Critical Reviews in Oncology / Hematology 137 (2019) 18–26

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Special considerations for the treatment of multiple myeloma according to advanced age, comorbidities, frailty and organ dysfunction

Muhammad Asad Fraz[a], Faiza Hassan Warraich[b], Sami Ullah Warraich[a], Muhammad Junaid Tariq[a], Zabih Warraich[c], Ali Younas Khan[a], Muhammad Usman[a], Awais Ijaz[a], Pavan Tenneti[d], Adeela Mushtaq[e], Faisal Akbar[f], Zaina Shahid[g], Zeeshan Ali[h], Hafiz Muhammad Fazeel[a], Cesar Rodriguez[i], Aboo Nasar[j], Ali McBride[k], Faiz Anwer[a,l,*]

[a] Department of Medicine, Division of Hematology Oncology, Blood and Marrow Transplantation, University of Arizona, Tucson, AZ, 85721, United States
[b] Department of Internal Medicine, McLaren-Flint Medical Center, Flint, MI, 48532, United States
[c] Department of Internal Medicine, United Health Services Wilson Memorial Regional Medical Center, Johnson City, NY, 13790, United States
[d] Department of Medicine, Banner University Medical Center, Tucson, AZ, 85724, United States
[e] Department of Medicine, University of Pittsburgh Medical Center, McKeesport, PA, 15132, United States
[f] Department of Medicine, Wake Forest Baptist Medical Center, Winston Salem, NC, 27157, United States
[g] Department of Medicine, Wilkes Medical Center- Wake Forest Baptist Health, Wilkesboro, NC, 28659, United States
[h] Department of Medicine, Southern Arizona Veterans Affairs Health Care System, Tucson, AZ, 85723, United States
[i] Department of Hematology Oncology, Wake Forest Baptist Medical Comprehensive Cancer Center, Winston Salem, NC, 27157, United States
[j] Department of Geriatrics, Tri-City Medical Center, 4002 Vista Way, Oceanside, CA 92056, United States
[k] Department of Pharmacy, The University of Arizona Cancer Center, Tucson, AZ, 85737, United States
[l] Taussig Cancer Center, Department of Hematology, Medical Oncology, Cleveland Clinic, Cleveland, OH, 44195, United States

ARTICLE INFO

Keywords:
Multiple myeloma
Personalized therapy
Elderly
Frailty
Dose reduction
Dose modifications
Comorbidities

ABSTRACT

Multiple Myeloma (MM) is primarily a disease of old age with a median age of sixty-nine years at diagnosis. The development of novel therapies for induction and use of autologous stem cell transplantation has resulted in improved clinical outcomes and better quality of life for MM patients. Elderly patients, comprising the majority of MM population, have a higher incidence of age-related comorbidities, frailty and organ dysfunction which complicates the coordination of treatment and limits the selection of therapies. Even in the era of multiple chemotherapeutic options, the clinical heterogeneity of the myeloma patients' demands personalized treatments which often require dose-adjustments or dose delays. The use of reduced-dose regimens and various comorbidity indices has improved clinical outcome and regimen tolerability in MM patients with renal, neurological and bone abnormalities. We focus on advancements in the treatment of multiple myeloma with the goal to guide clinicians towards patient-specific management.

1. Introduction

Multiple Myeloma (MM), the second most common hematologic malignancy, (Collins, 2005) had an estimated incidence of more than 30,000 cases in the United States of America in 2018 (Cancer Stat Facts: Myeloma, 2018). The median age for MM diagnosis is 69 years with the median age of death due to MM being 75 years (Ma et al., 2018). Increasing age, on one hand, confers a strong risk for acquiring malignancies, (mostly occurring in patients older than 65 years), on the other hand, increases the incidence of comorbidities and frailty risk (Palumbo et al., 2011). Presence of risk factors such as high-risk cytogenetics, advanced age, comorbidities and polypharmacy indicate management to be individualized to each patient's unique needs (Palumbo et al., 2011).

Comorbidity, the presence of two or more distinct disease entities in the same individual, is common in elder (> 65 years) patients. In the US, 27.5% men and 26.9% women of age > 65 years have three chronic conditions including arthritis, hypertension, and cancer (Ward and Schiller, 2013). Nephropathy, neuropathy, venous thromboembolism, osteolytic bone lesions, anemia, increased risk of infections and hypercalcemia are the common MM-associated morbidities with increased prevalence in elderly patients (Gregersen et al., 2017). In addition,

* Corresponding author at: Clinical Director of the Blood and Marrow Transplant Program, Division of Hematology & Oncology, Department of Medicine, University of Arizona Cancer Center, 1501 N Campbell Ave, AZ, 85721, United States.
E-mail address: anwerf@email.arizona.edu (F. Anwer).

https://doi.org/10.1016/j.critrevonc.2019.02.011
Received 28 August 2018; Accepted 24 February 2019
1040-8428/

elderly patients have a higher incidence of diabetes mellitus (DM), hypertension (HTN), heart failure (HF), cardiac arrhythmia, stroke and hyperlipidemia in the same patient population (Beltrán-Sánchez et al., 2013). Moreover, factors like advanced patient age (≥ 75 years), renal failure at presentation, drug discontinuation secondary to toxicity and grade 3–4 treatment-related infectious, cardiac or gastrointestinal adverse events (AEs) are found to be associated with reduced overall survival (OS) in MM patients (Bringhen et al., 2013).

Published literature in the PubMed database and guidelines by National Comprehensive Cancer Network (NCCN), (Kumar et al., 2017) International Myeloma Working Group (IMWG), (Palumbo et al., 2015) European Myeloma Network (EMN) (Terpos et al., 2015) and Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) (Mayo Stratification for Myeloma And Risk-adapted Therapy, 2018) highlight the importance of individualized management in comorbid elderly MM patients. The purpose of this review is to identify and summarize findings from original studies and guidelines for personalized therapy in the management of MM.

2. Selection of chemotherapeutic drug regimens in elderly MM patients

2.1. Frailty assessment

Frailty is commonly assessed by the presence of a decrease in any three out of the following five parameters: weight, gait speed, hand-grip strength, self-reported energy and physical activity (Fried et al., 2001). Various assessment tools like Charlson Comorbidity Index (CCI), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are used to stratify elderly MM patients on the basis of comorbidities and functional status. According to IMWG recommendations by Palumbo et al. (2015), age alone should not be used for dose-reduction. Utilization of the IMWG frailty score by considering other factors including medical comorbidities (assessed by CCI) and disabilities (assessed by ADL score and IADL score) for decision making in the elderly population is recommended. IMWG advised to categorize patients into groups of "fit" (cumulative IMWG frailty score = 0), "intermediate fit" (cumulative IMWG frailty score = 1) and "frail" (cumulative IMWG frailty score = 2–5 on the basis of age, CCI, ADL and IADL (Palumbo et al., 2015), as shown in Table 1 and is validated by many studies (Palumbo et al., 2015; Engelhardt et al., 2016).

An IMWG pooled analysis by Palumbo et al. (2015) evaluated 869 newly diagnosed multiple myeloma (NDMM) patients in 3 clinical trials with a median age of 74 years, which evaluated the utility of IMWG frailty score. Patients were classified into fit, intermediate fit and frail categories based on the IMWG frailty score; the 3-year overall survival (OS) was 84% (95% CI 78–89 %), 76% (95% CI 67–82), and 57% (95% CI 45–68%) respectively. The 3-year progression free survival (PFS) was 48% (95% CI 41–56%) for fit patients, 41% (95% CI 32–49%) for intermediate fit and 33% (95% CI 25–41%) for frail patients. This propensity score validating the use of IMWG frailty score by showing its prognostic role and clinical predictability (Palumbo et al., 2015). Engelhardt et al. (2016) analyzed a cohort of 125 NDMM patients with a median age of 63 years who were classified into fit, intermediate fit and frail categories using IMWG frailty score. For these patients, 3-year OS was 91% (95% CI: 78–100%) for fit, 77% (95% CI: 55–95%) for intermediate-fit and 47% (95% CI: 26–67%) for frail patients (Engelhardt et al., 2016). Engelhardt et al. (2017) developed a scoring system called revised Myeloma Comorbidity Index (R-MCI) for elderly MM patients on the basis of age, Karnofsky Performance Status (KPS), Estimated Glomerular Filtration Rate (eGFR), frailty, cytogenetics and lung dysfunction. Patients were classified into "fit" (R-MCI score = 0–3), "intermediate fit" (R-MCI score = 4–6) and "frail" (R-MCI score = 7–9). Eight hundred and one MM patients having the median age of 63 years, with 28% of patients aged 66–75 years and 13% aged > 75 years. 247, 446 and 108 of these patients were classified into fit, intermediate-fit and unfit categories based on R-MCI. The median overall survival rates of patients in these groups were 10.1 years, 4.4 years and 1.2 years; thereby validating the prognostic role of R-MCI for elderly MM patients (Engelhardt et al., 2017). EMN also recommends IMWG frailty index and R-MCI as reliable parameters to classify elderly MM patients into fit, intermediate-fit and frail categories, with R-MCI having a relatively inferior outcome and a higher rate of treatment discontinuation (Larocca et al., 2018).

Table 1
IMWG and R-MCI classification of elderly MM patients according to fitness profile and frailty score.

IMWG frailty score (2015)

Parameter		IMWG-frailty index points
Age (years)	≤75	0
	76- 80	1
	> 80	2
ADL	> 4	0
	≤4	1
IADL	> 5	0
	≤5	1
CCI	≤1	0
	> 1	1
Patient status		**Cumulative IMWG frailty score**
Fit		0
Intermediate-fit		1
Frail		2-5

R-MCI (2016)

Parameter		R-MCI points
Age (years)	< 60	0
	60-69	1
	≥ 70	2
KPS	100%	0
	80-90%	2
	< 70%	3
eGFR (ml/min)	≥ 60	0
	< 60	1
Frailty*	Mild	0
	Moderate/Severe	1
Cytogenetics	Missing	0
	Favorable**	0
	Unfavorable***	1
Lung dysfunction	No/Mild	0
	Moderate/Severe	1
Patient status		**Cumulative R-MCI frailty score**
Fit		0-3
Intermediate-fit		4-6
Frail		7-9

Abbreviations: ADL = Activities of daily life; CCI = Charlson Comorbidity Index; IADL = Instrumental activities of daily living; IMWG = International Myeloma Working Group; KPS = Karnofsky Performance Status; R-MCI = Revised Myeloma Comorbidity Index.

* Parameters: Karnofsky Index, Time Up/Go, IADL, Subjective fitness.

** Hyperdiploidie, t(11;14), NK, del(13q14).

*** t(4;14), t(14;16), t(14;20), del(17p), Hypodiploidie, c-myc, Chromosom1-aberrations.

2.2. Three drug versus two drug regimens in elderly myeloma patients

The FIRST trial performed by Benboubker et al. (2014) was the first randomized phase III study to compare the efficacy of two drug regimen containing lenalidomide and dexamethasone (Rd) with that of three-drug regimen containing melphalan, prednisone and thalidomide (MPT) in 1623 transplant-ineligible NDMM patients with median age of 73 years and 1531 (94.3%) patients with age ≥ 65 years. The patients were randomly assigned to three groups, 535 receiving continuous 28-day cycles of Rd until progression of the disease, 541 receiving 28-day cycles of Rd for 72 weeks (18 cycles) and 547 receiving MPT for 72 weeks. The median PFS was 25.5 months with continuous Rd, 20.7

months with 18 cycles of Rd, and 21.2 months with MPT. The OS at 4 years was 59% with continuous Rd, 56% with 18 cycles of Rd, and 51% with MPT. Eighty-five percent of patients in the continuous Rd group, 80% in the 18 cycle Rd group and 89% in the MPT group had at least one or more grade 3 or 4 AEs. This study showed a two-drug regimen of continuous Rd until disease progression having better efficacy and safety profile than MPT in transplant-ineligible patients, 94.3% of whom were ≥65 years (Benboubker et al., 2014). A phase 2 study by Larocca et al. (2016) in 152 NDMM patients aged ≥75 years, half of whom were frail, compared two-drug regimen of subcutaneous bortezomib with oral prednisone (VP) in 51 patients, three-drug regimen of VP plus cyclophosphamide (VCP) in 51 patients and three-drug regimen of VP plus melphalan (VMP) in 50 patients. Median PFS was 14.0 months, 15.2 months and 17.1 months while 2-year OS was 60%, 70%, and 76%, in patients receiving VP, VCP, and VMP. Twenty-two percent of patients treated with VP, 37% with VCP and 33% with VMP experienced at least one non-hematologic drug-related AE. The rate of drug discontinuation secondary to AEs was 12%, 14%, and 20% and the rate of deaths related to toxicity in 6 months was 4%, 4% and 8% with VP, VCP, and VMP respectively. No major difference in efficacy of VP, VCP and VMP regimens along with relatively better safety profile of VP compared to three-drug regimens favors the benefit of using two-drug regimen in very elderly and frail NDMM patients (Larocca et al., 2016). A study performed by Magarotto et al. (2016) with 662 NDMM patients, who were either aged ≥ 65 years or ineligible for ASCT, compared the efficacy of three-drug vs. two-drug regimens containing lenalidomide. Patients were randomized into three groups, two groups receiving three-drug regimens melphalan-prednisone-lenalidomide (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR) respectively and one group receiving two-drug regimen lenalidomide plus low-dose dexamethasone (Rd). A post hoc analysis classifying patients into fit, intermediate fit and frail on the basis of IMWG frailty score found 4 year OS to be 77% and 57% in fit patients receiving three-drug and two-drug regimens respectively while no significant benefit in 4 years OS with three-drug regimen was seen in intermediate fit and frail patients (Magarotto et al., 2016), suggesting improved efficacy of three-drug regimens only in fit elderly patients. Another study by Bonomo et al. (2016) with 117 MM patients with a median age of 75 years (range 70–95) and significant comorbidities including a patient group with 36% cardiac, 20% renal and 5% pulmonary involvement. They compared the efficacy of bortezomib-based two drug and three drug regimens. Patients receiving RVD (n = 34) showed an ORR of 94% and median PFS of 36 months as compared to the patients on VD (n = 17) showing an ORR and median PFS of 65% and 24 months respectively (Bonomo et al., 2016). The 34 patients receiving RVD received attenuated, not full doses, of this regimen which favors dose reduction in elderly MM patients.

The latest EMN guidelines by Larocca et al. (2018) recommend to treat elderly MM patients based on their classification into “fit”, “intermediate fit” and “unfit” as directed by IMWG frailty score and R-MCI with primary goal of treatment being achieving deep response, balancing efficacy and toxicity, and conservative approach along with low toxicity in fit, intermediate fit, and frail patients, respectively. It suggests the use of ASCT along with full dose of triplet or doublet regimens in fit patients, full-dosed doublet or reduced-dose triplet regimens in intermediate fit patients and reduced-dose doublet regimens along with palliative and supportive care in frail patients (Larocca et al., 2018).

3. Autologous Stem-Cell Transplantation (ASCT) in elderly MM patients

Almost all MM guidelines and studies consider patients aged ≤ 65 years suitable for ASCT, as evident from the phase III clinical trials (Palumbo et al., 2014a; Gaynon, 2006). In the recent years, many clinical studies performed regarding the clinical outcome of ASCT in MM patients aged > 65 years have shown promising results. Auner et al. (2015) compared the results of different studies regarding ASCT in elderly MM patients and established that eligibility for ASCT should not be decided on the basis of chronological age alone, other factors like overall health, functional reserve, and drug tolerability profile should also be considered (Auner et al., 2015). A study by Shah et al. (2015) for determining the cost-effectiveness of ASCT in MM patients aged ≥ 65 years compared the clinical outcome of ASCT by measuring the mOS and survival rate at five years in two groups of 270 MM patients each, one group received ASCT while the other did not. After a median follow-up of 3.5 years, mOS was 58 months vs. 37 months ($p < 0.001$) and 3-year survival rate was 73% vs. 50% ($p < 0.001$) in the ASCT group and non-ASCT group, respectively (Shah et al., 2015). A retrospective analysis by Desai et al. compared the toxicity of full dose melphalan (200 mg/m^2) among two groups of ASCT patients, age < 65 years (n = 47) and age 65–69 years (n = 49). No significant difference (p-value > 0.4) between cardiac, renal and hematological toxicity (infections, neutropenic fever) was seen between the two groups. The overall survival (OS) at 2 years and median progression free survival (mPFS) at 1.3 years were 88% and 60.5% respectively in these patients (n = 68) with a median age of 67 years (Desai et al., 2017).

Bashir et al. (2011) analyzed the safety of ASCT in MM patients (n = 84) age > 70 years with 21% of the patients ≥ 75 years of age. The 5 year OS and PFS was 67% (95% CI: 54–82%) and 27% (95% CI: 16–44%), respectively. Three different doses of melphalan (140, 180 and 200 mg/m^2) were used for conditioning regimen. No significant difference between response rate among the three doses (88%, 90%, and 82%) was noted. ASCT, if used as first line therapy, improves OS compared to use in patients with relapsed refractory disease (83% vs. 41% at 5 years, p-value = 0.001) (Bashir et al., 2012). Garderet et al. (2016) performed a study to analyze the efficacy and tolerability of high dose melphalan (200 mg/m^2) followed by ASCT after induction treatment in 56 NDMM patients age > 65 years. Among 56 patients, 6 were not able to receive ASCT after induction due to different reasons but were considered for post-transplant analysis on the basis of intention-to-treat. Ten out of 56 patients received low-dose melphalan (140 mg/m^2) while the remaining 46 patients received high dose melphalan (200 mg/m^2). After a median follow up of 21 months, 2-year PFS and OS rates were 76% (CI: 61.6–94.1%) and 88% (CI: 76.7–100%). PFS was found to be relatively better in patients receiving high-dose melphalan (Garderet et al., 2016). Straka et al. (2016) performed a multicenter trial on 434 NDMM patients randomized to 2 groups receiving ASCT, one with induction therapy and the other without induction. In 420 patients evaluable at the end of study for PFS and OS, the difference in median PFS and median OS was statistically insignificant in patients aged < 65 years and ≥65 years. Median PFS was found to be 19.5 months and 22.1 months in patients aged < 65 years and ≥65 years respectively (p-value = 0.23). Median OS was found to be 56.3 months and 53.1 months in patients aged < 65 years and ≥65 years respectively (p-value = 0.58) (Straka et al., 2016). Ozaki et al. (2014) retrospectively analyzed the clinical outcome of different treatment modalities in NDMM patients aged 65–70 years. Among 318 patients, 192 patients were treated with conventional chemotherapy regimens, 88 with novel chemotherapy regimens, 21 with conventional chemotherapy regimens plus auto-SCT and 17 with conventional chemotherapy regimens plus auto-SCT. Patients receiving auto-SCT showed statistically significant improvement in OS compared to those not receiving auto-SCT (OS being not reached vs. 57.9 months with $p < 0.02$ in both groups respectively), showing auto-SCT as an effective treatment option in eligible elderly MM patients aged 65–70 years (Ozaki et al., 2014). These studies suggest the feasibility of ASCT in elderly MM patients, making it a reliable therapeutic option in this patient population and don’t consider advanced patient age as exclusion criteria for ASCT. Latest EMN guidelines by Gay et al. (2018) recommend age < 65 years, Karnofsky Performance Status (PS) > 90%, Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-

CI) = 0 and Revised-Myeloma Comorbidity Index (R-MCI) 0–3 as a cut-off for receiving high-dose melphalan (200 mg/m^2) for all MM patients receiving ASCT. These also recommend high-dose melphalan (200 mg/m^2) for those aged 65–70 years with Karnofsky PS > 90% and those having Karnofsky PS < 90% related to the MM itself instead of other comorbidities, and consideration of melphalan dose reduction for more advanced age, Karnofsky PS < 90%, HCT-CI > 1 or R-MCI 4–6 (Gay et al., 2018).

4. Comorbidities and management of multiple myeloma

Gregersen et al. (2017) reported the presence of comorbid conditions like congestive heart failure (OR 2.8), chronic pulmonary disease (OR 1.7), renal dysfunction (OR 11) and DM with complications (OR 2.3) in myeloma patients compared to general population (p-value < 0.05) during the 1 year to 1 month before the diagnosis of MM (Gregersen et al., 2017). Management of MM patients with comorbidities is complicated because of drug-drug interactions and potential side effect profile of each of the prescription medication. The addition of a third factor, old age with frailty, adds unique challenges to the treatment strategy. There is potential for pharmacokinetic or pharmacodynamics interactions among medications for comorbidities and anti-myeloma drugs.

4.1. Renal impairment

Renal impairment (RI) is present in 20%–25% MM patients at the time of diagnosis (Knudsen et al., 1994) and 55% of patients develop RI during the course of their treatment (Kyle et al., 2003). Common factors that lead to renal impairment include hypercalcemia of malignancy, dehydration, amyloidosis, tumor lysis syndrome, age-related decline in renal function and exposure to nephrotoxic medications (Kleber et al., 2009; Kheder El-Fekih and Izzedine, 2016). Renal impairment requires dose adjustment for therapies according to the degree of renal function, use of alternatives to avoid nephrotoxic drugs, and plasmapheresis or dialysis if needed. Effective treatment of underlying pathology is the best management strategy for the complicated kidney dysfunction.

Bortezomib-based regimens are the mainstay of the treatment in patients with RI (Gay et al., 2018). Bortezomib is metabolized in the liver by deboronation, therefore, it does not require dose adjustment in patients with RI (Haynes et al., 2012; Dimopoulos et al., 2010a). Dimopoulos et al. (2009, n = 227) compared the efficacy of VMP (bortezomib, melphalan, prednisone) to MP in patients with renal dysfunction. Among 34 patients with CrCl < 30 ml/min, response rate with VMP was better (74%) than MP (47%). Improvement in GFR from < 50 ml/min to > 60 ml/min was seen in 44% patients on VMP than 34% patients on MP (Dimopoulos et al., 2009). Similarly, objective response rate (ORR) of 73% (Morabito et al., n = 117 with n = 82 having CrCl < 30 ml/min) (Morabito et al., 2010) and 67% (Ponisch et al., n = 36 with 16 patients on dialysis) (Ponisch et al., 2013) was reported in patients with renal impairment receiving bortezomib-based regimens. Lenalidomide, when used in combination with dexamethasone, in renal adjusted doses can improve renal function in about 40% of patients (Dimopoulos et al., 2010b). Renal dose adjustment of drugs used in multiple myeloma patients is summarized in Table 2.

4.1.1. ASCT in patients with renal impairment

ASCT is feasible in patients with renal impairment and can result in significant improvement in renal function. El Fakih et al. (2015) analyzed the role of ASCT in patients on dialysis (21 on hemodialysis and 3 on peritoneal dialysis). Three year OS and PFS were reported to be 64% and 36% respectively. Regarding improvement of the renal function, 32% of the patients showed improvement in GFR (by 25% from baseline) (El Fakih et al., 2015). Among 54 dialysis dependent patients, 13 (24%) patients did not require dialysis at a median of 4 months after transplant (Lee et al., 2004, 2004).

4.1.2. Supportive treatment

Along with the selection of appropriate chemotherapeutic drug and its dose adjustment, supportive therapy is also necessary. IMWG recommends high fluid intake (> 3 L/day) during myeloma treatment. Fluid challenge can be given to patients who are anuric as a way to reverse renal dysfunction. Nephrotoxic drugs like aminoglycosides, NSAIDs, iodine contrast, furosemide should be avoided (Dimopoulos et al., 2016).

4.2. Bone disease

4.2.1. Bisphosphonates

Osteolytic bone disease is present in 70%–80% of MM patients at the time of diagnosis (Terpos et al., 2013). Risk for skeletal-related events (pathological fractures and spinal cord compression) is increased in MM patients with bone disease (Coleman, 1997). Bisphosphonates (BPs) not only decrease the skeletal-related events (SRE) but may also provide survival benefits in MM (Berenson et al., 1996; Morgan et al., 2011). While personalizing the use of bisphosphonates in MM patients, the factors that need to be considered include grade of bone disease, stage of MM, route of administration, duration of treatment, adverse effects of bisphosphonates like osteonecrosis of jaw (ONJ) and renal function status of the patient. NCCN guidelines suggest the use of pamidronate (PAM) or zoledronic acid (ZOL) in MM patients with active disease at all stages with monitoring for renal function (CrCl) and osteonecrosis of jaw (Kumar et al., 2017). The mSMART guidelines recommend the initiation of BPs in patients with evidence of bone disease by conventional radiography whereas IMWG suggests the use of advanced imaging modalities like MRI, CT and PET scan in addition to plain radiographs for detection and monitoring of lytic lesions for BP therapy (Lacy et al., 2006; Durie, 2007). The recommended dose of zoledronic acid (4 mg) is infused over 15 min whereas that of pamidronate (90 mg) is infused over 2–4 h. EMN suggests that BPs should be administered once every 3–4 weeks; the duration of use is 2 years for PAM while ZOL should be used continuously (Terpos et al., 2015). Mayo consensus statement recommends the monthly dosing schedule of BPs for the first year and then decrease dosing frequency to once every 3 months for the second year. If disease relapse occurs, monthly dosing can be restarted (Bisphosphonates in Myeloma, 2018).

Adverse effects associated with BP use are electrolyte imbalance (hypocalcemia and hypophosphatemia), inflammatory reactions at the injection site, and acute-phase reactions after IV administration. Renal impairment and osteonecrosis of jaw are infrequent, but serious adverse effects associated with BPs. Hypocalcemia can be prevented with the daily administration of oral calcium and vitamin D3. Around 40% of myeloma patients have low vitamin D levels (Badros et al., 2008). Therefore, baseline and annual measurement of vitamin D level are recommended (Terpos et al., 2015; Calcium and Vitamin D Supplementation in Myeloma, 2018).

4.2.2. Management of bone disease in renal impairment

ZOL and PAM can cause renal impairment leading to acute renal failure (Morgan et al., 2010). Renal impairment depends on the concentration of BPs in bloodstream at a given time, therefore, rapid infusion rate and high dosage can potentially lead to renal failure. Established guidelines recommend the monitoring of renal function while administering BPs. Dose of ZOL should be reduced in patients with decreased creatinine clearance according to the manufacturer guidelines (Table 2) (Bisphosphonates in Myeloma, 2018). PAM may be administered over extended duration (> 4 h). No change in the duration of infusion of ZOL is advised. PAM and ZOL should not be used in patients with creatinine clearance less than 30 ml/min (Terpos et al., 2013). Denosumab, a monoclonal antibody, is recently approved by FDA for use in MM patients. A phase III trial with 1718 patients showed

Table 2
Dose modification of drugs used for the treatment of multiple myeloma according to Creatinine Clearance (CrCl).

Drug	> 60 ml/min	30-59 ml/min	15-29 ml/min	< 15 ml/min	On dialysis
Melphalan PO, mg/kg/d	0.15-0.25	0.11-0.19	0.11-0.19	0.0175-0.125	0.0175-0.125
Cyclophosphamide	300 mg/m^2	No dose adjustment required			
Doxorubicin	30 mg/m^2	No dose adjustment required			
Carmustine	150-200 mg/m^2 (single dose or divided in 2 days)	No dose adjustment required		Discontinue at CrCl < 10	
Plerixafor	0.24 mg/kg/d	≤50 CrCl, 0.16 mg/kg/d			
Dexamethasone	20-40 mg	No dose adjustment required			
Prednisone	According to regimen	No dose adjustment required			
Thalidomide	50-200 mg/d	No dose adjustment required			
Lenalidomide	25 mg/d	10 mg/d	15 mg/48hr	5 mg/d	5 mg/d, post-dialysis
Pomalidomide	4 mg/d	No dose adjustment required		NA	3 mg/d post-dialysis
Bortezomib	1.3 mg/m^2	No dose adjustment required			
Carfilzomib	According to regimen (20/27/56 mg/m^2)	No dose adjustment required			
Ixazomib	4 mg/d	No dose adjustment required	3 mg/d	3 mg	3 mg, pre or post dialysis
Panobinostat	20 mg/d	No dose adjustment required		Not studied	
Daratumumab	16 mg/kg	No dose adjustment required			
Elotuzumab	10 mg/kg	No dose adjustment required			
Pamidronate	90 mg monthly	No dose adjustment required	Not recommended		
Zoledronic acid (monthly)	4 mg	3 - 3.5 mg CrCl 50-60 ml/min: 3.5 mg, 40-49: 3.3 mg, 30-39: 3 mg.	Not recommended		
Denosumab	120 mg monthly	No dose adjustment required			
Enoxaparin	40 mg/d	No dose adjustment required	30 mg/d		

non-inferiority of denosumab over zoledronic acid for time to development of first skeletal-related event (Hazard ratio = 0.98, p-value = 0.010) (Raje et al., 2018). Denosumab is injected subcutaneously in a dose of 120 mg every 4 weeks. It is not renally cleared and thus its use can be considered in patients with RI (CrCl < 30 ml/min) (Anderson et al., 2018). In a recent study by Symonds et al., data revealed an increased risk of rebound vertebral compression fractures in patients who stop taking denosumab. A long-term follow up of participants (n = 1001) of FREEDOM trial showed a six-fold increased risk of vertebral fractures from 1.2 per 100 participant years while on the drug to 7.1 after discontinuation of denosumab, The risks and benefits of denosumab use must be reviewed with the patient before initiating or discontinuing therapy (Symonds and Kline, 2018).

4.2.3. Monitoring and management of osteonecrosis of jaw

Osteonecrosis of jaw (ONJ) is a serious complication resulting from the use of bisphosphonates and denosumab. It presents with exposed bone with tissue swelling, loosening of teeth and dental infections (Kalra and Jain, 2013). Incidence of ONJ is 4% to 11% in patients on BP therapy and risk is particularly increased in patients with use of ZOL (Dimopoulos et al., 2006). Longer duration of BP therapy, poor dental hygiene, dental infections, and corticosteroids are risk factors that lead to the development of ONJ. Utilization of BPs for more than 3 years causes increased incidence of ONJ (7.7%) compared to use for around 1 year (1.5%) (Bamias et al., 2005). Prophylactic use of antibiotics before dental procedures decreases the risk of ONJ significantly (p-value = 0.012) (Montefusco et al., 2008). EMN, IMWG, mSMART and NCCN guidelines advise patients to get complete dental exam before starting BP therapy (Kumar et al., 2017; Terpos et al., 2015, 2013; Bisphosphonates in Myeloma, 2018). The purpose of this exam is to identify any dental pathology that may need surgical treatment like dental extraction, incision & drainage or pulpectomy. Once BP therapy is started, if any dental problem arises it should be treated conservatively. If necessary, surgical intervention should be performed by an experienced maxillofacial surgeon. Physicians should stop BP one month before dental surgery and restart once complete healing has occurred (Lacy et al., 2006).

4.2.4. Role of kyphoplasty, radiation, and surgery

Balloon kyphoplasty (BKP) is an effective technique for immediate pain relief lasting up to 2 years in patients with painful vertebral fractures. BKP has shown better functional outcomes than vertebroplasty and prevented disability in MM (Bouza et al., 2009). For uncontrolled pain, imminent pathologic fracture or imminent spinal cord compression, surgical intervention or palliative radiotherapy (10–30 Gy) is recommended (Kumar et al., 2017).

4.3. Venous thromboembolism

Venous Thromboembolism (VTE) is a broad term that includes deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT) and thrombosis in other vessels. Factors that contribute to the development of VTE in MM are hyperviscosity induced by MM, immune modulators (lenalidomide, thalidomide, pomalidomide), steroids (dexamethasone) and patient related factors (Klovaite et al., 2015; Cancer Stat Facts: Myeloma, 2018). There is a strong risk of the development of VTE in the first year following the diagnosis of myeloma (Kristinsson et al., 2008). Therefore it is imperative to prescribe VTE prophylaxis to multiple myeloma patients with risk factors. Drugs commonly used for VTE prophylaxis are aspirin, low molecular weight heparin (LMWH) and warfarin. Novel anticoagulants like apixaban (factor X inhibitor) are in the trial phase to be used as primary prevention of VTE in myeloma patients on IMiDs (Apixaban for Primary Prevention of Venous Thromboembolism in Patients With Multiple Myeloma, 2019). Selection of VTE prophylaxis according to individual risk factors is necessary. Individual risk factors include smoking, obesity (BMI ≥ 30 kg/m^2), family history of VTE, comorbidities like renal insufficiency, diabetes, immobilization, cardiac disease, recent surgery, polycythemia, medications like tamoxifen, steroids and erythropoietin (Terpos et al., 2015). The summary of VTE prophylaxis guidelines by European Myeloma Network (EMN) and National Comprehensive Cancer Network (NCCN) is given in Table 3.

IMWG recommends the use of aspirin in patients with no or one risk factor. MM patients with multiple risk factors should receive LMWH or full dose warfarin (Palumbo et al., 2014b). NCCN recommends either monotherapy (LMWH, UFH, factor Xa inhibitors) or regimens (combinations of above with warfarin, dabigatran) if VTE develops. Selection

Table 3
Recommendation for VTE prophylaxis in MM patients on Immunomodulator drugs (IMiDs).

Risk factors (RF)	Recommended Therapy	
Individual RF[a]	NCCN, 2018	EMN, 2015
Myeloma-associated RF[b]	No or only one risk factor	
	Aspirin 81 to 325 mg/d	Aspirin 100 mg/d
	≥ 2 risk factors	
	LMWH or Warfarin[d]	LWMH (Switch to aspirin after 4 months) or Warfarin
IMiD based regimens[c]	LMWH or Warfarin[d]	LWMH (Switch to aspirin after 4 months) or Warfarin

Abbreviations: EMN = European Myeloma Network; IMiD = Immunomodulator drugs; LMWH = low molecular weight heparin; MM = multiple myeloma; NCCN = National Comprehensive Cancer Network; RF = risk factor.

[a] Individual risk factors are described in the text.

[b] Myeloma associated risk factors include diagnosis of myeloma and hyperviscosity.

[c] Immunomodulator drugs (lenalidomide, pomalidomide, thalidomide) in combination with dexamethasone (> 480 mg/month), doxorubicin or combination chemotherapy.

[d] Target INR 2–3.

of regimen should be based on factors like renal impairment (CrCl < 30 ml/min), mode of administration, bleeding risk and cost (Cancer-Associated Venous Thromboembolic Disease, 2018). IMWG and EMN agree to discontinue chemotherapy temporarily and start therapeutic anticoagulation if acute VTE develops (Terpos et al., 2015; Palumbo et al., 2014b).

4.4. Diabetes mellitus

Approximately 20% of the people above the age of 65 years in the United States are diagnosed with Diabetes Mellitus (DM) (National Diabetes Statistics Report, 2017). Hyperglycemia in the MM population can be due to either preexisting DM or steroid induced caused by the use of dexamethasone. Uncontrolled diabetes can cause nephropathy potentiating the renal dysfunction caused by MM. Wu et al. (2014, n = 1240) analyzed the impact of diabetes and its management on overall survival (OS) as primary endpoint. Diabetic MM patients had decreased median OS of 65.4 months compared to 98.7 months in patients without diabetes. Use of metformin was associated with increased OS compared to no use (74.3 vs. 60.1 months, p = 0.034). On the other hand, use of insulin resulted in shorter OS compared to no use (57 vs. 101 months, p < 0.001) (Wu et al., 2014). The possible mechanisms behind decreased OS due to insulin include induction of resistance to chemotherapy in cancer cells and activation of cell cycle signaling pathways resulting in growth of cancer cells (Feng et al., 2011). It is recommended to screen patients before starting treatment and monitor glucose levels during dexamethasone or prednisone therapy (Ahmed and Eltayeb, 2013). Dose reduction of dexamethasone should be considered in patients in uncontrolled hyperglycemia and those at risk of developing diabetes associated macrovascular and microvascular complications. Standard dose of dexamethasone 40 mg once per week can be changed to 20 mg twice weekly to achieve better glucose control. Further reduction to 20 mg once per week to 10 mg once per week can be done to decrease toxicity (Wildes et al., 2014).

4.5. Cardiovascular diseases

Multiple myeloma patients have been noted to have a higher incidence of cardiovascular diseases. One study reported that the incidence of cardiac adverse event is higher (Hazard Ratio = 2.2) in MM treated patients as compared to patients without the diagnosis (Kistler et al., 2017). Xiao and colleagues (2014, n = 4330) reported the overall incidence of all grade cardiotoxicity of 4.3% in bortezomib monotherapy versus 3.5% in bortezomib-based combination therapy for all cancer types. An analysis of six randomized clinical trials with bortezomib resulted in a pooled odds ratio for all grade cardiotoxicity of bortezomib is 1.15 with p-value = 0.41. This meta-analysis concluded that bortezomib does not increases the risk of cardiotoxicity during treatment (Xiao et al., 2014).

Cardiac adverse effects like dyspnea (2.8% vs. 1.8%), hypertension (4.3% vs. 1.8%) and cardiac failure (3.8% vs. 1.8%) have a higher incidence with carfilzomib based treatments (Stewart et al., 2015). Mushtaq et al. reported the range of cardiovascular side effects in patients for carfilzomib based combination regimens for hypertension at 3–25% and of heart failure at 3.4–20% (Mushtaq et al., 2018). In 24 prospective clinical trials, a total of 2594 MM patients were treated with carfilzomib from a range of doses of 15 to 88 mg/m^2. Various cardiovascular adverse events (CVAE) including hypertension, heart failure, cardiac arrhythmia, cardiac ischemia and cardiac arrest were assessed in these patients and reported as an aggregate outcome. All grade CVAE were reported in 617 (18.1%) patients and grade 3 or higher CVAE were seen in 274 (8.2%) patients. Increased rate of high-grade CVAE (11.9%) was reported in patients receiving increased dose of carfilzomib (≥ 45 mg/m^2) compared to 6.4% in patients receiving lower dose (< 45 mg/m^2), p = 0.02. These results indicated positive correlation between dose of carfilzomib and rate of CVAE (Waxman et al., 2018). Dimopoulos et al. (2017), n = 60) reported the incidence of cardiac event (left ventricle ejection fraction ≥ 20%) in 7 (12%) patients on carfilzomib combination regimens. Cardiac function returned to normal in all patients after a median of 60 days after drug discontinuation and appropriate treatment (Dimopoulos et al., 2017). Before starting carfilzomib, it is recommended to assess for baseline cardiac function, and manage preexisting hypertension and cardiac failure (Mikhael, 2016). In patients presenting with suspected signs and symptoms of cardiac dysfunction, carfilzomib and excessive fluids should be stopped and appropriate interventions and monitoring should be initiated. Consultation with a cardiologist should be considered for better management (Jakubowiak et al., 2017).

4.6. Peripheral neuropathy

MM patients have a relatively higher incidence of peripheral neuropathy (PN) resulting in increased risk of falls, neuropathic pain along with the higher incidence of loss of bowel/bladder control, ultimately causing functional impairment. About two-thirds of MM patients report pain including neuropathic pain (Kariyawasan et al., 2007) and more than half report varying intensities of PN at diagnosis (Plasmati et al., 2007). Neurological assessment tools including the 'Total Neuropathy Score'(Cavaletti et al., 2007) and 'National Cancer Institute (NCI) Common Toxicity Criteria'(Trotti et al., 2003) can be used in elderly MM patients at diagnosis to decide suitable treatment and assessment should be repeated periodically during the course of treatment to determine the need for changing therapy. MM patients with pre-existing PN at diagnosis need suitable drug selection and dose reduction for treatment because of relatively commonly reported bortezomib-induced PN (BiPN) and thalidomide-induced PN (TiPN) (Delforge et al., 2010). In a randomized controlled trial (RCT) by Palumbo et al. (2010), 511 elderly patients with newly diagnosed MM (NDMM) were randomly allocated to two groups, one receiving VMPT-VT and the other VMP. Initially, 134 patients in both groups were given twice-weekly bortezomib. Halfway through the trial, bortezomib dosing was reduced from twice-weekly to once-weekly in remaining 369 patients in both groups. In once-weekly vs. twice-weekly bortezomib arms, the rate of grade 3–4 non-hematological toxicities was 51% vs. 36% (p = 0.003) and the rate of grade 3–4 sensory PN was 16% vs. 3% (p < 0.001) respectively without any significant change in clinical outcome in both groups (Palumbo et al., 2010). In a phase III trial, 222 relapsed MM

Table 4
Recommended dose modifications in patients with peripheral neuropathy.

Bortezomib[a]	**Grade of PN**		**G1**	**G1 (painful) or G2**	**G2 (painful) or G3**
	IMWG[c]	Twice-weekly	↓ to 1 mg/m^2 or shift to once-weekly		D/C
		Once-weekly	↓ to 1 mg/m^2	D/C temporarily or ↓ dose to 1 mg/m^2	
	EMN[c]		NA	↓ to 0.7-1.0 mg/m^2 [d]	D/C till down-escalated to G1 Resume at 50% dose
Thalidomide[b]	**Grade of PN**		**G1**	**G2**	**G3-4**
	IMWG		50% dose reduction	D/C; Resume at 50% dose post resolution	D/C
	EMN		NA	50% dose reduction	D/C till down-escalated to G1 Resume at 50%

Abbreviations: D/C = discontinue; EMN = European Myeloma Network; G = grade; IMWG = International Myeloma Working Group; NA = not available; PN = peripheral neuropathy; ↓ = decrease.
[a] Dose of bortezomib is 1.3 mg/m^2.
[b] Dose of thalidomide is 100 mg.
[c] Discontinue if G4 develops.
[d] Preferably subcutaneous.

patients (half aged > 65 years) were randomized to receive either intravenous (IV) or subcutaneous (SC) bortezomib and the rate of grade 3 PN was 15% vs. 5% respectively, (Moreau et al., 2011), suggesting better safety profile of SC bortezomib than IV bortezomib with no significant difference in clinical outcome measured as PFS and OS between the two groups. IMWG (Ludwig et al., 2014) and EMN (Terpos et al., 2015) recommendations for dose-reduction in patients with drug-induced neuropathy is summarized in Table 4. The risk of peripheral neuropathy is lower as compared to the IMiDs such as lenalidomide (1.7%), (Weber et al., 2007) and pomalidomide (< 1%–2% grade 3/4 PN) (Martin, 2013). Among proteasome inhibitors, the incidence of grade 3 treatment-induced PN with carfilzomib was 1.3% (Martin, 2013) and ixazomib-related grade 3 PN occurred in 2% of patients (Offidani et al., 2014).

5. Conclusion

While making therapy decisions for MM patients, patient treatment should address a personalized approach with consideration for age, comorbidities, and frailty. In addition, ASCT should be considered in all MM patients based on their fitness profile and comorbidity index irrespective of the chronological age. Elderly patients, comprising the major part of MM patient population, are a clinically diverse group with specific and individual needs based on their drug tolerability profiles along with individual age-related and disease-related renal, neurological, endocrine and bone disorders. There is a need for clinical trials focusing on individualized treatment with special consideration for dose reduction and assessment of comorbidities in various subgroups of MM patients. More clinical trials should include very elderly MM patients as they are underrepresented in most of the completed clinical trials.

Authorship statement

FHW, SUW, FA and AM designed the study. All authors performed the study, contributed to data extraction, literature review, analyzed the data, and wrote the paper.

Conflict of interest

This manuscript is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. Authors declare no conflict of interest with this manuscript.

Funding source

U.S. Department of Health & Human Services, NIH, National Cancer Institute (NCI) Grant number - P30 CA023074 [Faiz Anwer]

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Muhammad Asad Fraz has his MD and is a graduate of King Edward Medical University (KEMU), Pakistan. Currently, he is working as research associate in Hematology/Oncology at University of Arizona Cancer Center (UACC).

Faiza Hassan Warraich has his MD and is a resident at Department of Internal Medicine, McLaren-Flint Medical Center, Flint, MI.

Sami Ullah Warraich has his MD and is a graduate of KEMU, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Muhammad Junaid Tariq has his MD and is a graduate of KEMU, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Zabih Warraich has his MD and is a resident at Department of Internal Medicine, United Health Services Wilson Memorial Regional Medical Center, Johnson City, NY.

Ali Younas Khan has his MD and is a graduate of Shifa College of Medicine, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Muhammad Usman has his MD and is a graduate of KEMU, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Awais Ijaz has his MD and is a graduate of Allama Iqbal Medical College, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Pavan Tenneti has his MD and is working as Clinical Assistant Professor at College of Medicine, University of Arizona.

Adeela Mushtaq has his MD and is a resident at Department of Medicine, University of Pittsburgh Medical Center, McKeesport.

Faisal Akbar has his MD and is working as Assistant Professor at Wake Forest Baptist Medical Center, North Carolina.

Zaina Shahid has her MD and working at Wilkes Medical Center - Wake Forest Baptist Health, North Carolina.

Zeeshan Ali has his MD and is working as Clinical Assistant Professor at College of Medicine, University of Arizona.

Hafiz Muhammad Fazeel has his MD and is a graduate of Services Institute of Medical Sciences, Pakistan. Currently, he is working as research associate in Hematology/Oncology at UACC.

Cesar Rodriguez has his MD and is working as Assistant Professor Hematology/Oncology at Wake Forest Baptist Medical Center, North Carolina.

Aboo Nasar has his MD and is working as geriatrician at Tri-City Medical Center, California.

Ali McBride has his PharmD and MS and is the Clinical Coordinator of Hematology/Oncology at UACC.

Faiz Anwer has his MD, is team leader for Multiple Myeloma program, Clinical Director of the adult Blood and Marrow Transplant Program and the Director of the Stem Cell Harvest Program in the Division of Hematology/Oncology at UACC and is an Associate Professor of Medicine at the University of Arizona, College of Medicine.