Advancements in the management of medically less-fit and older adults with newly diagnosed acute myeloid leukemia

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ABSTRACT

Introduction: Treating acute myeloid leukemia (AML) in older adults remains daunting. The unique biology often renders conventional chemotherapies less effective. Accurately predicting the toxicities of treatment is another unresolved challenge. Treatment planning thus requires a good knowledge of the current trial data and familiarity with clinical tools, including formal fitness and geriatric assessments. Both obstacles — disease biology and patient fitness — might be easier overcome with specific, AML cell-targeted agents rather than traditional cytotoxic chemotherapy. This may be the future of AML therapy, but it is not our current state.

Areas covered: Herein, the authors appraise the data supporting a standard induction approach, including an outline of how to predict treatment-related mortality and a review of the most up-to-date methods of geriatric assessment. They also discuss treatment expectations with less-intense therapies and highlight novel agents in development. Finally, they provide a basic approach to choosing treatment intensity.

Expert opinion: In an older and/or medically less-fit patient, treatment choice should begin with a thorough disease assessment, a formal evaluation of patient fitness and frailty. There should also be a clear communication with the patient and patient’s family about the risks and anticipated benefits of either an intense or nonintense treatment approach.

1. Introduction

In 2018, almost 20,000 people will develop acute myeloid leukemia (AML) in the U.S. alone [1]. AML remains difficult to treat [2,3] with an ongoing need for novel and more imaginative therapies. This is particularly true for less-fit, usually (but not invariably) older adults who may not tolerate intensive treatments, ironic as the median age at diagnosis is 67 years and 30% of patients are older than 75 years. Outcomes have not substantially improved in the last four decades in these patients [4–6], with recent median survival estimates of 4.5–6 months for 66–75 year-olds and 2–3 months for 76–89 year-olds found to have AML [7,8]. These analyses are impacted by the fact that many older adults with newly diagnosed AML do not receive disease-directed therapy (>50% of individuals aged >65 years and 80–90% of those aged >80 years, based on recent larger U.S. studies) [8–10], perhaps because of the presumption that treatment risks are not commensurate with potential benefits. Still, even after the receipt of some AML-directed therapy, the great majority of older patients – about 70% – will die within 1 year of diagnosis and long-term survival is rare, occurring in only about 5% of patients [4,7–9,11]. This contrasts sharply with the average expectation of a 65-year-old to live around 20 more years and a 75-year-old to live over 10 additional years [12]. With continuous population aging, the number of individuals at risk for AML will be higher for the years to come, underscoring the need for better approaches for this disease.

Disease biology and patient frailty make disease control in older patients difficult. With increasing age, the disease frequently demonstrates features associated with resistance to conventional chemotherapeutics such as adverse genetic or epigenetic abnormalities, drug transporter activity, inactivation of tumor suppressor genes, and history of antecedent hematologic disorder or prior chemo/radiotherapy [2,3,13–15]. In addition, medical fitness in older patients is remarkably heterogeneous, and accurately/reproducibly predicting who can tolerate intensive therapy has remained a challenge.

Ignoring this clinical reality, trials commonly exclude patients on the basis of age or comorbidities. Risks and benefits with any given therapy can, therefore, not easily be extrapolated to the typical patient encountered in the clinic. To complicate matters further, many older patients have unique logistical or emotional impediments to traditional leukemia treatments: an aging or dependent spouse or partner, restricted financial resources, or fatalism about the likelihood that therapy will provide benefits [16]. In this review, we will focus on the older...
Many older patients are not treated despite data demonstrating both safety and efficacy even in patients in their eighth decade. Tools exist to predict the rates of morbidity and mortality with classical induction therapy. Novel studies on the use of geriatric assessments in hematologic malignancy patients can provide patient-centered predictions for toxicity of therapy as well as interventions that can be implemented during the cytopenic phase to prevent physical decline. Cytotoxic induction algorithms have changed with several newly approved drugs, including GO, CPX-351, andenasidin. Novel approaches in clinical trials include the use of inhibitors of BCL2 and mutated IDH1 as well as antibody-based therapies. However, the latter will likely be more challenging in AML compared to ALL. The heterogeneity of the disease and of the population that develops it means that clinical trial in the future will need to be imaginative and nimble. It also underscores the importance of screening newly diagnosed patients for participation in these studies.

This box summarizes key points contained in the article.

2. Basic considerations regarding treatment approach

For younger, fit individuals, curative treatment typically starts with intensive chemotherapy (e.g. 7 + 3) and continues, if remission is obtained, with further chemotherapy and/or allogeneic hematopoietic cell transplantation (HCT) [2,3]. In contrast, in older patients, therapies less-intense than 7 + 3 (e.g. azanucleosides, low-dose cytarabine (LDAC) or supportive care alone) are often considered despite lack of randomized trials comparing more with less intensive therapy. However, even in older subjects, the principal cause of death is disease-based complications rather than treatment-related mortality (TRM) [17]. Evidence from a recent trial indicates that more than half of the early mortality with 7 + 3 is due to progressive leukemia, supporting the notion that insufficient treatment efficacy is an important contributor to short survival in older AML patients [18].

Population-based registry data from Europe and the U.S. support the use of intensive chemotherapy (vs. palliative or supportive therapy alone) in most AML patients up to age 80 [7,9,10]. Likewise, a retrospective analysis of >1,000 adults treated at five U.S. institutions showed that intensive therapy was associated with a better long-term survival than non-intensive therapy in older patients, including patients considered at higher risk for treatment complications and failure based on age, co-morbidities, and cytogenetics [19]. All these studies carry inherent risks of bias given only the fittest, or most-likely-to-respond patients may have been considered for intensive therapy and information on exact regimens, individual dose reductions, and supportive care measures is unavailable. A recent single-center retrospective study highlights the uncertainty regarding optimal treatment intensity by reporting better outcomes with azanucleosides than intensive chemotherapy in adults aged ≥70 years with nonproliferative AML and at least-as-good outcomes with lower-intensity treatment in individuals with proliferative disease [20]. Consistent with this, in the AZA-001 trial, post hoc analyses indicated a statistically nonsignificantly longer survival of patients ≥65 years when randomized to azacitidine rather than intensive chemotherapy [21].

Many times, physicians opt for nonintensive approaches with the goal of preserving a patient’s quality of life (QOL). Unfortunately, only a handful of efforts have been made to rigorously evaluate the relative effects of treatment on QOL and how patients weigh QOL relative to long-term disease control [22]. Three small randomized studies conducted over 20 years ago highlight these trade-offs. The first assigned 60 patients aged ≥65 years to either induction chemotherapy or supportive care including hydroxurea or LDAC and found a higher complete remission (CR) rate and longer survival for intensely treated patients but similar proportions of days spent in the hospital [23]. In contrast, the second reported, among 45 patients aged ≥70 years, that attenuated doses of chemotherapy – reducing daunorubicin to a single day’s dose of 50 mg/m² and giving twice daily subcutaneous cytarabine rather than five days of infusional cytarabine – resulted in similar remission rates but fewer early deaths and superior survival and QOL than higher doses of these same drugs [24]. Finally, the third showed higher remission rates with intensive chemotherapy than LDAC, but similar survival because the duration of these remissions was insufficient to offset an increased early death rate in a cohort of 87 patients aged ≥65 years; the less-intensive therapy also required less supportive care and shorter hospital stays [25]. These studies point to the delicate balance between competing positive (treatment efficacy) and negative (toxicity, hospitalization) effects and the importance of measuring QOL outcomes in clinical trials. Understanding how to optimize this balance might be ideally addressed with a randomized trial between intensive and less-intensive regimens – one that included real-world entry criteria, robust pretreatment stratification, patient-reported outcomes and, most importantly, efficacious treatment arms and a size sufficiently large to investigate differential treatment effects in various patient subsets. The latter is important because early mortality (TRM) and treatment efficacy differ widely among patients [26-28]. Needless to say, such a trial has not yet been conducted. One effort, the NCRI/MRC AML 14 trial, was designed to randomize between higher- and lower-intensity treatments, yet only 8 of 1,485 patients were randomized between the two approaches [29], indicating that there are strong, preconceived perceptions from physicians and/or patients regarding what treatment strategy might be best and, therefore, resistance to randomization.

3. Can we predict outcomes with standard therapy in older/unfit AML patients?

Being able to accurately predict both treatment toxicity and anti-leukemia activity at the individual patient level would
simplify treatment decision-making as it would inform who should receive standard therapy and who should be considered for alternative approaches. Such data could also guide discussions with patients. Available evidence suggests, paradoxically, most patients surveyed prior to intensive therapy overestimate both their risk of harm and their likelihood of benefit. A recent longitudinal study of patients >60 years at two academic hospitals assessed patients’ and oncologists’ perception of prognosis and TRM [30]. Interviewed within 72 h of consenting to therapy, the vast majority of patients reported it was at least ‘somewhat likely’ they would die from treatment. Their oncologists, on the other hand, overwhelmingly reported it was very unlikely the patient would die secondary to treatment. Once induction was completed, these same patients significantly overestimated their likelihood of cure, while physicians’ opinions reflected the poor outcomes more accurately. These data recapitulate those from a study published in 2004 [16], demonstrating that practitioners still appear to fail at communicating accurate treatment expectations to patients.

3.1. Early mortality (TRM) prediction

TRM is likely the result of numerous factors that reflect biologic (rather than chronologic) age. Several scoring systems have been developed to identify older patients suitable for intensive chemotherapy [17]. While differing in the details, the lesson learnt from these efforts is no single factor, e.g. age or performance status (PS), should be used. Rather, a combination of factors leads to most accurate prediction. One model used data from >2,200 patients to develop a ‘simplified’ score composed of 8 factors (PS, age, platelet count, serum albumin, type of AML [secondary vs. de novo], white blood cell count [WBC], peripheral blood blast percentage, and serum creatinine) [31]. An online calculator to compute this score (‘TRM score’) is available [32]. With these factors, TRM could be predicted with good, but not perfect, accuracy in patients undergoing intensive induction therapy. Of note, although >50% of the patients in the source cohort were older than age 60, it was not examined whether the model performed equally well across the subset of older patients.

3.2. Prediction of remission induction and survival

Resistance to treatment, i.e. failure to achieve CR or relapse from CR, remains the principal problem in adult AML. Most individuals want to know what their outcome expectations are if they proceed with standard intensive therapy. To this end, several large studies have examined variables to predict AML treatment outcomes. (Table 1 presents a select group of these studies.) For example, a group of German researchers analyzed just over 900 patients >60 years of age without severe comorbidities treated with two cycles of induction chemotherapy followed by postremission chemotherapy. Their aim was to develop a scoring system predicting treatment outcomes [33]. It was reported that 12% of patients died during induction and that 31% discontinued treatment prior to the second cycle of induction therapy due to death or toxicity. For individuals with intermediate-risk cytogenetics, the variables of blast percentage, WBC >20,000/µL, age >65 years, high LDH, and absence of NPM1 mutation accurately discriminated between a 3-year overall survival (OS) of 10% or 30%.

In 2014, European investigators developed and validated a prognostic model to estimate OS and disease-free survival (DFS) for patients with cytogenetically normal AML treated with intensive chemotherapy [36], utilizing PS, age, WBC count, and mutation status of NPM1, FLT3, and CAATT enhancer-binding protein alpha (CEBPA). Patients age >60 years could be stratified into low risk (9% of patients), intermediate risk (64%), and high risk (27%), with associated estimated 5-year OS of 57, 25, and 3%, respectively. Table 1 summarizes available models for predicting outcomes with intensive treatment in older adults with AML.

While such studies show patients can be stratified based on cytogenetic/molecular markers, it is important to distinguish associations between patient characteristics and treatment resistance at the cohort level, as described above, from resistance prediction at the individual patient level. We have yet to learn how to predict resistance with even moderate accuracy despite consideration of age, detailed cytogenetic/molecular data and comorbidities as well as posttreatment information (i.e. measurable residual disease [MRD] testing) at the time of CR achievement [37–40].

3.3. Need for ‘re-calibration’ of scoring systems over time

While the accuracy of prediction models for TRM and treatment resistance is imperfect even at the time of development – a limitation physicians and patients need to be aware of when utilizing these tools – it will likely further decrease over time with changes in AML care. For example, the rate of early death following intensive induction chemotherapy has declined considerably over the last 20 years because of improvement in supportive care [41–43]. Thus, TRM prediction tools need to be re-assessed and re-calibrated periodically, a task that becomes more and more difficult as death rates decline. Nonetheless, they offer an empiric approach of identifying older patients who will likely survive intensive AML chemotherapy. A second need for re-calibration may come from changes in therapy over time. While the treatment paradigm in AML has changed little between the early 1970s and 2016, the regulatory approval of four new drugs in 2017 and possible approval of additional drugs in the near future will change this paradigm. While models to predict resistance in AML may be agnostic to the specifics of the treatment to some degree, they may become outdated with the advent of novel therapies.

4. Role of geriatric assessment

As any practitioner knows, chronologic age and PS alone do not adequately reflect ‘physiologic age.’ Varying degrees of functional impairment and comorbidity render a ‘one size fits all’ approach inadequate and highlight the need for refined strategies to define ‘fitness.’ There is a clear clinical need to better define ‘fitness’ for a given therapy. One approach to defining ‘fitness’ is to identify methods that can help
<table>
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<tr>
<th>Reference</th>
<th>Study description</th>
<th>Variables</th>
<th>Model</th>
<th>Results</th>
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<td>[33]</td>
<td>Data derived from AML96 study, a trial of 909 patients with AML over the age of 60 yrs. All patients had an ECOG PS of 2 or less. Treatment included intensive induction therapy (2 cycles) and consolidation. The CR rate was 50%; the 5 years OS was 9.7%, the 30-day treatment-related mortality was 12%</td>
<td>Cytogenetics: Favorable and high-risk displayed markedly different OS times irrespective of other identified prognostic factors. Intermediate risk karyotype: subdivided into good risk and poor risk based on: CD34 expression more than 10% (+2) WBC more than 30/uL. (+2) Mutated NPM1 (−2) Age above 65 years (+3) LDH of more than 700U/L (+4)</td>
<td>Group 1: Favorable risk cytogenetics Group 2: Intermediate risk karyotype with favorable risk score (&lt;4) Group 3: Intermediate risk karyotype with favorable risk score (&gt;3) Group 4: Poor risk cytogenetics</td>
<td>3-yr OS Group 1: 39.5% Group 2: 30% Group 3: 10.6% Group 4: 3.3%</td>
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<td>[34]</td>
<td>Researchers analyzed prognostic factors derived from more than 1000 patients over the age of 60 years who were entered into the MRC AML11 trial and validated with data from the AML14 trial. Treatment included intensive induction (2 cycles) and consolidation. 1 year OS was 37–47%; 3 years OS was 15–19%</td>
<td>Multivariate analysis demonstrated significance of: Cytogenetics: favorable or intermediate (1), adverse (5), unknown (2) WBC(X 10^9/l) &lt;10 (1), 10–49.9 (2) 50–99.9 (3) 100+ (4) Age: 60–64 (1); 65–69 (2); 70–74 (3); 75+ (4) Type of AML: de novo (1) vs. secondary (3) PS: 0,1,2,3,4</td>
<td>Total score: Sum of score for cytogenetics, WBC, PS, age and AML type Good risk group: 4–6 Standard risk group: 7–8 Poor risk group: 9</td>
<td>1-yr OS (Intensively treated) Good risk group: 53–60% Standard risk group: 43–48% Poor risk group: 16–30%</td>
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<td>[35]</td>
<td>Researchers used data from two studies: AMLCG1999 and AML96 to develop and validate a web-based application to predict CR and early death in patients over 60 and who were otherwise medically healthy. Tested in 1406, validated in 801 patients. All received intensive induction</td>
<td>Key variables (pretherapeutic) Body temperature (≤38° C vs &gt;38° C) Hgm ≤10.3 vs. &gt;10.3 g/dl Platelets (≤20, &gt;28–&lt;53, 53–104, &gt;104 K/uL) Fibrinogen (≤150, &gt;150 mg/dl) LDH (&lt;700 or &gt;700) Age at diagnosis (60–64, &gt;64–67, &gt;67–72, &gt;72) Type of leukemia (de novo, secondary) Cytogenetic risk FLT3 and NPM1 mutation status</td>
<td>Web-based calculator developed – can estimate the likelihood of Complete Remission and Death within 60 days</td>
<td>CR rates from 7.6%–90.6% Early Death Rates from 6.1%–78.8% However, the statistical analysis demonstrated that even with these variables, the ability to accurately predict therapeutic resistance is relatively limited.</td>
</tr>
<tr>
<td>[36]</td>
<td>Data from 669 patients of all ages who received intensive induction therapy and had cytogenetically normal AML were analyzed.</td>
<td>Key variables: (1) Mutated NPM1 (2) Presence or absence of FLT3 ITD (3) Biallelic mutation in the CCAAT/enhancer binding protein α gene (absent, present) (4) WBC (G/L) (5) Age at diagnosis (year) (6) ECOG PS</td>
<td>Web-based calculator developed – can estimate the 5-year OS and 5-year RFS</td>
<td>5-yr OS 3%-74% 5-yr RFS 5%-55%</td>
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differentiate between those older adults who will tolerate standard therapies similar to middle aged patients (fit-no modifications) versus those who may benefit from therapies but require modification based on vulnerabilities (vulnerable) versus those for whom the risks of treatment will outweigh any benefits (frail). This approach can be helpful by providing: 1) a framework for personalized decision-making; 2) opportunities for subset selection and adaptive trial design investigating interactions between tumor and patient biology; and 3) identification of potentially modifiable vulnerabilities that can facilitate testing of supportive care interventions (i.e. physical function) to improve treatment tolerance. To adequately assess fitness, multiple characteristics, which can differ patient-to-patient, need to be accounted for and considered in conjunction with one another. Geriatric assessment (GA) is a method used to evaluate multiple characteristics in a standardized fashion (i.e. physical function, comorbidity, cognitive function, psychological state, social support, polypharmacy, and nutritional status) to fully characterize individual phenotypic complexity and optimally discriminate between fit, vulnerable, and frail patients in a given treatment context (see Table 2 for a summary of these characteristics). GA is recommended for assessment of older adults with malignancy by the current NCCN guidelines (44,45). A growing body of evidence has shown GA can predict chemotherapy toxicity and survival in a variety of tumor types including hematologic malignancies (46–49).

GA is feasible to perform during pretreatment assessment for older adults with AML, inclusive of multi-site settings (50–52), and can detect vulnerabilities, which are not routinely captured in standard testing otherwise. For example, in a single-institution observational study of adults ≥60 years scheduled to receive intensive induction for newly diagnosed AML, pretreatment GA detected the following impairments despite the patients all having been assigned ‘good’ performance status: cognitive impairment (24%), depression (26%), distress (50%), activity of daily living (ADL) impairment (34%), impaired objectively measured physical performance (31%), and significant comorbidity (40%) (50). Nearly all patients had at least one impairment, and approximately two-thirds met criteria for impairment in multiple characteristics. The cumulative effects of multiple impairments may be particularly relevant for poor treatment tolerance.

Small studies have demonstrated the added value of GA to predict outcomes for older adults with AML. These studies have shown using GA to account for patient characteristics such as physical function, cognition, comorbidity and symptoms markedly attenuates the impact of chronologic age on outcomes (51,53,54). In the abovementioned prospective study, two GA measures, objectively measured physical performance and cognitive impairment, were independently associated with OS after accounting for tumor and clinical characteristics. Physical performance was assessed using the Short Physical Performance Battery (SPPB). The SPPB is a validated measure of lower extremity function that predicts future disability, hospitalizations, and mortality among older patients with demonstrated reliability across diverse populations (55–60). Use of the SPPB as a frailty measure is recommended by

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**Table 2. Overview of geriatric assessment domains and content.**

<table>
<thead>
<tr>
<th>Geriatric assessment domains</th>
<th>Examples of domain specific content</th>
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<tbody>
<tr>
<td><strong>Physical function</strong></td>
<td>• Self-reported&lt;br&gt;- Activities of daily living (i.e. bathing, dressing, transfers)&lt;br&gt;- Instrumental activities of daily living (i.e. shopping, medication management, finances)&lt;br&gt;- Mobility (i.e. walk a city block, climb flight of stairs)&lt;br&gt;• Objectively measured&lt;br&gt;- i.e. Short physical performance battery (gait speed over 4 m, balance testing, repeat chair stands)</td>
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<tr>
<td><strong>Cognitive function</strong></td>
<td>• Cognition screen&lt;br&gt;• Capacity assessment</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td>• Number of conditions&lt;br&gt;• Comorbidity burden scale&lt;br&gt;• Compensated versus uncompensated&lt;br&gt;• Individual high risk conditions (i.e. congestive heart failure)</td>
</tr>
<tr>
<td><strong>Socioeconomic issues</strong></td>
<td>• Social support (caregivers, transportation)&lt;br&gt;• Income&lt;br&gt;• Financial constraints</td>
</tr>
<tr>
<td><strong>Psychological state</strong></td>
<td>• Depression screen&lt;br&gt;• Distress screen&lt;br&gt;• Anxiety screen</td>
</tr>
<tr>
<td><strong>Geriatric syndromes</strong></td>
<td>• Examples of geriatric syndromes&lt;br&gt;- Falls&lt;br&gt;- Delirium&lt;br&gt;- Dementia&lt;br&gt;- Failure to thrive</td>
</tr>
<tr>
<td><strong>Polypharmacy</strong></td>
<td>• Number of medications&lt;br&gt;• Potentially inappropriate medications (PIMs)&lt;br&gt;• Drug interactions</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>• Weight loss&lt;br&gt;• Body mass index&lt;br&gt;• Access to nutritional support</td>
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the European Medicines Agency [61]. The SPPB is comprised of a short walk (4 m), repeated chair stands, and balance tests. Each measure is scored from 0–4 (0 = unable to complete the test; 4 = highest performance level), with a total summed score ranging from 0–12 [56]. Cognitive function was assessed using the Modified Mini Mental State Exam, a validated screening tool to assess global cognition [62]. Patients with low physical performance at baseline had shorter OS (6.0 vs. 16.8 months). Individuals with poor cognitive function at baseline had a median OS of 5.2 vs. 15.6 months for those who scored higher on the cognitive test. Notably, chronologic age, PS, and comorbidity burden were not associated with OS. For patients who are prescreened and considered fit for intensive therapy using standard criteria, refined assessments, which capture objectively measured physical function and assess cognition, can help identify meaningful vulnerability. While the current data in AML support the SPPB as a screening tool for physical performance, alternate approaches in practice include use of gait speed alone or the Timed Up and Go Test which has been associated with mortality in hematologic malignancies (Table 3) [48,63–65]. With respect to cognition screening, shorter tools may be preferable in practice. A reasonable option would be integration of the 5-word delayed recall test into pretreatment assessment. This brief screening strategy is feasible and has demonstrated an association with overall survival among patients with varied hematologic malignancies [66]. Ongoing multi-site studies utilizing GA in AML treatment trials in the U.S. and Europe will provide important information to help refine the role of GA in research and practice.

The role of GA to predict outcomes in the nonintensive setting for older adults with AML has also been investigated to a limited extent. A multi-site observational study utilizing pretreatment GA among patients with myelodysplastic syndrome (MDS) or AML included patients who received best supportive care, azanucleosides, or intensive therapy per clinician discretion. Requiring assistance with ADLs, high fatigue score and impaired PS were independently associated with worse OS among patients receiving either best supportive care or low-intensity therapy [51]. A frailty score was created from these three variables ranging from 0 (low risk), 1–2 (intermediate) and 3 impairments (high risk). Risk scores (low, intermediate, high) were associated with median OS (774, 231, and 51 days). The frailty score did not predict survival among those treated intensively, suggesting that characteristics used to define fitness and vulnerability may differ by treatment setting. Validation of this frailty score is underway in the setting of nonintensive chemotherapy in a multi-site clinical trial in Europe [67].

Accumulating evidence demonstrates that comprehensive assessment of patient characteristics utilizing standardized measures comprised in GA can provide clinically meaningful information to assist in treatment planning. For example, a recent systematic review evaluating studies investigating geriatric assessment or frailty tools among older adults with varied hematologic malignancies found that 75% showed an association between objectively measured physical function and survival, 67% for nutritional status and 50% for comorbidity [49]. Thus, it is reasonable to incorporate enhanced assessments of physical function either with patient-reported outcomes or objective physical performance, cognition screening, standardized comorbidity burden scoring and evaluation of symptom burden into practice. Table 3 provides examples of screening tools to assess fitness or frailty studied in AML specifically and other hematologic malignancies [68]. Integration of core measures assessing fitness routinely into clinical trials and practice will be necessary to personalize treatment planning for each older adult.

5. ‘Standard’ treatment algorithm for older, fit adults with newly diagnosed AML

5.1. Conventional induction chemotherapy

While results are not as good as in younger patients, ‘7 + 3’ and similar cytarabine-based combination therapies have been considered as standard for older, fit patients [13,14,17]. Nonetheless, most remissions will last <6–12 months with such therapies [18]. Table 4 presents selected intensive induction therapies in older patients. Compared to younger patients, the value of postremission therapy is less-well established, and there is no generally accepted postremission treatment algorithm and, perhaps as another reflection of the balance between efficacy and toxicity, repeated doses of ambulatory chemotherapy may be equivalent or better than intensive postremission chemotherapy [13,14,17]. For example, in the ALFA 9803 study, French researchers randomized older patients in CR to a second induction cycle or 6 monthly courses of lower-dose anthracycline and subcutaneous cytarabine. DFS was better in the ambulatory arm [69]. Still, because of improvements in supportive care, intensive therapies can now be given more safely to older individuals. An observational study of 237 adults with newly diagnosed AML, 97 of whom were ≥60 years of age, evaluated global QOL, fatigue and physical function longitudinally over the course of one year following intensive chemotherapy and described significant improvements in QOL, fatigue and function over time among those who achieved remission. Trajectories were similar regardless of age suggesting that preservation and improvement of QOL is achievable for appropriately selected older adults with intensive chemotherapy [70].

5.1.1. Recent improvements to induction chemotherapy

The recent data suggest improvements can be achieved in some patients with addition of gemtuzumab ozogamicin (GO) to induction chemotherapy, use of high-dose cytarabine-containing regimens such as FLAG-idarubicin (FLAG-Ida), or replacement of standard induction chemotherapy with CPX-351, a liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio designed to deliver maximally synergistic drug ratios to leukemia cells.

5.1.1.1. Addition of GO to induction chemotherapy. GO, a first-generation antibody-drug conjugate consisting of a humanized anti-CD33 antibody linked to a calicheamicin derivative [74], has been tested in older as well as less-fit adults
<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
<th>Setting</th>
<th>Outcome predicted</th>
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<tr>
<td><strong>Acute Myeloid Leukemia (AML)</strong></td>
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<tr>
<td>Short Physical Performance Battery (SPPB) [53]</td>
<td>3 exam maneuvers inclusive of timed 4-meter walk, 3 timed balance tests, timed repeat chair stands. Requires &lt;5 min to administer. Each maneuver scored 0–4 with summary score 0–12. Higher scores indicate better physical performance. Training module publically available at: <a href="http://www.grc.nia.nih.gov/branches/ledb/sppb">http://www.grc.nia.nih.gov/branches/ledb/sppb</a></td>
<td>Intensive therapy for AML</td>
<td>Overall survival</td>
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<tr>
<td>Modified Mini-Mental State (3MS) Exam [53]</td>
<td>100-point cognition screen with score of &lt;77 considered impaired. In practice consider substitution of a shorter cognition screen (see 5-word delayed recall below).</td>
<td>Intensive therapy for AML</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Activities of daily living (Barthel Index) [51]</td>
<td>10-item survey of self-reported independence in feeding, bathing, grooming, dressing, continence, toileting, transfers, mobility. Scored 0–100, higher scores indicating greater independence.</td>
<td>Non-intensive therapy</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Frailty score [51]</td>
<td>Score derived from three items: 1) Barthel Index &lt;100 (self-reported activities of daily living); 2) EORTC QLQ C30 Fatigue scale &gt;50; and 3) Karnofsky Performance Status &lt;80. Score categories include 0 risk factors (low risk), 1–2 risk factors (intermediate risk) and 3 risk factors (high risk).</td>
<td>Non-intensive therapy (hypomethylating agents) and best supportive care for AML/MDS</td>
<td>Overall survival</td>
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<tr>
<td><strong>Hematologic Malignancies</strong></td>
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<td>Geriatric 8 (GB) [139]</td>
<td>8-item tool includes questions about food intake, weight loss, mobility, neuropsychological function, body mass index, number of prescriptions, self-reported health status and age. Available at <a href="http://www.sio.org/content/comprehensive-geriatric-assessment-cga-older-patient-cancer">http://www.sio.org/content/comprehensive-geriatric-assessment-cga-older-patient-cancer</a></td>
<td>Aggressive hematologic malignancies (i.e. AML, lymphoma, MDS, multiple myeloma)</td>
<td>Mortality</td>
</tr>
<tr>
<td>Geriatric Assessment in Hematology (GAH) [140]</td>
<td>30-item measure developed specifically for hematologic malignancies. Covers eight domains including medications, gait speed, mood, ADLs, subjective health status, nutrition, mental status, and comorbidity. Scoring still under development.</td>
<td>Varied hematologic malignancies</td>
<td>Responsive to clinical change in health status. Predictive utility for treatment outcomes under investigation.</td>
</tr>
<tr>
<td>Groningen Frailty Indicator (GFI) [141]</td>
<td>15-item survey that assesses physical, cognitive, social and psychological domains of frailty</td>
<td>Lymphoma</td>
<td>Early treatment termination, Overall survival</td>
</tr>
<tr>
<td>Timed Up and Go (TUG) [48,64,65]</td>
<td>Patient is asked to get up from a chair, walk a short distance (3 m), turn around and come back and sit down; Maneuver is timed and scored by number of seconds required. Time &gt;20 s considered impaired. Available at <a href="http://www.sio.org/content/comprehensive-geriatric-assessment-cga-older-patient-cancer">http://www.sio.org/content/comprehensive-geriatric-assessment-cga-older-patient-cancer</a></td>
<td>Varied hematologic malignancies inclusive of chronic lymphocytic leukemia and AML/MDS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>5-Word Delayed Recall [66]</td>
<td>Patients asked to repeat and remember five words. Recall is requested after approximately five minutes. Recall of 2 or fewer words is considered probable impairment.</td>
<td>Varied hematologic malignancies</td>
<td>Overall Survival</td>
</tr>
</tbody>
</table>

**Abbreviations:** MDS, myelodysplastic syndrome; EORTC QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ADLs: activities of daily living
Table 4. Selected trials of intensive induction in older patients.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Trial Description</th>
<th>Regimens</th>
<th>N</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[71] ALFA-9801</td>
<td>Patients between 50–70 years with de novo AML randomized to three different anthracycline doses</td>
<td>Cytarabine: 200 mg/m²/d1-7 and DNR 80 mg/m²/d1-3</td>
<td>468</td>
<td>CR</td>
<td>The CR rate was significantly higher in the standard IDA3 arm than in the high-dose DNR arm (p = .007). Patients with secondary or treatment-related disease were excluded.</td>
</tr>
<tr>
<td>[72] HOVON/AMLSG</td>
<td>SAKK Cooperative Groups Patients over 60 years with AML or RAEB (with high IPSS) randomized to low vs. high dose daunorubicin</td>
<td>Cytarabine: 200 mg/m²/d1-7 and DNR 60 mg/m²/d1-3</td>
<td>813</td>
<td>CR</td>
<td>Post hoc analysis with possible outcome improvement with high-dose arm among patients aged 60–65 years. Monosomal karyotype patients had CR rate of 34%</td>
</tr>
<tr>
<td>[80] ALFA-0701</td>
<td>Patients between the ages of 50–70 years received 7 + 3 and were randomized to low fractionated-dose gemtuzumab ozogamicin (GO)</td>
<td>Cytarabine: 200 mg/m²/d1-7 and DNR 60 mg/m²/d1-3 and Arm 1: No GO Arm 2: GO 3 mg/m² days 1, 4, and 7</td>
<td>271</td>
<td>CR/CRp</td>
<td>Patients with secondary or treatment-related disease were excluded. EFS, OS, and RFS were significantly improved with GO at 2 years in this study – this is one of the studies that prompted FDA approval of the agent. Median age was 60 and 62 years, respectively. Improved 3-yr OS and RFS in patients who received GO. Estimates of the benefit of GO were smaller in secondary disease, with high-risk MDS behaving similarly to de novo AML.</td>
</tr>
<tr>
<td>[73] MRC/NCRI AML 16</td>
<td>Patients, mostly above the age of 60 with newly diagnosed AML or high-risk myelodysplastic syndrome randomized to one of four arms, two of which included GO</td>
<td>Arm 1: DNR 50 mg/m² d1,3,5 + cytarabine 100 mg/m² BID on days 1 to 10 Arm 2: Above + GO 3 mg/m² day 1 Arm 3: DNR 50 mg/m² d1,3,5 + clofarabine 20 mg/m²/d 1-5 Arm 4: Above + GO 3 mg/m² day 1</td>
<td>1115</td>
<td>CR/CRI</td>
<td>There was no significant difference in EFS or OS. Both early death rate and 60-day mortality higher with sorafenib. Excess toxicity with sorafenib meant patients were less likely to undergo full therapy.</td>
</tr>
<tr>
<td>[91] ECOG 2906</td>
<td>Patients over 60 getting ≥ 7 + 3 (cytarabine: 100 mg/m²/d1-7 and DNR: 60 mg/m²/d1-3) randomized to sorafenib or placebo. Eligibility did not depend on FLT3 mutational status</td>
<td>Arm 1: Cytarabine: 100 mg/m²/d1-7 and DNR 60 mg/m²/d1-3 + placebo Arm 2: Cytarabine: 100 mg/m²/d1-7 and DNR 60 mg/m²/d1-3 + sorafenib 400mg BID d3 – d prior to next cycle</td>
<td>197</td>
<td>CR/CRI</td>
<td>Prior therapy for MDS with hypomethylating agents was an exclusion. Patients with intermediate risk had significantly better overall survival on standard therapy than on clofarabine (p = .001). There was no difference between the arms in unfavorable risk patients (p = .78). EPX-351 treatment resulted in superior overall survival, EFS, and CR+ response. 60-day mortality favored CPX-351 (13.7% vs. 21.2%). Grade 3–5 AEs were equal (92% vs. 91%) and were similar in frequency and severity in both arms. CPX-351 (Vyxeos) approved by FDA in 2017.</td>
</tr>
<tr>
<td>[87]</td>
<td>Patients over 60 years randomized to intermediate intensity clofarabine vs. traditional 7 + 3</td>
<td>Arm 1: Clofarabine 30 mg/m² d1-5 Arm 2: Arm 2: DNR 60 mg/m²/d1-3 + cytarabine 100 mg/m²/d1-7</td>
<td>727</td>
<td>CR/CRI</td>
<td></td>
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</table>
with AML. In early studies in which GO was given as monotherapy at 9 mg/m² typically for 2 doses 2 weeks apart, GO induced a CR or CR with incomplete platelet recovery (CRp) in up to 25–35% of patients with newly diagnosed or relapsed/refractory AML. Based on single-drug activity in patients with first relapse of AML, accelerated regulatory approval was given in 2000 by the US Food & Drug Administration (FDA) for the ‘treatment of patients with CD33-positive AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy’ [75]. A decade later, the drug manufacturer voluntarily withdrew the US New Drug Application because of the lack of efficacy and increased early deaths with GO in S0106, a randomized phase 3 trial testing the addition of GO to intensive chemotherapy that was developed to fulfill the postapproval commitment to the FDA [76].

In September 2017, GO received full approval by the FDA for the ‘treatment of newly diagnosed CD33-positive AML in adults and relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.’ This approval was largely based on results from five randomized studies testing GO together with induction chemotherapy for newly diagnosed AML [74,77]. Among the 3,325 participants of these five studies that were included in a meta-analysis of individual patient data, a significant portion of the patients was older than age 60. Overall, addition of GO did not improve remission rates with or without complete peripheral count recovery (odds ratio [OR] 0.91, 95% CI 0.77–1.07). However, the addition of GO reduced 5-year cumulative incidence of relapse and improved survival (OR 0.81, 0.73–0.90; p = 0.0001). The survival benefit was primarily seen with favorable-risk disease and, to a lesser degree intermediate-risk disease but not adverse-risk disease. For example, in the subset of patients with favorable cytogenetics, there was a 20.7% improvement in overall survival for the group allocated to GO. The improvement, still significant, was 5.7% in those with intermediate-risk cytogenetics. In exploratory analyses, the survival benefit was maintained across the entire age range. Of note, the induction regimens of the studies included in this meta-analysis differed. For example, the MRC AML15 study was one of the five trials included in the meta-analysis, and a proportion of patients in this study were treated with FLAG-Ida, a fludarabine-containing high-dose cytarabine-based backbone [27,78]. Data from this meta-analysis, and a later randomized trial [79] indicated a dose of GO of 3 mg/m² was as effective as 6 mg/m² but associated with fewer early deaths. Two of the randomized studies of GO with induction therapy specifically target older adults. French researchers, in the ALFA-0701 study, randomized patients between the age of 50–70 years, induced with 200 mg/m² of infusional cytarabine and 60 mg/m² of daunorubicin were then randomized to fractionated-dose GO. In this study, CR did not differ, but EFS and OS were improved in the GO arm. However, the median age of patients was only 60 and 62 years [80]. In the randomized phase 3 trial by the EORTC and GIMEMA consortium (AML17), patients between the ages of 61–75 were randomly assigned to induction chemotherapy with mitoxantrone, cytarabine, and etoposide preceded, or not, by GO (6 mg/m² on days 1 and 15). In remission, patients received two consolidation courses with or without GO (3 mg/m² on day 0). Treatment with GO provided no survival improvement in any prognostic subgroup, with the possible exception of patients age <70 years with secondary AML, but outcomes were significantly worse in the oldest age subgroup because of higher early mortality [81]. Together, in some older, fit adults with newly diagnosed AML, addition of GO to cytotoxic induction regimens is one strategy to reduce relapse risks and improve survival. GO is listed as one option for induction in the NCCN guidelines. Patient selection should be based on the eligibility criteria for the source trial.

5.1.1.2. Purine analogs in induction. Inclusion of purine analogs with induction therapy has long been explored as one strategy to improve treatment outcomes. Data from a randomized trial conducted in younger adults did not support value of fludarabine when added to standard 7 + 3 chemotherapy but indicated addition of cladribine (which, unlike fludarabine, has single agent anti-leukemia activity) to 7 + 3 might be beneficial [82]. Consistent with this, very recent data from a randomized trial in older adults with newly diagnosed AML indicate adding cladribine to standard induction chemotherapy can improve outcomes, at least in some patient subsets [83]. As mentioned above, fludarabine is a component of FLAG-Ida, a high-dose cytarabine-based regimen that resulted in reduced relapses and improved DFS compared to standard induction chemotherapy in a large randomized trial [27]. Less robust data are available with cladribine when used together with high-dose cytarabine, but multiple encouraging single-center experiences have been published with this combination with or without mitoxantrone or idarubicin [84–86]. A third purine analog is clofarabine, which was investigated in the ECOG-ACRIN led intergroup study, E2906. This trial compared clofarabine with 7 + 3 for patients ≥60 years [87]. This study was closed to accrual after 686 patients were randomized because survival was longer in the standard arm, effectively eliminating single-agent clofarabine from the options for newly diagnosed patients.

5.1.1.3. CPX-351. In August 2017, CPX-351 received FDA approval for ‘newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).’ Approval followed a randomized phase 3 trial against 7 + 3 [18]. The 309 enrollees aged 60–75 years were required to have therapy-related, secondary or cytogenetically high-risk AML. Patients on the investigational arm experienced higher remission rates (48% vs. 33%) and lived longer (median OS: 9.6 vs. 6.0 months). The 30-day mortality for the investigational arm was about 6% compared to 10.6% with 7 + 3. The 60-day mortality from non-AML-related causes was similar, but more deaths due to progressive disease occurred with 7 + 3 (11% vs. 3%). For the patients who went on to transplant, the survival curves separated rather distinctly. Of the 39 patients who got 7 + 3 and went to allografting, the median OS was about 10 months. In the 52 patients on the CPX arm who proceeded to transplant, the median OS was not reached. Including all clinical trials of this agent, 57% of recipients have been over the age of 65. When the FDA examined the data from all studies, no overall
differences in safety were observed between patients over 65 and younger patients, with the exception of bleeding events, which occurred more frequently in patients 65 years and older compared to younger patients (77% vs. 59%).

5.1.1.4. Tyrosine kinase inhibitors. The multi-institutional, multi-national, randomized, double-blind, placebo-controlled CALGB 10603 (RATIFY) trial tested the addition of the multi-targeted kinase inhibitor midostaurin [88] during induction, postremission, and as maintenance therapy in younger adults with newly diagnosed FLT3-mutated AML [89]. Among 717 patients aged 18–61 years at trial entry enrolled on this study, OS was significantly longer with midostaurin, as was EFS, with a benefit that was seen with FLT3/ITD, regardless of allelic burden, as well as FLT3/TKD mutations. Largely based on findings from this study, midostaurin was approved in the U.S. in April 2017 for ‘newly diagnosed AML that is FLT3-mutation positive, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.’ Of note, this approval carries no age limitation. Midostaurin could therefore be used in older adults, and providers may be tempted to do so, even though there are no published data available from randomized studies in this patient subset. While in the RATIFY trial midostaurin was well-tolerated, toxicities of tyrosine kinase inhibitors can be problematic, as evidenced by the clinical experience with sorafenib. In a multicenter randomized phase 2 trial (SORAML), addition of sorafenib to standard induction and postremission chemotherapy reduced the risk of relapse and improved EFS in younger adults despite increased toxicity in the experimental arm [90]. However, in a similar trial in older adults aged 61–80 years, addition of sorafenib did not improve survival but, rather, led to higher TRM and lower CR rates, and higher induction toxicity allowed less postremission chemotherapy in the experimental arm [91]. Unless positive data from a randomized trial become available, caution should therefore be advised with tyrosine kinase inhibitors in older adults.

5.2. Allogeneic HCT

A full outline of allogeneic transplantation in older individuals is beyond the scope of this review but is available elsewhere [92–94]. Suffice to say that reduced-intensity or nonmyeloablative conditioning regimens have extended the age range of patients suitable for allogeneic HCT to 70–75 years and perhaps older, but the recent population-based data indicate that only about 2–3% of adults with AML aged 65–74 years undergo allogeneic HCT [8,9]. As with induction chemotherapy, models that focus on factors other than age (e.g. comorbidities) have been used to select patients unlikely to incur TRM after HCT [95]. Allografting with various stem cell sources can produce long-lasting remissions, and chronologic age may not directly affect outcomes [96,97]. The exact value of HCT relative to conventional postremission chemotherapy is difficult to determine given the highly selected nature of HCT patients. Preliminary data from the CIBMTR and the CALGB revealed that, in adults ≥60 years, reduced-intensity HCT was associated with a significantly reduced risk of relapse and a trend toward longer RFS relative to conventional chemotherapy; however, HCT was associated with more TRM, resulting in similar OS [98], again emphasizing the intricate balance between disease control and TRM in this patient population. Indeed, while Markov decision analyses support the value of allogeneic HCT in intermediate and adverse-risk AML, this benefit was reduced once results were adjusted for QOL [99].

6. ‘Standard’ treatment strategies for medically unfit adults with newly diagnosed AML

For many years, LDAC served as relatively nontoxic standard regimen for older, often medically unfit, patients with newly diagnosed AML. However, CR and survival rates, while statistically significantly better than those with supportive care and hydroxyurea, are quite modest and benefit may not extend to patients with unfavorable-risk disease [29]. Today, the azanucleosides, azacitidine and decitabine, are the common off-study choices for patients judged to be too frail for cytotoxic induction therapy. An international phase 3 study randomized subjects to either decitabine 20 mg/m²/day for 5 days with either LDAC or supportive care. In that study, the CR rate for the decitabine arm was 18% with a median OS of 7.7 months. Decitabine therapy was not associated with a statistically significant improvement in OS in the planned analysis [100]. Azacitidine has also been compared with other conventional care regimens in patients over age 65 years. In 113 patients with AML and 20–30% blasts randomized to azacitidine 75 mg/m² for 7 days every 4 weeks or physicians’ choice of conventional care (supportive care-only, LDAC, or intensive chemotherapy), azacitidine was associated with longer median survival (24.5 vs. 16 months) and less time in hospital than conventional care regimens, although the number assigned to intensive therapy was too small to draw firm conclusions [21]. While both drugs are typically given in the same manner they are administered for MDS, there are some published reports of using a 10-day decitabine regimen. One study hinted that patients with TP53 mutations responded at improved rates compared to patients without this mutation with this regimen. In that single-arm study, 84 patients with AML or MDS were treated at a dose of 20 mg/m²/day for 10 consecutive days in monthly cycles. Bone marrow blast clearance occurred in 46% of patients. Neither an unfavorable-risk cytogenetic profile nor the presence of TP53 mutation was associated with a lower rate of OS than the rate of survival among study patients with intermediate-risk cytogenetics [101]. The exact role of the 10-day decitabine regimen remains unclear, however, in particular in light of preliminary data from an ongoing randomized study indicating no difference in outcomes between 5- and 10-day decitabine courses among adults ≥60 years with newly diagnosed AML [102]. Of note, in patients who have progressed on either decitabine or azacitidine, a common clinical question is whether or not they will derive benefit from changing to the alternative agent. There is scarce data for this strategy in acute leukemia. In one study of MDS patients, however, the ORR was just 20% in patients treated with
decitabine after progression or failure of azacitidine [103]. In our practices, we try to find novel therapies on clinical trial for such patients.

The role of GO in unfit adults with newly diagnosed AML is likely limited. In EORTC-GIMEMA AML-19, patients ≥61 years judged unsuitable to receive intensive chemotherapy were randomized between best supportive care or GO, 6 mg/m² on day 1 and 3 mg/m² on day 8 followed by up to 8 monthly doses of 2 mg/m². Survival was very modestly albeit statistically significantly prolonged with GO (median of 4.9 months vs. 3.6 months) [104]. However, while this regimen is listed in the package insert for GO, the outcomes may not be better than what has been observed with LDAC and are likely worse than with azacitidine [21,105]. There is also no clear evidence of benefit with GO when combined with nonintensive chemotherapy. In the only randomized comparison reported today of adults with newly diagnosed AML treated in the LRF AML14 and NCRI AML16 trials, addition of GO to LDAC almost doubled the CR rate but did not improve survival [105].

7. Novel/upcoming therapies

In 2017, the FDA approved 4 new agents for the treatment of AML. These include, as mentioned previously, CPX-351, GO, and midostaurin. Additionally, in relapsed/refractory AML carrying the isocitrate dehydrogenase-2 (IDH2) mutation [106], enasidenib (AG-221), an oral, selective, and highly potent inhibitor of mutated IDH2, was approved. In the pivotal phase 1/2, open-label, single-arm study, monotherapy with this agent at the recommended phase 2 dose (RP2D) resulted in CR in 20.2% of patients with relapsed/refractory AML [107]. Cellular differentiation appears to be the dominant mechanism of action of enasidenib, and responses were seen without reduction in IDH2 mutation burden, with a significant number of patients converting from undifferentiated to differentiated clonal IDH2 mutation-positive hematopoiesis [108]. This drug is now being tested as an upfront treatment in newly diagnosed patients with IDH2-mutated AML [109]. Even in the absence of upfront data, however, the latest version of the NCCN guidelines include enasidenib as an option for newly diagnosed patients with disease that is IDH2-mutated in whom intensive therapy is not desired [45]. Such an option provides additional incentive for molecular testing for IDH2 at the earliest diagnostic juncture.

Two promising-appearing agents currently in late-phase testing are ivosidenib and venetoclax. Ivosidenib (AG-120) is a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase-1 (IDH1) [110]. Similar to enasidenib, ivosidenib suppresses the abnormal production of the oncometabolite 2-hydroxyglutarate and leads to differentiation of AML cells [106]. Preliminary data from a large first-in-human phase 1 study indicates single-agent activity in patients with relapsed/refractory IDH1-mutated AML, with achievement of CR in 27/125 (21.6%) and CR duration of 9.3 months among patients treated at the RP2D [110] – results remarkably similar to those with enasidenib described above [107]. The selective BCL2 inhibitor venetoclax is a drug already approved for relapsed/refractory CLL with 17p deletion. While the drug has modest single-agent activity in relapsed/refractory AML [111], encouraging preliminary results are reported with venetoclax in combination with either LDAC or an azanucleoside in adults ≥65 years with newly diagnosed AML not considered candidates for intensive chemotherapy. In the latest update, 71 patients have been enrolled in the trial with LDAC [112]. A total of 26% patients achieved a CR and an additional 36% achieved CR with incomplete blood count recovery (CRI), with a median duration of CR/CRI of 14.9 months. The 12-month OS for the intention-to-treat population was 46%, with a median OS of 18.4 months in patients achieving CR/CRI. The most recent results in the trial with azanucleosides now include 145 patients [113]. In this single arm study, 67% of patients achieved either CR, CRI, or partial remission, and a median OS among all patients of 17.5 months was observed. Safety analyses from the initial cohorts have been published [114]. An international phase 3 randomized trial of venetoclax with azacitidine vs. azacitidine alone is ongoing (NCT02993523). Randomized studies will be critical in evaluating this agent, as both azacitidine and LDAC have some activity in these patients.

Another group of agents investigated in this group of patients are the histone deacetylase (HDAC) inhibitors such as valproic acid, vorinostat, panobinostat, and pracinostat. The hope of these combination trials is grounded on preclinical data demonstrating HDAC inhibitors can reactivate gene expression and promote cell-cycle arrest, differentiation and apoptosis – cooperating with azanucleosides to restore non-pathologic DNA transcription. Despite multiple trials [115–118], however, the agents have not made their way into common clinical practice. One agent that remains under investigation is pracinostat, a potent pan-HDAC inhibitor studied in MDS and acute leukemia (NCT03151304; NCT03151408).

There are a number of immunotherapeutic agents in development, though none have been approved by the FDA. In an effort to overcome some of the limitations seen with GO, vadastuximab talirine (SGN-CD33A) was developed as a novel CD33 antibody-drug conjugate employing a pyrolobenzoazepine dimer for cytotoxicity. Preclinical data showed very good activity of this agent [119], and the recent data from the phase 1 trial demonstrated single-agent anti-leukemia efficacy and acceptable safety [120]. However, a randomized, placebo-controlled, multicenter, phase 3 trial evaluating azacitidine or decitabine with SGN33A versus the azanucleoside alone (NCT02785900) was terminated early because of increased mortality in the combination arm, casting uncertainty on the future of this agent.

8. Considerations for trial design

Progress in the treatment of older and medically unfit adults with AML will require the conduct of trials that are relevant to daily practice, devoid of selection bias, account for possible subgroup effects, use meaningful, informative endpoints, and are comparative to the currently available (standard) therapy; the latter is no simple task now that we have several new AML drugs approved and supportive care measures constantly improve. Important considerations for drug evaluation in this patient population have been reviewed before [17,121]. Among the many challenges besides the choice of control
group, foremost may be the risk of selection bias. AML patients enrolled on clinical studies tend to have better PS and organ function and more favorable disease characteristics than other patients [122]. Stringent eligibility criteria, as often used in trials even when targeting patients ‘not considered candidates for intensive chemotherapy,’ will select subsets of older patient with significantly better survival expectations than other patients of the same age [6], complicating (or eliminating) the ability to extrapolate findings to the intended target patient population at large.

Especially, now that we see a rapidly increasing number of drug candidates entering the clinic, timely identification and validation of beneficial drugs is critical. This is problematic given the length and cost of the traditional drug development process that relies on ‘promising results’ from early phase, single-arm studies as the foundation of late-phase randomized studies. These, in turn, are often nonconfirmatory [121]. This drug testing paradigm is particularly inefficient when therapies need to be tailored to patient subsets, as will become increasingly common with use of targeted therapies in AML [123]. Platform trials have been developed as a long-lived, versatile screening tool to accelerate drug testing and limit patients’ exposure to inactive or harmful therapies [124]. One recent example of such a platform trial for less-fit older adults with AML in North America is S1612 (NCT03092674), a trial with participation of the Network Groups of the U.S. National Cancer Institute (NCI) National Clinical Trials Network (NCTN) conducting trials in adult leukemia (ALLIANCE, ECOG-ACRIN, and SWOG) and the Canadian Cancer Trials Group (CCTG) [125].

Most trials in older and unfit patients with AML focus on efficacy as primary endpoint, e.g. CR rates or, perhaps more desirably but less commonly, survival measures such as EFS, RFS, or OS [17,121,126]. So far neglected are endpoints of QOL, which as alluded to before are greatly impaired in AML patients on many levels [127–129] and may be the most important consideration along with life expectancy. Unfortunately, the lack of validated measures of QOL specific to AML and methodological limitations has hampered the use of such endpoints [22] although they can lead to drug approval in the U.S. [126]. An AML-specific QOL instrument is currently under development [130] and hopefully will spur inclusion of QOL measures as endpoint in future clinical trials.

9. Conclusion

Even with novel agents, the overall outcomes for patients over the age of 60 with AML remain woefully inadequate. Some have even advocated abandoning cytotoxic agents altogether in this age group [131] unless good risk features are present. Unfortunately, such a step requires that we have a much better set of alternative therapeutic options than the currently existing ones. Until that time, practitioners and their patients need to understand the expectations of both a standard induction and palliative approach and how to engage in clinical trials wherever possible.

10. Expert opinion

Older and/or unfit patients with AML present unique challenges when choosing a treatment regimen. All too often, in the older patient, little or no therapy is offered – perhaps due to a shared sense of therapeutic nihilism. The fundamental argument of this paper and of our practice is that age alone should not be the deciding factor in choosing the type of AML therapy. Rather, a thoughtful, tailored approach may mean that more patients have a chance to achieve the duration and quality of life benefits that accompany optimal therapy. We have provided, in Figure 1, an overview of how we approach decision-making with patients.

In our practices, we approach newly diagnosed older adults with AML with three initial questions: what is the likelihood that their disease will respond to therapy, what is the likelihood that they can tolerate an intensive treatment, and, following a careful discussion of risks and benefits, what are the patients’ wishes? The initial assessments should precede the last, as counseling patients and their families with data appropriately allows for more realistic expectations. We have provided an attached algorithm that attempts to summarize our approach utilizing disease-related and patient-related factors.

Upon diagnosis, disease should be assessed with a bone marrow biopsy, fluorescence-in situ hybridization for evidence of both good-risk and poor-risk cytogenetic features, and, as soon as possible, molecular testing. There is adequate support from the NCCN and the ELN for molecular testing of NPM1, FLT3, CEBPA, RUNX1, IDH2, TP53, and ASXL1 for prognostic markers and for targeted therapy although the prognostic value, at least for some of the markers, may be less pronounced in older individuals [132]. The ability to preserve blasts may allow DNA testing for additional mutations in the future. While these mutations may be available as a send-out panel, we typically find that local institutional assessment of at least NPM1, FLT3/ITD, and TP53 mutations may be quicker and allow for pretreatment assessment. We perform a bone marrow aspirate on all patients but can sometimes obtain earlier results by sending FISH on the peripheral blood at presentation. Simultaneously, an assessment of PS using accurate information from the patient and the patient’s family should be performed.

While we work up disease characteristics, we test for cardiac function, if not otherwise available, and have a geriatric assessment performed. This can be done through consultation with a geriatrics service or by the primary oncologist/team. While there is no gold standard approach for performing a more comprehensive patient assessment, multiple tools are available which can identify clinically relevant vulnerabilities and/or characterize frailty in a given treatment context. At a minimum, additional assessment of physical and cognitive function are important to inform risks and benefits of therapy. We also use on-line calculators to assess TRM and itemize comorbidities using either of the most commonly used indices the Charlson Co-morbidity Index or the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI). Both of these indices have been studied in AML patients [133,134]. In a retrospective study of 177 patients over age 60 getting induction chemotherapy, patients with HCT-CI scores of 0 had an early death rate of 3%, those with scores of 1–2 had an early death rate of 11% and 29% of those with a score of 3 or higher died within 28 days of initiating therapy. The OS was 45, 31, and 19 weeks, respectively [134]. Notably, these studies are more than 10 years old and, therefore, do not account for improvements in supportive care. Thus, screening for comorbidities should be performed alongside TRM calculations as
Figure 1. We generally approach patients with a three-question model. Can the patient tolerate intensive therapy; will the patient’s disease respond to therapy; does the patient desire intensive therapy? As indicated in the text of the article, we often try to answer the first two questions prior to consenting the patient, as this background can provide a better foundation for a shared decision-making model. The first question can be approached by geriatrics assessment, calculation of performance status, TRM as well as use of a published comorbidities index like the HCT-CI or the Charlson CI, as outlined in the text. With regard to the likelihood of disease response, one can use published data on prognostic models (see Table 1) or use the risk stratification as outlined in the ELN or NCCN guidelines. The top part of the algorithm reviews considerations for the treatment of patients with good-risk or intermediate-risk disease as delineated by the NCCN or ELN risk stratification guidelines. In these patients, we tend to favor an intensive approach unless there are clear contraindications due to patient health status or desire. The lower part of the algorithm reviews consideration for the treatment of patients with poor-risk disease delineated by the NCCN or ELN risk stratification guidelines. In these patients, if they are fit and desire induction therapy, we recommend a clinical trial or consideration of CPX-351, if supported by the indications in the FDA approval.
part of routine clinical practice and should be contextualized for the patient during consent discussion.

Once we have as much information as possible about the disease and patient characteristics, we then present to the patient (and family) the likelihood of disease response and the likelihood of treatment-related or early mortality. It is in that context that we frame our recommendations for intensive vs. less-intense induction. For example, in a patient with intermediate risk cytogenetics, low predicted TRM and a HCT-CI less than 3, we would advocate, in consent discussion, for a more intensive induction, either on a clinical trial of intensive induction or with a combination of cytarabine and anthracycline. In this patient, we would also recommend an evaluation for allogeneic HCT in first CR. In this same patient, if intensive induction was not consistent with their wishes, then we recommend a clinical trial of less intensive therapy with the understanding that if the disease progresses, or fails to respond, we would re-introduce the option of intensive induction therapy.

In a patient with disease anticipated to be less responsive to treatment, we are more circumspect with recommendations for intensive therapy. In fit patients with poor-risk disease features, we discuss available clinical trials for less intensive therapy and weigh that against the outcomes of intensive induction therapy with, for example, CPX-351. In this setting, given that randomized studies are not available, we carefully explore the patient’s wishes and try to use a shared decision-making model. We consider whether or not allogeneic HCT is a feasible or desirable next step (i.e. is transplant something that the patient could realistically undertake?). If so, that may tip the balance in favor of intensive induction therapy.

In the end, we tell our patients we have no firm data to support an intense vs. less-intensive approach, which is one of the more difficult parts of the care of these patients. This is what should spur us on, as a community, to improve on the availability of imaginative, safe and efficacious new agents in this devastating disease.

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   - Excellent concise review of AML by leaders in the field.
   - State-of-the-art recommendations for assessment, classification, and treatment of adults with AML.
   - Together with reference #7, provides important insight into AML on the population level.
   - Together with reference #6, provides important insight into AML on the population level.
   - Population based study highlighting the large proportion of older adults for whom no therapy is administered; this study makes clear the magnitude of treatment and outcome disparity by age.
   - Population based study highlighting the large proportion of older adults for whom no therapy is administered; this study makes clear the magnitude of treatment and outcome disparity by age.
   - based on November2016 SEER data submission, posted to the SEER web site, April 2017.
   - Comprehensive review of the management of AML in older adults.
   - Comprehensive review of the management of AML in older adults.


22. Randomized trial of azacitidine versus conventional care which has influenced practice.


25. One of the few studies randomizing older patients to intensive vs. non-intensive induction.


30. Large randomized study showing superior anti-leukemia efficacy of FLAG-Ida versus conventional induction chemotherapy.


32. Perez of the few studies randomizing older patients to intensive vs. non-intensive induction.


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