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ONCOLOGY GRAND ROUNDS

Optimizing Treatment for Elderly Patients With Newly Diagnosed Multiple Myeloma: A Personalized Approach

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The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

An 84-year-old woman presented with bone pain and lytic bone lesions in April 2010. Diagnosis of multiple myeloma was based on the presence of an immunoglobulin G lambda serum M protein (4,784 mg/dL) and confirmed by the findings of bone marrow plasma cell infiltration, with t(11;14) chromosomal abnormality detected by fluorescence in situ hybridization analysis. The patient's medical history was significant for hypertension; she had an Eastern Cooperative Oncology Group performance status of 1, International Staging System (ISS) stage of 1, and Durie–Salmon stage of IIIA. In May 2010, the patient was enrolled in a randomized phase III trial comparing different lenalidomide-based treatments and received induction with lenalidomide plus dexamethasone (nine cycles) followed by lenalidomide maintenance. The patient started treatment with lenalidomide 25 mg per day for 21 days and reduced-dose dexamethasone 20 mg per week per protocol because of age. Induction was well tolerated; no relevant complications occurred, except for grade 1 fatigue and grade 1 diarrhea. Best response was partial response. In March 2011, she started maintenance with lenalidomide 10 mg per day. A dose reduction of lenalidomide 5 mg per day was required because of grade 2 diarrhea. In July 2015, the patient experienced relapse, with painful collapse of L3 vertebral body.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Multiple myeloma (MM) is a neoplastic disease deriving from an abnormal proliferation of monoclonal plasma cells in the bone marrow and immunoglobulin or light chain overproduction that can cause end-organ damage.[1] Despite recent advances, MM remains incurable. Its natural history is characterized by subsequent relapses, with shorter disease-free and asymptomatic status intervals, until the disease becomes refractory to therapies.[1]

MM predominantly affects elderly patients; median age at diagnosis is 70 years, and almost one third of patients are older than 75 years of age, with the highest rates of diagnosis reported in the 80- to 89-year age group.[2] The International Staging System (ISS) stratifies patients into three prognostic groups.[3] Chromosomal abnormalities, such as deletion 17 or translocations (4;14) and (14;16), have been found to be associated with poor prognosis.[4]

Age has long been considered the leading criterion in defining patients' treatment. The cutoff age of 65 years defines eligibility for autologous stem-cell transplantation (ASCT; for patients age < 65 years) or combination regimens (for patients age ≥ 65 years). Since biologic age does not always correspond to chronologic age, this strict range may differ by approximately 5 years. Patients > 70 years of age are less likely to benefit from ASCT and are treated with combination regimens, and elderly patients (age > 75 years) are treated using gentler approaches, with therapeutic agents often administered at lower doses than in younger, fitter patients.[5]

Melphalan plus prednisone (MP) had long been the reference treatment for elderly patients, with a median survival of 29 to 37 months.[6] In the last decade, new effective treatments, including novel agents thalidomide, bortezomib, and lenalidomide, have replaced the formerly standard MP. Current standard treatment of patients > 65 years of age (or younger with significant comorbidities and unsuitable for ASCT) consists of MP plus either thalidomide (MPT) or bortezomib (VMP).[7,8] Recently, continuous lenalidomide and low-dose dexamethasone (Rd) was shown to be superior to MPT.[9]

Registry data show that 5-year OS has improved markedly in recent years for patients 45 to 64 years of age; however, less benefit was seen among patients 65 to 74 years of age, and no improvement was seen for patients > 75 years of age.[10] The elderly population is highly heterogeneous, and the well-known biologic and genetic prognostic factors, as well as age per se, are insufficient to explain this survival difference. One limitation is that elderly patients usually do not meet eligibility criteria and thus are under-represented in clinical studies.[11]

In hemato-oncology, the term frail often improperly refers to a person > 75 years of age, which sometimes leads to inadequate, undertreatment of fit patients or overtreatment of frail patients based only on age. Currently, chronologic age, performance status, and clinician judgment are commonly used in the decision-making process but do not account for the heterogeneity of the older population.[5] Furthermore, geriatric impairments are highly prevalent in elderly patients (even in those with good performance status); they may not be easily detected and may impact a patient's ability to complete treatment.[12,13]

SUMMARY OF THE RELEVANT LITERATURE

Geriatric Assessment

It is crucial to appropriately assess the frailty status of elderly patients, particularly those > 75 years of age, to identify frail patients and consequently determine their optimal treatment. An objective and reproducible tool that could assist clinicians in tailoring therapy, not only according to disease-specific parameters but also to a patient's health status, is fundamental.

The comprehensive geriatric assessment (CGA) is a systematic procedure to objectively appraise the health status of older people, focusing on somatic, functional, and psychosocial domains. It is a highly sensitive and specific tool, and it is more objective and reliable than clinical judgment.[12-14]

Recently, the International Myeloma Working Group (IMWG) conducted a pooled analysis of data on 869 individual patients from three prospective trials and proposed a score for the measurement of frailty in elderly patients with newly diagnosed MM. At diagnosis, a simplified geriatric assessment was performed including: the Activity of Daily Living (ADL) and the Instrumental Activity of Daily Living (IADL) scales to assess self-care activities, household management tasks, independence status, and the Charlson comorbidity index to evaluate the number and severity of comorbidities. The cutoff age to define frail patients was established at 80 years of age. An additive scoring system (range, 0 to 5) based on age and these three tools was developed, and three groups of patients were identified: fit (score, 0; 39%), intermediate (score, 1; 31%), and frail (score, ≥ 2; 30%). Frailty was associated with inferior overall survival (OS; 3-year OS, 57% v 84%; P = .042), progression-free survival (PFS; 3-year PFS, 33% v 48%; P < .001), and higher nonhematologic toxicities and treatment discontinuation, regardless of ISS stage, chromosome abnormalities, or treatment. Because performing a geriatric assessment can be manpower and time consuming, a computer application was also created to support clinicians.[15]

This frailty score was also validated in the phase III FIRST (Frontline Investigation of Revlimid Plus Dexamethasone Versus Standard Thalidomide) trial. Patients were categorized into three severity groups. Of 1,517 patients, 17% were classified as fit, 30% as intermediate, and 54% as frail. Similar breakdowns were observed

Table 1. Selected Studies in Elderly Patients With Myeloma

Regimen	Patient Age ≥ 75 Years (%)	ORR (%)	Median PFS (months)	OS	P for Survival
MP	25*	50	13	66% at 3 years	.25†
MPR	24*	68	14	62% at 3 years	.81†
MPR-R	24*	77	31	70% at 3 years	
Rd	35*	75	25.5	59% at 4 years	.02‡
Rd18	36*	73	20.7	56% at 4 years	
MPT	34*	62	21.2	51% at 4 years	
Rd	37*	74	21	58% at 4 years	.927§
MPR	39*	71	24	65% at 4 years	.448§
CPR	36*	68	20	68% at 4 years	
VD	50	73	14.7	49.8 months‖	.79
VTD	38	80	15.4	51.5 months‖	
VMP	37	70	17.3	53.1 months‖	
VP¶	84#	64	14.0	60% at 2 years	NA
VCP¶	67#	67	15.2	70% at 2 years	
VMP¶	76#	86	17.1	76% at 2 years	

Abbreviations: CPR, cyclophosphamide, prednisone, and lenalidomide; MP, melphalan plus prednisone; MPR, melphalan, prednisone, and lenalidomide; MPR-R, melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance; MPT, melphalan, prednisone, and thalidomide; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; Rd18, lenalidomide plus dexamethasone for 18 months; VCP, bortezomib, cyclophosphamide, and prednisone; VD, bortezomib plus dexamethasone; VMP, bortezomib, melphalan, and prednisone; VP, bortezomib plus prednisone; VTD, bortezomib, thalidomide, and dexamethasone.
*Age > 75 years.
†P = .25 for MPR-R v MPR and P = .81 for MPR-R v MP.
‡P = .02 for Rd v MPT.
§P = .927 for Rd v MPR and P = .448 for Rd v CPR.
‖Median values.
¶Low-dose regimens.
#Patients age ≥ 80 years: 21 (41%) in VP, 14 (27%) in VCP, and 15 (30%) in VMP arms.

across treatment arms. Frail patients were older and had higher ISS stage, worse performance status, higher lactate dehydrogenase levels, and worse renal function than fit or intermediate patients. Of note, fit patients had a significantly longer OS. This analysis demonstrated predictive clinical outcomes in patients with newly diagnosed MM, similar to the original scale. A majority of patients fell into the frail category, demonstrating that this trial studied an at-risk population with poor outcomes and unmet need.[16]

Treatment Options for Elderly Patients

MPT and VMP are the current standards of care for older patients with newly diagnosed MM.[7,8] Recently, the European and US regulatory authorities approved Rd for ASCT-ineligible patients.[9] To date, there have been no prospective trials evaluating geriatric assessment–driven treatments in elderly patients with newly diagnosed MM; the best strategy for frail patients remains to be defined.

The frequency of patients > 75 years of age was 22% to 30% in the MPT and VMP regulatory trials,[7,8] but in recent trials, this percentage has been growing (Table 1). The optimal therapy for elderly patients remains controversial; some favor less intensive treatments (eg, doublet) to minimize complications, whereas others support the use of full-dose therapies (eg, triplet) to maximize survival benefit. Several trials, also conducted in the community-based setting, have highlighted that a doublet therapy may be as effective as a triplet, considering both efficacy and treatment-related toxicities, particularly in patients > 75 years of age.

The MM-015 trial showed that MP plus lenalidomide (MPR) followed by lenalidomide maintenance significantly prolonged PFS (31 months) compared with MP (13 months; $P < .001$) or MPR without maintenance (14 months; $P < .001$). The rate of patients > 75 years of age in the trial was 24%. Patients 65 to 75 years of age benefited the most, whereas those > 75 years of age did not.[17]

Another phase III trial compared MPR versus cyclophosphamide, prednisone, and lenalidomide versus the doublet Rd in elderly patients with newly diagnosed MM. The three-drug alkylator-containing combinations were not superior to the two-drug combination Rd. In addition, grade 3 or greater neutropenia was significantly more frequent with MPR (64%) than with Rd (25%; $P < .001$).[18]

In the randomized phase III UPFRONT (Velcade, Thalidomide, and Dexamethasone Versus Velcade and Dexamethasone Versus Velcade, Melphalan, and Prednisone) trial, the doublet bortezomib plus dexamethasone was as effective as the triplets VMP and bortezomib, thalidomide, and dexamethasone and induced a lower rate of nonhematologic adverse events (22% v 33% to 37% with the three-drug combinations). Although all regimens produced good outcomes, neither bortezomib, thalidomide, and dexamethasone nor VMP offered any advantage over bortezomib plus dexamethasone in patients treated in US community practice.[19]

A phase II trial evaluated three low–dose-intensity subcutaneous bortezomib-based treatments in patients age 75 years or older. This study showed that bortezomib plus oral prednisone (VP), VP plus cyclophosphamide, or VMP, followed by bortezomib maintenance, were well tolerated and effective, with similar efficacy among VP, VP plus cyclophosphamide, and VMP. Rates of toxicity, discontinuation, and early death resulting from toxicity were higher with VMP, particularly in frail patients (defined according to the IMWG frailty score), who comprised 54% of the study population.[20]

In the report accompanying this article, Hulin et al[21] present an updated analysis of the FIRST trial, additionally examining the impact of age ($\leq 75 v > 75$ years), a stratification factor in the study, on efficacy and safety of continuous Rd versus MPT and Rd for 18 months (Rd18). After a median follow-up of approximately 4 years, continuous Rd reduced the risk of progression or death compared with MPT, independent of age. However, in patients > 75 years of age, median PFS was similar across treatment arms, even though the risk of progression or death with continuous Rd was reduced by 22% and 20% versus Rd18 and MPT, respectively, and 4-year PFS was more than double compared with Rd18 and MPT. Rd18 induced a similar PFS compared with MPT and a marginally inferior OS compared with continuous Rd. Median OS was longer with continuous Rd than MPT, including a 14-month difference in patients > 75 years of age. In the continuous Rd arm, grade 3 to 4 treatment-emergent adverse events were similar between patients < 75 years of age or > 75 years of age; however, older patients had more frequent lenalidomide dose reductions. Age-based dose adjustments likely contributed to a consistent safety profile between younger and older patients. Importantly, 35% of patients > 75 years of age who received continuous Rd continued to receive therapy for more than 2 years, compared with 41% of patients ≤ 75 years of age. This analysis establishes continuous Rd as a new standard of care for patients with newly diagnosed MM, regardless of age.

Table 2. Parameters to Consider in Decision-Making Process in Frail Patients With MM

Patient Characteristic	Medical History	Criteria to Start Treatment	Disease Characteristic	Goal of Treatment
Age	Cardiovascular disease	Myeloma-defining events:	Cytogenetics	Response (CR)
Functional and independence status (ADL and IADL)	Thromboembolism	Calcemia, renal impairment, anemia, bone lesions	Stage (ISS)	Disease control
Comorbidity (CCI)	Diabetes	or	Tumor aggressiveness	Quality of life
Psychosocial status	Renal impairment	Biomarkers of malignancy:		
	Peripheral neuropathy	≥ 60% clonal bone marrow plasma cells		
		Involved or uninvolved serum FLC ratio ≥ 100		
		> One focal lesion on MRI		

Abbreviations: ADL, Activity of Daily Living; CCI, Charlson comorbidity index; CR, complete response; FLC, free light chain; IADL, Instrumental Activity of Daily Living; ISS, International Staging System; MM, multiple myeloma; MRI, magnetic resonance imaging.
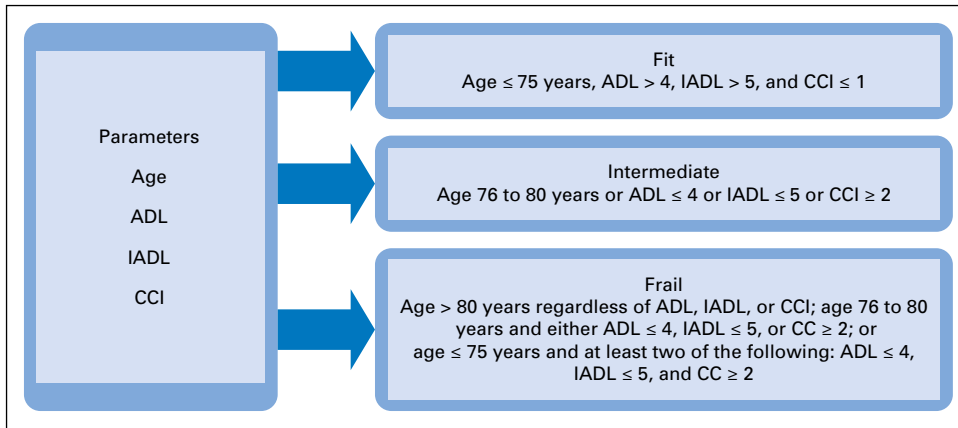
Fig 1. Framework for the definition of frailty status in elderly patients with myeloma. ADL, Activity of Daily Living; CCI, Charlson comorbidity index; IADL, Instrumental Activity of Daily Living.

SUGGESTED APPROACHES TO MANAGEMENT

In a pooled analysis of 1,435 elderly patients enrolled in four European phase III trials, advanced age ($\geq$ 75 years), occurrence of severe adverse events, and drug discontinuation predicted shorter survival in patients with newly diagnosed MM treated with MP alone or in combination with thalidomide and/or bortezomib. Therefore, avoiding treatment interruption and reducing the risk of adverse effects in the initial phase of therapy are fundamental, and low–dose-intensity treatments are appropriate options for these patients.[22]

Because the benefits obtained with new drug–based combinations may be limited in older patients, an approach that includes age and geriatric assessment should be adopted to appropriately define and identify frail patients (Table 2). Some frail patients are < 80 years of age, and conversely, some patients > 75 years of age are not frail. Indeed, the presence of either functional decline on ADL and IADL or the presence of comorbidities, rather than age per se, may identify frail patients (Fig 1). Practical strategies are necessary to recognize and appropriately manage frail patients to avoid the undertreatment of fit patients and the overtreatment of frail patients. Geriatric assessment is more accurate than traditional parameters such as age, performance status, and clinical judgment; thus, it is the most adequate tool and should be introduced into everyday clinical practice.[23] As an alternative to a full CGA, screening tools may be implemented to identify patients in need of a deeper evaluation by a CGA.[23,24] In MM, a simplified geriatric assessment that includes ADL, IADL, and CCI was recently introduced by the IMWG.[15]

On the basis of the results of a geriatric assessment, patients can be stratified into a fit group, suitable for full-dose therapy with three-drug combinations, or a frail group, requiring dose-adjusted therapies. Treatment strategies for frail patients should have minimal cumulative toxicity, which does not exacerbate any pre-existing pathologic conditions. In this setting, two-drug regimens have shown similar efficacy and limited toxicity as compared with multidrug combinations. Additional studies are needed to define more precise geriatric assessment–directed treatment selection.

The medical history of each patient, including cardiovascular disease, thromboembolism, diabetes, renal insufficiency, peripheral neuropathy, and psychosocial status, in addition to aggressiveness of disease, should be taken into account to decide the most appropriate drugs, dosing, schedule, and route of administration (oral, intravenous, or subcutaneous).[25] In the case of our patient, an 84-year-old (frail by definition) is considered at high risk for toxicity and early discontinuation. Our patient received lenalidomide plus reduced-dose dexamethasone. Treatment-related toxicities were limited, and benefit was long lasting because progression occurred after more than 60 months from diagnosis. The age-based dexamethasone dose reduction and the reduction of lenalidomide from 25 to 10 mg during maintenance likely contributed to good tolerability and an extended duration of treatment. Furthermore, lenalidomide has the advantage of oral administration, thus improving compliance and adherence to therapy.

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