Evidence-Based Minireview: Longitudinal geriatric assessment in quality care for older patients with hematologic malignancies

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A 65-year-old women was diagnosed with acute myeloid leukemia (AML; normal cytogenetics, NPM1 mutated, FLT3-ITD wild type). Preinduction screening geriatric assessment (GA) did not reveal any significant deficit, because she was independent of basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs), had normal cognition, and scored 10 (range 0-12) on the short physical performance battery (SPPB). She underwent standard 7 + 3 induction and achieved a complete remission, although her course was complicated by neutropenic sepsis and bacteremia. She is being evaluated for postremission therapy. Would you recommend a follow-up GA at this time?

Learning Objectives

- Appreciate dynamic, treatment-related changes in physical, emotional, and cognitive health of older patients with hematologic malignancies
- Discuss prognostic impact of changes in multidimensional geriatric assessment in older patients with hematologic malignancies and potential interventions

Introduction

Multidimensional GA plays an essential role in the care of older cancer patients, including risk stratification, toxicity prediction, prognostication, and management of nononcologic geriatric problems.[1] In hematologic malignancies, accumulating evidence demonstrates that pretreatment GA identifies prognostically important deficits, such as functional limitation and cognitive impairment, which may help decision making in treatment allocation and supportive care.[2-4] However, given current constraints in geriatrics resources and infrastructure, it remains unclear how to best integrate GA across the care continuum for older patients with hematologic malignancies, because most studies only used GA at baseline.[5]

Mechanistically, longitudinal GA is appealing in hematologic malignancies. First, chemotherapy has significant impacts on aging biology, which result in functional and cognitive decline.[6,7] Identifying such deficits can proactively direct interventions that may enhance subsequent treatment options and outcomes. Second, disease and remission status may lead to dynamic changes in GA, which could alter the choice of subsequent therapy, such as hematopoietic cell transplantation (HCT). Third, the accumulation of geriatric syndromes and geriatric deficits over time may contribute to poor quality of life (QOL) and frailty.[5] Fourth, GA is increasingly recognized as the ideal vehicle for advanced care planning and shared decision making for older patients.[8] In this review, we summarize available evidence to support longitudinal GA in care of older patients with hematologic malignancies (Table 1).

AML

In a prospective observational study, Klepin et al[9] measured short-term changes in GA domains and QOL of 49 older AML patients within 8 weeks of completing intensive induction chemotherapy. They found significant declines in physical function as measured by self-reported ADLs, IADLs, and mobility as well as a decrease in physical performance as measured by SPPB and grip strength. No significant change in cognition, depression, or distress was found. The authors concluded that serial GA was feasible during intensive induction chemotherapy and identified clinically meaningful declines in physical function that could be amendable to interventions. Importantly, with longer follow-up, the authors showed that, among 41 patients who achieved hematologic remission and subsequently received postremission therapy, a higher postinduction SPPB score (≥9) was associated with improved overall survival (medians of 3.9 vs 1.3 years) independent of performance status and types of postremission therapy.[10] These findings demonstrated that a simple test of physical functioning, SPPB, could predict postremission overall survival and suggested that interventions designed to maintain and improve physical performance during AML therapy may improve treatment tolerance and long-term outcomes.

Another follow-up study using the same cohort of patients correlated changes in GA findings with cytokine biomarkers.[11] They found that both increases in self-reported IADL limitation and declines in physical function measured by SPPB correlated significantly with increased soluble tumor necrosis factor-α receptor 1 level. Importantly, elevated baseline tumor necrosis factor-α and C-reactive protein were associated with worse survival, suggesting a potential serum biomarker platform for GA-based interventional trials.[11]

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Table 1. Summary of evidence

Study	Disease, N	Age, y	Timeframe	GA domains	Main findings
Klepin et al[9] 2016; Saad et al[10] 2017; Loh et al[11] 2019	AML, N = 49	≥60	At baseline and within 8 wk of completing induction	Physical function: ADL, IADL, mobility, SPPB, grip strength; cognition: 3MS; mood: CES-D, distress thermometer; comorbidity: HCT-CI	Physical function: decrease in all measures; cognition: no change; mood: stable CES-D, decrease in distress • Depression symptom correlated with greater decline in SPPB scores • Lower postinduction SPPB scores correlated with worse survival in patients who achieved remission • TNFα sR1 was a correlative biomarker for physical functioning • Baseline TNFα and CRP were associated with overall survival
Alibhai et al[12] 2015	AML, N = 97	≥60	At baseline and 7 time points the following year	Physical function: IADL, grip strength, 2MWT, chair stands; mood: Beck Depression Scale; QOL: EORTC QLQ-C30; fatigue: FACT-F scale	Physical function: IADL and grip strength worse in the first 3 mo and then improves steadily; other tests improve steadily; mood: improves steadily; QOL: improves steadily; fatigue: improves steadily • GA and QOL improvements were seen in patients in clinical remission • Similar trajectories were seen in younger patients (<60 y old)
Bonanad et al[13] 2015; Cruz-Jentoft et al[14] 2017	Various hematologic malignancy, N = 164	≥65	At baseline and on average, 1.4 y later	Physical function: ADL, gait speed; cognition: SPMSQ; mood: CES-D; nutrition: MNA; subjective health: VES-13; medications and comorbidities	GAH total score: no changes for the complete cohort from the baseline to the follow-up assessment • GAH score changes correlated with ECOG, KPS, and VAS score changes • Score changes were significantly different for patients in remission vs progressive/stable disease
Deschler et al[15] 2018	Allo-HCT, N = 108	≥60	At baseline and days +30, +100, and +180	Physical function: ADL, IADL, timed up and go; cognition: MMSE; nutrition: MNA; QOL: EORTC QLQ-C30; German short-form resilience; comorbidities	Physical function: nadir by day +30 to +100 → recover close to baseline by day +180; cognition: nadir by day +30 → improve; nutrition: nadir by day +30 → improve; QOL: nadir by day +30 → improve • Baseline timed up and go was predictive of overall survival • Changes in physical function or nutrition were associated with survival outcomes

Allo-HCT, allogeneic hematopoietic cell transplantation; CES-D, Center for Epidemiologic Studies—Depression Scale; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European organization for research and treatment of cancer quality of life questionnaire core; FACT-F, functional assessment of cancer therapy: fatigue scale; GAH: Geriatric Assessment in Hematology; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; KPS, Karnofsky performance scale; MMSE: Mini-Mental State Examination; MNA, mini-nutrition assessment; 3MS, Modified Mini-Mental State examination; 2MWT, 2-minute walk test; N, number; SPMSQ, short portable mental status questionnaire; TNFα sR1, tumor necrosis factor-α; TNFα sR1, soluble tumor necrosis factor-α receptor 1; VAS, visual analog scale; VES-13, vulnerable elders survey.

Another prospective observational study in older AML patients focused primarily on changes in physical function and QOL after intensive induction chemotherapy.[12] Alibhai et al[12] measured physical function by grip strength, 2-minute walk test (2MWT), and timed chair stands pretreatment and at 7 time points over the following year, and they collected patient self-reported IADL limitations, QOL, and

fatigue in 97 older AML patients. They found that IADL, grip strength, and QOL domain of physical functioning decreased initially, nadiring around 2 to 3 months postinduction; then, they gradually recovered to baseline by 1 year. Importantly, global QOL, fatigue, mood, 2MWT, and timed chair stands all improved steadily over time in patients who achieved clinical remission regardless of age, suggesting that disease status and therapy response maybe associated with improved physical functioning and QOL.

Various hematologic malignancies/transplantation

Spanish investigators developed a Geriatric Assessment in Hematology (GAH) scale and validated it in a mixed population of older patients with hematologic malignancies.[13,14] Among the subset of 164 patients who had survived to follow-up assessment 1 year later, they found no significant difference in total GAH scores for the overall cohort between these 2 assessments. However, patients with progressive disease had significant decreases in total GAH scores compared with patients with stable disease or in remission over the assessment period. These findings supported the longitudinal use of the GAH scale given its internal consistency over the course of treatment and its clinical responsiveness to disease status.

In the transplant setting, Deschler et al[15] performed a prospective observational study of GA and QOL in 108 older patients with advanced hematologic malignancies who underwent allogeneic HCT using a predominantly reduced-intensity conditioning regimen. GA and QOL were assessed at the baseline as well as days +30, +100, and +180. Not surprisingly, most GA domains, including physical functioning, cognition, nutrition, QOL, and self-reported resilience, nadired between days +30 and +60 posttransplant, and then, they slowly recovered thereafter in patients without relapse. By day +180, most GA and QOL domains scores returned or were close to the pre-HCT value. Most importantly, when used as a time-dependent covariate, changes in functional status (ADL and IADL), performance status, and nutrition were significantly associated with both progression-free and overall survival, thus providing a logical entry point for a GA-tailored intervention posttransplant to improve outcomes.

Conclusions and future directions

Available studies have consistently demonstrated significant declines across the GA physical functioning domain 2 to 3 months after intensive treatment in diverse populations of patients with hematologic malignancies that are associated with clinical response, QOL, and potentially survival (Table 1). Given prognostic implications of these findings and their potential to direct interventions, we, therefore, recommend a follow-up GA during this timeframe as illustrated in our case above (strength of recommendation: moderate).

In practice, we recommend a follow-up GA within ~3 months of intensive induction for older patients with acute leukemias or within 100 days after allogeneic HCT, especially if a subsequent therapeutic modality is planned, such as consolidative HCT or posttransplant maintenance. Specifically, we can use changes in physical and cognitive functions to guide management interventions, including referral to ancillary services (such as physical or occupational therapy) to enhance recovery and facilitate functional resilience. For patients with chronic myeloid or lymphoid malignancies or patients receiving low-intensity treatment, the need for and the optimal timing of follow-up GA remain unknown. We suggest repeating GA at the time of clinical remission to establish a new baseline; at disease progression to discuss prognosis and plan therapy, new clinical symptoms, or needs; or yearly during survivorship care.

Ultimately, longitudinal GA should inform ongoing supportive care interventions and/or subsequent treatment decision making, and interventional studies based on GA trajectory are needed. Biologically, the causal relationship between disease status, physical functioning, and QoL remains to be determined. In addition, various multidisciplinary care delivery models incorporating serial GA will need to be tested and refined in hematologic malignancies.[16] Finally, we strongly advocate for incorporating longitudinal GA as relevant end points in all clinical trials of older patients with hematologic malignancies.

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