R: Randomized Phase 3 study	• IQR 44–66 years • OS 6.2 mos versus 4.7 mos
Erba, 2022 [115]			7 + 3 + quizartinib vs 7 + 3 + placebo in newly diagnosed FLT3-ITD+ AML	QuANTUM-First: Randomized, double-blind, placebo-controlled Phase 3 study	• Median age 56 (10–75): CR/CRi 71.6% (quizartinib) vs 64.9% (placebo) • Medain OS: 31.9 mo (quizartinib) vs 15.1 mos (placebo)
DiNardo, 2018 [116] Roboz, 2020 [117]	Ivosidenib	IDH1 inhibitor	*Ivosidenib single agent 500 mg po daily in R/R and newly diagnosed AML with IDH1 mutation	Phase 1 dose-escalation/expansion study	• Median age 67 (18–87): ORR 41.6% (CR + Cri/CRp + MLFS+PR); • Median OS: 8.8 months
Montesinos, 2022 [118]			*Ivosidenib+azacitidine vs placebo+azacitidine in newly diagnosed AML with *IDH1* mutations	AGILE: Randomized Phase 3 study	• Median age, 76 (58–84) (ivosidenib arm) vs 75.5 (45–94) (placebo-controlled arm) • EFS: HR 0.33; [95% CI 0.16–0.69] (favoring ivosidenib) • 12 mo EFS 37% (ivosidenib arm) vs 12% (placebo-controlled arm) • Median OS 24 mos (ivosidenib arm) vs 7.9 mos (placebo-controlled arm)
Stein, 2019 [119] Pollyea, 2019 [120]	Enasidenib	IDH2 inhibitor	*Enasidenib single agent 100 mg po daily in R/R AML	Phase ½ study	• Median age 67 (19–100); ORR = 38.5% (CR + Cri/CRp + MLFS); Median OS 9.3 mos
de Botton, 2023 [121]			*Enasidenib versus convential care regimens (CCR) in R/R IDH2 mutated AML (2 or 3 prior AML-directed therapies)	Randomized Phase 3 study	• Median age 71 (60–86) • Median OS was not different (6.5 (Enasidenib) vs 6.2 mos (CCR)) • EFS 4.9 mos vs 2.6 mos • Confounded by early dropout and subsequent AML-directed therapies
DiNardo, 2021 [122]			*Enasidenib+azacitidine vs Azacitidine in newly diagnosed IDH2 mutated AML	Randomized phase 2 study	• Median age 75 (IQR 71–78) • ORR [CR + CRi + CRp + PR + MLFS]: 74% (enasidenib+azacitidine) vs 36% (azacitidine)
de Botton, 2023 [123]	Olutasidnib	IDH1 inhibitor	*Single agent 150 mg BID in R/R IDH1 mutated AML	Phase ½ study	• Median age 71 (32–87) • CR/CRh rate: 35% • ORR [CR + CRh + CRi + PR + MLFS]: 48% • Median OS 11.6 mos
Martinelli G, 2015 [124]	Glasdegib	Hedgehog inhibitor	Single agent 200 mg/day in R/R AML	Phase 1 study	• 1/28 patients with CR, not sufficient data for single-agent in any R/R AML regardless of age
Cortes, 2019 [125]			*Glasdegib (100 mg/day+ LDAC 20 mg/d x10 days vs LDAC	BRIGHT 1003 Randomized phase 2 (2:1)	• Median age 77, with 47 pts. older than 75 (132 pts. total). Median OS 8.8 (G + LDAC) vs 4.9 mos (LDAC) $p = 0.0004$
Sekeres, 2022 [126]			Glasdegib + azacitidine	BRIGHT 1012: Phase 2	• Median age: 74 years. CR rate 20%, no different than single-agent azacytidine
DiNardo, 2020 [36]	Venetoclax	BCL-2 inhibitor	*Venetoclax + Azacitidine versus placebo+Azacitidine	VIALE-A: Randomized 2:1, Phase 3 study	• Median age 76: Range 49–91. 174 pts. in Ven-Aza and 87 in Aza-placebo Ages 75 + . • Study showed improvement OS for all-comers and sub-group analysis in 75+ showed OS benefit HR 0.54 (0.39–0.73)
Wei, 2021 [127]			*Venetoclax + LDAC versus placebo + LDAC	Randomized, 2:1, Phase 3 study	• Median age 76 (range 36–93); aged 75+ LDAC-placebo- 40 and LDAC+ven – 82 • Improved CR, EFS, OS in Ven-LDAC arm
Konopleva, 2016 [128]			Single-agent in R/R setting	Phase 2, single-agent open-label monotherapy 800 mg daily	• Median age 71 (range 19–84) • ORR: 19%, no data specifically on pts. aged 70+
Lambert, 2019 [129]	Gemtuzumab ozagomicin	Anti-CD33 immunoconjugate	*Newly diagnosed AML 7 + 3+/-GO (3 mg/m2 D1,4,7)	Randomized, Phase 3	• 2-year EFS 40.8%(GO)vs 17.1% and OS 53.2% (GO)vs41.9%

(*continued on next page*)

Table 5 (*continued*)

	Mechanism	Regimen	Data Source	Data in Ages 70+
				• Ages 50–70 randomized but no patients over age 70
Burnett, 2012 [130]		Newly diagnosed AML 7 + 3 or daunorubicin/clofarabine +/− GO 3 mg/m2 Day 1	MRC-AML16: Randomized, Phase 3 study	• Median age 67 (range 51–84); 341 pts. >70 • Improved 3-year CIR and 3-year OS (25% vs 20%)
Hills, 2014 [131]		Newly diagnosed AML	Meta-analysis of MRC-AML-15 and AML-16	• No significant impact of OS in patients >70
Burnett, 2013 [132]		Newly diagnosed AML LDAC+GO 5 mg Day 1 vs LDAC alone	Randomized, Phase 3	• Median age 75 (range 54–90); age > 70 96% • GO improved CR rate but not 12-month OS
Amadori, 2016 [133]		*Relapsed/Refractory AML GO 6 mg/m2 on Day 1 and 3 mg/m2 on Day 8 versus BSC	Randomized, Phase 3	• Median age:77; >70 64%; Median age 4.9 months (GO) vs 3.6 months (BSC); 1 year OS 24.3% (GO) vs 9.7% (BSC). OS benefit of GO greater in the age 75+ population

A number of targeted therapies have not been tested in patients in their 70's, e.g. midostaurin etc.….

* Has agency approval in at least one country.

[2,78].There is no clear evidence that HRQOL post-treatment is better with lesser versus more intensive therapies, although randomized controlled trials (RCT) data are lacking. In an observational study of 100 older adults with AML, HRQOL, anxiety, and depression were similar pre- and post-treatment among those receiving intensive vs. non-intensive therapies [78]. Among older adults who received intensive induction on Alliance 361,006 [9,75], global HRQOL improved significantly post induction among those who were available for post-remission evaluation. Another longitudinal study suggests that older patients receiving both intensive and non-intensive therapy experience improvement in HRQOL over time [75]. A challenge in interpreting available HRQOL data from clinical trials is the bias associated with high attrition rates. Patients who experience morbidity and mortality often do not contribute HRQOL data with results reflecting those who have experienced better outcomes.

HRQOL and GA are not interchangeable. In a prospective study of older adults receiving intensive induction therapy, HRQOL improved significantly post induction therapy while GA measures of physical function (ADL/IADL), mood, and social activity declined. HRQOL improvement were driven largely by symptoms [2].

8.1.4. *HRQOL & Symptoms*

Older adults with AML experience significant symptom burden. In a cohort of 65 older patients with AML, 98% experienced some degree of fatigue prior to treatment, and between 92% to 97% reported fatigue up to six months post-treatment [79]. Fatigue was closely related to HRQOL. Not surprisingly, those who died had worse fatigue, but remission was not associated with significant improvement in fatigue. Induction chemotherapy for AML is more intensive than many other cancer treatments and may be associated with a different symptom burden. A study conducted among 43 inpatients with AML at initiation of induction chemotherapy assessed their symptoms, QoL, and distress weekly during their month-long hospitalization for induction, and monthly thereafter using three validated instruments: Patient Care Monitor v2.0 (PCM), FACT-Le, and the NCCN distress thermometer (DT). The patients reported a range of moderate to severe level symptoms such as poor appetite (35%), dry mouth (37%), difficulty sleeping (38%), dysgeusia (44%), fatigue (56%), diarrhea (35%), daytime sleepiness (30%), and nausea (27.5%). While these results are not specific to older adults, they highlight a high prevalence of symptoms that may have a significant impact on an older adult's treatment tolerability [80].

One concern in older patients with AML is the lack of resilience for recovering from severe complications as a result of AML and its treatment, or a higher likelihood of experiencing long-lasting effects affecting HRQOL. In a retrospective study of 330 older patients, 29% were admitted to the intensive care unit and 47% of those survived to hospital discharge with a one-year survival of 30%. Functional outcomes were reasonable among those who survived. This indicates that some older patients are resilient [77].

8.1.5. *Patient-Reported Outcome Measures in AML*

The importance of PROMs, which can form the basis for individualized treatment decisions and evaluate the benefits of treatment, is rapidly growing in healthcare systems and in clinical studies [71]. The overall high prevalence of poor HRQOL, symptom burden, and physical burden suggests sizeable unmet needs among patients with AML, arguing the need for interventions to enhance tolerability and outcomes [81].

The European Myelodysplastic Syndrome (MDS) Registry Group recently has established a core outcome set (COS) for MDS [82] which includes HRQoL, performance status, and function. There are ongoing projects to establish a COS for AML in the Harmony project.

8.1.6. *Supportive Care Interventions to Enhance Tolerability*

Several studies have evaluated/are evaluating the role of behavioral and supportive care interventions such as GA-guided interventions, exercise, and palliative care. In a single arm study by Klepin et al. [83], patients aged 50 years and above receiving intensive therapy performed exercises for four weeks, with 71% attending one or more sessions. As a result, HRQoL and depressive symptoms improved. On the other hand, in the study by Alibhai et al. among individuals aged 40 years and above who received intensive treatment, 28% underwent a 12-week home-based exercise regime with no observed benefits in HRQoL, fatigue, or physical fitness [2,78]. While non-specific to older adults, exercise has been shown to improve fatigue in patients with AML undergoing induction chemotherapy [84]. Recently, a pilot study presented at the American Society of Clinical Oncology annual meeting demonstrated feasibility of a symptom-adapted physical activity intervention for older adults (≥60 years) receiving intensive therapy for AML. Among participants who achieved remission, fewer older adults experienced a clinically meaningful decline in objectively measured physical function, supporting this line of investigation in a larger, fully powered study [85]. Feasibility of a mobile health exercise intervention has also been demonstrated for those receiving treatment in the outpatient setting, with patients experiencing stable physical function, fatigue, mood, and QoL [86].

8.1.7. *Geriatric Assessment-Guided Interventions*

GA has been shown to improve communication, improve QoL, and reduce toxicity [87]. In a randomized trial of embedded geriatric consultation for transplant-ineligible older adults (aged 75 years or older) with hematologic malignancies (including AML), no statistically significant changes were seen in one-year survival, unplanned hospitalizations, or emergency room visits compared with usual care [88]. Patients in the intervention arm were, however, more likely to complete a goals of care discussion. Ongoing studies are needed to assess the effects of non-oncological interventions on clinical outcome measures in

older patients with hematologic malignancies/AML, with the areas of nutritional counseling, social and psychological support, counseling on medications, and comorbidities being understudied.

8.1.8. Palliative Care

Older adults with AML spend a quarter of their time in the hospital and 14% attending outpatient clinic appointments since diagnosis with a median number of hospitalizations around 4.2 [89]. Those receiving intensive chemotherapy spend 30% more of their time in the hospital compared to others. Several studies have also shown that many older patients died in the hospital. Given the considerable amount of health-care utilization in addition to poor HRQOL, symptom burden, and physical burden, palliative care services should be considered. In a multicenter RCT, patients with high-risk AML including those aged 60 and above receiving intensive chemotherapy were randomized to receive integrated palliative and oncology care or usual care [90]. Those in the intervention arm reported better HRQOL and lower psychological distress, which sustained up until week 24. Patients who died and had been randomized to the intervention arm were more likely to discuss end of life care preferences and less likely to receive chemotherapy near end of life. These data are consistent with data in other settings, including those receiving transplants and those with solid tumors [91,92].

8.2. Expert Comments and Consensus

- Consider supportive care interventions such as palliative care integration, exercise, and geriatric co-management in the care of older patients with AML. (**Evidence: Moderate; Recommendation: Moderate**)
- PROs to assess HRQOL and symptoms should be incorporated and assessed longitudinally in clinical trials of older patients with AML undergoing treatments. **(Evidence: Low; Recommendation: Low)**
- Choice of PROMs is based on infrastructure and resources. In addition to baseline GA, consider inclusion of longitudinal GA (or at minimum assessment of functional status or physical performance), symptoms, and QoL measures. **(Recommendation: Consensus)**

9. Conclusion

In this paper we aimed to provide our colleagues with management recommendations for adults with AML aged 70 and older, a group largely underrepresented in clinical trials. We extracted information, combining evidence from systematic reviews/meta-analyses, decision models, individual trials targeting these patients, and subgroup data. Our recommendations are summarized in Table 6. Progress is continuously being made in intensive chemotherapy, cell therapies, and targeted therapies. It is our firm recommendation and hope that direct evidence should be generated for patients aged 70 and older as a distinct group in high need of improvement of their survival outcomes. Such studies should integrate information from a geriatric assessment to optimize external validity and outcomes.

Author Contributions

All authors contributed to the review of the evidence, determination of the consensus recommendations, and writing of the manuscript.

Declaration of Competing Interest

Disclosures: Dr. Extermann: Aileron, Alnylam (consultant), OncLive (honoraria). Dr. Artz: Abbvie, Magenta (consulting). Dr. Klepin: UptoDate (contributor). DrLoh: COI: Dr. Loh: Pfizer and Seagen (consultant), Pfizer (honoraria). Dr. Neuendorff: Janssen-Cilag, Medac, Novartis, Abbvie, and Jazz Pharmaceutical (honoraria, travel support). Dr. Santini: Abbvie, CTI, Celegne/BMS, Geron, Gilead, Novartis, Otsuka, Serveir, Syros (advisory boards), AIRC Foundation, Associazione Italiana

Table 6
Key recommendations.

Question asked	Expert recommendation	Evidence level	Recommendation
1) What baseline assessment is needed?	• Older patients with AML should undergo a GA in order to best determine their ability to tolerate and benefit from treatment. Validated tools and model summaries can be found for example in the SIOG screening and GA guidelines.	Moderate	Strong
	• In the setting of resource limitations, use of screening tools such as the Geriatric 8 or individual GA measures (such as dependence in instrumental activities of daily living, SPPB, or slow gait speed) provides a strategy to identify higher risk patients to inform clinical care and prompt referrals for full geriatric assessment if available.	Weak	Consensus
	• Geriatric impairments do not necessarily preclude treatment for AML but should be integrated in decision making	Strong	Consensus
	• Just as in younger patients, AML in older patients should be worked up according to general clinical guidelines (e.g., NCCN AML guidelines, ELN 2022) and patient preferences integrated. Exceptions may be made for patients with major impairments (e.g., severe dementia).		Strong
2) What should be used as frontline therapy?	• Leukemia-directed treatment should be offered to older patients with AML above the age of 70 with an expectation to improve 1-year survival.	Moderate	Strong
	• For patients with good functional status and low comorbidity, intensive chemotherapy or HMA-based regimens can be considered. Patients with specific targetable mutations may require a different treatment approach (see Section 5).	Moderate	Strong

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Table 6 (*continued*)

Question asked	Expert recommendation	Evidence level	Recommendation
	• Randomized trials directly comparing intensive chemotherapy- and HMA-based regimens should be conducted in fit patients above the age of 70, given similar survival results in a systematic review of published studies.	Moderate	Strong
	• In patients with ECOG PS 2+ and/or severe comorbidities, HMA-based regimens should be preferred in the absence of a specific targetable mutation.	Moderate	Moderate
	• *Comment:* Combinations of HMAs and targeted therapies are rapidly emerging, and physicians should follow updates as they may shift the balance of treatment preferences in the near future.		
3) What should be used as post-remission with or without transplant therapy?	• The evidence, albeit of low quality, suggests considering allogeneic HCT in remission for intermediate or unfavorable risk disease, at least up to age 75 years [45]. We recommend assessing HCT eligibility further based on anticipated tolerance to HCT, patient goals, donor availability, and local institutional HCT criteria. A GA may further inform candidacy.	Low	Consensus
	• For non-HCT consolidation, we recommend post-remission therapy over no therapy whenever feasible.	Moderate	Moderate
	• Consolidation after initial induction therapy is reasonable although individualization may be necessary based on patient fitness for treatment, goals, disease risk, and presence of MRD.	Moderate	Moderate
	• Maintenance: After intensive chemotherapy, a benefit in survival and relapse-free survival may exist for HMA maintenance. Consideration should be undertaken for HMA-based regimens either oral or injectable based on local practice for patients who cannot tolerate further intensive consolidative chemotherapy or have completed their consolidation courses as improvements in both DFS and OS have been seen. Maintenance should continue as long as continued response, acceptable toxicity, and aligned with patient wishes. Likewise, continuous regimens (e.g., HMAs) should be continued beyond CR.	Moderate	Moderate
	• Data are sparse for patients ≥70 years after CR1 from initial intensive therapy. For non-transplant candidates or when significant delay in HCT, we suggest intermediate dose Ara-C following intensive induction or CPX-351 to continue when successfully used for induction, to minimize anthracycline exposure.	Low/ moderate	Moderate
4) What treatments are available for relapse?	• Several studies suggest that for the patients who are fit with non-adverse cytogenetics, an intensive salvage should be considered as a bridge to transplant. It is worth noting that these studies are retrospective and that there is no established standard of salvage chemotherapy. The administration of IDAC alone or in combination with other drugs is consensual (NCCN).	Weak	Weak
	• The incorporation of GO in the salvage regimens has been shown to be associated with a better outcome in retrospective studies. The benefit seems to be restricted to patients with non-adverse cytogenetics. However, due to the small number of patients older than 70 included in these studies and the potential toxicity, the benefit of GO-	Weak	Weak

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Table 6 (*continued*)

Question asked	Expert recommendation	Evidence level	Recommendation
	containing regimens in this age group remains to be established.		
	• The proportion of patients older than 70 who are deemed fit for an intensive salvage is comprised between 10% to 20%. For most patients older than 70, treatment options rely on low-intensity therapies. Based on recent non-comparative studies, the combination of venetoclax and HMAs is recommended. However, best supportive care should also be considered for the oldest and most frail patients especially for second relapse and beyond.	Weak	Moderate
5) What are the available targeted therapies for use in older patients with AML?	• Gilteritinib, ivosidenib +/− azacitidine, enasidenib, olutasidenib, glasdegib+LDAC, venetoclax + HMA, venetoclax + LDAC all have sufficient data in the ≥70-year-old population to support the currently on-label indications.	Strong	Strong
	• Midostaurin +7 + 3 induction was not explored in patients 70 year and older, and therefore there is insufficient data to recommend in patients aged 70 and older.	Weak	Moderate
	• Data support post-transplant maintenance with sorafenib for improvement in relapse-free survival though this is an off-label indication.		
	• Quizartinib does not have sufficient data yet to support use in patients 70 years and older and currently is only available in Japan.	Strong	Strong
	• The incorporation of GO in the salvage regimens has been shown to be associated with a better outcome in retrospective studies. The benefit seems to be restricted to patients with non-adverse cytogenetics. However, due to the small number of patients older than 70 included in these studies, the benefit of GO-containing regimens in this age group remains to be established.	Weak	Weak
	• GO does not have sufficient data to support use in combination with 7 + 3 induction therapy based on meta-analysis results.	Weak Consensus	Weak Consensus
6) How does AML and its treatment affect patient reported outcomes and function? What supportive care interventions have been tested to enhance treatment tolerance?	• Consider supportive care interventions such as palliative care integration, exercise, and geriatric co-management, in the care of older patients with AML.	Moderate	Moderate
	• PROs to assess HRQOL and symptoms should be incorporated and assessed longitudinally in clinical trials of older patients with AML undergoing treatments.	Weak	Weak
	• Choice of PROMs is based on infrastructure and resources. In addition to baseline GA, consider inclusion of longitudinal GA (or at minimum assessment of functional status or physical performance), symptoms, and QoL measures.	Consensus	Consensus

AML: acute myeloid leukemia; GA: geriatric assessment; SIOG: International Society of Geriatric Oncology; SPPB: Short Physical Performance Battery; NCCN: National Comprehensive Cancer Network; HMA; hypomethylating agents; ECOG PS: Eastern Cooperative Oncology Group performance status; HCT: hematopoietic stem cell transplant; DFS: disease-free survival; OS: overall survival; CR: complete remission; CR1: first complete remission; IDAC: intermediate-dose Ara-C; GO: gemtuzumab ozogamicin; LDAC: low-dose Ara-C; PRO: patient-reported outcome; HRQOL: health-related quality of life; PROM: patient-reported outcome measure.

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