



Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: Report of CALGB 361006 (Alliance)[☆]

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ABSTRACT

Objective: To demonstrate feasibility of performing geriatric assessment (GA) in the National Clinical Trials Network (NCTN) and to explore the utility of GA to characterize treatment tolerance.

Materials and methods: We conducted a multisite companion study (CALGB 361006) to CALGB 11001, a phase 2 trial of adults ≥60 years old with newly diagnosed FLT3- mutated AML, testing the efficacy of adding sorafenib to intensive chemotherapy. On 361006, a GA was administered prior to induction and prior to post-remission therapy. The GA is divided into items requiring administration by a health care professional (HCP) and patient self-administered questionnaires. Feasibility outcomes were recruitment rate, time to GA completion, difficulty with GA administration, percent of patients requiring assistance, and satisfaction. Change in GA measures pre- and post-induction were compared using Wilcoxon signed rank test and McNemar's tests.

Results: The recruitment rate was 80% (N = 43, median age 68 years). Median completion time of the GA was 30 min; (10 and 21 min for HCP and patients, respectively). HCP reported no difficulty completing assessments (100%). Most patients completed questionnaires without assistance (77%), and were satisfied with the length (89%). Self-reported physical function, mental health, social activity and nutritional parameters worsened after induction.

Conclusion: GA is feasible to administer in the setting of intensive induction for older adults with AML in the NCTN and provides evidence of the impact of induction therapy on physical and emotional health.

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1. Introduction

Acute myeloid leukemia (AML) is a disease most commonly diagnosed in older adults. Survival for patients with AML is age dependent, with significantly lower survival rates reported for older adults [1,2].

While selected older adults may benefit from aggressive therapies, older adults, as a group, are at risk for increased toxicity from treatment [1,3,4]. Assessment tools are needed to better characterize fitness in the context of therapy and to capture how older adults feel and function prior to and after therapy. This information could assist clinicians in

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making treatment decisions, inform future trial design, and identify potentially modifiable risk factors for development of interventions to improve treatment outcomes and the quality of survivorship.

Geriatric assessment (GA) is a strategy that can characterize the heterogeneity of aging and capture important functional outcomes for older adults. Based on single institution data, pre-treatment GA for older adults with newly diagnosed AML appears feasible [5]. In this setting, GA detects significant, potentially unrecognized, impairments in the majority of patients scheduled to receive intensive therapy despite good performance status [5]. Importantly, GA measures such as objectively measured impaired physical function and cognitive performance are independently associated with worse survival among intensively treated patients [6]. Similarly, a fitness score derived from clinical and GA parameters has also been associated with survival among older adults with AML or myelodysplastic syndrome receiving non-intensive therapies [7]. Retrospective studies evaluating specific patient characteristics such as comorbidity, polypharmacy, and symptoms further support the importance of comprehensive and standardized risk assessment strategies for older adults [7–11]. However, the feasibility and utility of GA has not been demonstrated in multisite AML National Cancer Institute (NCI) National Clinical Trials Network (NCTN) studies.

A brief, comprehensive, standardized GA to characterize a patient's "functional age" was developed in the Alliance for Clinical Trials in Oncology (Alliance) Cancer in the Older Adult Committee and was previously piloted in a multisite trial among older adults scheduled to receive chemotherapy predominantly for solid tumors [12,13]. The assessment evaluates functional status, comorbid medical conditions, cognition, nutritional and psychological status, social support and social activities and was feasible to administer to patients enrolling on non-AML NCTN trials. A toxicity risk score derived from this GA predicts chemotherapy toxicity [14,15]. These published data, however, do not include patients with newly diagnosed AML. AML diagnosis and treatment represents a unique, often high-acuity setting, requiring rapid diagnosis and initiation of treatment commonly in the inpatient setting. It is uncertain whether data from non-AML studies can be extrapolated to the care paradigm for AML. To address this issue, the primary objective of this study was to evaluate the feasibility of performing GA in an AML NCTN treatment trial. Secondary objectives were to investigate the impact of induction chemotherapy on physical, cognitive, psychosocial factors and explore the association of baseline GA measures with overall survival.

2. Methods

Cancer and Leukemia Group B (CALGB) 361006 was a prospective multisite embedded companion study offered to patients enrolled on CALGB 11001 at the 15 participating CALGB institutions. CALGB 11001 was a phase II study of adults 60 years of age or older with newly diagnosed FMS-like tyrosine kinase-3 (*FLT3*) mutated AML testing the efficacy of adding sorafenib to intensive chemotherapy with daunorubicin and cytarabine open between 2011 and 2014 [16]. Any site participating in CALGB 11001 could enroll on 361006. This study, with the 361006 companion, was approved by the NCI Central Institutional Review Board and by the institutional review board (IRB) at each participating institution. CALGB is now part of the Alliance for Clinical Trials in Oncology.

2.1. Eligibility Criteria

Patients were eligible to enroll on the GA companion study (CALGB 361006) if they met eligibility criteria for and enrolled on CALGB 11001. Briefly, eligibility criteria for the treatment and companion study included: a new histologic diagnosis of AML excluding acute promyelocytic leukemia and core binding factor leukemia; documented *FLT3* mutation determined by central laboratory; 60 years of age or

older; and no prior chemotherapy for AML. The minimum acceptable performance status or laboratory parameters were not specified.

2.2. Procedures

Before patients were enrolled in CALGB 361006, the study principal investigator (HDK) trained research staff at each participating site (via telephone). Training calls (approximately 15–30 min) in length reviewed written standardized administration and scoring instructions for each GA measure and provided an opportunity for staff to ask clarifying questions. Then, patients who were eligible to enroll on CALGB 11001 were offered the opportunity to enroll on CALGB 361006. All patients who chose to participate in the GA companion study (361006) completed an IRB-approved, protocol-specific informed consent at the time of consent to the treatment trial (CALGB 11001). The GA and a quality-of-life questionnaire were completed at baseline (prior to initiation of induction chemotherapy) and again after induction at the time of evaluation for consolidation therapy either in the inpatient or outpatient setting. Patient registration, data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The study chair contacted site staff to obtain reasons for missing data when one was not provided.

2.3. Measures

The GA tool includes validated measures assessing the domains of physical function, comorbid medical conditions, psychological state, social activities and support, nutritional status, cognitive function and medications [12,13]. It was developed for use in the NCTN setting with a full description of measures previously reported. Modifications to the GA tool for this study include the addition of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) [17] and the substitution of the Mental Health Inventory-17 (MHI-17) to assess psychological health [18]. The HCT-CI was added because it is well validated in leukemia and provides more detailed information on comorbidity burden than the patient-reported comorbidity assessment included in the GA [19–21]. The MHI-17 was chosen as a substitute assessment for psychological health by the Alliance Cancer in the Older Adult Subcommittee due to the proprietary nature of the previously included measure.

The GA tool includes a healthcare provider (nurse or certified research associate) administered assessment and a self-administered patient questionnaire. The healthcare provider-administered questionnaire included the following 5 brief assessments: 1) HCT-CI (a validated comorbidity index associated with remission status and survival among older adults with AML) [17,19,21]; 2) Karnofsky performance status; 3) Timed up and Go (a performance based measure of physical function; time assessed in seconds for those who could complete the test or recorded as unable to perform) [22]; 4) Blessed Orientation Memory Concentration test (score ≥ 11 indicating impairment) [23]; 5) recording of height and weight (current and 6 months prior) to evaluate nutritional status including calculation of body mass index. Prior weight was collected by self-report if not recorded in the medical record. Intentionality of weight loss was not assessed.

The self-administered patient questionnaire included several validated surveys and demographic questions. The questionnaire included self-reported measures of physical function and activities (inclusive of activities of daily living, instrumental activities of daily living and mobility items), a patient-rated Karnofsky performance status, self-reported falls in the past 6 months, self-reported comorbid conditions and a rating of the degree to which each causes interference in activities, number and type of medications, assessment of psychological state (symptoms of anxiety and depression), social activity, and social support. A member of the health care team could assist those patients who needed help.

Health-related quality-of-life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [24,25]. Domains assessed included general physical symptoms, fatigue and malaise, and physical, social and emotional functioning. Time points for assessment were the same as for the GA questionnaires.

2.4. Outcomes

The primary outcome was feasibility evaluated by recruitment of participants, implementation (time to completion, difficulty with administration, percent of participants requiring assistance), and patient satisfaction with the assessment. Time to completion of the battery of tests was estimated in minutes by the health care professional for both portions of the evaluation. The research team completed survey questions about difficulty with administration. Staff was asked whether any items were difficult to administer or difficult to complete by the staff or participant. To determine patient satisfaction with the assessment, the patient questionnaire surveyed participants regarding difficulty understanding questions, length of the assessment, whether items were upsetting and whether important questions were left out. Similar to prior feasibility work in the NCTN setting, feasibility thresholds were recruitment rate of 70%, no difficulty in implementation reported by $\geq 70\%$ of participants and $\geq 80\%$ of research staff and $\geq 80\%$ of participants reporting satisfaction [12]. A time to completion indicating feasibility of the entire assessment was ≤ 40 min.

Secondary outcomes included: 1) evaluation of the change in GA measures from baseline to after induction assessment; 2) exploration of relationships between specific baseline GA measures and overall survival to inform larger trials; and 3) description of health care utilization by capturing hospitalizations, oncology clinic visits and nursing home use during the study from the medical record. OS was estimated from the time of signing the consent form.

2.5. Statistical Analyses

Descriptive statistics were used to summarize feasibility outcomes and GA measures. Continuous variables were described by mean (standard deviation) and median (range) and categorical variables by frequency and percentage. Changes from baseline to post-induction therapy were calculated using the Wilcoxon signed rank test for continuous variables and McNemar's test for categorical variables. Survival probabilities were estimated using the Kaplan-Meier estimator [26]. Associations between baseline GA measures and overall survival were explored by comparing survival probabilities between groups (dichotomized by the median score due to small sample size) using the log-rank test. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary NC, USA) and had a two-sided alpha level of 0.05. Data lock for trial data was on May 11, 2016. Due to the exploratory nature of this analysis, there was no adjustment for multiple comparisons.

3. Results

Among the 54 patients who enrolled on clinical trial CALGB 11001, 43 (80%) enrolled on the GA companion study (CALGB 361006) from 14 different institutions (Fig. 1). Of these, 40 completed at least one baseline assessment (93%). Twenty-eight patients (70%) performed a follow-up assessment after induction therapy. Of those who did not complete follow-up assessment, 3 were deceased, 3 came off study treatment (1 for resistant disease) and 6 assessments were missed (reasons not documented).

Baseline characteristics are presented in Table 1. Nearly 40% of participants were aged 70 years and above. Most were non-Hispanic, white males. The majority (75%) received one cycle of induction therapy. The remission rate was 78% and 64% received post-remission therapy. The early death rate was 10% and median overall survival was

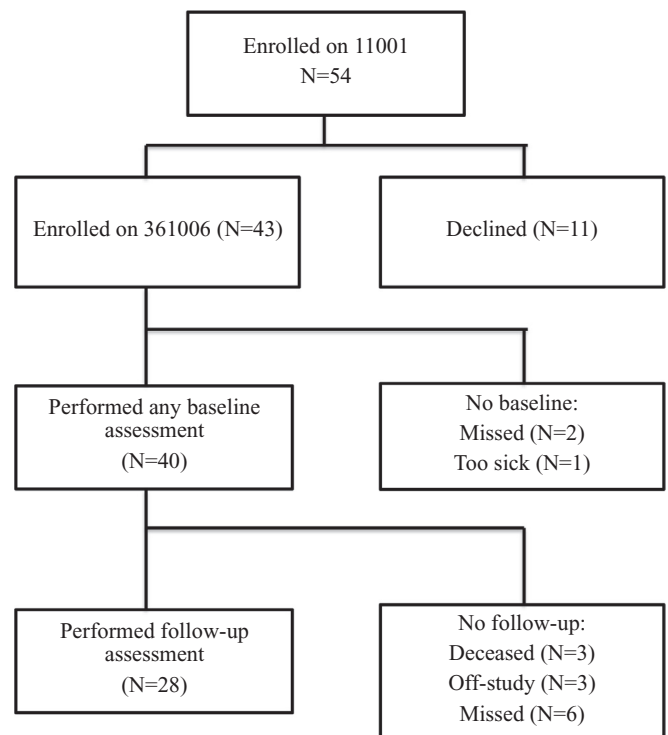


Fig. 1. Consort Diagram of enrollment and follow-up on A361006.

14.9 months (95% C.I. 12.6–23.3 months). Tumor and treatment characteristics of the GA cohort were similar to the overall study cohort [16].

The median time recorded for completion of the GA battery inclusive of both the health care professional and patient questionnaires was 30 min (Interquartile range 23–40 min). The median times recorded for completion of the health care professional questionnaire was 10 min (range 2–30 min) and for the patient questionnaire was 23 min (range 3–90 min). Among research staff, 100% reported no difficulty administering the healthcare professional component. The majority of patients reported no difficulty understanding questions (89%) and completed the assessment without assistance (77%). Patient satisfaction was high; 89% were satisfied with the length and no patients found the questionnaire upsetting.

Baseline values for each GA measure and the quality-of-life questionnaire (EORTC CLC-Q30) are presented in Table 2. Most participants reported independence in instrumental activities of daily living, had good performance status, had no history of falls, screened negative for cognitive impairment, were taking on average 4.5 medications and had modest comorbidity burden. Mean scores were low for psychological state, social activity and social support scales, and global quality-of-life measures (indicating prevalent psychological symptoms, less social activity and support, and poor quality of life). Mean scores on the Timed Up and Go test indicated impaired mobility (≥ 11 s) although the majority (90%) were able to perform the test.

For patients who completed post-induction assessment, change in GA measures and global quality-of-life is presented in Table 3. Receipt of induction therapy had a variable impact on GA measures for the 28 patients who survived induction therapy and returned for evaluation of post-remission therapy. Self-reported physical function (assessed by instrumental activities of daily living), psychological state, social activity, body mass index and unintentional weight loss significantly worsened. By contrast the global quality-of-life (EORTC CLC-Q30) score improved. Scores on the emotional, social, and several symptom-related subscales (pain, dyspnea, appetite) of the EORTC CLC-Q30 significantly improved after induction ($p < 0.05$ for all) and none showed significant worsening (data not shown).

Table 1

Baseline characteristics of older adults with AML on A361006 (N = 40).

Baseline characteristics	Median (range) or percent
Demographics	
Age (yrs) median (range)	68 (61–83)
% 60–64	30
% 65–69	30
% 70–74	23
% 75–79	10
% ≥80	8
% female	40
% white	98
% non-Hispanic	85
% married	62
% with ≥ college education	39
Clinical	
FLT3 mutation	
ITD	75
TKD	25
Onset of AML	
De novo	83
Therapy-related	8
MDS-related	4
ELN classification	
CN-AML	55
Intermediate II	28
ELN Adverse	5
Unconfirmed cytogenetics	13
Bone marrow blast percentage	58 (0–96)
White blood cell count ($\times 10^3/\text{mm}^3$)	15 (1–344)
Lactate dehydrogenase (U/L)	516 (103–2813)
Creatinine (mg/dl)	0.9 (0.4–1.7)

Abbreviations: AML: acute myeloid leukemia; FLT3; fms related tyrosine receptor kinase 3, ITD; internal tandem duplication, TKD; tyrosine kinase domain; AML; acute myeloid leukemia, MDS; myelodysplastic syndrome, ELN; European LeukemiaNet; CN; cytogenetically normal.

Exploratory analyses investigating the relationship between baseline GA measures and overall survival did not show any statistically significant associations. Univariate results are shown in Table 4; they can be useful to estimate effect size for larger studies. For example, the

hazard of mortality was higher for those with self-reported physical limitations (lower scores on MOS physical health subscale and Instrumental Activities of Daily Living) and for those reporting a fall. Similarly, there was no association between baseline global quality-of-life measured by EORTC CLC-Q30 and survival. However, the nausea/vomiting subscale of the EORTC CLC-Q30 was associated with worse survival; those with symptoms at baseline had an OS of 0.8 years compared to those without at 1.6 years ($p = 0.007$).

Health care utilization for participants who survived induction was high, with data available from 25 of 28 individuals. The median (range) number of days hospitalized for chemotherapy during the time between diagnosis and start of consolidation was 30 (7–61). In addition, roughly 27% were re-hospitalized for reasons other than chemotherapy during this period with a median of 25 (3–47) days. The median number of oncology clinic visits was 2.0 (0–4); 1 participant required care in a nursing facility for rehabilitation or long-term care.

4. Discussion

This is the first multisite NCTN study to demonstrate that GA is feasible and useful for older adults treated intensively for AML, despite the acuity and complexity of the disease setting. The wide range of scores for individual GA measures support the role of using this tool to better categorize the heterogeneity of aging and to identify potentially unrecognized vulnerabilities that can impact treatment outcomes and survivorship. GA measures post induction highlight the impact of treatment on functional domains and quality of life and provide potential targets for interventions to improve them. These findings support further investigation of GA in the context of clinical trials for AML to inform risk prediction and tailored supportive care [27].

This study is consistent with others demonstrating the feasibility of incorporating GA strategies into multisite trials in the non-AML setting [12,28]. Our results support the generalizability of incorporating GA into the evaluation of older adults receiving intensive therapy for AML, previously shown in a single institution trial [5]. Assessments were well received by both patients and research staff, and the time required was considered acceptable, with no reported concerns about

Table 2

Baseline geriatric assessment and quality-of-life measures (N = 40).

Domain	Measure	No. of items	Range of scores	Mean \pm SD	Median (range)
Functional status	Activities of daily living (subscale of MOS Physical Health)	10	0–100 (higher score: better physical function)	72.1 \pm 25.8	83.3 (50–94.4)
	Instrumental activities of daily living (subscale of the OARS)	7	0–14 (higher score: less need for assistance)	13.3 \pm 1.8	14 (4–14)
	^a Karnofsky self-reported performance rating scale	1	40–100 (higher score: better function)	83.2 \pm 15.1	90 (80–100)
	Karnofsky physician-reported performance rating scale	1	10–100 (higher score: better function)	84.9 \pm 13.5	90 (50–100)
	Number of falls in last 6 months	1	Higher score, worse performance	0.4 \pm 1.2	0 (0–7)
	Timed up and Go (seconds)	1	Higher score: worse performance	15.1 \pm 10	13 (5–60)
Cognition	Blessed orientation memory and concentration test (BOMC)	6	0–28 (score \geq 11 indicates impairment)	3.1 \pm 3.0	2 (0–12)
Comorbidity	Physician health section survey (subscale of the OARS)	13	0–39 (higher score: greater comorbidity)	3.2 \pm 3.1	2.5 (0–16)
	HCT-CI	17	0–29 (higher score: greater comorbidity)	1.8 \pm 1.9	1.0 (0–7)
Medications	^a Number of medications	1		4.5 \pm 3.7	4.0 (0–13)
Psychological state	Mental health inventory-17	17	0–100 (higher score: better mental health)	56.4 \pm 4.0	56.5 (49.4–67.1)
Social activity	MOS Social Activity Survey	4	0–100 (higher score: better social activity)	60.3 \pm 21.8	62.5 (6.3–93.8)
Social support	MOS social support survey: emotional information and tangible subscales	12	0–100 (higher score: better social support)	83.5 \pm 16.4	92.3 (15.4–92.3)
Nutrition	^a Percent unintentional weight loss in last 6 months	1		–1.9 \pm 11.7	–1.9 (–53.8–21.7)
Global quality of life	EORTC QLQ C30 Global	30	0–100 (higher score: better QOL)	46.8 \pm 30.7	50 (0–100)

Abbreviations: MOS = Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL = quality of life.

^a Represents score for number of subjects completing this assessment: Patient reported KPS, N = 37; Time up and go, N = 35; number of falls, N = 36; number of medications, N = 33; percent weight loss, N = 36.

Table 3

Change in geriatric assessment and global quality of life after induction (N = 28).

Measures	Baseline (mean ± SD)	Follow-up (mean ± SD)	Mean change from baseline ± SD	P-value
Activities of daily living (subscale of MOS physical health)	69.5 ± 27.8	60.5 ± 26.6	−9.0 ± 33.3	0.13
Instrumental activities of daily living (subscale of the OARS)	13.4 ± 1.1	12.3 ± 2.3	−1.1 ± 2.0	0.002
^a Karnofsky self-reported performance rating scale	81.9 ± 15.9	82.6 ± 17.9	0.7 ± 21.3	0.66
^a Karnofsky physician-reported performance rating scale	82.8 ± 13.1	84.8 ± 9.6	2.0 ± 13.2	0.52
^a No. of falls in last 6 months	0.2 ± 0.5	0.2 ± 0.5	0 ± 0.4	1.0
^a Timed Up and Go (seconds)	13.5 ± 4.3	12.1 ± 3.9	−1.4 ± 3.7	0.06
^a Blessed orientation memory and concentration test (BOMC)	4.0 ± 3.2	3.2 ± 4.2	−0.6 ± 3.6	0.18
^a Physician health section survey (subscale of the OARS)	3.4 ± 3.5	3.7 ± 4.6	0.3 ± 5.0	0.80
^a HCT-CI	1.9 (1.8)	1.7 (1.6)	−0.2 ± 1.2	0.51
^a Number of medications	4.0 ± 3.4	4.4 ± 3.6	0.4 ± 3.7	0.5
Mental health inventory-17	56.1 ± 3.4	54.2 ± 3.2	−1.9 ± 4.3	0.04
MOS social activity survey	62.3 ± 22.1	42.4 ± 23.1	−19.9 ± 24.7	0.0002
MOS social support survey: emotional information and tangible subscales	94.3 ± 10.5	91.7 ± 15.2	−2.4 ± 13.5	0.63
^a Body mass index	29.9 ± 5.5	28.1 ± 4.8	−1.8 ± 1.8	<0.001
^a Percent unintentional weight loss in last 6 months	−2.7 ± 12.5	−8.2 ± 13.4	−5.6 ± 17.3	0.03
^a EORTC QLQ C30	47.8 ± 29.8	67.9 ± 18.8	20.2 ± 29.4	0.001

Abbreviations: MOS = Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL = quality of life, KPS=Karnofsky performance status.

^a Represents score for number of subjects completing this assessment: Patient reported KPS, N = 27; Physician KPS, N = 25; number of falls, N = 25; Time up and go, N = 23; Blessed Orientation Memory Concentration Test, N = 23, physical health survey, N = 27, HCT-CI, N = 25, number of medications, N = 21; body mass index, N = 25, percent weight loss, N = 24.

participant or staff burden. Compared to implementation of the same GA in a predominantly solid tumor population, the median time required was slightly longer (30 vs. 22 min) with a small increase in the proportion of AML patients requiring some assistance (77% vs. 87%) and with similar high degrees of patient satisfaction [12].

This pilot also identifies opportunities to enhance efficiency, further minimize potential burden, and maximize value. First, training on measure administration using online educational modules that are now available for NCTN trials could enhance efficiency for sites when

opening trials that include GA. Second, the follow-up GA can be further streamlined by tailoring assessments to those measures demonstrating change over time. Use of tablets for direct data capture can further minimize missing data and staff time. [29,30] Attrition is a particular challenge in a dynamic patient population with high morbidity. While some attrition is unavoidable, collecting the GA/patient-reported outcome data as an integrated part of the treatment trial, rather than as a companion study requiring separate consent, can maximize participation and further minimize opportunities for missed assessments.

Similar to studies using GA in other settings, we demonstrate that older adults deemed fit for intensive chemotherapy have significant heterogeneity in physical function, cognition, comorbidity, emotional health, rates of polypharmacy, nutritional status, social activities and social support [31]. This observation provides proof-of-principle that incorporating GA into AML therapy can help characterize the heterogeneity of aging in this context. Compared to results from an observational study of older adults with predominantly solid tumor malignancy using the same GA, patients in the current study had slightly higher levels of self-reported physical function at baseline with higher levels of psychological distress [15]. However, similar to results among solid tumor patients, more than half had impaired objectively measured physical function (Timed Up and Go score > 10 s) reinforcing the importance of capturing objective measures to characterize vulnerabilities [6,15,32].

Our study adds to the literature by using GA and a global health-related quality-of-life measure concurrently as outcomes after intensive induction therapy to help characterize treatment tolerance. The impact of treatment on quality of life and independence is critical to inform decision-making and targeted supportive care for older AML patients. Yet only limited data have been collected in clinical trials for outcomes such as physical function, cognition, and psychological health. In a review of over 1000 clinical trials in hematologic malignancies, <10% collected endpoints related to quality of life, physical function or health care utilization [33].

In this study, participants evaluated for post-remission therapy reported increased physical limitations, worse mental health, decreased social activities and experienced decline in nutritional parameters measured by GA. Short-term decline in physical function after intensive induction for older patients with AML has been reported previously [34] although functional resilience may occur among longer term survivors [35]. The relationship between receipt of induction therapy on emotional health is less clear, with some studies showing lower levels of depressive symptoms and distress after treatment among older survivors

Table 4

Univariate association between baseline geriatric assessment measures and mortality.

Measure	Median score cut-point (N)	Hazard ratio for mortality (95% confidence interval)
Activities of daily living (subscale of MOS physical health)	≤83.3 (18)	1.6 (0.75–3.4)
Instrumental activities of daily living (subscale of the OARS)	>83.3 (21)	Reference
Number of falls in last 6 months	<14 (10)	1.7 (0.75–3.7)
	≥14 (29)	Reference
Karnofsky self-reported performance rating scale	≥1 (8)	2.02 (0.87–4.69)
	<1 (28)	Reference
Karnofsky physician-reported performance rating scale	≥90 (18)	0.8 (0.4–1.7)
	≥90 (19)	Reference
Timed up and Go (seconds)	<90 (15)	0.7 (0.32–1.6)
	≥90 (24)	Reference
Blessed orientation memory and concentration test (BOMC)	<13 (17)	0.7 (0.32–1.53)
	≥13 (22)	Reference
Physician health section survey (subscale of the OARS)	≤2 (24)	0.8 (0.4–1.7)
	>2 (15)	Reference
HCT-CI	≤2.5 (19)	0.9 (0.43–1.9)
	>2.5 (19)	Reference
Number of medications	≤1 (24)	1.23 (0.6–2.7)
	>1 (15)	Reference
Mental health inventory-17	≤4 (21)	0.8 (0.3–1.8)
	>4 (12)	Reference
MOS social activity survey	<56.5 (24)	0.7 (0.3–1.4)
	≥56.5 (15)	Reference
MOS social support survey	≤62.5 (22)	0.7 (0.3–1.4)
	>62.5 (17)	Reference
EORTC QLQ C30 global	≤92.3 (17)	0.8 (0.4–1.6)
	>92.3 (22)	Reference
	≤50 (21)	0.8 (0.3–1.7)
	>50 (16)	Reference

Abbreviations: MOS = Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL = quality of life.

[34,35]. Discrepant findings may relate to use of different measures versus varied timing of assessments or differences in patient populations [36]. Importantly, declines in physical function, mental health, and nutritional status can be addressed with supportive care if recognized. Interventions targeting maintenance of physical function during and after treatment are a particularly promising area of research [37–39]. Despite measured decrements in function by GA, global quality of life (QOL) scores were improved. Improved overall QOL after induction is consistent with results of other studies suggesting that achieving remission with improvements in symptoms has a positive effect on quality of life [34,35,40–43]. Thus, information gained from validated GA measures is complementary to global health-related quality-of-life assessment and provides insight into specific domains such as function and nutritional status which may otherwise be missed.

This study provides additional information to support testing the role of GA to enhance risk prediction in the context of intensive AML therapy. Identifying characteristics of patients who are more or less likely to tolerate and benefit from intensive chemotherapy is critical for both treatment decision-making, trial design and supportive care [44]. A single institution study showed that physical performance and cognition (measured by the Short Physical Performance Battery and Modified Mental State Exam) are associated with worse survival among older adults treated intensively, but confirmatory multisite studies are lacking. The GA measures included in this pilot study addressed the same domains but were less comprehensive to optimize implementation (i.e. use of the Timed Up and Go and a brief 6-item cognitive screen). Our exploratory analysis was not powered to demonstrate significant associations between GA measures and survival. However, promising candidate characteristics based on estimates of effect include measures of self-reported physical function and history of falls. Functional measures have been associated with survival in hematologic malignancies in many but not all studies investigating this domain [6,7,31,45]. Data collected in this study can be used to support development of fully powered multisite studies investigating individual risk factors and risk profiles derived from GA. Larger studies will be needed to determine if more comprehensive measures of cognitive or physical function are needed to discriminate risk. Finally, the observed relationship between baseline nausea and vomiting and survival in this cohort may relate to the impact of symptom burden on outcomes which has been suggested in other studies although warrants confirmation in larger studies [7,8].

This study has several strengths. This is the first multisite NCTN study to investigate feasibility and provide preliminary evidence for the utility of GA in the context of intensively treated patients with AML. All patients received the same therapy, limiting treatment confounding present in other studies. Collection of both GA and global quality-of-life measures provides an opportunity to better understand how to use these tools most effectively in future studies and highlights that they are not interchangeable. Finally, this study included a relatively high proportion of patients aged 70 or older (41%) which is uncommon in the literature.

This study also has limitations. The small sample size limits power to investigate the association of GA measures and treatment outcomes including overall survival and treatment-related mortality. Findings related to survival are exploratory and hypothesis generating. The sample size is inadequate to investigate which combinations of risk factors might optimally characterize fit or unfit individuals. However, the goal of this pilot was to provide preliminary data to support the feasibility of this line of investigation in larger studies. The optional nature of this ancillary study may have introduced some bias. Patients who opted not to enroll on the study may have been different in some way from those who enrolled. However, when comparing patient characteristics from those enrolled on the ancillary study to the entire clinical trial population, we see no significant differences in measurable baseline characteristics. Missing data is another limitation, with eight consented participants missing assessments without documentation of reason for

missed visits. It is reasonable to expect that those who were missing data may have differed from those who provided data. In particular, if those 6 patients missing follow-up GA data had experienced worse treatment tolerance the negative impact on functional outcomes and quality of life may be under-represented. The optional nature of the study may have contributed to missing data. Finally, patients enrolled on this study were considered fit enough for intensive chemotherapy and feasibility results may differ among populations perceived to be less fit. For example, it would be expected that the time to administer this GA among frail patients may be longer regardless of the treatment setting. Results from the GA ancillary study included in Alliance 11002 clinical trial (NCT01420926) which enrolled less fit patients will provide this information in the future and can help identify strategies to further streamline GA for frail populations [46]. Similarly, feasibility results may differ in community practices compared to academic institutions. However, these results provide a framework to estimate resource/time allocation for patients and staff to conduct GA in the treatment evaluation of older adults, which is now guideline recommended [47]. Use of a primarily self-administered GA enhances the usability in varied settings and minimizes staff resource requirements.

In summary we have demonstrated the feasibility of performing GA in the context of an NCTN AML intensive treatment trial for older adults. Our results provide evidence to support further investigation of the use of GA in this setting and highlight the role for use of post-treatment GA to understand the impact of treatment on multiple domains of function. Larger studies can confirm these findings and inform on clinically meaningful changes for older patients. We also highlight opportunities to streamline efficiency when integrating GA into multisite trials. Next steps include validation of the utility of GA to inform risk prediction in larger multisite studies, collection of GA measures in treatment trials to characterize survivorship, and testing of interventions targeting GA-identified vulnerabilities to decrease morbidity.

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Author contributions

H.D.K. and E.R. designed the research, performed research, interpreted analyses, and wrote and edited the manuscript. B.S. and K.B. designed research and edited the manuscript. B.M.E., J.L.R., analyzed data, contributed to manuscript preparation and edited the manuscript. D.S., L.S., S.G. W.Z. analyzed data and edited the manuscript. G.M., B.L., M.B., W.S., R.S., R.L., G.U. contributed to study design, performed research and edited the manuscript. H.J.C. contributed to research design, data interpretation and edited the manuscript.

Declaration of Competing Interest

None.

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