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HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

Frailty in Hematologic Malignancy

Thuy T. Koll[1] · Ashley E. Rosko[2]

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Abstract

Purpose of Review Older adults with hematologic malignancy are a growing demographic. Estimating risk of chemotherapy toxicity based on age alone is an unreliable estimate of quality of life, functional capacity, or risk of treatment complications.

Recent Findings Dedicated geriatric assessment tools can aid the clinician in identifying geriatric syndromes such as frailty, resulting in improved prognostication to decrease morbidity and mortality. Frailty is not synonymous with individual performance status and is dynamic.

Summary Establishing the patient goals, values, and preferences is central to the consideration of malignant hematology decision process. Careful considerations of available data on the patient's prognosis based on estimated life expectancy, geriatric assessment data, and age-specific cancer mortality, with and without treatment, can reconcile the risks and benefits. Assessments of frailty can aid the clinical feasibility and burden of the treatment to the patient and family in the context of each patient's unique needs.

Keywords Hematologic malignancy · Frailty · Older adults · Geriatric assessment

Introduction

Aging adults with hematologic malignancy are a growing demographic. The majority of hematologic malignancies are diagnosed in the older adult [1] Few clinical trials are dedicated to aging adults specifically, resulting in limited data to gauge risk of chemotherapy toxicity or tolerability in older adults with hematologic malignancy. Clinical trial enrollment for aging adults with blood cancer is estimated to be 11% for adults > 75 years old and 85% of all clinical trial participants are *less* than 65 years of age [2•]. Without supporting data, clinicians are left to estimate the risk for chemotherapy toxicity based on clinical factors such as age, comorbidities, and performance status. Yet these metrics alone are not a reliable estimate of life expectancy, functional capacity, or risk of treatment complications [3, 4]. Moreover, aging is heterogeneous and health status cannot be summarized by chronologic age alone. One of the greatest challenges in caring for older adults with hematologic malignancy is to individualize therapy, balancing treatment efficacy with tolerability. As such, many oncologists have sought to work within the disciplines of oncology and geriatrics to optimize care for aging adults with cancer. Consequently, many tools and assessments from the discipline of geriatrics are being incorporated into routine oncology care. Here we provide an overview of our current understanding of frailty in older adults with hematological malignancy, as it applies to therapeutic decision, emerging therapies and outcomes for frailty in hematology.

Frailty in Geriatric Population

While there is a lack of consensus on the definition of frailty, most experts agree that frailty is measurable and is a clinical representation of the underlying dysregulation across multiple physiologic systems [5]. This dysregulation causes a decrease in the capacity to adapt and results in increased vulnerability to minimal stressors in older adults. Frailty is a result of age-related physiological changes and is a state of diminishing reserve that can be exacerbated by diseases such as blood

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✉ Ashley E. Rosko
Ashley.Rosko@osumc.edu

[1] Division of Geriatrics, University of Nebraska Medical Center, Omaha, NE, USA

[2] Division of Hematology, Department of Medicine, Ohio State University College of Medicine, A345 Starling Loving Hall, 320 W. 10th Avenue, Columbus, OH 43210, USA

cancer. The physiological systems implicated in frailty include increase in inflammatory markers, decrease in hormones needed to maintain muscle mass and strength, and increase clotting activity, among others [6–9]. Frailty status is classified into three categories: non-frail (fit), pre-frail, and frail. The pre-frail state signifies high risk of progression to a frail state. Importantly, frailty is dynamic, and the progression from fit, pre-frail, to frail is not always linear and is potentially reversible and amendable to interventions [10]. The clinical consequences of frailty include falls, worsening mobility, disability, hospitalizations, and death [11]

Clinical management of frailty should focus on several notable factors: (1) prevention, delay, or reduction in severity of frailty and (2) minimize the consequences of adverse outcomes in frail older adults [12]. A comprehensive Geriatric Assessment (GA) is a multidisciplinary in-depth evaluation that can assess risk of morbidity and mortality in cancer patients and identify geriatric syndromes in an aging population [13, 14] [15]. Frailty is a geriatric syndrome and is considered the most common marker of adverse outcomes [11], [16]. Components of a GA may include the following domains of health: (1) medical: evaluation of comorbidity, polypharmacy, sensory loss, and nutritional status; (2) mental health: evaluation of cognition, depression, anxiety, and delirium; (3) functional status: assessment of activities of daily living (ADL), instrumental activities of daily living (IADL), mobility (physical performance), and falls; and (4) social: evaluation of environment, resources, and social support/network. Comprehensive geriatric assessments (CGAs) can improve health outcomes for frail older adults because it addresses abnormalities of multiple systems and the multifactorial etiologies that contribute to the frailty syndrome [10, 17–20].

Frailty Distinct from Comorbidity and Disability

Comorbidity and disability are often correlated with frailty but these concepts are distinct [21]. Comorbidity is defined as the concurrent presence of two or more chronic diseases in an individual. Chronic diseases contribute to the development of frailty and perhaps worsen the underlying decrease in reserve if not adequately managed. Disability is defined as difficulty or dependency in ADL. Disability may exacerbate comorbidity and frailty [21]. Geriatric syndromes (e.g., osteoporosis, dementia, delirium) are common health conditions in the geriatric population and can also drive the development of the frailty syndrome [12]. There is a complex interaction between age-related physiological changes, comorbidity, and geriatric syndromes such as frailty, blood cancer, and treatments. There is heterogeneity in the aging process resulting in variable loss of reserve in multiple health domains. The likelihood of multiple chronic health conditions (comorbidity), geriatric syndromes, specifically frailty, increases with age and is compounded by unique psychosocial needs in the aging population. Geriatric assessment consists of validated tools to evaluate the physiologic reserve across multiple health domains affected by aging including social support and resources. Importantly, optimizing care for older adults with blood cancer is not dependent on a single factor such as age, disease, or frailty but rather dependent on the intersection of many common health-related factors (Fig. 1).

Identification of Frailty in Clinical Practice

Frailty occurs in 15–25% of community-dwelling older adults (≥ 65 years and older) [22]. Clinicians caring for older adults recognize frailty as an important marker of poor outcomes. The integration of frailty measurements and clinical algorithms in subspecialty practice is evolving [23•]. There are two major conceptual operationalizations of frailty with proposed clinical measurement tools: frailty phenotype also known as Fried's frailty or Cardiovascular Health Study definition [11] and the Frailty Index [24]. Fried and colleagues used data from the Cardiovascular Health Study to define frailty as a distinct clinical syndrome characterized by unexplained weight loss, low physical activity, weak grip, slow

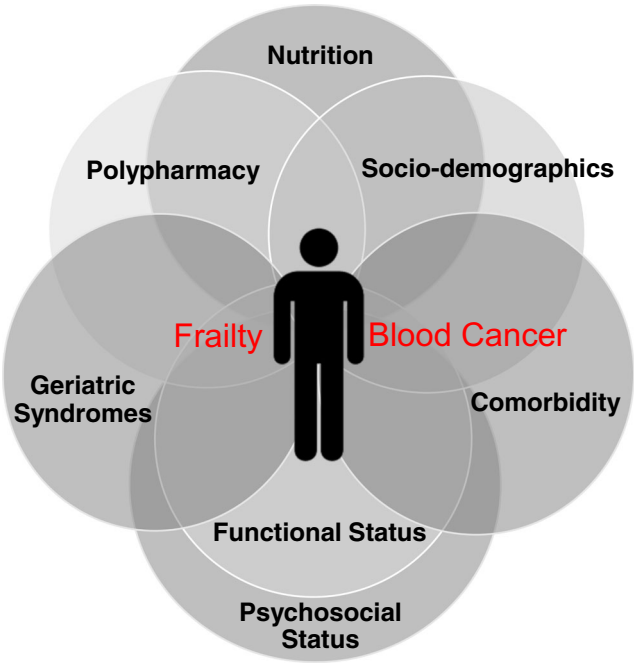

Fig. 1 Complex interaction between age-related physiological changes, comorbidity, geriatric syndromes such as frailty, and hematologic malignancy. Here we demonstrate overlapping geriatric domains of nutrition, polypharmacy, socio-demographics, comorbidity, functional status, psychosocial status, and geriatric syndromes

gait, and self-reported exhaustion [11]. Individuals with three or more of these characteristics are considered frail, those with one or two characteristics are considered pre-frail, and those with none of the mentioned characteristics are considered non-frail [11]. Rockwood and colleagues proposed to look at health deficits and developed the Frailty Index based on CGA data (24). The index is calculated by counting the number of health deficits including comorbidity, disability, cognitive impairment, psychosocial risk factors, and other geriatric syndromes. The Frailty Index represents the number of deficits over the total number of deficits considered. This model predicts outcomes with greater precision due to inclusion of factors that likely contribute to poor outcomes such as comorbidity and disability [25, 26]. There are a number of other screening tools available to help clinicians identify those in need of further assessment including Fatigue, Resistance, Ambulation, Illnesses, Loss of Weight (FRAIL) [27], Groningen Frailty Indicator [28], and the Clinical Frailty Scale [29]. Frailty assessments are commonplace in older adults; however, it is necessary to denote that frailty is prevalent in childhood cancer survivors and associated with an increased risk of mortality in young hematopoietic cell transplant populations [30, 31].

Frailty in Hematological Malignancies

Oncologists are acutely aware of the impact of a cancer diagnosis on health status and well-being. This has been summarized in clinical terms as performance status and quantified dating back to the 1950s as the Karnofsky Performance Status (KPS) or alternatively using the Eastern Cooperative Oncology Group (ECOG) system. The system was developed to estimate a patients' tolerability of chemotherapy. The KPS is embedded into numerous prognostication scoring systems such as the International Prognostic Index for non-Hodgkin Lymphoma [32] or for determining eligibility for allogeneic transplant for myelodysplastic syndrome [33]. In reality, it is unlikely that differences between KPS are clearly acknowledged in routine oncology care. Moreover, frailty is not synonymous with individual performance status. Frailty, a distinct clinical syndrome, is both dynamic and physiologic, whereas traditional oncology metrics of performance status focus on functional status and scales of disability. Recently, frailty has been described in several cohort studies of older adults with hematologic malignancies (Table 1). In hematologic malignancy, there is a movement towards recognizing the clinical state of vulnerability and the role in treatment tolerance. There is not one method for identifying frailty. Frailty signifies a state of vulnerability to poor outcomes and there is heterogeneity in measurement of frailty in hematologic malignancies, with most studies using a GA to identify frailty. Individual GA domains can ascertain risk for chemotherapy toxicity in the oncology setting [34–36] and provide intervention targets to improve the ability of patients to undergo treatment for their cancer. Interventions to intervene and improve on frailty are many and are personalized to the deficits identified on the GA (Table 2). The interventions are designed to improve quality of life and to optimize overall health with aging. Deficits are variable in older adults and can be localized to only one domain across domains.

GA are underutilized in hematologic malignancy. In 2014, a systematic review evaluated the use of a GA in hematologic malignancy where a minimum of two GA domains was included [37]. In summary, 18 publications from 15 studies were identified and concluded that geriatric deficits were associated with a shorter overall survival. In most studies, age and performance status lost their predictive value of mortality by multivariate analysis, whereas comorbidity, physical function, and nutritional status retained their predictive value. More recently, many studies have reported outcomes of the predictive value of GA domains in specific hematologic malignancy populations (Table 1). Here we provide our current understanding of frailty in older adults with common hematological malignancies.

Multiple Myeloma

Multiple myeloma interest groups have sought to examine the predictive ability of GA tools in clinical evaluation. The International Myeloma Working Group (IMWG) used a simplified GA tool based on age, comorbidities (Charlson Comorbidity Index), ADL, and IADL for newly diagnosed older adults with multiple myeloma [38•]. The IMWG score was developed from patients registered on three prospective myeloma trials ($n = 889$), which classified patients as fit (score = 0, 39%), intermediately fit (score = 1, 31%), and frail (score ≥ 2, 30%). The IMWG frailty score was predictive of mortality, treatment discontinuation, and non-hematologic toxicities independent of treatment type, cytogenetics, or stage. Furthermore, other groups [39] have sought to examine prognostic scores combining end organ function, performance status, frailty, and age in older adults with multiple myeloma. In multiple myeloma, the standard of care is autologous stem cell transplant (ASCT). The challenge for the myeloma community is standardizing the approach of fitness for ASCT. Balancing the toxicity and efficacy of ASCT is of particular relevance, given that transplant does not result in a cure. Major limitations for understanding the role of transplant in older adults are hindered by past clinical trial designs based on age or vague descriptors of fitness for transplant.

Table 1 Predictors and outcomes of geriatric assessment and frailty studies in hematologic malignancies

Author	Year of pub	Number of patients	Cancer type(s) Age [mean, median years]	Assessment	Patient characteristics	Outcome	Conclusions
Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS)							
Klepin et al. [55]	2013	$N = 70$	AML 70 years	GA	Cognitive impairment: HR 2.5 [1.2, 5.5] Impaired physical function: HR 2.2 [1.1, 4.6]	Survival	Survival at 30 days was inferior for patients with impairment in cognition and physical function
Deschler et al. [72]	2013	$N = 195$	AML and MDS 71 years	GA and Quality of Life	Impairment in activities of daily living (ADL): HR 2.10 [1.13, 3.89] Quality of life (QOL)-fatigue: HR 2.09 [1.17,3.71] KPS < 80%: HR 2.45 [1.23, 4.87]	Survival	Survival was inferior for patients with impairment in ADL and QOL-fatigue score of ≥ 50
Sherman et al. [73]	2013	$N = 368$	AML ≥ 65 years 65–70 (40.6%)	Quality of Life Comorbidity	Comorbidity: HR 1.92 [1.18, 3.11] Difficulty with strenuous activity: HR 2.18 [1.19, 4.0] Reports of pain: HR 2.17 [1.19, 3.97]	Survival	Patients with higher baseline comorbidity score; difficulty strenuous activity and pain had inferior survival
Fega et al. [74]	2015	$N = 114$	MDS 73 years	Quality of Life Clinical-pathologic data	Low serum albumin: HR 2.3 [1.06,5.14] Ease of taking a long walk: HR 0.44 [0.23, 0.90]	Survival	Low serum albumin and ease of taking a long walk added important prognostic information to survival
Buckstein et al. [75]	2016	$N = 445$	MDS 71 years	Rockwood Frailty Scale Comorbidity (Charlson comorbidity score)	Frailty: HR 2.7 [1.7, 4.2] Comorbidity: HR 1.8 [1.1, 2.8]	Survival	Survival was significantly shorter for patients with higher frailty and comorbidity scores
Klepin et al. [76]	2016	$N = 49$	AML 70 years	GA	Baseline depression and cognitive impairment	Decline in physical function (SPPB)	Patients with depressive symptoms before and during chemotherapy had greater decline in SPPB scores at baseline and on follow-up
Diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL)							
Merli et al. [77]	2014	$N = 99$	DLBCL 78 years	GA	GA "frail": HR 3.09 [2.20, 4.33]	Survival	Survival was inferior for frail patients even if they were treated with rituximab containing combination chemotherapy
Aaldriks et al. [46]	2015	$N = 44$	DLBCL 78 years	GA, Groningen Frailty Indicator (GFI), and laboratory markers	GFI: OR 9.2 [1.5, 55.8], HR 2.6 [1.1, 6.1]	Treatment withdrawal Survival	Abnormal nutrition, GFI scores, and low hemoglobin level were associated with not being able to complete intended chemotherapy Patients with frailty classification on GFI and low hemoglobin had inferior survival.
Tucci et al. [45]	2015	$N = 173$	DLBCL 77 years	GA International Prognostic Index (IPI)	IPI: HR 4.60 (1.35, 15.64] GA, 3.69 [1.09, 12.51]	Survival in "fit," "unfit," and "frail"	Curative treatment in unfit patients showed a clear trend towards better 2-year overall survival (75 vs. 45%) but not in frail patients (44 vs. 39%) IPI and CGA are associated with survival
Yoshida et al. [78]	2016	$N = 135$	DLBCL 72 years	GA	GA "unfit": HR 2.23 [18,4.22]	Survival	Survival was inferior for patients with ADL impairment and "unfit" classification on CGA

Table 1 (continued)

Author	Year of pub	Number of patients	Cancer type(s) Age [mean, median years]	Assessment	Patient characteristics	Outcome	Conclusions
Multiple myeloma							
Engelhardt et al. [79]	2017	$N = 801$	Myeloma 63 years	Revised Myeloma Comorbidity Index	Index > 6 "frail": OS 1.2 years Index 4–6 "intermediate fit": OS 4.4 years Index ≤ 3 "fit": OS 10.1 years	Survival	*Fit* (revised Myeloma Comorbidity Index of 1–3): OS 10.1 years *Intermediate fit* (revised Myeloma Comorbidity Index of 4–6): OS 4.4 years *Frail* (revised Myeloma Comorbidity Index of > 6) 1.2 years
Fiala et al. [80]	2017	$N = 340$	Myeloma 75 years	Frailty index (FI)	Lowest tertile of FI 48 vs. 23 months for the highest tertile of FI	Survival	Each 10% increase in FI was associated with a 15% increased risk of death
Li et al. [81]	2017	$N = 12,547$	Myeloma 66 years	Frailty defined as poor claims—based disability status (PDS)	PDS frail vs fit: 3-year OS: 34 vs 61% ($P = 0.01$) who began first-line therapy	Survival	Frail patients were older, had higher comorbidity, and worse OS
Nathwani et al. [82]	2017	$N = 210$	Myeloma 72 years	Modified GA including Palumbo frailty score	Frailty score influences provider decision-making 50% of the time	Treatment decision	Preliminary data support feasibility, usability, and acceptability of modified GA
Schutz et al. [83]	2017	$N = 150$	Myeloma 77 years	Edmonton frailty score	Frailty status: OR 8.2 [1.9, 34]	Early mortality	Frailty was associated with early death Frailty criteria independently associated with death include incontinence, polypharmacy, and previous hospital admissions
Hematologic malignancies (mixed)							
Velghe et al. [84]	2016	$N = 59$	Hematologic malignancies	Hand grip strength (HGS)	HGS: AUC 0.800 (women) and 0.847 (men)	Abnormal GA	HGS was associated with concurrent abnormal CGA
Hshieh et al. [85]	2016	$N = 235$	Hematologic malignancies 78 years	Cognition by Montreal Cognitive Assessment (MOCA)-delayed recall and Clock in Box (CIB)	Cognitive impairment per CIB: OR 1.89 [1.07, 3.34] MOCA delayed recall: OR 1.86 [1.02, 3.40]	Pre-frail or frailty status	Cognitive impairment likely contributes to overall frailty status
Teran et al. [86]	2017	$N = 32$	Hematologic malignancies 81 years	GA G8 screen	Frailty score influences therapeutic decisions in 34% of the time	Initial therapeutic decisions	Treatment was adjusted in 34% of the cases because of frailty score
Hematopoietic cell transplantation (HCT)							
Rosko et al. [66]	2015	$N = 55$	Myeloma autologous HCT 61 years	GA *p16 mRNA*	Objective physical function ($P = 0.04$) Self-reported physical function ($P = 0.05$)	Length of stay	Objective and subject measures of physical function may help identify older adults at high risk for adverse outcomes after autologous HCT
Wildes et al. [87]	2015	$N = 40$	Myeloma 69.5 years	GA	Age ($P = 0.047$) Slow time on TUG ($P = 0.048$) CCI ≥ 1 ($P = 0.002$) Poor baseline QOL ($P = 0.006$)	Not eligible for autologous HCT	In addition to age and comorbidity, TUG and patient self-reported quality of life were associated with autologous HCT eligibility
Muffly et al. [60]	2014	$N = 203$	Hematologic malignancies Allogeneic HCT 58 years	GA Phenotypic frailty Hematopoietic Cell Transplant Comorbidity Index (HCT-CI)	Limitations in IADLs: HR 2.38 [1.59, 3.56] Slow walk speed HR = 1.80 [1.14, 2.83] High HCT-CI: HR 1.56 [1.07, 2.28] Low mental function: HR 1.67 [1.12–2.48] Elevated C reactive protein: HR 2.51 [1.54, 4.09]	Survival	Patients with limitations in IADLs, slow walk speed, high HCT-CI, low mental function, and elevated serum CRP had inferior survival. This association is more pronounced in the cohort 60 and older IADL adds prognostic significance to HCT-CI

Table 1 (continued)

Author	Year of pub	Number of patients	Cancer type(s) Age [mean, median years]	Assessment	Patient characteristics	Outcome	Conclusions
Arora et al. [88]	2015	$N = 96$	Autologous and allogeneic HCT	GA Phenotypic frailty	Time from HCT: OR 3.7 [1.9, 7.2] Pre-HCT employment status (retirement): OR 7.3 [1.2–46.2] Pre-HCT medical leave/disabled: OR 11.2 [1.8, 67.7] Limitations in social activities: OR 1.04 [1.01, 1.07] Allogeneic HCT: OR 3.1 [0.9, 10.2]	Frailty status	The prevalence of frailty was 8% at baseline and increased to 39% by 6 months. This study identifies factors associated with frailty after HCT
Arora et al. [58]	2016	$N = 998$	Autologous and allogeneic HCT 42.5 years	Phenotypic frailty	Frailty status: OR 2.76 [1.7, 4.4]	Survival	HCT survivors were 8.4 times more likely to be frail than siblings Prevalence of frailty among young adult HCT survivors (8.4%) approaches that seen in the elderly general population (10%)

GA geriatric assessment, *ADL* activities of daily living, *KPS* Karnofsky performance status, *IADL* instrumental activities of daily living, *SPPB* Short Physical Performance, *TUG* Timed Up and Go, *OR* odds ratio, *HR* hazard ratio, *AUC* area under the curve, *OS* overall survival

Diffuse Large B Cell Lymphoma

Non-Hodgkin lymphoma (NHL) is a disease of older adults with a median age of onset of 71 years [40, 41]. Evaluating treatment intensity in the aging adult with NHL is a priority given the possibility of curative intent chemotherapy. In the most common NHL, diffuse large B cell lymphoma (DLBCL) full-dose treatment is associated with improved outcomes but must be balanced by the tolerability and safety of the therapy [42, 43]. Tucci et al. demonstrated that a GA utilizing age, ADL, comorbidities, and geriatric syndromes was better than clinical judgment in identifying patients fit for curative intent chemotherapy [44]. Prospective studies in DLBCL confirm unfit and frail patients who received palliative vs. curative intent had similar outcomes [45]. Others have demonstrated in older adults with both aggressive and indolent NHL that geriatric factors such as malnutrition and frailty had predictive value for treatment discontinuation and frailty and hemoglobin were independent predictors of mortality [46].

Chronic Lymphocytic Leukemia

In chronic lymphocytic leukemia (CLL), many novel therapies and studies have been targeted specifically for older adults. Half of all patients diagnosed with CLL are 70 years and older. Many frontline strategies are available for older adults with CLL and several studies have focused on understanding the impact of end organ function and comorbidities on therapeutic outcomes. As an example, prognostic factors in older adults with CLL (median age 70) identified that two or more comorbidities were associated with inferior PFS and OS [47]. The CLL9 trial implemented a comprehensive GA prior to fludarabine treatment to identify risk of treatment toxicity. Functional deficits using the objective Timed Up and Go (TUG) and screening tests for dementia (DEMTECT) were associated with inferior survival [48]. Advances in care for older adults for CLL are a result of dedicated clinical trials for older adults with comorbidities leading to a better understanding of treatment tolerance and response [49]. Furthermore clinical trials designed for aging adults with CLL led to the approval of ground-breaking treatments, such as ibrutinib [50].

Acute Myelogenous Leukemia

Older adults with acute myelogenous leukemia (AML) are among the most vulnerable patient population with the most diagnoses and deaths in those aged 65 years and older [51]. Older AML patients are more likely to have high risk cytogenetic features and overall poor outcomes [52, 53]. Moreover, the undertreatment (or no treatment) of older adults with AML is highly prevalent, where 60% of older adults in real-world analysis do not receive any therapy [54]. The goal of therapy for older adults with AML may be highly variable (curative vs.

Table 2 Interventions for geriatric syndromes

Domains	Common tools	Interventions
Function	ADL, IADL TUG, 4 m walk, SPPB, functional gait assessment, 5 times sit to stand, fall risk assessment, handgrip	Physical therapy, occupational therapy, aquatic therapy, durable medical equipment, falls education, home-safety evaluations (e.g., grab bars), medications for chemotherapy-induced neuropathy, compression stockings for chemotherapy-induced lower extremity edema, driver rehabilitation
Social support and function	Illness-specific subscales of social support (ISSS), MOS-SSS, MOS-SAS	Personal medical alert devices, medication assistance for financial restrictions, implement advance directives, arrange for transportation for medical appointments, home health care arrangements (nursing, home health aid) evaluation of elder mistreatment, respite needs, partnership with local aging agencies for community resources (e.g., silver sneakers, eldercare)
Cognition	Mini-mental state examination, MOCA, BOMC, DemTect, mini-COG, SLUMS, clock-drawing test	Medications for memory loss, if hearing loss: hearing aids for improved sensorium, identification of chemotherapy-induced cognitive impairment and longitudinal assessment
Psychologic	GDS Mental health inventory Mini GDS	Medications for anxiety, depression, coping and support, sleep recommendations, referral for psychology or psychiatry input
Nutritional status	Mini-nutritional assessment, anthropometrics	Dental evaluation for dentures, medications for appetite stimulants, improved medication control of nausea, calorie/protein/fluid recommendations
Polypharmacy	Beers criteria for potentially inappropriate medications, > 5 medications	Deprescribe, discontinue supplements/herbal remedies, provide education on drug-drug duplicates and interactions, provide safe alternatives for drugs that should be avoided in older adults, pillbox use, and reconciliation

MOS-SSS, Medical Outcome Survey-Social Support Survey; MOS-SAS, Medical Outcome Survey-Specific Adherence Scale; MOCA, Montreal Cognitive Assessment; BOMC, Blessed Orientation-Memory-Concentration; SLUMS, Saint Louis University Mental Status; GDS, Geriatric Depression Scale

palliative). Geriatric assessments in AML have identified that patients who receive traditional cytotoxic chemotherapy with impaired functional performance and/or cognitive impairments have inferior overall survival [55] Real-world analysis has demonstrated improved early mortality with intensive treatment over palliative treatment, independent of age or performance status at diagnosis [56]. Emerging personalized therapy for AML based on molecular abnormalities combined with physiologic age may transform our approach to older adults with AML.

Hematopoietic Cell Transplant

Increasingly, many older adults are undergoing autologous and allogeneic hematopoietic cell transplant (HCT). Older adults account for 39% of patients 60 years and older who undergo HCT, compared to < 10% during the years 1999–2005. HCT is associated with a serious toll on health status in older adults with hematologic malignancies and understanding goals of care is imperative for the patient–physician relationship.

The proportion of allogeneic HCT recipients ≥ 70 years increased from 0.1 to 3.85% from 2000 to 2013 due to lower-intensity conditioning regimens and more accurate human leukocyte antigen typing [57]. Two-year overall survival significantly improved from 26% in 2000–2007 to 39% in 2008–2013. Similarly, 2-year progression-free survival improved from 22 to 32% [57]. However, the 2-year transplant-related mortality and complications such as graft-versus-host disease remain unchanged thus highlighting the need to improve patient selection and improvement in the transplant process to minimize toxicity and morbidity for older patients [57].

The prevalence of frailty among young adult HCT survivors (8.4%) approaches that as seen in the older general population (10%) [58]. The prevalence of frailty and pre-frailty is 28 and 51%, respectively, in adults over age 50 prior to receiving allogeneic HCT [59]. In 203 patients with median age of 58 years who underwent allogeneic HCT, limitations in IADL (HR 2.38; $P < 0.001$), slow gait speed (HR 1.80; $P = 0.01$), and low mental health by short-form-36 mental component (HR 1.67; $P = 0.01$) pre-HCT were associated with worse survival [60]. Allogeneic HCT patients are faced with many limitations that can have a negative impact of resuming important life activities post-HCT. Patients' goal in the first year after allogeneic HCT is to regain physical, mental, and social function so they can participate in normal life. Addressing the impairment in these domains presents an opportunity for the healthcare team to maximize the benefit of HCT [61].

Recent studies showed that older HCT survivors are more vulnerable to cognitive impairment [62, 63]. Specifically, at 3 years post-HCT, reduced-intensity HCT recipients' scores declined significantly ($P < 0.003$) for executive function, verbal fluency, and working memory compared to non-cancer controls [63]. The ability to manage a complex medication regimen,

enjoy a hobby, and return to prior social roles is more difficult with cognitive impairment [64]. Given that allogeneic HCT survivors are at risk for accelerated aging, high burden of morbidity, and high prevalence of frailty and subclinical neurocognitive disorders such as mild cognitive impairment, screening for cognitive impairment is imperative to avoid further neurotoxicity that can lead to disability and loss of independence.

Autologous HCT is increasingly being implemented for older adults where 44% of patients who receive autologous HCT are > 60 years of age [65]. The number 1 indication is for multiple myeloma, a disease with rising incidence in older adults. Recently, several studies have sought to examine frailty and GA metrics in older adults undergoing autologous HCT. Recovery from autologous HCT in myeloma is related to functional performance status either by objective measures such as the short physical performance battery or IADL [66, 67]. Autologous transplant is also indicated in patients with lymphoma. Sun et al. retrospectively evaluated 170 patients with a median age of 72, 2-year PFS was 58% (95% [CI], 48–67%), and overall survival was 65% (95% CI, 55–74%) [68]. Interestingly, comorbidity scores were not predictive of NRM (7% NRM) further confirming the complexity and interdependence of a host of patient and disease factors on outcome. Implementing standardized metrics of the GA, including frailty, can identify individuals who are at greater risk for morbidity following autologous HCT.

Decision-Making for Older Adults with Hematologic Malignancy

Establishing the patient and family treatment goals (i.e., life prolongation, cure of disease, or symptom management), values, and preferences (i.e., functional independence, quality of life) is central to the consideration of malignant hematology decision process. This is followed by careful considerations of available data on the patient's prognosis based on estimated remaining life expectancy and age-specific cancer mortality with and without treatment. Finally, together with patient and family, the physician should help reconcile the treatment options risks and benefits with patient's treatment goals, values, and preferences. GA can also inform cancer management decision by assessing clinical feasibility (tolerance) and burden of the treatment to the patient and family in the context of each patient unique psychosocial needs. Once shared decision is made regarding a treatment, implementation of appropriate supportive care with the goal to maintain health, function, and quality of life is crucial in older adults. The Multinational Association for Supportive Care in Cancer defines supportive care in cancer as: "supportive care in cancer is the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. Supportive care aims to improve the quality of rehabilitation, secondary cancer prevention, survivorship, and end-of-life care" [69]. A hematologic malignancy diagnosis abruptly changes health status. In many cases, by treating the underlying illness, patients can and do improve allowing for potential treatment or transplant options that were not considered at diagnosis. Supportive care management will vary within the continuum of the disease.

Here we propose an integrated geriatric supportive care strategy starting at the time of diagnosis and throughout the continuum of care (Fig. 2). Treatment for hematological malignancies can worsen underlying chronic health conditions and may potentiate functional dependence and geriatric syndromes such as depression, malnutrition, and falls. Supportive care management of older patients with hematologic malignancies needs an approach that systematically assesses health status, functional abilities, and evaluation of geriatric syndromes unique to the individual. There is an opportunity to intervene with supportive care strategies at all time points along the cancer care continuum using validated GA tools. There is a need for a proactive approach to partner with geriatricians, palliative care, primary care physicians, physical therapy, occupational therapy, dieticians, and social work to leverage their expertise to improve outcomes for older adults. Finally, active participation and engagement of patients and family to increase self-efficacy in self-management of their health and decision-making is important to execute such a program.

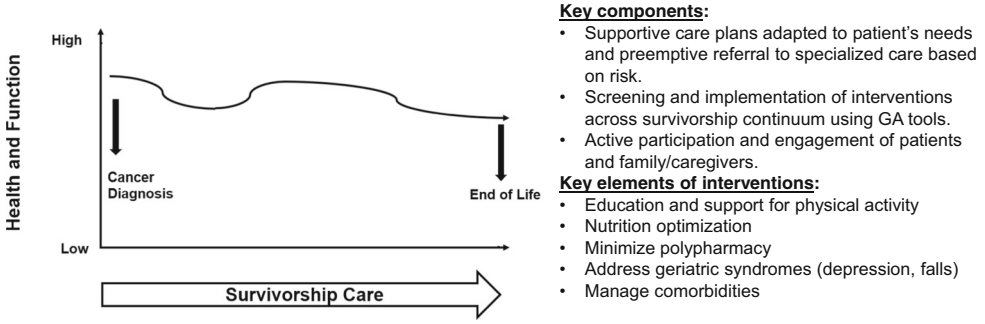

Fig. 2 An integrated geriatric supportive care strategy

Conclusions

Identifying frailty in patients with hematologic malignancy is relevant to both optimize best therapy and quality of life in older adults. Barriers to incorporate frailty metrics into best clinical practice are multifactorial. Older adults in general, including those with hematologic malignancy [70], are under enrolled and understudied in clinical trials [2•]. Requiring aspects of frailty in clinical trial design are necessary to advance the care of aging adults. Moreover, including translational science in the biology of aging, or geroscience, is important to the field of geriatric hematology/oncology research [71]. The need for assessments of physiologic age is increasingly necessary in the era of cellular therapy and intensive treatment such as transplant. These efforts to advance the biology of aging with geriatric research will improve the disease course and ideally mitigate treatment toxicity. The reviewed literature demonstrates the interdependence of health factors on treatment outcomes with aging. No single individual factor will determine health outcomes with aging, rather identifying patients who are vulnerable to toxicity and intervening on those factors can improve outcomes. In summary, the following key concepts can help guide the clinician when addressing frailty in hematologic malignancy.

- Aging is heterogeneous and health status cannot be summarized by chronologic age alone.
- Frailty is dynamic. A hematologic malignancy diagnosis abruptly changes health status. In many cases, by treating the underlying illness patients can and do improve allowing for potential treatment or transplant options that were not considered at diagnosis.
- A Geriatric Assessment is an established tool to identify frailty and assess for etiologies contributing to the frailty syndrome.
- Objective measures of health status using geriatric assessments partnered with subjective measures are better than clinical judgment alone.
- Partner with geriatricians or specialized care teams dedicated to aging adults to optimize health factors with aging.
- Preserving quality of life is meaningful in the older adults. Shared decision-making is made to establish goals and expectations regarding prognosis. Implementation of appropriate supportive care with the goal to maintain health, function, and quality of life is crucial in older adults.

Compliance with Ethical Standards

Conflict of Interest Thuy Koll and Ashley E. Rosko declare that they have no 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.

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