

Multiple myeloma in the very elderly patient: challenges and solutions

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Abstract: Diagnosis and management of myeloma in the very elderly patient is challenging. Treatment options have vastly improved for elderly myeloma patients but still require the clinician to personalize therapy. In this paper, we offer evidence-based, pragmatic advice on how to overcome six of the main challenges likely to arise: 1) diagnosis of myeloma in this age group, 2) assessment of the need for treatment, and the fitness for combination chemotherapy, 3) provision of the best quality of supportive care, 4) choice of combination chemotherapy in those fit enough for it, 5) treatment of relapsed myeloma, and 6) provision of end of life care. With an increased burden of comorbidities and a reduced resilience to treatment and its associated toxicities, the management of myeloma in this age group requires a different approach to that in younger patients to maximize both quality and length of life.

Keywords: myeloma, elderly, diagnosis, treatment

Introduction

Plasma cell myeloma is a clonal disorder of malignant plasma cells and is a disease of the elderly, with a median age of onset of 70 years.^{1,2} Development of newer therapeutic agents over the last decade has led to improvements in survival in younger patients;^{3,4} however, such benefits have yet to be realized in the very elderly (>80 years) who continue to have poor outcomes.⁵ There are potential reasons for this. First, aging is associated with organ dysfunction, poorer resilience to physiological stressors, reduced functional status, and an increasing burden of comorbidities.⁶ Second, the elderly are at increased risk of frailty, a poorly defined syndrome characterized by a state of increased vulnerability to minor stressors with cumulative deficits in multiple physiological systems, resulting in an increased risk of hospitalization, dependency, and reduced life expectancy.

Elderly patients comprise a heterogeneous group of variable fitness from the very frail to the remarkably fit.⁷ Adequate assessment of fitness prior to treatment in this cohort is vitally important: inadequate assessment will inevitably lead to instances where frail patients are overtreated, and fitter patients are undertreated. In both situations, this can reduce the quality and length of life. The use of age and performance status (eg, the Eastern Cooperative Oncology Group [ECOG] score) alone is unsatisfactory, and there is a clear benefit to using geriatric assessment scores combining factors such as age, comorbidity burden, and assessments of functional status.⁸ Further increasing the difficulties in managing myeloma in this group is the paucity of clinical trial data. Stringent trial entry criteria typically exclude the majority of very elderly patients due to reduced performance status, comorbidities, or organ dysfunction.⁹ Trial candidates over the age of 80, therefore, tend to be unusually fit and are not representative of the typical very elderly patient.

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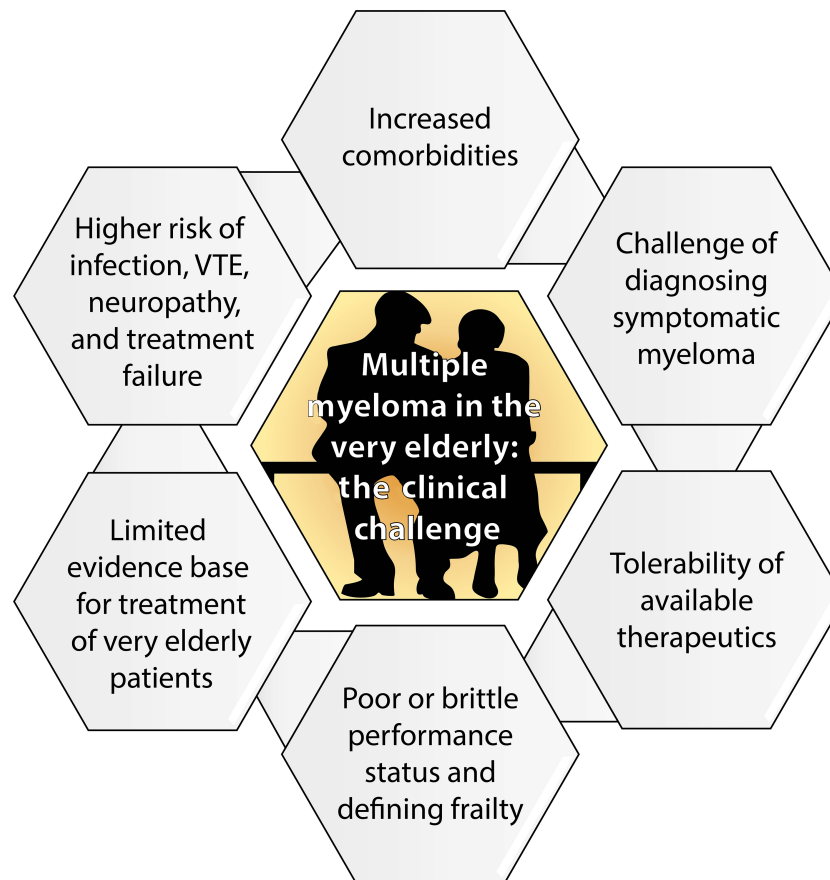


Figure 1 The challenges of diagnosis and treating the very elderly patient with multiple myeloma.
Abbreviation: VTE, thromboembolism.

Reaching a diagnosis of myeloma, assessing the need for treatment, and choosing the relative treatment intensity in the very elderly are consequently highly complex (Figure 1). This review will address six main challenges to clinicians treating myeloma in the very elderly and discusses the strategies to overcome them.

Challenge 1 – How is multiple myeloma diagnosed in the very elderly?

Myeloma is preceded by an asymptomatic monoclonal gammopathy of undetermined significance (MGUS) in all patients, although only a small proportion of myeloma patients have this diagnosed, with the vast majority presenting *de novo*. In those diagnosed with MGUS, most do not progress to myeloma: a paraprotein is found in 4%–5% of people in their 80s,¹⁰ whereas the incidence of myeloma in this group is only 40 per 100,000.¹¹ It is therefore of fundamental importance to consider whether a patient has myeloma or incidental MGUS with unrelated organ dysfunction (Figure 2).

Myeloma can present with a plethora of clinical features including unexplained anemia, bone pain, hypercalcemia, renal dysfunction, fatigue, spinal cord compression (SCC), recurrent bacterial infections, and rarely, symptoms of hyperviscosity.^{12,13} Up to 40% of myeloma patients present acutely with unexplained renal impairment, SCC, fracture, or profound hypercalcemia. A subset of patients present with a paraprotein or light chain excess and a full set of “CRAB” criteria (HyperCalcemia, Renal impairment, Anemia, and Bone lesions). In such patients, the diagnosis is usually considered early and rapidly confirmed, and so the treatment can begin promptly under the direction of a hematologist.

Diagnosis of a very elderly patient presenting insidiously with mild anemia, renal impairment, or bone pain, all of which can often be attributed to another etiology, requires detailed evaluation. There is often a lengthy delay between symptom onset and diagnosis of myeloma, with the average duration being around 6 months.¹⁴ Access to secondary care for assessment is significantly delayed, with over 50% of newly diagnosed patients requiring three visits to a general practitioner (GP) before a referral is made.¹⁵

Clinical features of myeloma

HyperCalaemia (present in 13% at diagnosis)

- Increased osteoclastic bone resorption
- Increased renal tubular calcium reabsorption

Renal failure (present in 19% at diagnosis)

- Light chain cast nephropathy ("myeloma kidney")
- Hypercalcaemia (with or without nephrocalcinosis)
- Monoclonal immunoglobulin deposition disease
- Plasma cell infiltration of the kidneys
- Concurrent amyloidosis
- Drug-induced (NSAIDs, bisphosphonates)
- Recurrent urinary tract infections

Anemia (present in 35% at diagnosis)

- Bone marrow infiltration by plasma cells
- Cytokine-mediated suppressive effect on erythropoiesis (anemia of chronic disease-type of anemia)
- Renal failure (decreased erythropoietin production)

Bone pain (present in 58% at diagnosis)

- Increased osteoclast activity causing lytic bone lesions, osteoporosis and pathological fractures
- Plasmacytomas affecting the bone

Other features:

- **Spinal cord compression:** (occurs in 5% of patients)
- Due to plasmacytomas or due to pathological fractures

Recurrent infections:

- Due to hypogammaglobulinemia and leukopenia

Hyperviscosity symptoms:

- Due to high levels of circulating paraprotein

Alternate diagnoses that can mimic myeloma

HyperCalaemia

PTH-mediated hypercalcaemia

- Primary hyperparathyroidism
- Tertiary hyperparathyroidism (eg, due to CKD or vitamin D deficiency)

Non-PTH-mediated hypercalcaemia

- Malignancy (bone metastases, humoral hypercalcaemia of malignancy)
- Drugs (eg, thiazides, lithium, vitamin D, vitamin A)
- Endocrine conditions (eg, thyrotoxicosis, Addison's disease)
- Granulomatous conditions (eg, sarcoidosis, tuberculosis)
- Other (eg, prolonged immobilisation, milk-alkali syndrome)

Renal failure

AKI (acute kidney injury)

- Prerenal causes
 - eg, dehydration, sepsis
- Renal causes
 - eg, drug-induced, infections
- Postrenal causes
 - eg, acute urinary retention

CKD (chronic kidney disease)

(affects ~60% of >80 year olds)

- Age-related decrease in eGFR
- Hypertension
- Diabetic nephropathy
- Drug-induced (eg, diuretics, NSAIDs)
- Obstructive uropathy (eg, due to BPH)
- Glomerulonephritides

Anemia (affects ~25% of >80 year olds)

- Anemia of chronic disease
- Iron deficiency (dietary and/ or blood loss)
- Vitamin B12 or Folate deficiency
- Chronic kidney disease
- Myelodysplasia
- Others (eg, bone marrow infiltration, haemolytic anemia, thalassemia)

Bone pain

Nonmalignant causes

- Osteoporosis
- Osteomalacia
- Osteomyelitis
- Paget's disease
- Injury (eg, fractures)

Malignant causes

- Primary bone cancer
- Bony metastases:
 - eg, breast, prostate, lung, thyroid
 - kidney, testicular, ovarian

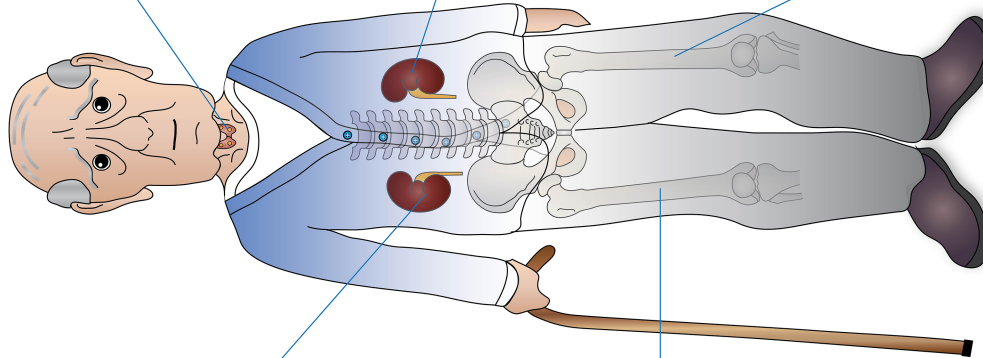


Figure 2 Clinical features of myeloma and other diagnoses which may mimic myeloma.

Notes: The incidences of calcium ≥ 2.75 mmol/L (11 mg/dL), hemoglobin ≤ 100 g/L, creatinine ≥ 177 μ mol/L (2 mg/dL), and bone pain at initial diagnosis of myeloma are shown.

Abbreviations: BPH, benign prostatic hypertrophy; CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs; eGFR, estimated glomerular filtration rate.

Table 1 Investigations required in very elderly patients with possible plasma cell myeloma

To make the diagnosis		
First-line investigations	FBC, U&E, creatinine, calcium, protein electrophoresis, urinary electrophoresis, SFLC ratio ^a	This should be performed in all patients suspected of having myeloma
To exclude mimics	PTH, blood film, hematinics, fasting glucose	As appropriate to exclude other causes for symptoms and abnormal blood results
Radiology	Skeletal survey MRI spine and pelvis in patients with back pain	All patients, but in the very frail may just target areas of pain
To confirm diagnosis		
Bone marrow	Aspiration and trephine	All patients, but consider omitting trephine in frail patients, particularly if combination chemotherapy is inappropriate
Bone marrow	Flow cytometry	Assessment of clonality
To assess disease status		
Blood	β_2 -microglobulin, albumin, LDH	To assess tumor burden and prognosis
Bone marrow	FISH panel	To assess prognosis

Note: ^aSFLC should be done if light chain myeloma or nonsecretory myeloma is suspected.

Abbreviations: FBC, full blood count; U&E, urea and electrolytes; SFLC, serum free light chains; PTH, parathyroid hormone; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization; MRI, magnetic resonance imaging.

Normally, GPs or general medical teams discover an incidental paraproteinaemia or note an abnormal imaging result; hematologists are then involved for advice regarding interpretation and further investigation. A thorough evaluation in secondary care is often required in this situation. In such situations, further investigations listed in Table 1 should be considered.

Eighty percent of patients with myeloma have a detectable paraprotein; the vast majority of the remainder have light chain only myeloma (where the malignant clone produces a monoclonal light chain rather than the full immunoglobulin molecule).¹⁴ Less than 2% of patients have nonsecretory myeloma where there is neither a paraprotein nor significant light chain production. Immunoparesis, where the normal immunoglobulin levels are decreased (due to impaired production of normal functioning plasma cells), leads to an increased risk of infection in myeloma patients and can provide an important clue to light chain or nonsecretory myeloma when a paraprotein is not present.

Diagnosing myeloma (Table 2) requires the demonstration of a clonal population of plasma cells either within the bone marrow, or less commonly, within a bony or extramedullary plasmacytoma. Bone marrow sampling is generally well tolerated in the elderly; however, its necessity must be carefully considered in the frail patient. Such patients may be at increased risk of side effects including significant bleeding, not only as they may be unable to lie in the optimal position and are more likely to be taking antiplatelet agents, but also because a paraprotein can interfere with fibrin production. The relative risk of bleeding must, therefore, be carefully considered. Osteoporosis in a proportion of myeloma patients could make trephine biopsy sampling difficult. In a frail elderly patient, the clinician may choose to perform

aspiration alone, or alternatively to omit the test altogether when palliation is considered.

Patients are routinely staged according to the International Staging System for myeloma using a combination of albumin and β_2 -microglobulin to assess overall prognosis.¹⁶ Certain cytogenetic abnormalities are associated with poor prognosis including deletions of chromosome 17p (*TP53* deletion), t(4;14) and t(14;16) and these are normally assessed by fluorescence in situ hybridization (FISH) at diagnosis.¹⁷ A retrospective analysis of outcomes in older patients with chromosomal abnormalities (median age 72 years; range 66–94 years) demonstrates that these high risk cytogenetic features predict poor outcomes regardless of age.¹⁸

There should be a low threshold for magnetic resonance imaging (MRI) of the whole spine in proven cases of myeloma

Table 2 Diagnosis of symptomatic myeloma

Clonal population of plasma cells >10%, or biopsy proven plasmacytoma plus one or more of

Evidence of end-organ damage that can be attributed to the plasma cell disorder

Hypercalcemia: calcium >0.25 mmol/L above normal range or >2.75 mmol/L

Renal impairment: creatinine clearance <40 mL/min or creatinine >177 μ mol/L

Anemia: hemoglobin >20 g/L below lower limit of normal or <100 g/L

Bony lesions: one or more osteolytic lesions on plain XR/CT/PET-CT
Myeloma defining events in the absence of end-organ damage

Clonal plasma cell population >60%

Ratio of involved: uninvolved SFLC >100 with involved SFLC >100 mg/L
>1 focal lesion of >5 mm in size on MRI

Note: Data from Rajkumar et al.⁶²

Abbreviations: PET-CT, positron emission tomography-computed tomography; SFLC, serum free light chains; MRI, magnetic resonance imaging.

with back pain to help guide areas suitable for radiotherapy or vertebroplasty, assess for SCC, and exclude multifocal plasmacytomas. Whole-body imaging including MRI and positron emission tomography-computed tomography (PET-CT) may be of value, alongside close monitoring in clinic to determine the trajectory and pace of organ dysfunction. A PET-CT requires a patient to move to and from a bed unaided; an important consideration in a very elderly patient.

Challenge 2 – How should the need for treatment and the fitness for treatment be assessed in the very elderly?

MGUS patients are normally monitored in primary care with pre-agreed guidelines for re-referral and specialist hematology input as required.¹⁷ Similarly, patients with smoldering myeloma (patients meeting the diagnostic criteria for myeloma in terms of their paraprotein level and/or marrow plasma cell percentage but without resulting end-organ damage) do not require treatment, although they have a 50% risk of requiring treatment over the next 5 years.^{19,20} Patients with high-risk smoldering myeloma should be closely monitored or recruited into appropriate clinical trials unless the patient is very frail and active treatment would be inappropriate.

The decision to initiate combination chemotherapy should be taken by a specialist myeloma multidisciplinary team considering all available diagnostic and clinical information, and in discussion with the patient and their family. Once end-organ damage attributable to myeloma has been identified, treatment is recommended.

Comprehensive geriatric assessment (CGA) tools have been created to help guide treatment decisions in elderly patients with cancer.⁸ A specific CGA has been developed for myeloma which aims to divide patients at diagnosis into groups of variable fitness to help guide treatment schedules.²¹ This score was developed by pooled analysis of 869 patients prospectively treated in three different clinical trials in which several methods of assessment had been performed at baseline.^{22–24} The most useful tools to predict outcome were the Katz Activities of Daily Living, the Lawton Instrumental Activities of Daily Living, and the Charlson Comorbidity Index. These were combined with patient age to categorize individuals into three groups: fit, intermediate fitness, and frail. The single factor that best predicted a reduced overall survival (OS) was age over 80 years (hazard ratio [HR]: 2.4). This particular tool automatically allocates the maximum score for frailty to all patients over 80 years based solely on

their age and therefore is unable to distinguish the fitter from the more frail.²¹ An alternative CGA tool combining performance status with assessment of renal and respiratory function and validated in patients with myeloma may be a useful alternative means of assessment.²⁵ Other geriatric assessment tools have been developed and applied to hematological cancers in general, and it is likely that a geriatric assessment score will be incorporated into future international trials.^{26–28} There is a clear need to gather further prospective evidence in this older age group, and to develop and validate new scoring systems that may guide practice in the future.

Pragmatically, the treating clinician should take into account age, performance status, a CGA tool, and importantly the views of the patient and their family when planning treatment. These should be combined with their own clinical judgment to arrive at an overall assessment of which treatments should be offered. Regardless of their fitness for combination chemotherapy, all elderly patients require careful management of both disease-related and treatment-related symptoms. A principal aim in the very elderly is the maintenance or improvement of quality of life with improved OS.

Combination chemotherapy may be more effective in controlling symptoms such as lytic bone pain than traditional palliative care, and such regimens can be offered with this intent. If chemotherapy regimens are carefully attenuated, then it is possible to reduce drug discontinuations, which commonly occur in the very elderly patients population.²¹ Despite this, there will be a small portion of the very elderly who are not fit even for the most attenuated treatment. Such patients should be identified early and managed according to the best principles of palliative care, treating symptoms while minimizing invasive investigations.

Challenge 3 – How can supportive care best be provided in the very elderly?

Providing appropriate supportive care to myeloma patients is of vital importance, both for symptom control and management of disease-specific complications. Input from specialists in pain medicine, orthopedic surgery, interventional radiology, and palliative care is often required.

Management of skeletal complications and pain

Myeloma-related skeletal complications in the elderly can be severe and debilitating; a variety of treatment approaches may be combined in addition to disease modification. Importantly, SCC occurs in 5% of patients with myeloma and may be the

presenting problem. High-dose dexamethasone should be commenced upon suspicion and definitive treatment planned with either surgery or radiotherapy after appropriate imaging; radiotherapy is pragmatically favored in the very elderly.

Provision of adequate analgesia is vital and specialist pain team input may be required. Paracetamol is safe, but nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with extreme caution due to the risk of nephrotoxicity. Opiates are often needed, but their side effects are more pronounced in the elderly and as such doses should be titrated carefully.

Radiotherapy and occasionally orthopedic surgery may be appropriate in the management of skeletal disease. Low-dose radiotherapy may be effective in the treatment of isolated painful bony lesions; typically, only a single dose (8 Gy) is required for adequate control.²⁹ Kyphoplasty or vertebroplasty may help when vertebral compression fractures results in pain unresponsive to analgesia or to stabilize vertebrae at risk of fracture.

Bisphosphonates reduce the risk of new skeletal-related events and are routinely given to all patients with symptomatic myeloma. Data from the Myeloma IX trial suggested an improved OS of zoledronic acid over clodronate,³⁰ and this is generally preferred to pamidronate, which takes longer to infuse. A pragmatic approach of infrequent infusions is sometimes needed in treating elderly myeloma patients who may find monthly visits to hospital for infusions tiring and impractical. Intravenous (IV) bisphosphonates are contraindicated in chronic renal impairment where the creatinine clearance is <30 mL/min.

Osteonecrosis of the jaw is a rare complication of bisphosphonate treatment; the risk is higher in patients with poor dentition, following invasive dentistry, and with IV preparations. Patients should be reviewed by a dentist pretreatment, and dental work should be avoided where possible once treatment is initiated. In patients who achieve complete remission with treatment, bisphosphonates can reasonably be stopped after 2 years, although this is unfortunately rare in the elderly. Calcium and vitamin D supplementation should be routinely given to all patients taking bisphosphonates to avoid hypocalcaemia, but care should be taken that their use does not exacerbate hypercalcemia in certain patients.

Anemia

Anemia is one of the hallmark features of myeloma, present in 35% at diagnosis. It may be exacerbated by chemotherapy. Management includes judicious red blood cell transfusion,

consideration of IV iron infusion, and in selected patients, erythropoietin-stimulating agents.¹²

Renal failure

Renal failure in myeloma is multifactorial in nature, occurring due to damage to renal tubules by free light chains, inappropriate NSAID usage, dehydration, hypercalcemia, and infection. Renal function declines with age, and so the elderly are less resilient to such insults. Dexamethasone should be commenced as soon as multiple myeloma is suspected; prompt treatment can reverse renal dysfunction in about 50%.³¹ If dialysis is indicated, a frank discussion involving the patient, their family, renal physicians, and myeloma specialists is necessary to determine the appropriateness of such an intervention.

Thromboembolic disease

Patients with myeloma are at increased risk of venous thromboembolism (VTE).³² VTE is more common with increasing age, and the use of the immunomodulatory agents (IMiDs) thalidomide and lenalidomide further increase this risk.³³ Low-molecular-weight-heparin prophylaxis should be considered in patients judged to be at high risk; however, this can be logistically difficult in the very elderly due to poor eyesight, lack of dexterity, and low confidence with self-injecting. Aspirin may be a suitable, evidence-based compromise.³⁴ Novel oral anticoagulants are used in clinical practice with limited evidence as prophylactic treatment for patients on IMiDs, due to their convenience.

Infectious complications

Analysis of registry data from 1980 to 2002 concluded that 10% of myeloma patients die of infection within 60 days of diagnosis due to deficits in cellular and humoral immunity.³⁵ Elderly patients are particularly prone to infection. Prophylactic fluconazole (to prevent candidiasis) and aciclovir (to prevent herpes simplex and/or zoster) are typically coprescribed with chemotherapy. There is no good evidence for the use of antibacterial prophylaxis at present. The UK-wide “Tackling early morbidity and mortality in myeloma” (TEAMM) trial is currently recruiting, and will determine whether primary fluoroquinolone prophylaxis is beneficial. Clarithromycin has some anti-myeloma properties and has been used in some experimental combination regimens, while providing antibacterial prophylaxis.³⁶ Neutropenia may be managed by the use of granulocyte colony stimulating factor.

Challenge 4 – How should fitter very elderly patients be treated with combination chemotherapy?

Summary of trial evidence

Large, multicenter, randomized controlled trials published in high-impact journals lay the foundation for an evidence-based approach to treating patients who are not deemed eligible for an autologous stem cell transplant (ASCT) in first remission (Table 3).^{37–41} This is typically defined as those over 65 years or those younger than 65 years with prohibitive comorbidities. These large trials are typically performed at major tertiary referral centers across Europe and America, and as such it is unsurprising that the median age in such trials is approximately 70 years, with only between a third to a quarter of patients over 75 years. As a result, extrapolating the evidence base to the very elderly must be done with caution. The data do, however, allow some conclusions to be drawn to guide clinicians in the management of very elderly patients.

Novel agents are now commonly used in all age groups in myeloma. Although steroid and alkylator therapy formed the backbone of induction treatment for many years, the IMiDs thalidomide and lenalidomide and the first-generation proteasome inhibitor bortezomib (velcade) have significantly changed the treatment landscape and outcomes over the last decade.

A large meta-analysis of six clinical trials has shown a clear survival benefit from the use of thalidomide in addition to MP (melphalan, prednisolone) in those unfit for ASCT.⁴² Thalidomide, however, is known to be poorly tolerated at high doses, particularly in the very elderly. Constipation, cardiac events, excessive somnolence, peripheral neuropathy (PN), and VTE are well-described side effects that are prevalent and poorly tolerated in the very elderly.⁴² A substantial proportion of patients across these six trials either had thalidomide stopped prematurely or its dose reduced. As such, it is critical to assess tolerability and use appropriate dosage (typically 50–100 mg once daily maximum) in the very elderly.

The randomized controlled VISTA trial investigated whether the addition of bortezomib (velcade) to MP (VMP) improved outcomes in those unfit for ASCT as first-line treatment.³⁸ The addition of bortezomib showed a significantly improved duration of remission, progression-free survival (PFS), and ultimately 5-year OS (56.4 months vs 43.1 months).⁴³ Notably, the VMP schedule was protracted, requiring regular visits to hospital for IV bortezomib for up to 54 weeks. The length of any regimen and outpatient time investment given must be considered in a group with

a shorter all-cause life expectancy. In view of this, many clinicians now use subcutaneous bortezomib due to evidence of reduced PN, increased speed of delivery, and equivalent efficacy.⁴⁴

The UPFRONT trial addresses whether triple therapy is of benefit when bortezomib is used in the very elderly.⁴⁵ The trial included a higher proportion of patients with comorbidities and elderly patients (42% ≥ 75 years and 18% ≥ 80 years) and recruited from US community-based settings as opposed to large, tertiary referral units. Velcade–dexamethasone (VD) was compared with VTD and VMP. All patients who responded to induction received bortezomib maintenance. This is the largest study to date that intentionally reflects the elderly population in the “real-world” clinic setting. There were no differences between the three arms in terms of median PFS or median OS (OS: VD 49.8 months vs VTD 51.5 months vs VMP 53.1 months; global $P=0.46$ and $P=0.79$). The most toxicities were seen in the VTD arm. Velcade maintenance resulted in limited additional toxicity compared to induction, while sustaining responses in 89%.

Lenalidomide is a more potent IMiD than thalidomide, and recent trials have investigated its use upfront in those unfit for ASCT. In the largest and most relevant trial, melphalan, prednisolone, thalidomide (MPT; $n=547$) was compared with up to 18 cycles (28 day) of lenalidomide–dexamethasone (LD18) ($n=541$) and continuous lenalidomide–dexamethasone (cLD) ($n=535$) to progression. cLD proved superior in terms of PFS compared to both MTP and LD18 (median PFS 25.5 months with cLD vs 20.7 months with LD18 vs 21.2 months with MPT; $P<0.001$ with cLD compared to both MTP and LD18). The improved PFS with cLD resulted in a superior OS compared to MTP (4-year OS 59% vs 51%; HR, 0.78; $P=0.02$) but not compared to LD18 (4-year OS 59% vs 56%; HR, 0.90; $P=0.31$). This trial supports the use of continuous lenalidomide therapy. Low-dose dexamethasone with lenalidomide is associated with reduced toxicity and improved survival compared to high-dose dexamethasone.⁴⁶ Where LD is used continuously in the very elderly, it is critical to monitor for adverse effects, particularly from long-term steroid exposure. No increase in second primary malignancy was noted in this trial in the lenalidomide arms. Recently presented updated data from the FIRST trial show that RD continuous therapy performs poorly in patients with high-risk disease, compared to those with standard risk.⁴⁷ SWOG trial S0777 trial supports this finding, as patients randomized to VRD had a better OS in comparison to those treated with cLD.⁴⁸

Table 3 A summary of the results of large randomized controlled trial treatment in transplant-ineligible patients with myeloma

Source	Regimens tested	Eligibility	Age (range)	Comorbidities	ORR	OS	PFS	Toxicity
San Miguel et al ^{38,60}	Nine 6-weekly cycles of VMP (n=344) vs MP alone (n=338)	≥65 years or <65 years and ineligible for ASCT	Median 71 years (48–91) Age ≥75 years 30%	5.5% CrCl <30 mL/min 33% history of cardiac condition	PR or better: 71% VMP vs 35% MP CR: 30% VMP vs 4% MP (P<0.001)	Median OS: VMP 56.4 vs MP 43.1 months 5 year OS: VMP 46.0% vs MP 34.4% (P<0.001)	Median TTP: VMP 20.7 months vs MP 15.0 months (HR, 0.54, P<0.001)	Incidence SPM was similar and consistent with background rates
Mateos et al ⁶¹	Six cycles of VMP (n=130) vs six cycles of VTP (n=130) as induction, responders: Maintenance VP (n=87) vs VT (n=91)	≥65 years ECOG 0–2	Median 73 years (68–77) Age ≥75 years 34%	Not discussed	105 (81%) in VTP vs 104 (80%) in VMP: PR or better (P=0.9) 36 (28%) in VTP and 26 (20%) VMP: CR (P=0.2)	3-year OS: VMP 74% vs VTP 65% (P=0.3) 25 months (P=0.1)	Median PFS: VMP 34 months vs VTP 25 months (P=0.1)	VTP: serious AEs (31% vs 15%, P=0.01) and discontinuations (17% vs 12%, P=0.03) vs VMP
Fayers et al ⁶²	Meta-analysis of MPT trials vs MP: (n=1,685 across trials) Thalidomide: 100–400 mg od	>65 years in 3 trials, >55 years in 1 trial, >75 years in 1 trial, 65–75 years in 1 trial	Median ages: 72.5, 72.6, 69.4, 78.5, 74.4, 70.6 years, respectively		1-year ORR (PR or better) 59% MPT vs 37% MP (P=0.0001)	Median OS: MP 32.7 months vs MPT 39.3 months (P=0.004)	Median PFS: MP 14.9 months vs MPT 20.3 months (P<0.0001) No PFS advantage if presenting creatinine >176 (HR, 0.87, P=0.6)	Not detailed
Morgan et al ⁶³	CTDa (n=426) vs MP (n=423)	Nonintensive arm of Myeloma IX trial >18 years, unfit for ASCT	Median 73 years (57–89)	Not discussed, although clear data that those over 80 years have significantly worse OS	ORR: CTDa 63.8% vs MP 32.6% (P<0.0001) CR: CTDa 13.1% vs MP 2.4% VGPR: CTDa 16.9% vs MP 1.7%	Median OS: MP 30.6 months vs CTDa 33.2 months (HR, 0.89, P=0.24)	Median PFS: MP 12.4 months vs CTDa 13.0 months (HR, 0.82, P=0.01)	CTDa associated with higher rates of thromboembolism, constipation, infection, and PN vs MP
Palumbo et al ⁶⁰	MPR-R (nine 4-weekly cycles of MPR, followed by lenalidomide maintenance to PD) (n=152) vs MPR (n=153) vs MP (n=154)	≥65 years or <65 years and ineligible for ASCT	Median 71 years (65–91) Age ≥75 years 2.4%	Not discussed	ORR: MPR-R (77%) vs MPR (68%) vs MP 50% (P<0.001 and P=0.002, respectively, for comparison with MP)	3-year OS: MPR-R 70% vs MPR 62% vs MP 66% (HR MPR-R vs MPR: 0.79, P=0.25. HR MPR-R vs MP: 0.95, P=0.81)	Median PFS: MPR-R 31 months vs MPR 14 months (HR, 0.49, P<0.001) vs MP 13 months (HR, 0.40, P<0.001). PFS benefit with MPR-R in 65–75 years of age but not >75 years	Most AEs hematologic; Grade 4 neutropenia: MPR-R 35% vs MPR 32% vs MP 8%. 3 year rate SPM: MPR-R 7% vs MPR 7% vs MP 3%

Benboubker et al ³⁷	cLD to PD (n=535) vs LD18 for 72 weeks (18 cycles; n=541) vs MPT 72 weeks (n=547)	≥65 years or <65 years and ineligible for ASCT	Median 73 years (44–91) Age ≥75 years 35%	9% CrCl <30 mL/min	75% cLD vs 73% LD18 vs 62% MPT (p<0.001: both comparisons with MPT)	4 year OS: 59% cLD vs 56% LD18 vs 51% MPT (HR, cLD vs MPT, 0.78; P=0.02. cLD vs LD18, HR, 0.90, P=0.31)	Median PFS: cLD 25.5 months vs LD18 20.7 months vs MPT 21.2 months (HR, 0.72 cLD vs MPT and 0.70 cLD vs LD18, P<0.001 for both comparisons)	Grade 3–4 AEs cLD 70% vs MPT 78%. Compared with MPT, cLD associated with fewer hematologic and neurotoxicity, increased infections, and fewer SPMs
Magarotto et al ⁴⁹	Rd and lenalidomide–prednisone plus melphalan (MPR) or CPR (n=222). MPR (n=218) or CPR (n=222)	≥65 years	Rd 37%, MPR 39%, CPR 36% ≥75 years	Not discussed	Not discussed	Median OS in ≥75 years: Rd NR vs MPR 37 months vs CPR 43 months (Rd vs MPR P=0.04; Rd vs CPR P=0.430; MPR vs CPR P=0.323)	Median PFS in ≥75 years: Rd 22 months vs MPR 18 months vs CPR 21 months in CPR (Rd vs MPR P=0.572; Rd vs CPR P=0.699, MPR vs CPR P=0.914)	≥1 hematologic Grade 3–4 AE in ≥75 years subgroup: Rd 29% vs MPR 70% vs CPR 33% (MPR vs Rd/CPR, P<0.0001). No difference in extra-haematologic AEs
Palumbo et al ³⁹	VMPT plus VT maintenance (VMPT-VT) (n=254) vs VMP (n=257)	≥65 years or <65 years and ineligible for ASCT	Median 71 years Age ≥75 years 27%	Not discussed	CR: 38% VMPT-VT vs 24% VMP	5 year OS: VMP 51% vs VMPT-VT 61% (HR, 0.70; P=0.01)	3 year PFS: VMP 41% vs VMPT-VT 56% median PFS: VMP 24.8 months vs VMPT-VT 35.3 months (HR, 0.58; P=0.001)	Grade 3–4 AE in VMPT-VT: neutropenia (38%), thrombocytopenia (22%), PN (11%), and cardiac events (11%). All except thrombocytopenia, were significantly more frequent in VMPT-VT
Niesvizky et al ⁴⁵	Eight 21-day cycles VD (n=168) vs VTD (n=167) vs VMP. All arms received V-maintenance	≥65 years or <65 years and ineligible for ASCT	Median 73 years (48–91) Age ≥75 years 42%	48% comorbidities, 19% Charlson comorbidity index ≥2, including DM 21%, renal disease 15%, and chronic pulmonary disease 8%	ORR: VD 73% vs VTD 80% vs VMP 70% CR: VD 3% vs VTD 4% vs VMP 4%	Median OS: VD 49.8 months vs VTD 51.5 months vs VMP 53.1 months (global P=0.79)	Median PFS: VD 14.7 months vs VTD 15.4 months vs VMP 17.3 months (global P=0.46)	PN: VD 50% vs VTD 60% vs VMP Grade ≥2 PN: 35% VD vs VTD 47% vs VMP 35%. Grade ≥3 infection: VD 21%, VTD 16% vs VMP 18%. Grade ≥3 sepsis: VD 3% vs VTD 3% vs VMP 2%

Abbreviations: AEs, adverse events; ASCT, autologous stem cell transplantation; cLD, continuous lenalidomide–dexamethasone; CTDA, attenuated cyclophosphamide, thalidomide, dexamethasone; CPR, cyclophosphamide; CR, complete response; CrCl, creatinine clearance; DM, Diabetes Mellitus; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MP, velcade, melphalan; MPT, melphalan, prednisolone, thalidomide; MPR ± R, melphalan, prednisolone, revlimid ± revlimid maintenance; NR, not reached; od, once daily; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response; Rd, lenalidomide–dexamethasone; SPM, secondary primary malignancy; TTP, time to treatment failure; VD, velcade, dexamethasone; VGPR, very good partial response; VMP ± T ± VT, velcade, melphalan, prednisolone ± thalidomide ± velcade–thalidomide maintenance; VTP, velcade, thalidomide, prednisolone; VMPT, velcade, melphalan, prednisolone, thalidomide; VTD, velcade, thalidomide, dexamethasone.

Table 4 Choice of therapeutic agent in patients with comorbidity

Comorbid condition	Advice on therapeutic agent
Renal impairment	Prefer bortezomib-based regimes Need to reduce dose if use lenalidomide
Polyneuropathy	Avoid or reduce dose if use bortezomib
Cardiac arrhythmia/ dysfunction	Caution with thalidomide and high-dose steroids
Diabetes	Caution with high-dose steroids
Psychiatric/behavioral problems	Caution with high-dose steroids
Bone marrow insufficiency	Caution with cytoreductive drugs Consider single-agent dexamethasone
Poor immune function	Caution with cytoreductive drugs
Poor cognitive function or compliance	Consider subcutaneous and/or hospital-delivered regimes

A subgroup analysis of patients over 75 years in a large trial comparing lenalidomide–dexamethasone (low dose; Rd) and lenalidomide–prednisone plus melphalan (MPR) or cyclophosphamide (CPR) was recently published in abstract form.⁴⁹ The addition of an alkylating agent provided no additional benefit beyond lenalidomide–dexamethasone alone, and Rd appears to have a survival advantage compared to MPR (median OS not reached in Rd vs 37 and 43 months in the MPR and CPR arms, respectively [Rd vs MPR $P=0.04$; Rd vs CPR $P=0.430$]). The OS difference was primarily due to a higher efficacy of salvage treatment.

Recommendations for first-line treatment

On the basis of age, CGA, performance status, and overall clinical assessment, it is possible to stratify patients into fit patients suitable for two or three drug combination therapies, frail patients requiring significantly attenuated therapies, and those suitable only for palliative care. In general, given the greater toxicity with thalidomide and alkylating agents, these are avoided in this age group whenever possible. Pre-existing comorbidities as well as disease characteristics must be considered when selecting a treatment regime (Table 4).

This trial data support the use of lenalidomide–dexamethasone as first-line treatment for fit patients continued until disease progression. This has the advantage of limiting visits to hospital to outpatient visits, and it can be used in pre-existing PN. In patients with significant renal disease, or aggressive disease requiring rapid paraprotein reduction, subcutaneous bortezomib–dexamethasone is preferred.

In frail patients, lenalidomide may also be used as initial therapy, although dose reduction to typically no more than

15 mg once daily is necessary. The dexamethasone dose should also be reduced, to around 10 mg once per week. Careful monitoring is necessary, and granulocyte colony stimulating factor can be used to minimize neutropenia. If bortezomib–dexamethasone is selected, dexamethasone should be dose reduced, and patients should be carefully monitored for bortezomib toxicity.

In patients with severe cognitive impairment or very poor functional status, palliation may be preferred. In such situations, low-dose steroids may offer symptom relief.

Challenge 5 – How should relapse be treated in the very elderly?

Patients with asymptomatic serological relapse can have treatment delayed until they develop evidence of organ dysfunction, akin to the approach described with asymptomatic myeloma. A rapidly rising paraprotein (doubling in 2 months) is an indication of progressive disease requiring re-treatment, and as such, serological relapse should be monitored closely. The goals of treatment are again to improve quality of life and survival. Further treatment may be inappropriate depending upon the patient's frailty and wishes.

Novel agents again form the mainstay of treatment at relapse. Rechallenge with lenalidomide or bortezomib may be appropriate if a response >12 months was previously achieved.⁵⁰ In refractory disease or short-term response only (<12 months), switching regimes (lenalidomide-based with bortezomib-based) is recommended. Good evidence exists for lenalidomide in relapsed disease,⁵⁰ with a smaller study indicating benefit in patients over 75 years with a median PFS of 14 months.⁵¹ Data also support the use of bortezomib at relapse,^{52,53} with one small trial indicating a clear benefit in elderly patients.⁵⁴

Patients relapsing after bortezomib and lenalidomide may occasionally still be fit enough for further treatment. Treatment in clinical trials should be considered in such situations.

There are a number of emerging treatments that are likely to benefit elderly patients in the future. Carfilzomib, a novel proteasome inhibitor, is effective in newly diagnosed and relapsed myeloma.^{24,55} It is associated with a reduced toxicity compared to bortezomib (particularly PN) and may therefore take the place of bortezomib first line in the future, although its use should be avoided in patients with significant pre-existing cardiac disease. Ixazomib, another new proteasome inhibitor, has the advantage of oral administration. A Phase III trial has recently reported data in abstract form demonstrating improved survival in relapsed/refractory patients when ixazomib is used together with Rd in

comparison to Rd alone. The side-effect profile was overall felt to be acceptable, although PN rates were increased in the ixazomib arm.⁵⁶ The monoclonal antibodies daratumumab (an anti-CD38 monoclonal antibody) and elotuzumab (an anti-CS1 monoclonal antibody) are also in advanced clinical trials.^{57,58} Both have good tolerability and are also likely to particularly benefit the elderly should they prove effective in Phase III clinical trials. Relapsing disease often impacts on performance status of patients; in selected individuals, palliation may be appropriate.

Challenge 6 – the management of end-of-life care

“End of life” is now considered as the last 12 months of life⁵⁹ (National Institute for Health and Care Excellence), and for some elderly myeloma patients, this may be from the point of diagnosis. A holistic needs assessment is therefore a vital tool from the outset, allowing patients to openly convey their needs and wishes. An honest discussion about prognosis both at diagnosis and each relapse is crucial for the patient and their family to make the appropriate choices with regard to their treatment. It is becoming increasingly difficult to determine when a patient has reached the terminal stages of their disease due to the increasing palate of treatment options and trials available, and patients are sometimes treated until their last few days. Myeloma remains incurable, and so stopping chemotherapy and focusing on palliative care can be the most appropriate decision for the patient and their family. Advice from the palliative care team is often beneficial in the final stages as patients become increasingly weak and bedbound. Analgesia can be given subcutaneously, often in the form of syringe drivers to help control refractory pain and prevent periods of inadequate analgesia. Close communication between clinicians, nurse specialists, the palliative care team, social services, and GPs is of paramount importance to support the needs of the patient and their family.

Conclusion

Diagnosing and treating myeloma in the very elderly is challenging, requiring careful consideration of when to treat and how aggressively. A careful assessment of fitness for therapy must be conducted to allow treatment to be provided at an appropriate intensity. Close attention from a multidisciplinary team to provide adequate supportive care is essential to allow the patient to benefit from combination chemotherapies. Particular care must be taken to minimize toxicities, reducing doses if required to allow continuation of treatment when appropriate. As the population ages, the incidence of myeloma in the very

elderly will increase. Novel and emerging therapies are likely to provide significant benefits to this patient group, with potent anti-myeloma activity combined with easier administration and lower toxicity. There is an urgent need to increase recruitment of patients in this age group to clinical trials to increase the evidence base and to allow the clinician and patient to make informed, evidence-based decisions on treatment strategies. Treating myeloma in the very elderly is challenging, but with judicious use of supportive and active treatments, compassionate and effective care can be provided to these patients.

Acknowledgments

TE is funded by the Julian Starmer-Smith research fund and has received honorarium from Takeda. AK is funded by Wellcome Trust. KR is supported by the NIHR Biomedical Research Centre (Oxford). The views expressed are those of the authors and not necessarily those of the Department of Health.

Author contributions

TE, JW, AK, CW, and FB wrote the manuscript. TE produced Table 3 and Figure 1. CW produced Figure 2. KR, TE, JW, and AK edited the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors critically reviewed the manuscript and agreed on the final version.

Disclosure

TE has received consultancy honoraria from Janssen. KR has received honoraria from Janssen, Celgene, Takeda and Amgen. The authors report no other conflicts of interest in this work.

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