Published in final edited form as:

Curr Hematol Malig Rep. 2015 June ; 10(2): 118–125. doi:10.1007/s11899-015-0257-2.

Elderly acute myeloid leukemia: Assessing risk

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Abstract

Treatment of older adults with acute myeloid leukemia (AML) is challenging in part due to the difficulty of accurately predicting risks and benefits of available therapies. While older patients represent the majority of those with newly diagnosed disease, there remains no consensus regarding optimal therapy. Older age is associated with increased risk of treatment-related toxicity and worse survival compared to younger adults. Age-related outcome disparity in the setting of AML therapy is clearly attributed in part to differences in tumor biology conferring resistance to therapy. However, physiologic changes of aging that decrease treatment tolerance also influence outcomes and vary among patients of the same chronologic age. Measurable patient characteristics such as comorbidity and physical function can reflect the heterogeneity of physiologic aging among older patients and help predict resilience during and after the stress of diagnosis and treatment. To improve outcomes for older adults with AML it will be critical to investigate the predictive utility of patient characteristics in parallel with tumor biology to improve decision-making, inform trial design, and identify actionable targets for supportive care interventions. This review will focus on available data addressing risk assessment for older adults treated for AML with a focus on patient characteristics that may reflect vulnerability to poor treatment tolerance.

Keywords

acute myeloid leukemia; elderly; geriatric assessment; fitness; older

Introduction

Most patients diagnosed with AML are over age 65 years yet optimal treatment strategies for older adults remain unclear(1). Uncertainty regarding therapy stems from concerns regarding the efficacy and tolerability of available treatments among older adults. When compared to middle-aged individuals treated for AML, older adults (usually defined by age 60 or 65 years) experience increased treatment-associated morbidity and shorter survival. Age-related differences in tumor biology are a major factor influencing treatment

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Conflict of Interest

Dr. Heidi Klepin declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

outcomes for older adults. However, physiologic changes of aging which decrease resilience during the stress of treatment also impact outcomes for older patients. Many of these changes are manifest in the inherent phenotypic complexity of older adults presenting with comorbidity and functional impairments. Some of the implications of physiologic aging are more difficult to measure including effects of aging on drug metabolism and the interaction between the aging microenvironment and the tumor itself. It is clear, however, that both tumor biology and physiologic reserve vary widely among patients of the same chronologic age requiring individualized assessment strategies.

To maximize outcomes for individual older adults it is necessary to identify those measurable patient characteristics that can predict physiologic reserve capacity in the context of a given treatment strategy. Similar to risk stratification applied to tumor biology, categories of fit (similar treatment tolerance to middle-aged patients), vulnerable (at higher risk for toxicity), and frail (likely to experience significant toxicity) can be developed. This information, in combination with increasing knowledge of tumor biology, can inform patient-centered decision-making, novel trial design, and optimize supportive care during and after therapy. This review will highlight existing data regarding patient characteristics which influence treatment outcomes, including the role of geriatric assessment in this context.

The age controversy: Outcomes and treatment patterns for older adults with AML

Optimal treatment for older adults with AML remains controversial due to the dramatic age-related outcome disparities seen in both population-based data and clinical trials. Estimates of treatment-related mortality range from 10–30% in many clinical trials(2–6). Survival from diagnosis decreases dramatically from middle age to late life. For example, data from the Surveillance End Epidemiology End Results (SEER) show 5-year survival rates from the time of diagnosis declining from 39% to 8.5% to <2% for people <65, 65–74, and 75 years of age respectively(1). Concerns regarding the poor efficacy and high toxicity associated with therapy have resulted in fewer than 40% of newly diagnosed adults 65 years of age receiving any chemotherapy for AML in the United States(7).

Despite poor outcomes in aggregate, data from both population registries and clinical trials have shown that intensive therapy can improve survival for selected older adults(4, 5, 7–9). For example, data from the Swedish Acute Leukemia Registry inclusive of 998 patients 70–79 years of age diagnosed between 1997–2006 showed a survival advantage for intensive versus palliative therapy in this age group regardless of performance status(10). A landmark randomized trial comparing intensive induction to supportive care alone demonstrated a small but measurable improvement in survival for patients 65 years of age(4). Survival has improved over time in both registry data and clinical trials although to a greater extent among younger patients compared to older adults(1, 7, 11–14).

Few studies have characterized the impact of induction therapy on patient-centric outcomes such as quality of life, functional status, emotional well-being or health care utilization specifically among older patients. These outcomes are not routinely collected in clinical

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trials to help inform decision-making. Alibhai and colleagues have investigated the impact of intensive therapy on quality of life and functional status among older adults. In a small prospective study of 65 adults ≥ 60 years of age self-reported quality of life and functional status (activities of daily living) did not appear to differ significantly in survivors over 6 months between patients receiving intensive versus palliative therapies(15). A more recent study (N=103) suggests the impact of intensive induction on quality of life and objectively measured physical function is similar among younger and older adults(16). While these studies are small they represent an important area of research and suggest that for selected older adults chronologic age alone may not negatively impact quality of life or functional status during survivorship.

Individualizing risk prediction

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Rather than making treatment decisions based on chronologic age and aggregate outcomes, treatment decisions should be individualized. Ideally, data collected in a pre-treatment evaluation should help inform who is fit (i.e. expect similar treatment tolerance to middle-aged individuals) versus vulnerable (i.e. at higher risk for clinical or functional decline that may mitigate some of the treatment benefit) versus frail (i.e. likely to experience significant toxicity with resultant low probability of benefit). This information can be used in several ways. First, it is necessary for an informed patient-centered treatment decision. Second, it can inform clinical trial designs targeting specific subsets of patients for novel therapies or including fitness characteristics in adaptive trial designs investigating subsets of patients who benefit more or less from given therapies. Finally, it can provide specific targets for supportive care interventions to improve treatment tolerance for older adults.

Prognostic models: Improving outcome estimation for older adults

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Several prognostic models have been developed from clinical trial data to improve pre-treatment risk stratification specifically for older adults with AML. Using algorithms derived from these models demonstrates a wide range of outcome estimates for older patients treated with induction therapy. For example, estimates of early mortality range from 16% to 71%, complete remission rates range from 12% to 91%, and 3-year survival ranges from 3%–40% depending on presence of specific risk factors. Kantarjian et. al showed that age>80, complex cytogenetics, ECOG performance status >1, and creatinine >1.3mg/dl were predictive of 8-week induction mortality for patients ≥ 70 years(6). Presence of risk factors ranging from none (28%), 1 (40%), 2 (23%) and ≥ 3 (9%) were associated with 8-week mortality rates of 16%, 31%, 55%, and 71% respectively. Rollig et al. identified age, karyotype, NPM1 mutational status, white blood cell count, lactate dehydrogenase (LDH) levels, and CD4 expression as risk factors associated with overall survival and categorized patients into 4 groups with 3-year OS ranging from 3.3% to 39.5%. Krug et al. identified body temperature, age, secondary leukemia or antecedent hematological disease, hemoglobin, platelet count, fibrinogen and LDH as variables predictive of complete remission rates ranging from 21–80%. These risk factors have been used to develop a web-based application for ease of use in clinical practice. Malfuson et. al developed a decisional index to inform survival after intensive induction therapy which included high-risk

cytogenetics and/or presence of at least two of the following variables: age ≥ 75 years, ECOG performance status ≥ 2 , and white cell count $\geq 50 \times 10^9/L$.

Each of the proposed models provides important information to help individualize treatment outcome expectations for specific patients. One limitation of these data is the reliance on chronologic age as the primary measurable patient characteristic. Chronologic age is in part a surrogate for other measurable patient characteristics such as comorbidity, physical function, cognition, and nutritional status which can vary widely among individuals of the same chronologic age. These variables may confound the impact of age on outcomes but with the exception of oncology performance status scales are not routinely measured in most clinical trials. Addition of measured patient characteristics to existing models may further refine risk stratification estimates.

Individualizing patient assessment: Deconstructing chronologic age

Physical Function

Assessment of physical function is critical to prediction of treatment tolerance. Physical function in oncology is typically estimated using a performance status scales (Eastern Cooperative Oncology Group [ECOG] or Karnofsky performance status [KPS]). Multiple studies have shown that older adults with poor performance status at the time of treatment are more likely to experience toxicity associated with treatment and are less likely to derive benefit (2, 6). The prognostic importance of poor performance status appears increase with higher chronologic age (2). Clinical trial data from the Southwest Oncology Group suggests that 30-day mortality rates are similar for adults with increasing age in the setting of excellent performance status (ECOG 0). However, rates of 30-day mortality during induction therapy increase dramatically with age for those patients who have a poor performance status (ECOG 3) at the time of diagnosis; for patients aged 56–65, 66–75, >75 rates of 30-day mortality were 29%, 47% and 82%, respectively (2). Similarly, overall survival also declines with worse performance status at the time of diagnosis and treatment. In a study of 998 older adults treated intensively, one year survival rates were at 35 percent, 25 percent and 7 percent for adults with an ECOG performance status of 1, 2 and 3 respectively.

Oncology performance status scales when applied to older patients are useful in identifying those who are frail. However, they are suboptimal to help differentiate between patients with clinical vulnerability and those who are fit. This is due in part to subjectivity of the scales as well as a lack of task-specific questions to enhance sensitivity. More refined measures are needed to better estimate treatment tolerance associated with physical function. The addition of simple task-specific questions may improve assessment of physical function at the time of diagnosis. For example, questions regarding a patient's ability to perform basic activities of daily living (ADLs) or instrumental activities of daily living (IADLs), which are necessary for living independently at home or in the community, can be useful. A prospective study of 63 adults with newly diagnosed AML suggested that impairment in IADLs was associated with decreased overall survival independent of age and KPS (17). Simple questions regarding activities such as shopping, managing finances, housekeeping and taking medications could add information to data gathered from KPS. Similarly, a multi-site study

investigating pretreatment geriatric assessment among older adults with newly diagnosed MDS or AML found that those patients requiring assistance with the most basic activities of daily living experienced shorter survival independent of age, cytogenetic risk or KPS(18). Finally, in a retrospective study of 101 adults 65 year of age with newly diagnosed AML, patients who reported difficulty in strenuous activities (i.e. lifting a heavy shopping bag) on a quality of life questionnaire had a two fold increase in risk of death compared to those reporting less difficulty independent of tumor biology, ECOG score, comorbidity and treatment type(19). Taken together these data suggests that simple questions regarding specific activities may provide additive information to oncology performance status assessment and could be readily incorporated into clinical practice.

However, optimal assessment of physical function for older adults with adequate performance status (ECOG 0-2) may be best assessed with objective measures. Even task-specific self-report questions are subject to bias and may not be the most sensitive measures of functional reserve capacity. In a single institution study of older adults treated with intensive therapy significant physical impairments were detected among patients with an ECOG 1. Specifically, 48 percent required some assistance with activities of daily living and 54 percent had impairment in objectively assessed physical performance(20). The physical performance measure utilized was the validated short physical performance battery (SPPB) that includes a timed 4 meter walk, chair stands and balance testing which is scored from 0 (worst) to 12 (best)(21–23). This measure has been shown to predict disability, hospitalizations and mortality among elderly patients without AML. Importantly a SPPB score less than 9 was associated with a shorter median survival (6.0 versus 16.8 month) in this intensively treated cohort of older adults with AML. The association of baseline SPPB score with survival was independent of age and cytogenetic risk group. The SPPB can be performed by a trained nurse either in the inpatient or outpatient setting and training modules are publically available on-line. While these results require validation it is reasonable to consider incorporation of the SPPB or similar objective physical function testing in pretreatment evaluations of older adults, particularly among those with good ECOG performance status.

Comorbidity

Older AML patients often have comorbidity (18, 19, 24–27). For example, a study using population data (SEER) including over 5000 adults diagnosed with AML (median age 78) showed that half had atleast one major comorbidity based on claims data(7). Despite this, many multi-site AML treatment trials do not consistently capture or report upon comorbidity. This limits the evidence base to smaller studies and population-based data. Comorbidity burden is often measured using standardized indices. The most commonly used indices are the Charlson Comorbidity index (CCI) and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI)(28, 29). Many studies of older adults with AML have shown a relationship between increased comorbidity burden (measured by CCI or HCT-CI) and worse outcomes including decreased remission rates, increased risk of 30-day mortality and worse overall survival (OS) (18, 24–26, 30, 31). Several studies, however, have not shown such a clear relationship (27, 32, 33). Cross study comparisons are limited

due to the heterogeneity of populations studied with differences in patient selection and treatment received.

Studies investigating the predictive value of comorbidity burden specifically among older adults treated intensively have typically shown an association with outcomes. Etienne et al. retrospectively analyzed 133 older adults (age ≥ 70 years) treated intensively and showed an association between pre-treatment CCI and lower remission rates(25). Studies using the HCT-CI, which includes additional conditions compared with the CCI, have shown an association of higher comorbidity scores with early mortality and shorter survival. For example, in a study of 177 patients ≥ 60 years who received induction chemotherapy, the HCT-CI score was 0 in 22%, 1 to 2 in 30%, and ≥ 3 in 48%, corresponding to early death rates (3%, 11%, and 29%) and OS (45, 31, and 19 weeks, respectively)(26). Similarly, HCT-CI score ≥ 3 was associated with shorter survival among 416 older adults enrolled on an intensive therapy trial (ALFA-9803)(34).

Available evidence and clinical experience would support screening for major comorbidity as a method for identifying frail older adults during a pre-treatment evaluation. Either the CCI or HCT-CI is a reasonable choice. Inclusion of comorbidity indices routinely in clinical trials would inform risk prediction for older adults who are considering specific therapeutic options. Available data does not clearly inform how to tailor treatment or supportive care in the setting of comorbidity. The prognostic implications of many individual comorbid conditions are still largely unknown. Research focused on the risk attributable to individual comorbid conditions may be helpful in design of supportive care interventions to improve treatment tolerance.

Cognition

The prevalence of cognitive impairment increases with age and is often unrecognized. Cognitive impairment in the setting of a new AML diagnosis could represent preexisting mild cognitive impairment, early dementia, or delirium. Any of these conditions may increase the risk of complications during and after intensive therapy for AML. While data are limited, available evidence suggests cognitive impairment is prevalent among patients receiving chemotherapy for AML. A study of 54 patients with AML or myelodysplastic syndromes identified impaired performance on a battery of cognitive tests in up to 40 percent of the patients before treatment (35). Similarly, a second small prospective study which enrolled only patients deemed fit for intensive induction detected undiagnosed cognitive impairment in 28.8 percent of patients (mean age 69) prior to treatment using a standardized screening test (27). In this study patients with cognitive impairment had a significantly shorter median survival (5.2 versus 15.6 months; hazard ratio [HR] 2.5, 95% CI 1.2–5.5) which was independent of age, cytogenetic risk and other patient characteristics captured in a geriatric assessment. While validation is required, simple and efficient screening tools to assess cognitive function may be important predictors of treatment tolerance. Awareness of cognitive vulnerability may result in changes in management that can ultimately prevent or treat delirium.

Polypharmacy

Polypharmacy represents another potentially modifiable risk factor that could be included in pretreatment assessment. Polypharmacy is common among older adults with cancer and many patients are taking more than 5 medications(36–40). Among older adults with AML treated intensively a retrospective study of 150 patients >60 years of age the median number of medications at presentation was 4 (range 0–15)(41). After adjustment for age and comorbidity, increased number of medications at diagnosis (4 vs. 1) was associated with increased 30-day mortality, lower odds of complete remission and shorter survival. Polypharmacy warrants further study as a modifiable marker of vulnerability among older adults with AML. In clinical practice review and discontinuation of any medications without strong clinical indication may decrease risk of drug interactions and adverse events.

Symptoms

Specific symptoms assessed at the time of pretreatment evaluation may be prognostic in the setting of AML diagnosis. A multi-site study investigating pretreatment geriatric assessment for older adults with MDS or AML identified a high level of fatigue (score >50 on the EORTC-QLQ C30 fatigue subscale) as an independent predictor of poor overall survival(18). A retrospective single institution study of older adults with newly diagnosed AML identified pain (reported as more often versus less often) as an independent predictor of mortality(19). In addition to improving risk stratification, identification of specific symptoms associated with poor outcomes can inform supportive care interventions to improve quality of life and treatment tolerance.

Comprehensive assessment: accounting for complexity

To adequately assess fitness, we need sensitive and efficient screening tools and a more comprehensive approach. In considering only select characteristics such as performance status and comorbidity we are missing multiple other measurable characteristics that may influence treatment tolerance. It is equally important to recognize that vulnerabilities do not always exist in isolation. Geriatric assessment (GA) is a method used to evaluate multiple patient characteristics in a standardized fashion (i.e. physical function, comorbid disease, cognitive function, psychological state, social support, polypharmacy, nutritional status) to help characterize individual complexity and discriminate between fit, vulnerable, and frail patients. Prospective studies have shown that GA can predict chemotherapy toxicity and survival in multiple tumor types(42–44).

GA is feasible to perform in the setting of pre-treatment assessment for older adults with newly diagnosed AML(20). GA can detect significant variability in patient characteristics which are not routinely captured by typical clinical assessments(20). In a prospective single institution study of older adults (age ≥ 60 years) with newly diagnosed AML treated intensively, pre-treatment GA detected high prevalence of impairments even among those with ECOG 0–1: cognitive impairment, 24%; depression, 26%; distress, 50%; ADL impairment, 34%; impaired physical performance, 31%; and comorbidity using the HCT-CI, 40%(20). Importantly, most patients were impaired in one (92.6%) or more (63%) measured characteristics. The cumulative effects of multiple impairments may be more important than

individual conditions and the implications of these impairments may differ by treatment intensity.

There is evidence that GA measures can inform risk stratification for older adults with AML(45–47). When accounting for individual patient characteristics such as function, comorbidity and symptoms measured by GA, the impact of chronologic age loses significance (atleast among those aged 60–80). In the above mentioned single institution prospective study of adults ≥60 years of age treated with intensive induction therapy, two GA measures performed at diagnosis were associated with overall survival(46). Specific measures assessed in this study (N=74) were physical function (self-reported and objectively measured); cognitive function; comorbidity; distress, and depressive symptoms. Most participants had a good ECOG PS (78% ECOG = 1) at the pretreatment assessment. As described in the previous sections both objectively measured physical performance (SPPB score <9) and cognitive impairment (Modified Mental State Exam score<77) were independently associated with overall survival after accounting for tumor and clinical characteristics. Age and ECOG PS score were not independently associated with survival in this study. These data suggest that among patients considered fit for intensive therapy using standard clinical criteria, measurement of physical performance and cognition may help identify meaningful vulnerability. Efforts to validate these assessment strategies in the multi-site cooperative group setting in the US and Europe are on-going and will further inform generalizability of GA administration in practice.

The predictive utility of GA has also been investigated among older adults with AML receiving non-intensive therapy. A multi-site study investigated the role of pre-treatment GA among patients with myelodysplastic syndrome (N=63) and AML (N=132). Patient received treatment at the discretion of their physician inclusive of best supportive care (N=47), hypomethylating agents (N=73), and intensive induction (N=75)(45). The GA included measures of physical function by self-report (ADL and IADL) and objective assessment (Timed up and go test), cognition, mood, and quality of life. Many patients screened positive for impairment in each of the assessment domains. As expected, patients in the non-intensively treated group were more impaired on the GA measures than those in the intensively treated group. When considering the non-intensively treated patients the following characteristics were independently associated with worse overall survival: KPS<80, requiring assistance with ADLs, and high fatigue score from the quality of life questionnaire score (>50 on the EORTC-QLQ C30 fatigue subscale). A fitness score was derived from these three variables; 0 (no impairments, low risk), 1–2 (intermediate), and 3 (high risk). Median overall survival differed for patients in the low risk, intermediate and high risk groups (774 versus 231 versus and 51 days respectively, $p<0.01$). The fitness score did not predict survival for those treated intensively (N=75), suggesting that characteristics used to define fitness and vulnerability differ by treatment setting and population studied.

Finally, a retrospective study (N=101) utilized registry data to reconstruct a GA by mapping specific questions collected on a quality of life survey to typical GA domains inclusive of physical, social, cognitive, psychological function, nutritional status and pain (47). A comorbidity score was also collected. Patients were ≥65 years of age with only 35% receiving intensive therapy. In multivariate analysis, higher comorbidity (HCT-CI>1), self-

reported difficulty with strenuous activity and pain were associated with higher mortality after controlling for adverse cytogenetics, ECOG PS and secondary AML. This study suggests that simple targeted questions regarding specific symptoms or physical functioning may help identify vulnerability.

Available evidence suggests that assessment of multiple patient characteristics using standardized methods can provide clinically meaningful information to assist in treatment planning. The most promising predictors of vulnerability are measures of physical function (task specific or objectively measured) and cognition although symptom burden may be critically important. Data specific to AML is limited to small sample sizes with few patients >80 years of age represented. While validation is needed, it is reasonable to utilize existing data in clinical practice to help differentiate between fit, vulnerable, and frail patients in the context of AML therapy.

Considerations for risk stratification: fit, vulnerable, frail

An evolving risk stratification schema can be proposed with the understanding that our knowledge base continues to evolve. Characteristics of frailty include any of the following: ECOG 3, requiring assistance with ADLs, major comorbidity (CCI or HCT_CI>1). Vulnerable patients are those with ECOG<3 and no major comorbidity but have detectable impairments in physical function (SPPB score<9) or cognition (3MS<77). Fit patients are those with none of the above risk factors. Clearly this schema requires validation and will be informed by data collected in on-going multi-site clinical trials.

In most circumstances assessment of SPPB, 3MS and comorbidity by a nurse can be done in approximately 15 minutes. Screening questions addressing fatigue and pain can be readily incorporated into usual care. Shorter screening tools are under investigation but have yet to be validated in AML(48). It would be reasonable to substitute measurement of gait speed alone(49, 50), mobility questions (i.e. difficulty with strenuous activity, difficulty walking one block(43, 51)) and a shorter cognition screen such as the Blessed Orientation-Memory-Concentration Test in practice(43, 51, 52). This could inform clinical decision-making and would require less than 10 minutes to perform.

Moving from prediction to intervention: Can we decrease vulnerability?

Improving risk prediction for older adults is a worthy goal. However, it should not be the terminal goal for this line of inquiry. Ideally, identification of factors contributing to vulnerability during therapy should lead to interventions to improve treatment tolerance. Many of the risk factors discussed above are potentially modifiable. For example, if impaired physical performance is associated with poor outcomes, can intervention targeting physical function during therapy mitigate this risk? Studies investigating the feasibility of performing physical activity in the setting of intensive induction therapy have been conducted and this is an active area of investigation(53, 54). In addition to physical function many patient characteristics lend themselves to intervention including but not limited to management of specific comorbid conditions, polypharmacy, nutritional status, and symptom burden. Design of active supportive care strategies may improve the chances that older adults will tolerate and benefit from therapies.

Conclusion

Treatment outcomes for older adults are influenced by measureable patient characteristics. Comprehensive assessment of multiple patient characteristics can enhance prediction of treatment tolerance and better reflect physiologic rather than chronologic age. Incorporation of standardized assessment of patient characteristics in clinical trials and practice will be needed to best individualize treatment decisions for older adults.

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