CLINICAL GUIDELINES

blood advances

American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

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Background: Older adults with acute myeloid leukemia (AML) represent a vulnerable population in whom disease-based and clinical risk factors, patient goals, prognosis, and practitioner- and patient-perceived treatment risks and benefits influence treatment recommendations.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about management of AML in older adults.

Methods: ASH formed a multidisciplinary guideline panel that included specialists in myeloid leukemia, geriatric oncology, patient-reported outcomes and decision-making, frailty, epidemiology, and methodology, as well as patients. The McMaster Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre supported the guideline-development process, including performing systematic evidence reviews (up to 24 May 2019). The panel prioritized clinical questions and outcomes according to their importance to patients, as judged by the panel. The panel used the GRADE approach, including GRADE's Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 6 critical questions in managing older adults with AML, mirroring real-time practitioner-patient conversations: the decision to pursue antileukemic treatment vs best supportive management, the intensity of therapy, the role and duration of postremission therapy, combination vs monotherapy for induction and beyond, duration of less-intensive therapy, and the role of transfusion support for patients no longer receiving antileukemic therapy.

Conclusions: Treatment is recommended over best supportive management. More-intensive therapy is recommended over less-intensive therapy when deemed tolerable. However, these recommendations are guided by the principle that throughout a patient's disease course, optimal care involves ongoing discussions between clinicians and patients, continuously addressing goals of care and the relative risk-benefit balance of treatment.

Summary of recommendations

These guidelines are based on original systematic reviews of evidence conducted under the direction of the McMaster Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre. The panel followed best practice for guideline development recommended by the Institute of

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Table 1. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not; decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences
Clinicians	Most individuals should follow the recommended course of action; formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences; decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences
Policy makers	The recommendation can be adopted as policy in most situations; adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	Policy making will require substantial debate and involvement of various stakeholders; performance measures should assess whether decision-making is appropriate
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation; on occasion, a strong recommendation is based on low or very low certainty in the evidence; in such instances, further research may provide important information that alters the recommendations	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research; an evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps

Medicine and the Guidelines International Network (GIN).[1-4] The panel used the GRADE approach[5-11] to assess the certainty in the evidence and formulate recommendations.

The following criteria were used to identify older adults with acute myeloid leukemia (AML) included in the clinical trials forming the basis for these recommendations.

Inclusion criteria

1. Newly diagnosed de novo, treatment-related, and secondary AML (ie, not relapsed or refractory AML);
2. Patients 55 years and older;
3. Patients had to have received intensive or less-intensive antileukemic therapy depending on the specific question being addressed;
4. Patients were treated as part of randomized controlled trials (which were prioritized) and comparative observational studies; and
5. Studies had to include 20 or more patients.

Exclusion criteria

1. Acute promyelocytic leukemia,
2. Myeloid neoplasms associated with Down syndrome, and
3. Studies in which >75% of patients did not meet an eligibility criterion based on characteristics of the patients or the intervention, or in which the results were not reported separately for those who met the criteria.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel *recommends*" are used for strong recommendations, and "the guideline panel *suggests*" for conditional recommendations. Table 1 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Recommendations

Recommendation 1. For older adults with newly diagnosed AML who are candidates for such therapy, the American Society of Hematology (ASH) guideline panel *recommends* offering antileukemic therapy over best supportive care (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 2. For older adults with newly diagnosed AML considered candidates for intensive antileukemic therapy, the ASH guideline panel *suggests* intensive antileukemic therapy over less-intensive antileukemic therapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Recommendation 3. For older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allogeneic hematopoietic stem cell transplantation (HSCT; allo-HSCT), the ASH guideline panel *suggests* postremission therapy over no additional therapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). **Remarks:** In some settings, patients may receive 2 cycles of intensive antileukemic therapy even if they achieve remission after the first one. In those settings, the panel considered the second cycle of intensive therapy to be postremission therapy.

Recommendation 4a. For older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy, the ASH guideline panel *suggests* using either of the options when choosing between hypomethylating-agent monotherapy and low-dose-cytarabine monotherapy (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 4b. For older adults with AML considered appropriate for antileukemic therapy (such as hypomethylating agents [azacitidine and decitabine] or low-dose cytarabine) but not for intensive antileukemic therapy, the ASH guideline panel *suggests* using monotherapy with 1 of these drugs over a combination of 1 of these drugs with other agents (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). **Remarks:** For patients treated with combination therapy, the agents for which there is evidence of effectiveness are low-dose cytarabine in combination with glasdegib, based on a small randomized trial, and hypomethylating agents or low-dose cytarabine in combination with

venetoclax, based on promising data from phase 2 trials. These recommendations may change (favoring combination therapies over monotherapy) with upcoming reporting of results from randomized trials.

Recommendation 5. For older adults with AML who achieve a response after receiving less-intensive therapy, the ASH guideline panel *suggests* continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 6. For older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care), the ASH guideline panel *suggests* having red blood cell (RBC) transfusions be available over not having transfusions be available (conditional recommendation based on very low certainty in the evidence of effects). There may be rare instances where platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in end-of-life or hospice care (⊕◯◯◯).

Introduction

Aim(s) of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations for management of older adults with newly diagnosed AML, from the time of their diagnosis, through post-remission therapy, and considerations for end-of-life/hospice care. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that answer critical questions regarding managing older adults with AML, mirroring real-time practitioner-patient conversations and disease natural history. These guidelines do not address treatment in the relapsed/refractory setting. Through improved education of providers and patients regarding the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making that will result in optimal treatment decisions in older adults with AML that meet patient goals of care.

The target audience includes patients, hematologists, general practitioners, internists, other clinicians, and decision-makers. Policy makers who may be interested in these guidelines include those involved in developing local, national, or international plans with the goal of providing optimal management of older AML patients, including those no longer receiving antileukemic therapy. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem(s)

An average 75-year-old living in the United States today can expect another dozen years of life, with a 96% to 97% chance of being alive in 1 year.[12] A 75-year-old developing AML has, however, an average life expectancy measured in months, with only 1 in 5 surviving 1 year after diagnosis and 3-year survival rates of under 4%.[13] Advances in treatment, therefore, should be contextualized to this sobering reality. The prognosis for those aged 65 to 74 years is only slightly better, with most still dying in the year or 2 following AML diagnosis but up to 1 in 5 surviving to 3 years and beyond.[13] Thus, on average, being diagnosed with AML at age 65 years or older in the United States means dying a decade too soon.

Although each individual AML diagnosis in an older adult is devastating, the cumulative impact across the population is also considerable. The median age at AML diagnosis in the United States is 68 years, with >75% of cases developing in those aged 55 years or older.[14] The "baby boomer" generation, born in the period from 1946 to 1965, are currently aged 55 to 74 years and will help drive an ~50% expansion in the number of adults aged 65 years and older (over 73 million, >20% of the US population) projected to be living in the United States by 2030.[15,16] There are already >18 000 adults aged 65 years or older with AML in the United States, with associated health care costs measured in the billions of dollars. The expected demographic changes over the next 10 years make evidence-based recommendations on the optimal treatment of older adults with AML both urgent and important. Based on World Bank estimates,[17] 7% of the population of low- and middle-income countries are now aged 65 years or above, with the global proportion within this age range increasing by 50% since 1980, making the optimal care of older adults with AML a growing international concern.

The poor prognosis associated with AML in older adults is likely multifactorial, including patient, disease biology, and health system influences.[18-20] Patient factors include reduced capacity to tolerate therapy not only due to diagnosed medical comorbidities but also because of physiological, functional, and social factors associated with aging but not determined exclusively by chronological age.[21,22] It is also clear that AML disease biology differs in older adults compared with younger adults, with unfavorable genetic factors contributing to treatment resistance.[23-26] Finally, health care system factors include physician and patient reluctance to initiate therapy, with more than one-half of AML patients age 65 years or older not receiving any treatment,[27-29] and unequal access to allogeneic transplant for those achieving remission.[30]

Initial options include no treatment, hospice or supportive care only, and low-intensity, targeted, or cytotoxic therapy. Patient preferences, available support from family and friends, and any existing caregiver responsibilities may factor into decisions regarding predominantly inpatient treatment options. Given the lack of an invariably curative therapy, enrollment in a clinical trial should be considered for all patients.[19] An informed discussion between patient and physician, carefully weighing patient goals in the context of realistic expectations regarding risks and benefit,[31] to create a personalized plan is arguably the most important aspect of care for older adults diagnosed with AML. These guidelines should help with that conversation.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[5-11] The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to

meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[1-4]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided by the ASH Guideline Oversight Subcommittee, which reported to the ASH Committee on Quality. ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process, including the use of the GRADE approach. The membership of the panels and the McMaster GRADE Centre is described in supplemental File 1.

The panel included hematologists, oncologists, and internists with clinical and research expertise on the guideline topic. This included clinicians with expertise in leukemia, epidemiology, palliative medicine, and geriatric oncology. One cochair was a content expert; the other cochair was an expert in guideline-development methodology.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline-development process, including determining methods, preparing meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (www.surveymonkey.com and www.gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. The panelists received no other payments. Through the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed through disclosure, panel composition, and recusal, which were recommendations of the Institute of Medicine and GIN.[1-4] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. At the time of appointment, a majority of the guideline panel, including the cochairs, had no such conflicts. Some panelists disclosed new interests or relationships during the development process. After the clinical questions were selected and before the panel met to formulate recommendations, some panelists disclosed new interests. These new disclosures changed the balance of the panel so that a majority of the panel had direct financial conflicts of interest. To address this, and to maintain a majority of panelists with no direct financial conflicts, 3 additional panelists with clinical and methods expertise and no conflicts were appointed to the panel. None of the McMaster-affiliated researchers who contributed to the systematic reviews or who support the guideline-development process had any such conflicts.

Recusal was also used to manage conflicts of interest. During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting about individual factors (eg, magnitude of desirable consequences) and the direction and strength of the recommendation. The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2020, after the guideline panel had agreed on recommendations, it was discovered that 1 panelist had a direct financial conflict with an affected company (a meal in 2018) that had not been previously reported. Members of the Guideline Oversight Subcommittee reviewed the guidelines in relation to this late disclosure and agreed that this conflict was unlikely to have influenced any of the recommendations.

Supplemental File 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years prior to appointment; in part B, indirect financial interests were disclosed; and in part C, not mainly financial interests were disclosed. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplemental File 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel convened in February 2018 for a 1-day in-person meeting to brainstorm and then prioritize the questions described in Table 2.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[32] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach.[32] Given the variation in definition of response between studies, panel members agreed that response should broadly include components of the International Working Group criteria for response. The panel considered the outcomes listed in Table 3 as critical for clinical decision-making across questions.

Evidence review and development of recommendations

For each guideline question, McMaster researchers prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[5,6,11] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability,

Table 2. Clinical questions formulated and prioritized

Questions determined by the panel
1. Should older adults with newly diagnosed AML who are candidates for antileukemic therapy receive antileukemic therapy instead of best supportive care only?
2. Should older adults with newly diagnosed AML considered candidates for antileukemic therapy receive intensive antileukemic therapy vs less-intensive antileukemic therapy?
3. Should older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy receive postremission therapy vs no additional therapy?
4. Should older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy receive gemtuzumab ozogamicin, low-dose cytarabine, azacitidine, 5-d decitabine, or 10-d decitabine as monotherapy or in combination?
5. Should older adults with AML who received less-intensive antileukemic therapy and who achieved a response continue therapy indefinitely until progression/toxicity or be given therapy for a finite number of cycles?
6. Should older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life or hospice care) receive RBC transfusions, platelet transfusions, or both, vs no transfusions?

and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (presented in supplemental File 4) were updated on 24 May 2019, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions.

Under the direction of the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting new systematic reviews of intervention effects. Risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk-of-bias tool for randomized trials or nonrandomized studies.[33] In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences and costs, equity, acceptability, and feasibility and summarized findings within the EtD frameworks[5,6,11] Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[7-9]

During a 2-day in-person meeting, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus, based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 27 November 2019 to 20 December 2019 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. The document was revised to address pertinent comments, but no changes were made to recommendations. On 10 March 2020, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline-development process was followed, and on 13 March 2020, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary-of-findings tables in each section.

Prognosis in older adults with AML

The decision to treat a patient with AML and, if so, whether to use less- or more-intensive therapy depends in part on patient- and disease-specific factors, which together determine prognosis in AML. Of all patient-specific clinical factors, advancing age (≥60 years) at the time of AML diagnosis has been associated consistently with

Table 3. Critical outcomes for decision-making

Outcomes
Q1.
• Mortality/survival
• Quality-of-life impairment
• Functional-status impairment
• Severe toxicity
• Morphologic CR (or CR)
• Allogeneic hematopoietic cell transplantation
• Hospitalization (non–intensive care unit)
• Burdens on caregivers
Q2.
• Mortality/survival
• Quality-of-life impairment
• Functional-status impairment
• Recurrence or duration of response
• Morphologic CR (or CR)
• Allogeneic hematopoietic cell transplantation
• Severe toxicity
• Burdens on caregivers
Q3.
• Mortality/survival
• Quality-of-life impairment
• Functional-status impairment
• Recurrence or duration of response
• Severe toxicity
• Hospitalization (non–intensive care unit)
Q4.
• Mortality/survival
• Quality-of-life impairment
• Functional-status impairment
• Recurrence or duration of response
• Morphologic CR (or CR)
• Severe toxicity
• Burdens on caregivers
Q5.
• Mortality/survival
• Quality-of-life impairment
• Functional-status impairment
• Severe toxicity
• Burdens on caregivers
Q6.
• Mortality/survival
• Functional-status impairment
• Burden on caregivers
• Hospice care
• Major bleeding
• Platelet transfusion refractoriness

worse survival in cooperative group trials and in population-based studies.[26,34-38] Regardless of treatment intensity, the outcomes in older adults with AML are worse than those in younger cohorts, and the differential age-dependent responses persist when analyzed by specific cytogenetic categories, including favorable risk.[39] Long-term outcomes in older adults with AML are dismal, with 5-year survival rates of 5% to 8%.[35,37,38] The biological underpinnings for poor outcomes in older AML patients include a high prevalence of unfavorable cytogenetic abnormalities, such as monosomal and complex karyotypes[26]; increased expression of multidrug resistance (*MDR1*) genes, which encode an efflux pump that expels chemotherapeutic agents from cells[26]; reduced sensitivity to anthracyclines[24]; a higher prevalence of adverse molecular abnormalities[40,41]; and a higher prevalence (24% to 40%) of secondary AML arising from antecedent myelodysplastic syndromes or myeloproliferative neoplasms or following prior chemotherapy or radiation for a prior cancer.[38] These disease characteristics in older adults with AML confer inherent resistance to conventional chemotherapy, which translates into a higher incidence of early death, lower complete remission (CR) rates, higher rates of cytopenias with bleeding and infectious complications, higher rates of refractory disease, and inferior disease-free survival and overall survival (OS).[42-49]

Several other factors confound the treatment decision-making process in older adults with AML, including a high prevalence of significant comorbidities,[26,37,49] heterogeneity in performance status (PS),[26,37,49] and age-related decline in organ function, all factors that render older adults vulnerable to treatment toxicities and increase the likelihood of their being offered no treatment at all. A higher comorbidity burden is associated with lower remission rates, early mortality, and worse long-term survival.[50-55] In registry studies of unselected older AML patients, a higher Hematopoietic Cell Transplant–Comorbidity Index (HCT-CI) predicted an increased likelihood of not receiving chemotherapy.[49-51]

PS interacts with age to influence treatment outcomes. In contrast to the modest effect of age on the risk of mortality for patients with an excellent Eastern Cooperative Oncology Group (ECOG) PS score, those with a reduced PS (ECOG score of >2) display a worse prognosis independent of age.[37] The combination of age and PS is highly predictive of 30-day mortality after intensive induction of antileukemic treatment in older patients.[26] PS, like comorbidity, independently predicted selection of intensive chemotherapy compared with nonintensive approaches and appeared to be a better predictor of short-term survival and OS than comorbidity for patients assigned to intensive induction.[49] There is increasing evidence that frailty[56] and its composite domains, such as independence in instrumental activities of daily living,[57] cognition,[58] and gait speed,[59] are all highly predictive of survival for older patients with blood cancers, such as AML.

Concerns regarding perceived treatment intolerance in older patients with AML are thought to play a large role in the reluctance of some hematologists to endorse antileukemic therapy. Registry studies show that a substantial proportion of older patients with AML, estimated to be as high as 50%, do not receive any antileukemia therapy.[42] The reasons for undertreatment or nontreatment of older adults with AML may be influenced by perceptions of decreased benefits and increased risks of treatment in older age groups. For those for whom treatment is recommended, less-intensive therapies (such as

low-dose cytarabine or hypomethylating agents) are frequently preferred, a practice that contrasts with the findings from population registries that demonstrate a survival benefit for older AML patients with receipt of antileukemic therapy.[37,42,50] Considering the large proportion of older AML patients who go untreated despite a demonstrated survival benefit with antileukemic therapy, there is a great unmet need for specific guidelines for selecting treatments for patients based on patient-related prognostic factors, notably older age, comorbidities, and PS.

To further inform the development of these guidelines, a systematic review was done to explore the associations among age, comorbidities. frailty, performance status, functional status and mortality, and quality of life or fatigue for patients with AML 55 years or older receiving antileukemic therapy. We included observational studies in which researchers addressed this question using any type of statistical analysis and in which researchers included at least 50 patients. We considered antileukemic therapy to include both cytotoxic induction and less-intensive regimens and considered hydroxyurea in the category of best supportive care. There were 69 eligible studies. High-quality evidence showed that the risk of death was 1.17 times higher when patients 5 years younger were compared with patients 5 years older than the median age (hazard ratio [HR] [95% confidence interval per 5-year increase in age], 1.17 [1.11-1.23]).[29,56,60-72] High-quality evidence showed that the risk of death was 1.72 times higher when patients with worse performance status (ECOG score of 2+) were compared with those with better performance status (ECOG score of <2) (HR [95% confidence interval], 1.72 [1.47-2.01]).[60,64,73-83,123] There was also high-quality evidence showing that the risk of death was 1.59 times higher when patients with more comorbidities (HCT-CI score of 3+) were compared with those with fewer comorbidities (HCT-CI score of <3) (HR [95% confidence interval], 1.59 [1.28-1.98]).[54,84] Studies in which researchers assessed these associations using other methods for measuring the variables suggested similar increases in the risk of death.

Recommendations

Should older adults with newly diagnosed AML who are candidates for antileukemic therapy be offered antileukemic therapy instead of best supportive care only?

Recommendation 1

For older adults with newly diagnosed AML who are candidates for such therapy, the ASH guideline panel *recommends* offering antileukemic therapy over best supportive care (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Summary of the evidence. A total of 15 studies were included in the evidence syntheses regarding benefits and harms for identified health outcomes.[62,64,85-97] Eighteen additional studies were reviewed but excluded from the meta-analyses due to lack of data on the outcomes prioritized by the expert panel.[98-116] Given the challenges in randomizing patients to intensive or less-intensive treatments, most of the included studies were observational.[62,85,86,93,95,96] Two were randomized clinical trials (RCTs).[94,96] One study was an RCT[64] in which patients were preselected by their physicians as appropriate candidates for either intensive therapy, less-intensive therapy, or best supportive care and then randomized to their preselected conventional-care treatment or to azacitidine. Within this study, patients preselected for less-intensive therapy and then randomized to receive azacitidine or best supportive care were used for RCT data in our analyses. Data from the same study comparing intensive therapy vs best supportive care were considered observational, as patients did not undergo a formal randomization to receive best supportive care vs intensive therapy.

Eleven studies, all classified as observational, addressed the comparison between intensive antileukemic therapy and best supportive care.[62,64,85-93] These studies provided evidence for mortality and serious adverse events. Ten studies addressed the comparison between less-intensive antileukemic therapy and best supportive care.[62,64,88-90,92,94-97] These studies provided evidence for mortality, hospitalization, and serious adverse events. The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/Lfz8s2r0kpE and https://guidelines.gradepro.org/profile/Uiwz0FeE2z8.

Benefits. The panel judged that antileukemic therapy, compared with best supportive care, provides a benefit. For the comparison between intensive antileukemic therapy and best supportive care, low-quality evidence suggests that the hazard of death for patients who receive intensive antileukemic therapy may be 0.36 times that of the patients who receive best supportive care, over time (HR, 0.36; 95% confidence interval, 0.26-0.50).[62,64,85-93]

Low-quality evidence suggests that the risk of death for patients who receive intensive antileukemic therapy may be lower than that of the patients who receive best supportive care at 30 days,[62,88,89,92,93] at 6 months,[86,91] and at 1 year[64,86,87,90-92] (relative risk [RR] [95% confidence interval], 0.28 [0.14-0.58] at 30 days, 0.57 [0.45-0.72] at 6 months, and 0.69 [0.60-0.80] at 1 year).

For the comparison between less-intensive antileukemic therapy and best supportive care, moderate-quality evidence from randomized clinical[64,94,97] trials and low-quality evidence from observational studies[62,96] suggests the likelihood of a lower risk of death over time for patients who receive less-intensive antileukemic therapy than in those who receive best supportive care (HR [95% confidence interval], 0.74 [0.60-0.91] for randomized trials and 0.22 [0.16-0.29] from observational studies).

Very low-quality evidence suggests that the risk of death of patients who receive less-intensive antileukemic therapy compared with that of patients who receive best supportive care may be lower at 30 days[62,88,89,92] (RR, 0.45; 95% confidence interval, 0.25-0.81), and moderate-quality evidence suggests that it is likely lower at 6 months[94,95] (RR, 0.76; 95% confidence interval, 0.63-0.92) and 1 year[64,94] (RR, 0.85; 95% confidence interval, 0.77-0.94).

The studies not included in the meta-analyses[98-115] reported outcomes similar to those described herein.

With consideration of the quality of evidence and the thorough meta-analysis, the data presented herein confirm what many practitioners, if not patients, know from experience: that any therapy is better than no therapy if the goal is prolongation of life, even in an older, less "fit" patient cohort.[117] These studies and others demonstrate that with careful consideration by providers

regarding patients' tolerance of more- or less-intensive therapy, treatment beyond best supportive care extends survival of older AML patients. In fact, the principal cause of death in this population, even in older subjects, is disease rather than treatment-related mortality[118] or noncancer mortality. For the observational studies, the panel acknowledges the likely selection bias that contributed to benefits for those patients receiving antileukemic therapy compared with those receiving best supportive care. The panel also recognizes that the definition of a "candidate" for such therapy includes a thorough understanding and acknowledgment of patient goals.

Harms and burden. For the comparison between intensive antileukemic therapy and best supportive care, low-quality evidence suggests that the risk of febrile neutropenia is likely higher with intensive antileukemic therapy than with best supportive care[64] (RR [95% confidence interval], 1.13 [0.57-2.21]).

For the comparison between less-intensive antileukemic therapy and best supportive care, very low-quality evidence suggests that there may be an increased risk of febrile neutropenia and pneumonia with less-intensive antileukemic therapy.

Low-quality evidence suggests that hospitalization may be 2 days longer, on average, when patients receive less-intensive antileukemic therapy rather than best supportive care.[90]

In addition, patients who receive antileukemic therapy may experience more burden related to how the treatment is administered, particularly the intensive antileukemic therapy.

Contextualizing the ramifications of treatment is a critical part of the physician role in chemotherapy consent. Many patients approach therapy with apprehension, keeping in mind the classical toxicities of treatment like nausea, infection, and bleeding. These analyses demonstrate that for patients receiving either intensive or less-intensive therapy, treatment may be associated with higher rates of febrile neutropenia and hospitalizations. This finding is consistent with data showing that, even for patients with pancytopenia, severe neutropenia accompanies antileukemic therapy when either intensive or less-intensive agents are used. However, the analyses show that the magnitude of additional harm attributable to therapy is small.

Such information should inform conversations with patients. Patients who choose to be treated need to know that hospitalization or complications of therapy at some point, even with less-intensive treatment, is more likely. Though the increase in risk may be small given the inherent complications of untreated disease, careful consideration of patient comorbidities, values, and resources should guide treatment decision-making.

Protocols for the prevention and management of febrile neutropenia largely derive from patients treated intensively but are applicable to patients receiving less-intensive treatment given the validity of similar management of the same underlying disease with the same degree of adverse event, even with different provoking factors. The panel acknowledges that in unblinded studies, patients receiving antileukemic therapy and best supportive care may have also received differential management of complications, including recommendation for hospitalization.

Other EtD criteria and considerations. Three studies addressed patients' values and preferences regarding the outcomes of interest.[116,119,120] These showed that patients placed a high value on achieving CR (health state median, 0.70, on a scale from 0 to 1, where 0 is dead and 1 is totally healthy)[116] and consider relapse an outcome with a negative value (health state and utility ranged from 0.10 to 0.50 across studies).[116,119,120] The panel judged that patients are likely to place a high value on the potential benefits of the treatment, as well as on being offered treatment when there is no certainty about the benefits. There were no studies providing evidence regarding cost and cost-effectiveness that were applicable to this context. There were also no studies providing evidence regarding feasibility. One study provided evidence regarding acceptability of antileukemic therapy, suggesting that the value of the health state of receiving therapy is 0.50.[116]

The importance of patient-reported outcome research is recognized now more than ever, but there remains a paucity of information on how older AML patients view their therapeutic options and goals of treatment. Existing data illustrate that patients recognize the importance of therapeutic milestones such as CR. Furthermore, the analyses underscore the idea that patients highly value the potential for control of their disease, ranking relapse as a concern higher than no CR, indicating a preference for treatment. The studies also demonstrated that patient preferences align with clinician judgment of importance and severity of these health states.

Unfortunately, no data are available regarding the costs of treatment in comparison with best supportive care, but the costs were deemed to be significant and variable in both scenarios. Our conversations with patients should emphasize that treatment is associated with longer survival and with a decrease in transfusion burdens, cancer-related fatigue, and symptomatology. The panel also recognized that both antileukemic treatment and best supportive care are associated with logistical burdens, such as commuting to and from the physician's office or hospital and depending on others for care. Therefore, after careful discussion between provider and patient, should the patient choose antileukemic treatment, the option for treatment, more- or less-intensive, is considered beneficial over the risk of harm from the treatment.

Conclusions and research needs for this recommendation. The panel determined that there is a net benefit of antileukemic therapy over best supportive care in older adults with AML who are candidates for therapy. This recommendation places a high value on the potential benefits of antileukemic therapy over best supportive care with regard to mortality. The quality of the evidence is moderate for the comparison between less-intensive antileukemic therapy and best supportive care and low for the comparison between intensive antileukemic therapy and best supportive care. Because there is no evidence, nor a reason to believe, that less-intensive therapy is more effective than intensive therapy compared with best supportive care, the overall quality of the evidence for this recommendation is moderate.

This recommendation also places a high value on the likelihood that most patients would choose to be offered therapy and that they place a high value on the potential benefits of therapy. The potential harms and burden were considered to be small. This recommendation applies to patients who are candidates for both intensive and less-intensive antileukemic therapy.

This meta-analysis confirms what clinical experience indicates, that intensive and less-intensive chemotherapeutic treatment of AML in older patients has an OS advantage over best supportive care. This

survival advantage is coupled with an increased risk of adverse events, such as febrile neutropenia, pneumonia, and hospital length of stay with treatment, although the magnitude of these harms is small. Furthermore, health outcome research, though severely limited, indicates that patients prefer the opportunity to attain CR or cure and opt to seek treatment despite risks of treatment-related morbidity and mortality.

The decision to pursue treatment in older AML patients should be made only after careful consideration of individual patient values, availability of resources, and clinical context for treatment. However, with physician discretion, the balance of these considerations tips the scale for clinicians to comfortably consider treatment in older AML patients regardless of age and/or vulnerability, with the balance in risk/benefit shifting accordingly at extremes of age and frailty.

These recommendations are formed on the basis of often limited and uncertain evidence. Although the available data showed that patient preference and clinical perspective aligned, there is clear need for further patient-reported-outcome research. Although health care cost was considered an important factor and outcome by the panel, the analyses were void of information regarding any health care cost analysis for both treatment and best supportive care because of a lack of available data. As novel treatment options emerge for older AML patients, it is imperative that rigorous cost analyses accompany new clinical trial development.

Should older adults with newly diagnosed AML considered candidates for antileukemic therapy receive intensive antileukemic therapy vs less-intensive antileukemic therapy?

Recommendation 2

For older adults with newly diagnosed AML considered candidates for intensive antileukemic therapy, the ASH guideline panel *suggests* intensive antileukemic therapy over less-intensive antileukemic therapy (conditional recommendation based on low certainty ⊕⊕◯◯).

Summary of the evidence. There were 20 studies addressing this question, reported in 21 publications,[54,62,64,76,80,90,92,101,104,121-132] the majority of which were observational.[54,62,76,80,90,92,101,104,121-132] One study was an RCT[64] in which patients in the standard-of-care arm were preselected by their physicians to receive either intensive (induction) therapy, less-intensive therapy, or best supportive care, vs less-intensive therapy with azacitidine. For this study, for outcomes in which the researchers presented data comparing intensive therapy to azacitidine among patients preselected for intensive therapy, we used this as RCT data. For outcomes in which all standard of care was combined, we used data as observational. Studies provided data about mortality, allogeneic hematopoietic stem cell transplantation, serious adverse events, and hospitalization. The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/ccZbiHTtIRU.

Benefits. Very low-quality evidence suggests that patients who receive intensive antileukemic therapy may be at lower risk of death than those who receive less-intensive antileukemic therapy, over time (HR, 0.78; 95% confidence interval, 0.69-0.89).[62,80,90,101,104,121,124,125,129,132] Very low-quality evidence suggests that the risk of death may also lower at 1 year (risk ratio, 0.93; 95% confidence interval, 0.85-1.01).[54,62,76,90,92,104,121,123,127-129,132] Low-quality evidence suggests the likelihood that patients who receive intensive antileukemic therapy are 6.6 times more likely to receive an allo-HSCT than those who receive less-intensive antileukemic therapy (risk ratio, 6.65; 95% confidence interval, 4.13-10.71). Very low-quality evidence suggests that, counterintuitively, those who receive more-intensive antileukemic therapy may be less likely to have pneumonia (RR, 0.25; 95% confidence interval, 0.06-0.98) than those receiving less-intensive therapy, up to 2 years.[64]

The panel was limited by the lack of randomized data addressing this critical question of whether older patients considered fit for chemotherapy actually have outcomes superior to those of similar patients receiving less-intensive therapy. Historically, treatment of older adults with AML involved a subjective determination of whether a patient was considered fit for intensive chemotherapy, and if the patient was considered fit, the recommendation was generally to proceed with intensive chemotherapy.

Although fitness is still a major factor driving initial treatment recommendations, the consideration for intensive chemotherapy over a less-intensive regimen includes a more holistic assessment of the most appropriate induction regimen and is driven by the physician's assessment of disease and patient characteristics and by an analysis of patient goals in the context of anticipated outcomes with each treatment approach. For example, patients with certain adverse molecular characteristics, such as a *TP53* mutation, may not be offered intensive chemotherapy out of a belief by treating physicians that it is not likely to benefit these patients more than less-intensive approaches, such as hypomethylating agents.[133] Although those who receive more-intensive antileukemic therapy are more likely to proceed with stem cell transplant than those who receive less-intensive therapy, the difference may be due to factors influencing the decision regarding initial treatment rather than a higher success rate with intensive chemotherapy, although a higher efficacy (eg, remission) enabling transplant is quite possible.

Newly approved therapeutic approaches, including hypomethylating agents combined with venetoclax as well as targeted therapies, may increase the efficacy of less-intensive therapies (but may also increase their intensity) and thus mandate a reexamination of this question.[134] The seemingly paradoxical lower death rate, cumulative lower adverse events, and lower pneumonia rates with intensive chemotherapy from 1 study may be due to a more common, faster, or more complete return to normal hematopoiesis than was achieved with formerly (but not necessarily currently) available nonintensive therapies.

Harms and burden. Very low-quality evidence suggests that patients who receive intensive antileukemic therapy may be more likely to experience treatment-emergent adverse events, particularly during the induction phase of therapy (RR, 1.34; 95% confidence interval, 1.03-1.75),[79] and to be hospitalized for longer (mean difference, 6.84 days; 95% confidence interval, 3.44-10.24)[76] than patients who receive less-intensive antileukemic therapy. Patients who receive intensive antileukemic therapy must receive it in the hospital, which is a burden to the patients and the system compared with less-intensive antileukemic therapy.

Insofar as nonintensive chemotherapy can be administered more often in the outpatient setting, it is expected that intensive

chemotherapy, with its attendant myelosuppression and gastrointestinal toxicity requiring hospitalization, would lead to a longer time in the hospital. Moreover, many patients given nonintensive chemotherapy would not be considered intensive care unit (ICU) candidates based on personal goals of care. However, exposure to intensive chemotherapy tends to be brief compared with the indefinitely repetitive cycles of nonintensive therapy. Such ongoing therapy may be difficult for patients to tolerate psychologically, physically, and financially.

Other EtD criteria and considerations. There were 3 studies addressing patients' values and preferences regarding the outcomes of interest.[116,119,120] These showed that patients placed a high value on achieving CR (health state median, 0.70, on a scale from 0 to 1, where 0 is dead and 1 is totally healthy)[115] and consider relapse an outcome with a negative value (health state and utility ranged from 0.10 to 0.50 across studies).[116,119,120] There were 3 studies providing evidence regarding costs[54,135,136] and 1 providing evidence relevant to equity.[137] Because these 2 factors did not have an important bearing on the recommendation, their results are presented only in the EtD.

The panel appreciates the value that patients place on achievement of remission. However, we also recognize that some of the weight that patients place on these outcomes is due to how they are educated about their disease and what can be achieved with treatment. As our treatment options are increasing, the conversations with and education of patients are changing. We recommend that as new treatments are evaluated, patient-reported outcomes, quality of life, and assessment of patient goals and preferences be studied.

Conclusions and research needs for this recommendation. The panel determined that there may be a net benefit of intensive antileukemic therapy over less-intensive antileukemic therapy in older adults with AML who are candidates for intensive antileukemic therapy. This recommendation places a high value on the potential benefits of intensive over less-intensive antileukemic therapy. Even though there is low to very low-quality evidence of such benefits, there is no higher-quality evidence that less-intensive antileukemic therapy results in better health outcomes. Although values and preferences are likely to vary, it is likely that most patients value the uncertain benefits more than the uncertain harms. Intensive antileukemic therapy is an option likely to be acceptable to stakeholders where it can be implemented. Costs did not have a bearing on this recommendation.

The evidence includes patients with both intermediate and poor prognosis. Because of the way in which studies are reported, we could not separate these subgroups. Even though at the study level there seem to be no differences in outcomes between them, the panel believes that studies that explore this issue at the patient level (randomized controlled trials and observational studies with proper subgroup analyses and systematic reviews with individual patient data) may help inform this question when these recommendations are revised and updated.

Finally, the panel felt strongly that use of potentially more efficacious combination therapies that may be less intensive than traditional, "3 + 7" cytotoxic therapy, particularly those based on the addition of venetoclax, could alter these conclusions. However, supportive randomized data are not currently available, and the addition of new agents may increase the toxicity of so-called nonintensive therapies. The panel advocated for future research priorities focusing on better determination of "fitness" for intensive chemotherapy, as the panel could not clearly define a patient population "unfit" for intensive chemotherapy, despite models that have been developed to help in this determination.

Should older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy receive postremission therapy vs no additional therapy?

Recommendation 3

For older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allo-HSCT, the ASH guideline panel *suggests* postremission therapy over no additional therapy (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: In some settings, patients may receive 2 cycles of intensive antileukemic therapy even if they achieve remission after the first one. In those settings, the panel considered the second cycle of intensive therapy to be postremission therapy.

Summary of the evidence. Twelve studies addressing different postremission therapy strategies informed this question.

In 2 studies, researchers compared no postremission therapy to 1 cycle of consolidation therapy (evidence profile 1). One was a RCT in which researchers reported mortality and time to recurrence in 297 participants,[138] and another was an observational study in which researchers reported time to recurrence in 132 participants.[139]

In 1 observational study, researchers reported the outcomes for 48 patients who received 1 cycle of consolidation plus 1 cycle of postremission therapy with gemtuzumab ozogamicin or 1 cycle of consolidation therapy plus autologous HSCT (auto-HSCT; evidence profile 2).[140]

In 4 studies, 3 RCTs with 258 participants[70,141,142] and 1 observational study with 126 patients,[106] researchers compared mortality and time to recurrence between patients who received 2 cycles of consolidation therapy and patients who received 1 cycle (evidence profile 3).

In 1 RCT, researchers compared the outcomes of 6 cycles of ambulatory postremission therapy vs those of 1 cycle of consolidation therapy in 164 participants (evidence profile 4).[66]

In 1 RCT, researchers compared 3 cycles of postremission therapy with those of 2 cycles of consolidation plus auto-HSCT in 25 participants (evidence profile 5).[143]

In 1 RCT, researchers compared 3 cycles of postremission therapy with gemtuzumab ozogamicin vs no therapy in 232 participants (evidence profile 6).[144]

In 2 observational studies, researchers compared auto-HSCT vs no therapy in 503 patients (evidence profile 7).[145,146]

The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/YvrJkjrzFzs.

Benefits. Patients who receive more postremission therapy seem to do better than patients who receive less postremission therapy.

There is moderate-quality evidence that patients who receive 1 cycle of consolidation have lower mortality (RR, 0.96; 95% confidence interval, 0.89-1.03), have a longer survival time by a median of 3 months and a longer time to recurrence by a median of 1 month than patients who do not receive consolidation.[138]

Low-quality evidence suggests that patients who receive 6 months of low-dose outpatient ambulatory postremission therapy may have 0.63 times the risk of dying (95% confidence interval, 0.64-1.07) and moderate-quality evidence of borderline significance suggests that they have 0.66 times the risk of recurrence (95% confidence interval, 0.44-1) than people who receive 1 cycle of intensive inpatient consolidation therapy. There is also moderate-quality evidence that the risk of febrile neutropenia is lower with 6 cycles of low-dose outpatient ambulatory postremission therapy (RR, 0.39; 95% confidence interval, 0.30-0.52).[66]

Low-quality evidence suggests that patients who do not receive postremission therapy may have higher mortality than those who receive 3 cycles of gemtuzumab ozogamicin (RR, 1.05; 95% confidence interval, 0.89-1.24).[144]

Very low-quality evidence suggests that patients who do not receive consolidation therapy may have a higher risk of death (RR, 1.75; 95% confidence interval, 0.96-3.20) and a higher risk of recurrence (RR, 2.24) than patients who receive auto-HSCT.[145,146]

Although the data demonstrate that postremission therapy is of modest benefit for older patients who achieve CR following intensive induction chemotherapy, the best postremission strategy, in terms of both the chemotherapy regimen and treatment duration, remains to be determined. The use of allogeneic hematopoietic cell transplantation as a postremission curative therapy in older patients has increased with the development of reduced-intensity conditioning regimens, but no RCTs have compared this treatment modality to chemotherapy in older adults. This treatment modality, however, is used in a minority of patients, whereas the majority of older patients receive either chemotherapy or no postremission treatment, leaving open the question of relative efficacy. The greater part of research efforts to date related to older adults with AML has been directed at improving the induction strategy and the identification of novel agents and their addition to low-intensity or high-intensity therapy. The panel considers it a priority and an opportunity to design and conduct clinical trials that will identify the best postremission strategy/strategies.

Harms and burden. Very low-quality evidence suggests the possibility of greater harms of more postremission therapy than less postremission therapy. In addition, patients who receive more postremission therapy have the additional burden of such therapies.

The panel recommends that in addition to discussions with patients regarding prolonging survival and treatment-related mortality associated with any postremission modality, decisions about postremission treatment should include the patient's expectations in relation to the intensity of postremission therapy, the patient's social circumstances, the impact on the patient's quality of life, and the availability of family support.

Other EtD criteria and considerations. Three studies addressed patients' values and preferences regarding the outcomes of interest. These showed that patients placed a high value on being in CR (utility, 0.88, on a scale from 0 to 1, where 0 is dead and 1 is totally healthy)[120] and consider relapse an outcome with a negative value (health state and utility ranged from 0.10 to 0.50 across studies).[116,119,120] In 2 of these studies, the researchers also explored how patients accept postremission therapy and reported that the median health state attributed to consolidation therapy ranged from 0.47 to 0.70.[116,119] There was no research evidence regarding costs and feasibility.

The data support the value patients place on attaining CR and demonstrate the distress associated with the risk of disease relapse. The panel concluded that postremission therapy is a beneficial treatment approach and one that likely is acceptable to patients, their families, and health care providers.

Conclusions and research needs for this recommendation. The panel determined that there may be a benefit of postremission therapy over no additional therapy in older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allo-HSCT. The panel acknowledged that the evidence is not sufficient to make a recommendation for a specific number of cycles beyond 1 cycle. It is likely that there is little variability among patients in the value of prolonged survival and remaining in remission for a longer time. Postremission therapy is likely to be accepted by all stakeholders. The panel also recognized that maintenance therapy with a hypomethylating agent may be an alternative to or improvement over traditional consolidation therapy, based on a recent randomized study showing a survival advantage to a maintenance hypomethylating agent following intensive, induction chemotherapy.[147]

The panel highlighted the unmet need for well-conducted prospective and standardized research to inform this recommendation. The definition of "postremission" and the therapy regimens vary considerably across settings, which was reflected in the studies used to inform this recommendation. Furthermore, as novel therapies are introduced into the frontline treatment of older patients with AML, consideration must be given to the use of such agents beyond remission induction. Of particular importance will be studies to determine the comparative value of such therapies, both within and between specific patient populations.

Should older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy receive gemtuzumab ozogamicin, low-dose cytarabine, azacitidine, 5-day decitabine, or 10-day decitabine as monotherapy or in combination?

Recommendation 4a

For older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy, the ASH guideline panel *suggests* using either of the options when choosing between hypomethylating-agent monotherapy and low-dose cytarabine monotherapy (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Recommendation 4b

For older adults with AML considered appropriate for antileukemic therapy (such as hypomethylating agents [azacitidine and decitabine] or low-dose cytarabine) but not for intensive antileukemic therapy, the ASH guideline panel *suggests* using monotherapy with 1 of these drugs over a combination of 1 of these drugs with other agents (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). **Remarks:** For patients who choose combination therapy, the agents for which there is evidence of effectiveness are low-dose cytarabine in combination with glasdegib, based on a small, randomized trial, and hypomethylating agents in combination with venetoclax, based on promising phase 2 data and preliminary reports of a significant improvement in OS and CR/CR with incomplete count recovery (CRi) in a randomized trial.

Summary of the evidence. Twenty studies[64,96,101,122,125,130,148-168] informed this recommendation question. For Recommendation 4a, 3 RCTs provided evidence for the comparison between azacitidine monotherapy and low-dose cytarabine monotherapy,[64,101,130] and 1 RCT[156] and 1 observational study[155] compared the effects of low-dose cytarabine monotherapy with the effects of decitabine monotherapy. In addition, there was 1 observational study comparing the effects of low-dose cytarabine monotherapy and either 1 of the hypomethylating agents.[96] Within the category of hypomethylating agents, 3 observational studies compared the effects of decitabine monotherapy and azacitidine monotherapy.[153,159,162] We did not find any randomized data comparing 5-day and 10-day decitabine monotherapy that met inclusion criteria (though 1 study of 71 patients[169] undergoing Bayesian randomization to 5-day or 10-day decitabine monotherapy showed similar overall response rates and OS) and thus were not able to make formal recommendations about these 2 decitabine regimens. Similarly, although there were some data suggesting superiority of azacitidine to decitabine, we did not find a compelling difference between the 2 drugs, and the panel does not recommend 1 drug over the other.

For Recommendation 4b, 6 RCTs compared low-dose cytarabine monotherapy with low-dose cytarabine combination,[148-150,152,154,161] 3 RCTs compared the effects of azacitidine monotherapy with those of azacitidine combinations[151,157,158] and 1 RCT compared the effects of decitabine monotherapy with a decitabine combination.[160] In addition, 1 observational study compared the effects of low-dose cytarabine combination and hypomethylating agents.[122] The EtD frameworks for these recommendations are available online at https://guidelines.gradepro.org/profile/iwpSkokb6O4 and https://guidelines.gradepro.org/profile/53Ky1kep1dI.

Benefits. The evidence profiles present detailed results regarding how each of the interventions compares to others. Here, we focus on the benefits relevant to the comparisons for which recommendations were made. When azacitidine monotherapy is compared with low-dose cytarabine monotherapy, patients who receive azacitidine monotherapy probably have a lower risk of death over time (HR, 0.81; 95% confidence interval, 0.63-1.04)[64,103] and a lower risk of death at 2 years (risk ratio, 0.78; 95% confidence interval, 0.64-0.94) (moderate-quality evidence). The panel judged that these potential benefits particularly when considering death over time, are minimal. When low-dose cytarabine monotherapy is compared with a low-dose cytarabine combination, patients who received low-dose cytarabine may have a lower risk of febrile neutropenia (risk ratio, 0.51; 95% confidence interval, 0.25-1.03) (low-quality evidence).[150,154,161] The panel considered these benefits small in the context of largely unsuccessful combination partners.

Although the panel considered hypomethylating agents and low-dose cytarabine to be on a par with each other, certain clinical situations exist that might favor the use of 1 of the agents. For patients with adverse disease biology, including complex karyotype, history of myelodysplastic syndromes, and *TP53* mutations, hypomethylating agents are favored, as the clinical efficacy of these agents is considered agnostic to adverse biological subtypes of AML. AML with adverse biology is considered resistant to chemotherapy, thus making low-dose cytarabine less favored. Similarly, patients with a recent exposure to hypomethylating agents as treatment of antecedent hematological conditions are not likely to respond to induction with another hypomethylating agent, and cytarabine can be considered in this situation, though rigorous data supporting this approach are lacking.[170]

With regard to combination therapies, low-dose cytarabine-based combination therapies have largely not shown an important benefit compared with low-dose cytarabine monotherapy, and combinations should not be used unless there is evidence through randomized data from large phase 3 trials to support their use. Preliminary reports from the phase 3 VIALE-C trial, in which AML patients considered ineligible for intensive chemotherapy were randomized to low-dose cytarabine vs low-dose cytarabine and venetoclax, show no difference in survival for the combination vs monotherapy (a median of 7.2 months vs 4.1 months, $P = .11$). The combination of low-dose cytarabine and glasdegib was tested in a randomized phase 2 study, with a survival advantage for the combination. However, the relatively small number of patients enrolled in the study makes it difficult to generalize these data. For hypomethylating-based combinations, the compelling data showing high response rates from early-phase trials of venetoclax combined with hypomethylating agents have led to widespread adoption of this regimen. Preliminary reports from the phase 3 VIALE-A study, in which AML patients considered ineligible for intensive chemotherapy were randomized to azacitidine vs azacitidine and venetoclax, report a CR/CRi and an OS advantage to the combination (though no data have been made available at the time of this publication). These guidelines will be updated when data from phase 3 trials are formally reported. Gemtuzumab ozogamicin has been approved as monotherapy in older patients with AML. However, there are no randomized data comparing it to other monotherapy regimens. The efficacy of gemtuzumab ozogamicin is also limited for patients with adverse disease biology.

Harms and burden. There was moderate-quality evidence suggesting the likelihood that no important differences in harms exist between azacitidine monotherapy and low-dose cytarabine monotherapy. There was high-quality evidence that decitabine monotherapy results in a higher risk of neutropenia than low-dose cytarabine monotherapy (risk ratio, 1.61; 95% confidence interval, 1.16-2.27) and moderate-quality evidence that it likely results in a higher risk of febrile neutropenia (risk ratio, 1,30; 95% confidence interval, 0.96-1.75).

With regard to Recommendation 4a, the panel did not find any harm in choosing 1 regimen over the other and suggests that treatment decisions should be based on disease biology and other factors, as discussed in the previous and next sections. For Recommendation 4b, the majority of data did not favor combination therapies over monotherapy largely due to similar efficacy and the potential for more toxicity.

Other EtD criteria and considerations. For the comparison between azacitidine monotherapy and low-dose cytarabine monotherapy, the panel discussed the implementation and administration of the drugs. There was agreement that there is regional variation, with hypomethylating agents being more difficult to access in some settings but not in others, given that they have to be administered in cancer centers. The panel also discussed that the route of administration of low-dose cytarabine may be preferred by some patients, but there is no convincing evidence that this is the case. Low-dose cytarabine is likely to be less costly; however, this factor did not have an important bearing on the recommendation.

For the comparison between monotherapies and combinations, the panel discussed the costs associated with administering 2 drugs (in the case of combinations) instead of just 1 (in the case of monotherapies) when considering the lack of convincing evidence of important benefits in health outcomes based on randomized data. The panel also discussed the idea that acceptability of combination therapies may vary across physicians and patients and how several factors, including age, disease biology, and medical comorbidities, can play a role in this decision-making. Although the published data from nonrandomized phase 2 studies on venetoclax-based combinations are encouraging, long-term survival data in a randomized setting are not yet available and might have an impact on these recommendations in the future.

Conclusions and research needs for this recommendation. The panel concluded that there is insufficient evidence of important benefits in choosing between hypomethylating agents and low-dose cytarabine. In addition, the conditional recommendation for either of the options acknowledges that issues regarding disease biology, patient values and preferences, acceptability, and feasibility are likely to vary importantly across settings and that the balance of potential desirable and undesirable consequences does not favor either treatment approach.

The panel concluded that there is insufficient evidence that adding a secondary agent to any of the monotherapies results in an important benefit and that toxicity and expense need to be weighed when combination regimens are being considered. However, 2 regimens can be considered for combination therapies. Although low-dose cytarabine combined with glasdegib did demonstrate a moderate survival benefit compared with low-dose cytarabine monotherapy, the unexpectedly low CR rate in the control arm, in addition to the added costs, have to be considered against the potential benefits. Venetoclax combinations also have been approved by the US Food and Drug Administration for the treatment of older adults with AML. The panel did not consider these data in depth as part of the recommendations, because results from ongoing randomized trials, with a deeper consideration of toxicities and benefits, are still pending (azacitidine, clinical trial NCT02993523; cytarabine, clinical trial NCT03069352). The panel highlighted the need for additional randomized data regarding less-intensive approaches to treating older patients with AML, particularly for combinations that include agents targeting specific genetic abnormalities.

Should older adults with AML who received less-intensive antileukemic therapy and who achieved a response continue therapy indefinitely until progression/toxicity or be given therapy for a finite number of cycles?

Recommendation 5

For older adults with AML who achieve a response after receiving less-intensive therapy, the ASH guideline panel *suggests* continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We did not find any comparative studies addressing this question in older adults with AML. The panel used 2 sources of indirect evidence to inform the judgments regarding desirable and undesirable effects. First, 2 RCTs compared the outcomes for patients who received less-intensive antileukemic therapy with those for patients who received conventional care, including best supportive care.[64,101] In both studies, patients received at least 6 cycles of azacitidine for 7 consecutive days (each cycle was 28 days). The researchers do not describe how many patients achieved a response after a specific number of cycles (and thus, we could not determine how many cycles beyond response patients received) and report only that, overall, 27.8% of patients achieved a hematologic response (CR or CRi) in 1 study[64] and 18% did in the other study.[101]

Second, we conducted a survey among the panel members to systematically collect their experiences. The survey was based on the panelists' best recollection of experiences because it was not feasible to collect information from clinical records given the timelines for the development of these guidelines. The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/HUZFFv_yyDU.

Benefits. Based on the systematic collection of panel members' experience, there is very low certainty evidence that continuing therapy indefinitely may result in longer survival and sustained responses. The difference was estimated to be ~10% in survival up to 2 years. The panel judged that the magnitude of these benefits was moderate.

No study has prospectively demonstrated that continuing less-intensive therapy beyond best response ad infinitum provides a survival or quality-of-life advantage over stopping therapy at a defined time point after best response. Continuing less-intensive therapy beyond best response has become a de facto standard of care based, however, on the design of clinical trials in older adults with AML, in which this practice is supported, the noncurative nature of these agents, and the personal experience of providers. Anecdotally, for patients for whom less-intensive therapy was stopped following CR, relapse occurred shortly thereafter, and reinstitution of the same less-intensive therapy was unsuccessful in re-achieving CR. A survey among panel members reinforced these facts, as almost 100% of members reported continuing therapy until progression or toxicity.

Harms and burden. The collection of the panel members' experience suggested similar proportions of patients and caregivers who are perceived to experience an acceptable burden when continuing treatment.

The panel decided that the potential benefit of continuing therapy beyond best response was sufficient to justify the additional toxicities, costs, and patient and provider burden associated with the additional therapy. However, the panel acknowledged that the potential consequences of continuing therapy were not completely dismissible, estimating in a survey of panel members that 30% of patients would have a poor quality of life and 48% of caregivers would have an unacceptable burden whether therapy continued indefinitely or was finite, and urged further prospective study of the value of continuing therapy that would include these endpoints.

Other EtD criteria and considerations. There is no research evidence regarding patient values and preferences and acceptability. The panel perceived that most patients do not place a high value on the burden of treatment and care more about the potential benefits for survival. There is limited research evidence regarding costs, resources, and cost-effectiveness specific to AML in older adults. The panel discussed potential resource needs and how continuing treatment is more likely to result in more costs than stopping treatment. Continuing treatment is probably feasible, as observed in regimens that researchers gave to patients in the clinical trials that have investigated the effects of less-intensive antileukemic therapy vs best supportive care[1,2] and in the survey completed by panel members, which showed that all of them use this option most of the time.

Indirect data support the value patients place on improved OS, which outweighs even moderate toxicities of therapy. The panel felt that long-term use of nonintensive therapy is generally well tolerated and available in both community and academic settings.

Conclusions and research needs for this recommendation. The panel determined that there is likely to be a net benefit of continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy in older adults with AML who achieve a response after receiving less-intensive therapy. The conditional recommendation places a high value on the potential benefits of survival when therapy is continued indefinitely and on the acceptability of the intervention to clinicians and researchers, who seem to continue therapy as the default option. It also places a lower value on the moderate costs that are likely to result from continuing therapy indefinitely and considers there to be clinical equipoise in quality of life and functional status between these 2 strategies. Values and preferences of patients are likely to play an important role: patients who are likely to accept burden of treatment are likely to benefit more from continuing over stopping therapy. Patients who are likely to be toxicity-averse or treatment burden–averse with uncertain benefit will likely benefit more from stopping therapy.

The panel highlighted the need for prospective, adequately powered comparative studies addressing this question Such a study ideally would include randomization to continuing therapy ad infinitum vs stopping therapy at a defined time point beyond best response (eg, 3 cycles beyond best response). This is an important research, health economics, regulatory, and patient satisfaction question, as it offers the opportunity to minimize unnecessary treatment, akin to studies determining duration of anticoagulation therapy following a thromboembolic event. There was general agreement among panel members that any retrospective study attempting to show an advantage to continuing therapy indefinitely until progression or toxicity vs stopping therapy at a finite time point would likely report findings that are unreliable and not valid, as selection bias and confounding by indication for subjects included in each study arm could not be controlled for adequately.

Should older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life or hospice care) receive RBC transfusions, platelet transfusions, or both, vs no transfusions?

Recommendation 6

For older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care), the ASH guideline panel *suggests* that RBC transfusions be available over not having transfusions available (conditional recommendation based on very low certainty in the evidence of effects). There may be rare instances where platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in end of life or hospice care (⊕◯◯◯).

Summary of the evidence. We did not find any comparative studies addressing this question in older adults with AML. The panel decided to use indirect evidence, obtained from 2 published systematic reviews of the literature, neither of which was focused on older adults with AML, to inform this question.[163,164] The first systematic review focused on the effects of RBC transfusions for patients receiving palliative care.[163] The mean age of patients included in the studies ranged from 64 through 70 years, and it was specified (only in some of the studies) that the patients had terminal malignancies or advanced nonmalignant disease.

The second systematic review focused on the effects of transfusions, both RBC and platelets, in palliative-care patients with cancer.[164] The authors described the outcomes for patients of all ages, with hematological malignancies and solid tumors. The outcomes of interest were measured in different ways across studies and therefore could only be summarized narratively. For most of these outcomes, there are only noncomparative data, given that most of the studies included in both systematic reviews were case series. The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/9hbiwr14sb8.

Benefits. The evidence about benefits was obtained from case series of patients receiving RBC transfusions. Very low-quality evidence suggests that the median or mean survival after transfusion may range from 42 days to 3 months; however, 3 of the 4 studies reported a time of <50 days. There is also very low-quality evidence that transfusions may yield an improvement in well-being scores. One study reported a change from 4.2 to 5.8 and another from 3.9 to 6.0 (measured using a 10-point visual analog scale, with higher scores reflecting improved well-being). The proportion of patients for whom

an improvement in well-being was reported (by the patients themselves or the clinicians) was 65% in 1 study and 51.4% in another. Finally, there is very low-quality evidence that 70% of patients may perceive an improvement in fatigue after transfusion. The panel judged that the magnitude of these benefits was moderate.

In addition to potential improvements in well-being and fatigue, the panel determined that 1 of the most important reasons to allow transfusions for older adults with AML who are no longer receiving antileukemic therapy is that it may help facilitate timely hospice enrollment for the transfusion dependent, as many hospice programs do not allow transfusions. Moreover, the lack of evidence that such transfusions prolong life for patients at this stage argues that for patients who experience quality-of-life benefits, they are palliative and not disease focused.

Harms and burden. The studies did not measure burden on patients and caregivers or potential downsides of transfusions. The panel felt that the most important considerations were complications that may lead to hospitalization and burden but that the effects of transfusions on these were likely to be small.

The panel specifically pointed out 2 issues that should be considered when transfusion are advised for older adults with AML who are no longer receiving antileukemic therapy, following an established framework for risk consideration for transfusions. First, to initiate or continue these, patients need to show some benefit in terms of well-being. Second, patients need to understand, especially when they are in hospice, that such transfusions come with a "package" of potential downsides. This includes need to travel to clinics, potential transfusion reactions, and well-meaning but anxiety-provoking potential reassessments of goals of care by transfusion providers. Indeed, days spent in the outpatient clinic has been successfully used as a proxy for poor quality of life for older adults with AML.[125]

Other EtD criteria and considerations. There is no research evidence regarding patients' values and preferences and acceptability regarding palliative transfusion support. The panel discussed and agreed that in their experience, patients place a high value on receiving transfusions and their potential benefits. There is no research evidence regarding costs, resources, and cost-effectiveness. The panel discussed potential resource needs and implications, including resources for transfusions and potential impact on blood banks, as well as potential savings, if transfusions could be provided in hospice. Transfusions are likely to be feasible in hospice care and possibly even in the home, regardless of potential threats identified by the panel, such as systemic obstacles and the need to be hospitalized in some rural settings. Platelet transfusions have a limited role in the palliative setting and should be administered only in the setting of clinical signs of bleeding, as opposed to "treating a number."

Evidence suggests that limited availability of transfusions for patients electing hospice care stands as a significant barrier to hospice referral. In a national survey study of hematologists, more than one-half of respondents agreed that they would refer more patients to hospice care if palliative transfusion support were available.[165] Other evidence suggests that patients with leukemias who are transfusion dependent at the end of life ultimately receive lower-quality end-of-life care when they do not elect hospice care.[166] Moreover, patients with myelodysplastic syndromes who are dependent on transfusions have been shown to be less likely to use hospice care.[167] Because patients often value the palliative benefits of transfusions, and transfusion availability may be a barrier to high-quality end-of-life care for older adults with AML who are no longer receiving antileukemic therapy, efforts are warranted to explore the feasibility and benefits of transfusion support for this population when on hospice. This includes explorations of the feasibility of providing transfusions in the home. ASH has released a policy statement about the problem of transfusion support availability for hematology patients, including older adults with AML, receiving hospice care at the end of life, calling for attention to this issue.

Conclusions and research needs for this recommendation. The panel determined that there is likely to be a net benefit of making RBC and platelet transfusions available to older adults with AML who are no longer receiving antileukemic therapy. The conditional recommendation for these interventions over no transfusion places high value on the potential benefits of RBC and platelet transfusions on health-related quality of life and on how important patients and clinicians perceive these treatments to be, as well as their potential benefits. The potential burden, costs, and feasibility concerns were judged to be less important than the desirable consequences mentioned above.

The panel highlighted the need for comparative studies addressing this question. The optimal study design to inform this recommendation question is a well-designed RCT comparing the options of interest (including a no-transfusion arm) and measuring the outcomes that are important to patients (particularly health-related quality of life but also symptom burden, survival, and the quality of end-of-life care provided). One such study could compare platelet transfusions to use of, for example, tranexamic or aminocaproic acid. Observational studies in which similar groups of older adults with AML received transfusions and others did not could also be helpful.

Absent higher-quality data that answer these important clinical questions about the benefits and burdens of palliative blood product transfusions among patients with AML no longer receiving antileukemic therapy, clinicians will continue to provide care on an "n of 1" basis, doing what they think is best for the patient, in accordance with their personal values and wishes. This status quo usually means that transfusion support is the default, until there is a catastrophic event leading to sudden decline and death, or until patients and family opt to stop transfusions when it becomes too burdensome to come to the clinic to receive them. This is complicated by the fact that the feasibility and safety of home transfusions has not been well-studied in this context. As such, referrals to hospice care, which are often discouraged or delayed for patients continuing to receive palliative transfusion support, will continue to be made late or not at all. This seems unacceptable for older patients with AML, as hospice care is heralded as the gold standard way to provide high-quality care at the end of life in the United States, in the place where most Americans state they would prefer to be at the end of life: their home. Even among patients with leukemias, when they elect hospice care, the end-of-life care quality measures reflect significantly improved care. Absent more definitive evidence about the benefits of palliative transfusion support, older adults with AML will likely continue to suffer lower-quality end-of-life care outcomes compared with patients with solid tumors, as numerous studies have highlighted.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions. Much of the management of older adults with AML is based on single-arm trials or observational studies. Far more randomized trials have reported results that do not favor 1 approach compared with another than have clearly demonstrated superior outcomes for a new treatment. As the criteria for data consideration in these recommendations included and prioritized randomized studies over single-arm trials, the panel was limited in supporting certain strategies that have widespread use despite the lack of high-quality data. Consequently, these guidelines could not adequately address the use of certain molecularly targeted agents in up-front therapy for older adults with AML. There are many nuanced or controversial aspects of the management of AML in older adults that were not covered in these guidelines, either due to lack of data to make a formal recommendation, or to the guideline-development process, in which the panel winnowed down an initial list of 30 potential question to the 6 they felt most important to address. In addition, 1 question may have included a different relative balance of risk and benefit of an intervention, as enumerated in the EtD framework, than another, which may lead to the appearance of a contradictory conclusion despite a similar HR for, for example, survival. The panel considered the totality of data contributing to outcomes, such as quality-of-life impairment, functional status impairment, recurrence/duration of response, remission rates, toxicities, caregiver burden, etc in reaching its recommendations. The panel at times turned to indirect evidence to support recommendations when higher-quality studies were not available. This included surveys of panel members themselves. The panel felt strongly that recommendations still need to be given in these instances to provide guidance to practitioners for management aspects that are challenging, such as transfusion support at the end of life. These limitations should be viewed as a call to action for more rigorous studies in older adults in AML, so future iterations of these guidelines can provide higher levels of evidence for recommendations. Given the paucity of high-quality data to support strong recommendations in many instances, older adults with AML should be considered for enrollment to clinical trials whenever possible.

Finally, the panel was composed of clinicians from the United States and Canada. This was done for practical reasons regarding drug availability and approvals. ASH expects for these guidelines to be adapted for various international settings with different drug availability.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[168]

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