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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1615725 since 2023-02-10T17:57:24Z

Published version:

DOI:10.1200/JCO.2016.68.6113

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03 February 2025

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This is the author's version of the contribution published as:

Larocca A, Palumbo A. Optimizing Treatment for Elderly Patients With Newly Diagnosed Multiple Myeloma: A Personalized Approach. J Clin Oncol. 2016 Oct 20;34(30):3600-3604. doi: 10.1200/JCO.2016.68.6113. PMID: 27601551.

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The publisher's version is available at:
https://ascopubs.org/doi/pdf/10.1200/JCO.2016.68.6113?role=tab |
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Optimizing treatment for very elderly patients with newly diagnosed multiple myeloma: a personalized approach.

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A 84-year old woman presented with bone pain and lytic bone lesions in April 2010. MM diagnosis was based on the presence of an IgG-lambda serum M-protein (4784 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 (FISH) analysis,. The patient's medical history was significant for hypertension; she had an Eastern Cooperative Oncology Group (ECOG) performance status of 1, International Staging System (ISS) stage 1, and Durie and Salmon IIIA. In May 2010 the patient was enrolled in a randomized phase 3 trial comparing different lenalidomide-based treatments, and received induction with lenalidomide-dexamethasone (9 cycles) followed by lenalidomide maintenance. The patient started treatment with lenalidomide 25 mg/day for 21 days and reduced dose dexamethasone 20 mg/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/d. A dose reduction of lenalidomide 5 mg/d was required due to grade 2 diarrhea. In July 2015 the patient relapsed 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 still 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 a third of patients are older than 75 years, with the highest rates of diagnoses reported in the 80-89-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 a poor prognosis.[4]

Age has long been considered the leading criterion to define patients' treatment. The cut-off age of 65 years defines eligibility for autologous stem cell transplantation (ASCT) (for patients younger than 65 years) or

combinations regimens (for patients older than 65 patients). Since biologic age does not always correspond to chronologic age, this strict range may differ by approximately 5 years. Patients over the age of 70 years are less likely to benefit from ASCT and are treated with combination regimens, and very elderly patients (>75 years) are treated using gentler approaches, with therapeutic agents often given at lower doses than in younger, fitter patients.[5]

Melphalan-prednisone (MP) had long been the reference treatment for elderly patients, with a median survival of 29-37 months.[6] In the last decade, new effective treatments including novel agents thalidomide, bortezomib and lenalidomide, have replaced the former standard MP. Current standard treatment for patients older than 65 years (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) showed to be superior to the MPT.[9]

Registry data show that 5-year OS has improved markedly in recent years for patients aged 45-64 years; however, there was a lower benefit seen among patients aged 65-74 and no improvement for patients over 75 years.[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 underrepresented in clinical studies.[11]

In hemato-oncology often the term "frail" improperly refers to a person >75 years, which sometimes leads to an inadequate under-treatment of fit or over-treatment of frail patients based only on age. To date, chronological 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 on the 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, to identify frail patients and consequently determine their optimal treatment. An objective and reproducible tool that could assist clinicians tailor therapy not only according to disease-specific parameters but also to 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) has conducted a pooled analysis of 869 individual patient data from 3 prospective trials and proposed a score for the measurement of frailty in elderly newly diagnosed myeloma (NDMM) patients. 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, tasks of household management, and independence status; and the Charlson Comorbidity Index (CCI) to evaluate number and the severity of comorbidities. The cut-off age to define frail patients was established at 80 years. An additive scoring system (range 0-5) 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 survival (3-year OS: 57% versus 84%, P=0.042), progression-free survival (3-year PFS: 33% versus 48%, P<0.001), and higher non-hematologic toxicities and treatment discontinuation, regardless of ISS stage, chromosome abnormalities, and treatment. Because performing a

geriatric assessment can be manpower- and time-consuming, an application for computer was also created to support clinicians.[15]

This frailty score was also validated in the phase 3 FIRST trial. Patients were categorized into three severity groups. Of 1517 patients, 17% were classified as fit, 30% as intermediate, and 54% as frail. Similar breakdowns were observed 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 NDMM similar to the original scale. The 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 very elderly patients

MPT and VMP are the current standards of care for older NDMM.[7, 8] Recently, the European and American regulatory authorities approved Rd for ASCT-ineligible patients.[9] To date, there are no prospective trials that evaluate geriatric assessment-driven treatments in elderly NDMM and so the best strategy for frail patients still remains to be defined.

The frequency of patients >75 years was 22-30% in the MPT and VMP regulatory trials, but in recent trials this percentage is growing (Table 1). The optimal therapy for very elderly patients remains controversial, some favor less intensive treatments (such as doublet) to minimize complications, while others support the use of full-dose (such as triplet) therapy to maximize survival benefit. Several trials, also in the community-based setting, highlighted that a doublet therapy may be as effective as a triplet, considering both efficacy and treatment-related toxicities, in particular in patients >75 years.

The MM-015 trial showed that melphalan-prednisone-lenalidomide (MPR) followed by lenalidomide maintenance (MPR-R) significantly prolonged PFS (31 months) compared with MP (13 months; P<0.001) or MPR without maintenance (14 months; P<0.001). The rate of patients >75 years was 24%. Patients age 65 to 75 years benefited the most, while those older than 75 years did not.[17]

Another phase 3 trial compared MPR versus cyclophosphamide-prednisone-lenalidomide versus the doublet Rd in elderly NDMM. The three-drug alkylator-containing combinations were not superior to the two-drug combination Rd. In addition, grade ≥3 neutropenia was significantly higher with MPR (64%) than with Rd (25%; P<0.0001).[18]

In the phase 3 randomized, UPFRONT trial, the doublet bortezomib-dexamethasone (VD) was as effective as the triplets VMP and bortezomib-thalidomide-dexamethasone (VTD), and induced a lower rate of non-hematologic adverse events (22% compared with 33-37% with the three-drug combinations). Although all regimens produced good outcomes, VTD and VMP did not offer any advantage over VD in patients treated in US community practice.[19]

A phase 2 trial evaluated three low-dose intensity subcutaneous bortezomib-based treatments in patients aged 75 years or older. This study showed that bortezomib and oral prednisone (VP) or plus cyclophosphamide (VCP) or VMP, followed by bortezomib maintenance were well tolerated and effective, with similar efficacy between the VP and the VCP and VMP. Toxicities, discontinuation rate and early deaths due to toxicity were higher with VMP, particularly in frail patients (defined with the IMWG frailty score) who were 54% of the whole study population.[20]

In their accompanying article, Hulin et al. presented an updated analysis of the FIRST trial, and additionally examined the impact of age (≤75 versus >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 versus MPT, independently of age. However, in patients

>75 years, 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. In the continuous Rd arm, grade 3-4 treatment-emergent adverse events were similar between patients ≤75 and >75 years; 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 who received continuous Rd remained on therapy for >2 years compared to 41% of patients ≤75 years. This analysis established continuous Rd as a new standard of care for patients with NDMM, regardless of age.

Suggested Approaches to Management

In a pooled analysis of 1435 elderly patients enrolled in four European phase III trials, advanced age (≥75 years), the occurrence of severe adverse events, and drug discontinuation predicted shorter survival in NDMM patients treated with MP alone or in combination with thalidomide and/or bortezomib. Therefore, avoiding treatment interruption and reducing the risk of side effects in the initial phase of therapy are fundamental, and low-dose intensity treatments are appropriate options for these patients.[21]

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). A portion of frail patients are younger than 80 years and conversely some patients older than 75 years are not frail. Indeed, the presence of either a functional decline on ADL and IADL, or the presence of comorbidities, rather than age per se may identify frail patients (Figure 1). Practical strategies to recognize and appropriately manage frail patients and to avoid under-treatment of fit patients and over-treatment of frail ones are necessary. The geriatric assessment is more accurate than traditional parameters such as age, performance status and clinical judgment, thus it is the most adequate tool and it should be introduced in everyday clinical practice.[22] As an alternative to a full CGA, screening tools may be implemented to identify patients in need for a deeper evaluation by a CGA.[22, 23] In MM, a simplified geriatric assessment that includes ADL, IADL and CCI has been recently introduced by the IMWG.[15]

Based on the results of the geriatric assessment, patients can be stratified into fit patients suitable for full-dose therapy with 3-drug combinations, or frail patients 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 2-drug regimens showed similar efficacy and limited toxicity as compared to multi-drug combinations. Further studies are needed to define a more precise geriatric assessment-directed treatment selection.

The medical history of the patient, including cardiovascular disease, thromboembolism, diabetes, renal insufficiency, peripheral neuropathy and psyco-social status, beside aggressiveness of the disease, should be taken into account to decide the most appropriate drugs, dosing, schedule, route of administration (oral, intravenous or subcutaneous) for each patient.[24]

In our patient's case, an 84 year old patient (frail by definition) is considered at high risk for toxicity and early discontinuation. The patient received lenalidomide plus reduced-dose dexamethasone. Treatment-related toxicities were limited and the benefit was long lasting, since the progression occurred after more than 60 months from diagnosis. The age-based dexamethasone dose reduction and the reduction of lenalidomide from 25 mg to 10 mg during maintenance likely contributed to a good tolerability and an extended duration of treatment.

Furthermore, lenalidomide has the advantage of the oral administration thus improving compliance and adherence to therapy.

Conflicts of interest disclosure: Alessandra Larocca has received honoraria from Celgene and Janssen-Cilag. Antonio Palumbo has received honoraria and consultancy fees from Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, Merck; research funding from Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, Merck and Binding Site; and participated in a speakers' bureau for Bristol-Myers Squibb.

Acknowledgment: the authors thank Giorgio Schirripa for assistance in the preparation of the manuscript.

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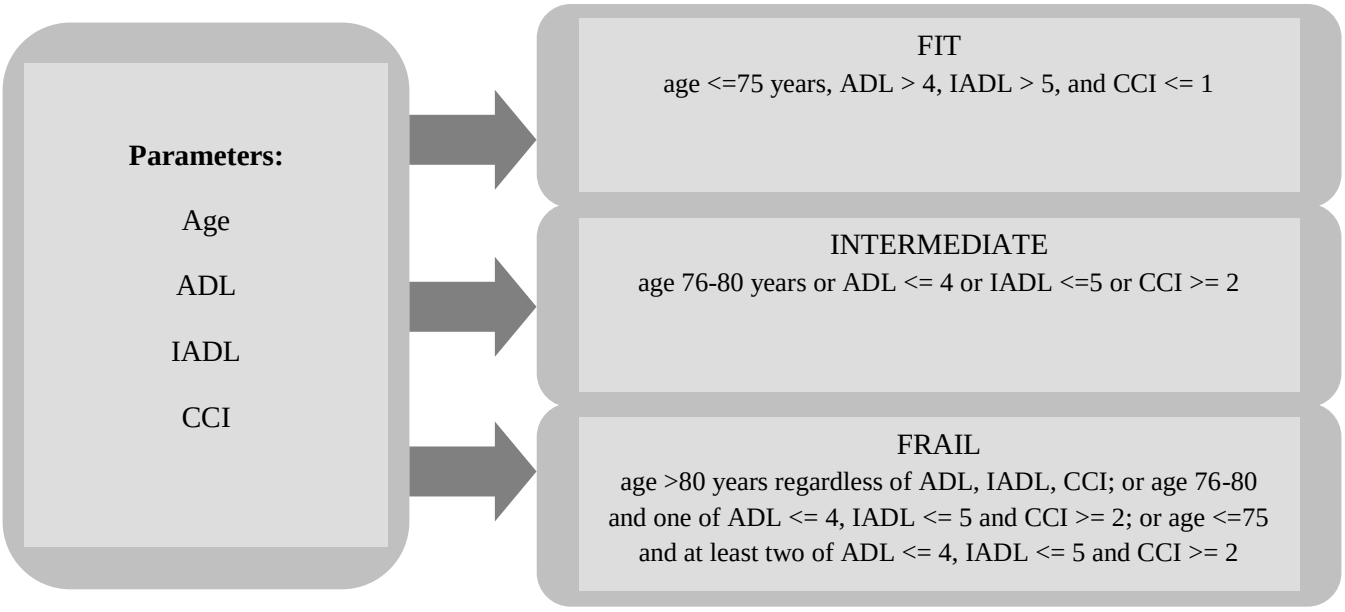
Figure 1 Framework for the definition of frailty status in elderly myeloma patients



ADL, activity of daily living; IADL, instrumental activity of daily living; CCI, Charlson comorbidity index

Table 1 Selected studies in elderly patients with myeloma

Regimen	Patients ≥75 years old	Overall response rate	Median progression-free survival (months)	Overall survival	*P* for survival
MP	25%[§]	50%	13	66% at 3 years	0.25°°
MPR	24%[§]	68%	14	62% at 3 years	0.81°°
MPR-R	24%[§]	77%	31	70% at 3 years	
Rd	35%[§]	75%	25.5	59% at 4 years	0.02°
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	0.927[#]
MPR	39%[§]	71%	24	65% at 4 years	0.448[#]
CPR	36%[§]	68%	20	68% at 4 years	
VD	50%	73%	14.7	49.8 months[b]	0.79
VTD	38%	80%	15.4	51.5 months[b]	
VMP	37%	70%	17.3	53.1 months[b]	
VP[a]	84%*	64%	14.0	60% at 2 year	NA
VCP[a]	67%*	67%	15.2	70% at 2 year	
VMP[a]	76%*	86%	17.1	76% at 2 year	

Rd, lenalidomide-dexamethasone; Rd18, lenalidomide-dexamethasone for 18 months; MPT, melphalan-prednisone-thalidomide; MPR, melphalan-prednisone-lenalidomide; CPR, cyclophosphamide-prednisone-lenalidomide; VD, bortezomib-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone; VMP, bortezomib-melphalan-prednisone; VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone. [§]Age >75 years; NA, not available. [a]Low-dose regimens. [b]Median values. °p=0.02 for Rd versus MPT. [#]p=0.927 for Rd versus MPR and p=0.448 for Rd versus CPR. *Age ≥80 years, 21 (41%) in VP, 14 (27%) in VCP and 15 (30%) in VMP patients. °°p=0.25 for MPR-R versus MPR and p=0.81 for MPR-R versus MP.

Table 2 Parameters to consider in the decision-making process in frail patients with MM

Patient characteristics	Medical history	Criteria to start treatment	Disease characteristics	Goals of treatment
Age Functional and independence status (ADL and IADL) Comorbidity (CCI) Psycho-social status	Cardiovascular disease Thromboembolism Diabetes Renal impairment Peripheral neuropathy	Myeloma-defining events (CRAB): ✓ ***C****alcemia* ✓ ***R****enal impairment* ✓ ***A****nemia* ✓ ***B****one lesions* *or* Biomarkers of malignancy: ✓ *≥ 60% clonal bone marrow plasma cells* ✓ *Involved/uninvolved serum FLC ratio ≥ 100* ✓ *>1 focal lesion on MRI*	Cytogentics Stage (ISS) Tumor aggressiveness	Response (CR) Disease control Quality of life

ADL, activity of daily living; IADL, instrumental activity of daily living; CCI, Charlson comorbidity index; FLC, free-light chain; MRI, magnetic resonance imaging; ISS, international staging system; CR, complete response.