Biol Blood Marrow Transplant 23 (2017) 193–200

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Aging: Treating the Older Patient

Ashley Rosko [1,†], Andrew Artz [2,*,‡]

[1] Department of Internal Medicine, Ohio State University, Columbus, Ohio
[2] Department of Medicine, University of Chicago, Chicago, Illinois

Article history:
Received 28 September 2016
Accepted 4 November 2016

Key Words:
Multiple myeloma
Acute myeloid leukemia
Transplant
Elderly
Geriatric assessment
Autologous
Allogeneic

THE OLDER MYELOMA PATIENT: EVALUATING AGING AND UNDERSTANDING FITNESS

Overview

Multiple myeloma (MM) is an incurable plasma cell malignancy of older adults. The median age at diagnosis is 69 years, and in the next 15 years the incidence of MM is expected to double in this age demographic [1,2]. Novel therapeutics and the routine use of autologous stem cell transplant have led to substantial improvements in overall response rates and durable remissions [3]. In contrast with younger MM patients, older patients have only modest improvements in overall survival [4-6]. MM deaths overall are highest in patients aged 75 years and greater, and early mortality is most common in those 70 years and older [3,7]. The disparity in overall survival for aging adults is multifactorial and is secondary to comorbidities, treatment strategy, toxicities, physiologic reserve, and therapy discontinuation.

Transplant "eligibility" is an active and important area of MM investigation. Autologous stem cell transplant is established in younger populations to improve survival over nontransplant therapy [8,9] and has progression-free survival advantages over delayed transplant [10]. Autologous stem cell transplant is feasible and an efficacious component of therapy for older patients with MM as well [11]. Older adults mobilize sufficient numbers of stem cells and can tolerate transplant with excellent outcomes, resulting in increased numbers of older adults undergoing autologous transplant [11]. Nearly half of autologous transplants are done in adults 60 years and greater, and this number will only increase as the population ages [12]. Referral bias for transplant still exists, likely because of historic reports depicting conflicting tolerance, response rates, and survival [13].

Transplant Eligibility

Transplant eligibility is matter of estimating a patients' physiologic reserve for an intensive therapy [14]. Identifying and intervening on factors that contribute to vulnerability in pretransplant MM patients is imperative to balance quality of life with an efficacious therapy. One method to identify and resolve occult health factors is a geriatric assessment (GA), which is a global evaluation of the health of older adults. A GA goes beyond the disease-focused history and aims to identify unrecognized issues to intervene and prevent future complications. GA tools are established metrics to accurately assess risk of morbidity and mortality in cancer populations [15,16]. The GA consists of a multidimensional evaluation of functional status, fall history, social support, cognitive and psychological status, sensory loss, nutritional status, comorbidities, and a polypharmacy evaluation.

Table 1 depicts a set of tools often used in a cancer-specific GA. GAs have been shown to predict mortality and toxicity, independent of performance status and age [17]. Traditional metrics, such as Karnofsky performance status, are often overestimated by clinicians and are a poor indicator of treatment toxicity risk [18].

Financial disclosure: See Acknowledgments on page 198.
* Correspondence and reprint requests: Andrew Artz, MD, MS, University of Chicago, Chicago, IL 60637.
E-mail address: aartz@medicine.bsd.uchicago.edu (A. Artz).
† The Older Myeloma Patient: Evaluating Aging and Understanding Fitness.
‡ The Older AML Patient: Candidacy and Optimization for Allogeneic Transplant.

http://dx.doi.org/10.1016/j.bbmt.2016.11.007

Table 1
Geriatric Evaluation for Older AML Candidacy for Allogeneic Transplant

Domains	Common Tools	Additional Geriatric Questions
Comorbidity	HCT-CI	Remote cancer, urinary problems, visual or hearing impairment, diastolic dysfunction, prior renal impairment, osteoporosis
Function	IADL Timed up and go, grip strength, 4-m walk	Arthritis, falls, maximum ability for physical activity, exercise, balance
Social support and function	Illness-specific subscales of social support Center-specific tool	Backup caregiver, alcohol use, stairs at home, person preparing meals, power of attorney
Cognition	Mini-Mental State Exam or Montreal cognitive assessment	Prior confusion, memory impairment and duration Assess retention of information without family member interjection
Psychological	Geriatric Depression Scale Mental Health Inventory 17	Sleep problems, motivation for transplant, coping skills, preparation for setbacks, life goals (eg, specific event)
Nutritional status	Weight loss, body mass index	Last dental evaluation, dentures, use of supplements, effect of prior therapy on nutrition and weight
Polypharmacy	>5 medications	Over-the-counter medications, side effects from prior medication, clarify remote allergies

The treatment approach for MM is heterogeneous because of concerns for frailty and tolerance in older adults. Primary dose reductions and therapy discontinuations result in worse outcomes in older adults with MM [19,20]. Although it is known that functional assessments can improve on outcomes in cancer patients, feasibility, practicality, and disease specificity are barriers to implementation [21-23]. Nonetheless, a simple GA based on age, comorbidities, cognition, and physical function can predict mortality in the MM population. Frailty assessments in MM patients were predictive of death independent of treatment, cytogenetics, or stage [20].

Biomarkers of Physiologic Age

Novel aging biomarkers are being explored to provide a rapid measure of physiologic fitness [24,25]. Ideally, an aging biomarker would capture vulnerability by estimating physiologic reserve and risk for chemotherapy and/or transplant toxicity. Exploring biomarkers of aging in a cancer population is particularly challenging, because many aging biomarkers are evaluated in a community-dwelling population without a cofounding factor of cancer. Despite these challenges, many potential biomarkers of aging are being explored to evaluate the relationship among chronologic aging, frailty syndromes, and cancer. Candidate biomarkers include molecular markers, inflammatory markers, immunosenescence panels, serum and hematologic parameters, and hormones (Table 2). Each of these biomarkers has associations with aging and frailty and variable relationships with autologous hematopoietic stem cell transplant and myeloma. Inflammatory markers such as IL-6, C-reactive protein, tumor necrosis factor-α, and D-dimer have reported associations with frailty in oncology studies [26]. Inflammatory panels such as the senescence-associated secretory phenotype has a well-established relationship with aging, gerontologic conditions, and frailty [27].

Distinct changes in the immune system are reported with aging [28,29] and are being explored with frailty [30,31]. Many of the distinct changes in T cell dysfunction found in MM patients parallels that of aging and frail populations. T cell dysfunction is commonly reported in MM where markers of immunosenescence are associated with relapsed disease [32]. Clonal expansions of T cells are common with aging and are also present with long-term survival in MM [33], although the biology of clonal expansions may differ. Anemia, inherent to MM, has been independently associated with functional disability in older adults [34]. miRNA expression profiles have been shown to correlate with age in healthy populations [35], cardiovascular disease [36,37], but not frailty in solid tumor cancer populations [38]. Other biomarkers, such as N-terminal fragment of B-type natriuretic peptide, have recently been shown as useful predictors of survival, independent of age and performance status in MM patients [39]. Markers of T cell immunosenescence and exhaustion have recently been reported to have an association with relapse after MM transplant [40].

A molecular marker of cellular senescence is peripheral blood T cell $p16^{INK4A}$ (*p16*). *p16* mRNA accumulates in aging tissues and increases with chronologic aging and with internal and external stresses [41-44]. Over the human lifespan,

Table 2
Aging and Frailty Assessments

		Aging	Frailty	Transplant	Myeloma
Molecular markers	$p16^{INK4A}$	x		x	
	Leukocyte telomere length	x			
	DNA methylation	x			
	miRNA				
Immune dysregulation	Immunosenescence	x	x		x
	SASP	x	x		
Heme parameters	Anemia	x	x		
Serum markers	IL-6	x	x	x	x
	CRP	x	x		
	NT-proBNP		x		x
	Albumin	x	x	x	
	D-dimer	x	x		
	TNF				
	sICAM-1		x		
Clinical tools	GA metrics	x	x	x	x

SASP indicates senescence-associated secretory phenotype; CRP, C-reactive protein; NT-pro-BNP, N-terminal fragment of B-type natriuretic peptide; TNF, tumor necrosis; sICAM-1, Soluble intercellular adhesion molecule-1.