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MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Challenges and Strategies in the Management of Multiple Myeloma in the Elderly Population

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Abstract

Purpose of Review Approximately one half of the patient-population in multiple myeloma (MM) is > 70 years at diagnosis. Despite notable strides in the management and improved survival, MM remains incurable, with an increasing proportion of elderly patients comprising the relapsed-refractory cohort.

Recent Findings The arbitrary age cutoff at 65 years to define the elderly patient-population has evolved to a more nuanced categorization, incorporating a comprehensive assessment for determining frailty prior to commencing treatment. This step is critical in determining the therapy-intensity, including transplant-eligibility, to minimize toxicity. Dose-modifications are crucial, as the merits of continuous therapy are becoming evident in this patient-population. Bortezomib, lenalidomide, and dexamethasone (VRd) combination has emerged as standard of care for newly diagnosed MM. Fixed-duration Rd followed by reduced-dosed continuous R may be considered in select frail patients with standard-risk MM.

Summary Herein, we review the unique challenges encountered in elderly MM and discuss strategies for optimal management.

Keywords Frailty · Supportive care · Geriatric assessment · Comorbidities · Toxicity · Anti-myeloma therapy

Introduction

Multiple myeloma (MM) is a plasma cell proliferative disorder, accounting for approximately 1.8% of all newly diagnosed malignancies in the USA [1]. The median age at diagnosis of MM is 69 years, with approximately two-thirds of the patients being older than 65 years, and one-third of the patients over 75 years of age at presentation [1, 2]. Various arbitrary age cutoffs have been used to categorize patients as elderly, the most common being 65 years. However, an arbitrary chronological age cutoff is not ideal, and categorization of a myeloma patient as elderly is more nuanced with its dependence upon a multitude of factors besides age. With a rapidly aging population and a steady decline in MM-related mortality, the proportion of elderly MM patients is expected to rise in the coming years. In this article, we review the evaluation and treatment strategies for elderly MM, focusing on up-to-date literature pertaining to the elderly population.

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Diagnostic Challenges with MM in the Elderly

The diagnosis of MM is based on documentation of ≥ 10% plasma cells in the bone marrow and the presence of at least one myeloma defining event. Traditionally, the CRAB criteria (C = elevated serum **c**alcium; R = renal insufficiency; A = anemia; B = lytic bone lesions) had been used as markers of active disease [3]. Recently, newer criteria have included 3 additional myeloma defining events (MDEs) in the absence of CRAB features. These include the presence of either clonal bone marrow plasma cells ≥ 60% by conventional examination, an involved to uninvolved serum free light chain ratio ≥ 100 and/or presence of > 1 lytic lesion on MRI [4]. These biomarkers in the setting of smoldering MM were incorporated into the definition of active disease on the basis of a significantly short progression-free survival (PFS) to active disease at a rate of approximately 40% per year, indicating that the

vast majority of such asymptomatic patients, if merely observed, would require therapy within 2 years of diagnosis [5–7]. These criteria for treatment initiation may be even more important in the context of the elderly MM population as starting therapy early in such situations may prevent debilitating skeletal complications or renal failure that could potentially preclude use of some therapies subsequently.

Importantly, the baseline renal function might be deranged in the elderly, usually secondary to other comorbidities such as diabetes mellitus and hypertension and it is imperative to establish a link or lack there-of between plasma cell disorder and renal dysfunction prior to initiating therapy. In a report by Dimopoulos et al., 63% of patients with age > 80 years at the diagnosis of MM had a creatinine clearance < 60 ml/min/1.73 m^2 [8]. Elderly patients with poor renal function reserve are more prone to light chain associated renal damage. Myeloma-associated renal dysfunction can present as an acute on chronic kidney injury with progressive decline in renal function from cast nephropathy, hypercalcemia, light chain deposition disease, or coexisting AL amyloidosis [9]. Although a renal biopsy is not required in every case, it is particularly important in ambiguous cases where other potential factors, including exposure to nephrotoxins such as NSAID or iodine contrast are felt to play a role.

Frequently, old undetected compression fractures may be visualized during evaluation for lytic lesions for MM. Presence of osteopenia, with an asymptomatic vertebral collapse in the absence of any other lytic lesions may point towards non-myelomatous etiology. MRI and PET-CT imaging techniques can be particularly helpful in differentiating pathological fractures due to myelomatous etiologies versus compression/insufficiency benign fractures [10, 11]. Alternative explanations to non-specific presentations can delay the diagnosis and referral for starting treatment [12]. A population-based study from the UK reported the average time from symptom onset to start of treatment for MM was approximately 6 months [13].

Impact of Age on the Prognosis of Patients with MM

The therapeutic options for MM have expanded tremendously over the past decade, and its impact has been reflected in the improvement in outcomes for patients with MM in the recent years, including the elderly population [14, 15]. Despite this observation, the survival of elderly MM patients continues to be inferior compared to the younger patient population [16, 17]. An explanation for inferior outcome of elderly MM patients may be the lower rates of autologous stem cell transplantation (ASCT) in this group [18, 19]. In a study of 10,549 patients with newly diagnosed MM, patients under 50 years of age had a better survival with favorable prognostic features. Age was an independent predictor of survival in patients not undergoing ASCT, suggesting that factors apart from rates of ASCT utilization also influence the outcomes in elderly MM [20]. The process of aging reduces the organ function reserve, leaving elderly patients more vulnerable to organ damage from MM. Additionally, the tolerability to chemotherapy and novel agents is poorer in elderly patients [21, 22]. The presence of comorbidities increases with old age and again has been seen to confer poorer outcomes in patients with MM [22, 23].

Evaluation

Goals of Therapy: The goals of therapy in a fit patient with newly diagnosed MM are to achieve rapid and deep response, through aggressive induction therapy preferably followed by ASCT as elaborated by multiple studies previously [24–26]. Elderly patients, especially frail patients, are often underrepresented in clinical trials as most of the elderly patients that are included in clinical trials tend to be fitter, with less comorbidity [27]. Therefore, extrapolating treatment strategies tested in such patients to those in the community can be difficult. Frequent dose reductions or premature treatment discontinuations are encountered [28, 29]. Achieving a deeper response with induction therapy, even in the elderly transplant ineligible patients, has been shown to correlate with improved survival in patients undergoing transplant [30–32]. Thus, goals of therapy of achieving deep and sustained responses are fairly similar to those in the young population, but the balancing act of matching efficacy with acceptable toxicity plays a significant role, particularly when it comes to choosing induction therapy in elderly MM.

Geriatric Assessment in the Care of Elderly MM: Evaluation of fitness for therapy of an elderly patient with MM requires a detailed assessment and incorporation of comprehensive geriatric assessment (CGA) adds value beyond routine assessment of performance status alone [33]. Comprehensive geriatric assessment is a multidimensional tool focused at assessing an elderly patient's medical, psychological, social, and functional capacity, giving a more holistic picture of geriatric health. Tailoring therapy on the basis of CGA has been shown to improve various health outcomes impacting both morbidity and mortality [34–36]. However, it is quite time consuming and often becomes impractical in busy clinics. Palumbo et al. attempted to address this issue and proposed a simplified geriatric assessment scale for assessing frailty based on analysis of 869 elderly patients with newly diagnosed MM that were enrolled in three clinical trials across 72 institutions in Europe [37••]. Three different scales were administered to these patients, the Katz Activities of Daily Living, Lawton Instrumental Activities of Daily Living, and the Charlson Comorbidity Index. Age was also incorporated and based on the results of these, a combined additive score (range 0–5) was

formulated. Patients were divided into fit (score 0), intermediate fit (score 1), and frail (score ≥ 2) categories. This score was predictive of OS with 3-year OS of 84% in the fit group, 76% in the intermediate fit group, and 57% in the frail group (hazard ratio 3.57; $p < 0.01$). The risk of grade 3/4 non-hematologic toxicities was also significantly increased in the frail group (HR 1.57; 95% CI 1.12–2.2) compared to the fit group. Performance status was not shown to be predictive for OS in this study. On the other hand, the frailty score was shown to have greater impact on survival than the cytogenetic profile of the patients, further highlighting its importance. A limitation of this study, however, was the lack of an independent validation cohort as well as use of the data to devise a proposed index in patients who were fit enough to be enrolled in trials. Nonetheless, this appears to be a promising and easier-to-use tool that can help to better stratify elderly patients and personalize treatment. The score can be calculated using a web-based application at http://www.myelomafrailtyscorecalculator.net/. Among other scores, the Freiberg Comorbidity Index was studied and validated in 466 MM patients and combining this information with the International Staging System, it was found to be predictive for 5-year OS in that cohort of patients. [37••] However, this study was not restricted to elderly population and needs to be independently validated for elderly MM patients [38]. To summarize, utilization of some form of validated geriatric assessment tool is of paramount importance in the management of elderly myeloma.

Treatment of Newly Diagnosed Elderly Myeloma Patient

The introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors has dramatically reshaped the treatment landscape for MM over the past decade [39]. The treatment of newly diagnosed elderly MM patients can be segregated into transplant and non-transplant based. Potential transplant candidates are best approached by utilization of stem cell sparing therapies. For the transplant-ineligible population, alkylator-based therapy, typically melphalan-prednisone (MP), used to be the standard of care in the prenovel agent era. As many as seven randomized clinical trials (RCT) tested the addition of thalidomide to MP in elderly or transplant ineligible population [40–46]. The improvement in PFS was quite consistent across these trials and four out of these seven trials also showed an improvement in OS with the addition of thalidomide. A meta-analysis of 1571 patients from 5 prospective RCTs comparing MP and MPT (melphalan-prednisone-thalidomide) regimens demonstrated significantly better outcomes for the MPT arm with pooled hazard ratio (HR) of 0.68 ($p < 0.001$; 95% CI 0.55–0.82) and 0.80 ($p = 0.07$; 95% CI 0.63–1.02) for PFS and OS, respectively [47]. Subsequently, an individual patient data meta-analysis of six studies comparing MP versus MPT demonstrated a statistically significant OS benefit, with median OS improving from 32.7 months for MP to 39.3 months for MPT [48•]. Addition of thalidomide, however, was associated with significant adverse effects, including increased peripheral neuropathy and deep venous thrombosis, and frequent treatment discontinuations [47, 49]. Lenalidomide, a second-generation IMiD, has supplanted thalidomide in the current treatment schema for frontline treatment of MM. It has a superior toxicity profile, with lower rates of neuropathy, making it more suitable for continuous therapy. A few retrospective and indirect comparative studies have demonstrated improved outcomes with lenalidomide compared to thalidomide [50, 51]. The ECOG E1A06 was a non-inferiority trial that randomized patients to either MPT or melphalan-prednisone-lenalidomide (MPR). Maintenance with thalidomide or lenalidomide was used in respective arms and median PFS was the primary endpoint. After a median follow-up of 40.7 months, there was no significant difference in the PFS or OS in the two arms. However, the lenalidomide arm had better tolerability, with significantly less grade 3 or 4 non-hematologic toxicities and significantly improved quality of life (QoL) compared to the thalidomide arm, establishing lenalidomide the preferred IMiD in this setting [52]. Lenalidomide in the frontline setting was evaluated in the three-arm double-blinded randomized controlled MM-015 trial [53••]. Continuous lenalidomide after 9 cycles of melphalan-prednisolone-lenalidomide (MPR-R) was found to have significantly improved median PFS compared to the other two arms of MPR and MP. Notably, there was no statistically significant difference in the PFS between the MPR and MP arm. This lack of benefit was attributed to the high rates of grade III/IV hematologic toxicities in the MPR arm, especially in patients above 75 years of age. The overall rates of grade 4 neutropenia and thrombocytopenia were 32% and 12% in the MPR arm versus 8% and 4%, respectively in the MP arm. Thus, this study was only able to demonstrate a PFS advantage with the use of maintenance lenalidomide in the elderly transplant-ineligible patient population. Another important finding was the unacceptably high rate of hematological toxicity with the combined use of lenalidomide and melphalan, indicating that lenalidomide is not necessarily an optimal partner drug to be utilized with alkylating agent and highlighting the need for combining drugs with non-overlapping toxicities in the elderly patient population. The FIRST trial was a three-arm randomized phase III study that included 1623 newly diagnosed elderly (≥ 65 years) patients or younger patients that were ineligible for ASCT [54••]. The study randomized patients to either 28-day cycles of lenalidomide-dexamethasone (Rd) till progression or Rd for a fixed 18 cycles (Rd18) or to 42-day cycles of MPT for 72 weeks (12 cycles). The primary end-point of the study was PFS. With a median follow-up of 37 months, the median PFS with continuous Rd was 25.5 months, and was

significantly longer compared to the median PFS of 21.2 months with MPT (HR 0.72; 95% confidence interval [CI] 0.61–0.85; $p < 0.001$) and 20.7 months with Rd18 (HR 0.7; 95% CI 0.6–.082; $p < 0.001$). There was however no statistically significant difference in the PFS between Rd18 and MPT arms. The 4 year OS was 59%, 56%, and 51% with Rd, Rd18, and MPT arms, respectively. Although there was some improvement in survival with Rd over MPT (HR 0.78; $p = 0.02$), this endpoint did not reach the prespecified superiority limit of $p < 0.0096$. The incidence of grade 3 or 4 neutropenia was significantly lower with Rd compared to MPT (28 vs 45%) and overall incidence of high-grade toxicities was comparable in the three arms (85% for Rd, 80% for Rd18 and 89% for MPT). The incidence of second malignancies was 3% in the Rd arm, 5% in the MPT arm, and 6% in the Rd18 arm. On exploratory subgroup analysis, the benefit of Rd was seen even in age group of > 75 years. Importantly, the starting doses were lower in patients > 75 years of age, with the dose of melphalan reduced from 0.25 mg/kg/day to 0.2 mg/kg/day day 1 to day 4 of a 42-day cycle, thalidomide dose reduced from 200 mg/day to 100 mg/day every day of the cycle, and weekly dexamethasone dose reduced from 40 to 20 mg. Rd regimen also led to a significant improvement in health-related quality of life compared to MPT [55]. Thus, a common theme from the conclusions of the MM-015 and the FIRST trials was that continuous therapy appears to be superior to fixed-duration therapy, a finding confirmed subsequently by a combined analysis of patients enrolled in three different trials comparing continuous versus fixed-duration therapy [56]. The continuous therapy was shown to improve PFS, OS as well as PFS 2 (time from initial randomization till second progression) as compared to fixed-duration therapy [56]. Bortezomib, a proteasome inhibitor, has also been studied in combination with melphalan and prednisolone (VMP) in newly diagnosed, untreated, transplant-ineligible patients with MM and the combination demonstrated a significant improvement in OS (56 with VMP vs 43 months with MP; HR 0.7, $p < 0.001$) compared to MP [57, 58]. Addition of bortezomib to thalidomide and dexamethasone was also studied in the population-based randomized phase III UPFRONT trial, which included newly diagnosed transplant ineligible MM patients that were being treated in the US community-based centers [59•]. Patients were randomized to bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone (VTD), or bortezomib-melphalan-prednisone (VMP) and the primary endpoint was PFS. This study had a higher proportion of elderly patients (42% > 75 years), and was designed to give a more real-world assessment combining a proteasome inhibitor with an IMiD for induction therapy in transplant ineligible population in the community setting. This study failed to show any significant difference in the PFS (median PFS of 14.7 months for VD versus 15.4 months for VTD versus 17. months for VMP; global p value = 0.46) or OS (median OS: VD 49.8 months vs VTD 51.5 months vs VMP 53.1 months; global $p = 0.46$ and $p = 0.79$) between the three arms.

Bortezomib-lenalidomide-dexamethasone (VRd) is one of the standard induction regimens in young fit MM patients [24, 25]. There is a good preclinical evidence of synergistic activity with the addition of bortezomib to Rd that is now reflected in the high response rates associated with this regimen in the newly diagnosed MM patients [60]. The SWOG S0777 trial was designed to answer the question of whether the addition of bortezomib to lenalidomide-dexamethasone (VRd) in induction therapy would improve outcomes compared to lenalidomide-dexamethasone(Rd) in newly diagnosed MM patients treated without an intent for immediate ASCT [61••]. There was no age cutoff for this study and 525 patients were randomized to two arms. All patients received maintenance with lenalidomide and dexamethasone after completion of induction therapy. The baseline characteristics were well matched in the two arms except a higher proportion of patients > 65 years in the Rd arm (48% in the Rd arm versus 38% in VRd arm). After a median follow-up of 55 months, there was not only a significant improvement in the median PFS with VRd (43 months with VRd arm versus 30 months with Rd; HR 0.712; $p = 0.0038$), but also OS, a prespecified secondary endpoint, that improved with VRd (median 75 months with VRd versus 64 months with Rd; HR 0.709; two-sided $p = 0.025$). Notably, the median OS in both arms remained unchanged even after censoring the patients that withdrew from the study for stem cell harvest or transplant (median OS of 75 vs 64 months; $p = 0.036$ in favor of VRd arm). The benefit from VRd for PFS and OS remained significant after an age-adjusted multivariate analysis. The rate of grade III/IV neurologic toxicity, as expected, was higher in VRd arm (33%) compared to Rd arm (11%). This study, however, had used the twice-weekly intravenous bortezomib schedule, which was the standard practice at the time of conception of this trial. Grade 3 and 4 toxicities were observed in 82% with VRd arm and 75% with Rd arm. The median age of the study population was 63 years. In the subset patients > 75 years of age, the median PFS was 39 months versus 20 months in favor of VRd (p = not significant) and the median OS of 63 months versus 31 months in favor of VRd (p = significant; not specified in the study report). The data regarding the cytogenetics were incomplete at the time of publication. The use of subcutaneous bortezomib, which is the current standard practice, would further reduce the rates of neuropathy from bortezomib with this combination [62, 63].

A published report from the European Myeloma Network recommends dose modification of anti-myeloma agents for elderly patients with MM based on certain risk factors. In frail patients, those with an age > 75 years or presence of cardiac, hepatic, pulmonary or renal dysfunction, a dose reduction has been recommended. Further dose reduction by one additional level is recommended upon occurrence of grade 3 or 4 non-

hematologic toxicity [2]. A dose-reduced combination regimen of lenalidomide, bortezomib, and dexamethasone, commonly referred to as RVD-lite, has shown impressive overall response rates of 81.8% in a phase II study ($n = 41$) with good tolerance in an elderly newly diagnosed MM population [64]. RVD-lite was administered over a 35-day cycle as opposed to the conventional 21-day cycles of RVD. Lenalidomide was administered as a single daily oral dose of 15 mg days 1–21 compared to a dose of 25 mg per day for days 1–14 with the conventional RVD regimen; bortezomib was administered at a dose of 1.3 mg/m^2 once weekly subcutaneously on days 1, 8, 15, and 22 and dexamethasone was dosed at 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 for patients ≤ 75 years and days 1, 8, 15, 22 for patients older than 75 years. The median age in this study was 73 years (range 65–91 years). Major grade ≥ 3 toxicities included hypophosphatemia (32.3%), skin rash (11.8%), mood changes (5.9%) fatigue (2.9%), and neuropathy (2.9%). Three patients were withdrawn from the study prior to completion of cycle 1 due to toxicity.

Carfilzomib is an irreversible proteasome inhibitor without the adverse effect of peripheral neuropathy [65]. The CLARION trial compared carfilzomib in combination with melphalan and prednisone (KMP) to VMP in transplant-ineligible NDMM [66]. KMP or VMP were given in 42-day cycles until cycle 9 or till progression/unacceptable toxicity. Carfilzomib was given in a twice-weekly schedule (day 1, 2, 8, 9, 22, 23, 29, and 30) at a dose of 20 mg/m^2 on cycle 1 day 1 and day 2 followed by 36 mg/m^2 subsequently. Progression-free survival was comparable between the 2 regimens (KMP median 22.3 vs 22.1 months with VMP; HR 0.9, $p = 0.16$) as was the rate of grade ≥ 3 AEs (75% with KMP and 76% with VMP). As expected, the grade ≥ 2 peripheral neuropathy was lower with KMP (2.5%) compared to VMP (35%), but KMP was associated with higher incidence of all-grade cardiac failure (11 vs 4%). Recent data from the ALCYONE trial comparing VMP with or without daratumumab (D-VMP) demonstrated a higher ORR with D-VMP (91 vs 74%, $p < 0.001$), along with improvement in deeper responses (CR or better 43 vs 24%, $p < 0.001$). There was a significant improvement in the 18-month PFS (72 vs 50%; HR 0.5, 95% CI: 0.38–0.65, $p < 0.001$) with the addition of daratumumab to VMP, but the OS data are not mature yet [67••]. The highlights of some of the important studies in newly diagnosed transplant-ineligible MM patients are shown in Table 1.

In summary, the progress in the field, as outlined above, has been rather systematic with the establishment of superiority of VRd regimen over Rd which in turn was found to be superior to MPT, a regimen with greater efficacy over the long-standing standard of care, MP. Consequently, our approach has been to use VRd in this patient population. Fixed-duration Rd followed by reduced-dosed continuous R may be considered in select frail patients with standard-risk MM. While daratumumab-VMP has recently been approved for newly diagnosed patients, melphalan-based regimens have fallen out of favor in the USA. Whether carfilzomib, lenalidomide, and dexamethasone or daratumumab in combination with VRd regimens are equally well tolerated and superior to the current standard of care, VRd, in this subset of patients remains to be established.

Role of High-Dose Chemotherapy with Autologous Stem Cell Transplant in Elderly Patients ASCT continues to be an integral part of the management of young, fit patients with MM and remains the standard of care even in the era of novel agents [72, 73]. Traditionally, ASCT has been avoided in elderly MM patients due to the risks involved. However, the arbitrary chronological age cutoff for ASCT appears to be changing over the years and a group of fit elderly patients with less comorbidity can be considered as candidates for transplant [74, 75]. In an analysis of 29,489 first autologous transplants for MM between 1995 and 2010 by the Centre for International Bone Marrow Transplant Research (CIBMTR), the median age for ASCT has steadily increased over the years from 54 years between 1995 and 1999 to 59 years between 2005 and 2009. Also, the proportion of patients over the age of 65 years has risen from 8% to 24% in those time frames, respectively [19].

Transplant in the elderly appears to be a feasible option in carefully selected candidates. In a CIBMTR analysis of ASCT in elderly MM, the 1-year non-relapse mortality was 0% among the 946 patients over the age of 70 years that underwent ASCT within 2 years of diagnosis of MM [76•]. Various other retrospective single-institution studies have demonstrated the feasibility and efficacy of ASCT in the elderly population [77–79]. Also, age at diagnosis does not seem to impact outcome in patients undergoing transplant, with elderly patients deriving similar benefit from ASCT compared to younger patients in various retrospective studies [77, 79, 80]. Few studies have prospectively evaluated the role of ASCT in the elderly population. Induction therapy followed by tandem ASCT with melphalan 100 mg/m^2 was compared with MP in patients aged 50–70 years in a randomized trial. The ASCT arm showed significant improvement in PFS and OS [81]. In a prospective, multicenter study of 56 elderly patients (> 65 years) with MM treated in the era of novel agents, ASCT was feasible and efficacious, with no transplant-related mortality. The PFS was 77% and OS was 88% at 2 years [82]. The impact of dose reduction to 140 mg/m^2 or 100 mg/m^2 has not been addressed in a randomized trial. There is conflicting evidence for dose reduction on outcomes after ASCT in MM. In the CIBMTR analysis, melphalan at 140 mg/m^2 had similar outcomes to those who received melphalan at 200 mg/m^2 [76•], whereas in the prospective multicentre single-arm French trial, patients who received melphalan at 200 mg/m^2 had better outcomes compared to

Table 1 Selected studies for frontline therapy in elderly/transplant ineligible multiple myeloma

Study	Regimen	Median age in years (range)	Overall response rate (%)	Grade ≥ 3 AE rates (%)	Median PFS (months)	Median OS (months)
Kapoor et al. [47]	MPT vs MP meta-analysis of five randomized trials ($n = 1568$)	Median age range for the studies: 72–78.5 years	NR (OR 3.4; 95% CI: 2.2–5.1, $p < 0.001$ for responding to MPT vs MP)	NR [OR for grade ≥ 3 PN 6.6 ($p < 0.001$) with MPT vs MP; Or for DVT 2.4 (p-0.02) with MPT vsMP]	NR (pooled HR 0.68; 95% CI 0.55–0.82; $p < 0.001$ for MPT vs MP)	NR (pooled HR 0.80; 95% CI 0.63–1.02; $p = 0.07$ for MPT vs MP)
Fayers et al. [48•]	MPT vs MP individual patient data meta- analysis of six randomized trials ($n = 1685$)	Median age range for the studies: 72–78.5 years	NR	NR	20.3 m vs 14.9 m (HR 0.68; $p < 0.001$)	39.3 m vs 32.7 m (HR 0.83; $p = 0.004$)
San Miguel et al. [57]; Mateos et al. [68]	VMP versus MP ($n = 682$)	71 (57–90) vs 71 (48–91)	PR or better: 71 vs 35%	Grade ≥ 3 AEs81 vs 71	Median TTP: 20.7 m vs 15 m (HR 0.54; $p < 0.001$)	56 m vs 43 m (HR 0.7; $p < 0.001$)
Palumbo et al. [53••]	MPR×9 f/b R maintenance vs MPR × 9 vs MP × 9 ($n = 459$)	71 (65–87) vs 71 (65–86) vs 72 (65–91)	77 vs 68 vs 50	Grade 4 neutropenia/thrombocytopenia during induction: 35%/11% vs 32%/12% vs 12%/4%	31 m vs 14 m (HR 0.49; $p < 0.001$) vs 13 m (HR 0.40; $p < 0.001$ compared to MPR-R)	3-year OS: 70% vs 62% (HR 0.79; $p = 0.25$) vs 66% (HR 0.95; $p = 0.81$ compared to MPR-R)
Benboubker et al. [54••]	Rd × 72 weeks vs Rd18 × 72 weeks vs MPT ×72 weeks ($n = 1623$)	73 (44–91) vs 73 (40–89) vs 73 (51–92)	75 vs 73 vs 62	Grade ≥ 3 AEs 85 vs 80 vs 89	25.5 m vs 20.7 m (HR 0.70;$p < 0.001$) vs 21.2 m (HR 0.72; $p < 0.001$)	4-year OS: 59% vs 56% (HR 0.9; $p = 0.31$) vs 51% (HR 0.78; $p = 0.02$ compared to cRd)
Niesvizky et al. [59•]	VD ×8 vs VTD ×8 vs VMP ×8 Bortezomib maintenance in all arms ($n = 502$)	74 vs 73 vs 72	73 vs 80 vs 70	Grade ≥ 3 AEs 78 vs 83 vs 87	14.7 m vs 15.4 m vs 17.3 m ($p = 0.46$)	49.8 m vs 51.5 m vs 53.1 m ($p = 0.79$)
Durie et al. [61••]	VRd × 8 vs Rd. × 6 Maintenance Rd. inboth arms ($n = 525$)	63 (56–71)	82 vs 72	Grade ≥ 3 AEs 82 Vs 75	43 m vs 30 m (HR 0.71; $p = 0.002$)	75 m vs 64 m (HR 0.709; 2 sided $p = 0.025$)
Magarotto et al. [69]	MPR ×9 vs CPR ×9 vs Rd. followed maintenance with RP vs R ($n = 643$)	74 (63–91) vs 73 (63–87) vs 74 (50–89)	71 vs 68 vs 74	Grade ≥ 3 AEs; hematologic: 68% vs 32% vs 29% non-hematologic: 31% vs 30% vs 30%	22 m vs 22 m vs 21 m (HR, 0.906; $p = 0.3$)	4-year OS: 67% vs 67 vs 58% (HR, 0.945; $p = 0$ .7)
Facon et al. [66]	KMP vs VMP ($n = 955$)	72 vs 72	84 vs 79	Grade ≥ 3 AEs: 75 vs 76	22.3 m vs 21.1 m (HR 0.9; $p = 0.16$)	OS data immature
Mateos et al. [67••]	D-VMP vs VMP ($n = 700$)	71 (40–93) vs 71 (50–91)	91 vs 74	SAEs: 41.6 vs 32.5	18-month PFS: 72 vs 50% (HR 0.5; $p < 0.001$)	OS data immature
Facon et al. [70••]	DRd vs Rd. ($n = 737$)	73 (45–90)	≥ VGPR: 79 Vs 53	NR	NR Vs 31.9 m (HR 0.55; $p < 0.0001$)	OS data immature
Larocca et al. [71••]	Rd × 9 f/b R vs Continuous Rd. [$n = 199$ intermediate fit patients (frailty score = 1)]	75 vs 76	≥ VGPR: 43 Vs 35		Median EFS 9.3 m vs 6.6 m (HR 0.72; $p = 0.04$)	18-month OS: 85% vs 81% (HR 0.73; p-NS)

ASCT, autologous stem cell transplant; *CPR*, cyclophosphamide-prednisolone-lenalidomide; *CR*, complete response; *cRd*, continuous lenalidomide-dexamethasone; *HR*, hazard ratio; *D-VMP*, daratumumab-bortezomib-melphalan-prednisone; *EFS*, event free survival; *MP*, melphalan prednisone; *MPT*, melphalan prednisone thalidomide; *MPR*, melphalan prednisone lenalidomide; *NR*, not reported; *NS*, not significant; *ORR*, overall response rate (partial response or better); *OS*, overall survival; *PFS*, progression free survival; *PN*, peripheral neuropathy; *PR*, partial response; *R*, lenalidomide; *Rd*., lenalidomide-dexamethasone; *Rd18*, lenalidomide-dexamethasone for 18 cycles; *RP*, lenalidomide-prednisolone; *SAE*, serious adverse events; *SPM*, second primary malignancy; *TTP*, time to progression; *VD*, bortezomib-dexamethasone; *VRd*, bortezomib lenalidomide dexamethasone; *VTD*, bortezomib thalidomide dexamethasone; *VMP*, bortezomib melphalan prednisolone; *VGPR*, very good partial response

melphalan at 140 mg/m^2 [82]. In general, among elderly patients, especially above the age of 70 years, dose reduction of melphalan to 140 mg/m^2 is an option and the decision about the dose reduction should be made on a case by case basis. Generally, if an elderly patient is ACST eligible at diagnosis, it is best to proceed with ASCT rather than harvest and cryopreserve stem cells for future use, as patients' comorbidities may preclude this approach in future.

Treatment at Relapse

Disease relapse is invariable in patients with MM. The risk status, rate of disease progression, extent of symptoms and patient comorbidities aid in deciding the aggressiveness of the salvage therapy. A rapidly increasing paraprotein concentration or evidence of extramedullary disease indicates an aggressive disease, and merits early reinstitution or change of therapy. In general, drugs with non-cross resistant mechanism of actions should be used. Asymptomatic slow relapses without the presence of the CRAB criteria (biochemical progression) may be observed carefully, with a close 'watch and wait' strategy [83]. Alternatively, patients with an asymptomatic biochemical relapse may be managed by increasing the dose(s) of the ongoing therapies [84]. Patients with an interval response lasting more than 6 to 12 months from last dose of bortezomib or lenalidomide may benefit from re-challenge (retreatment) with these drugs [85, 86]. The cytogenetic profile can also guide treatment, with proteasome inhibitors being the agents of choice in patients with high-risk features [57, 87]. Venetoclax has shown a response rate of 40% in a phase I study involving multiply pretreated refractory MM patients with t(11;14) [88]. Carfilzomib, a second-generation ketoepoxide irreversible proteasome inhibitor, has important advantages include lower neurotoxicity, although its cardiorenal toxicity needs to be factored prior to selecting carfilzomib [65, 89]. It has been studied in combinations with lenalidomide and melphalan appears to be safe and efficacious [90, 91]. Ixazomib is a novel orally administered proteasome inhibitor that is chemically and structurally distinct from bortezomib and has been found to be safe and efficacious in both relapsed and frontline treatment of MM. Oral route of administration make ixazomib a particularly attractive option in elderly patients [92–94]. It is currently approved by the FDA and EMA for relapsed MM patients who have received at least one prior line of therapy. Pomalidomide is a highly potent third generation IMiD that been approved for treatment of relapsed/refractory MM. It appears to be safe and well tolerated with various combinations [95–97]. Pomalidomide may partially be able to overcome the negative impact of 17p deletion [98]. Daratumumab is a monoclonal antibody targeting CD38 antigen on myeloma cells. It is approved both as a single agent in patients with at least three prior lines of therapy or double refractory to proteasome inhibitor and IMiD as well as in combination therapy in relapsed refractory myeloma with at least one prior line of therapy. It is very well tolerated and efficacious even in heavily pretreated patients with myeloma [99, 100]. Elotuzumab is another monoclonal antibody that targets SLAMF7. It has shown to improve survival when used in combination with lenalidomide and dexamethasone in relapsed MM and is approved in patients who have received at least 1 prior line of therapy [101, 102]. These novel antibodies are quite safe, with tolerable infusion reactions as the most common toxicities [103, 104]. There are a multitude of other options, including B cell maturation antigen (BCMA)-directed therapies and CAR-T cell therapies that are being evaluated currently in clinical trials. A second-generation BCMA-directed CAR-T cell therapy has shown exciting results, with an ORR of 94%. Ten of the 18 patients treated at a dose of 150×10^6 achieved a CR or unconfirmed CR [105]. GSK2857916 is an antibody targeting BCMA with highest single agent activity, to date, in heavily pretreated MM. It has demonstrated an ORR of 60% at a dose of 3.4 mg/kg in 35 heavily pretreated and refractory MM patients, with a median PFS was 8 months at the time of reporting [106]. With the search for optimal biomarkers in MM still proving to be elusive, it is critical to evaluate optimal strategies for sequencing these agents appropriately to derive the maximum benefit possible. Some of the important studies in relapsed/refractory MM with an emphasis on outcomes in elderly population have been depicted in Table 2.

Supportive Care for Old and Frail Patients

Myeloma bone disease puts the patients at high risk for pathologic fractures, pain, hypercalcemia and spinal cord compression. These complications can be devastating, with significant worsening of QoL. The use of bisphosphonates is integral in maintaining bone health and is an important part of the management of MM. In the MRC Myeloma IX trial, the use of zoledronic acid (ZA) was found to have improved survival when compared to clodronate [110]. Also, the infusion time for ZA is shorter compared to pamidronate making it the more convenient and preferred option among bisphosphonates. The standard dosing schedule for ZA is every 4-weekly. A recent study of 1822 patients with a diagnosis of either breast or prostate cancer with bone metastasis and multiple myeloma with bony lesions compared the 4-weekly infusion schedule of ZA to a 12-weekly infusion schedule for the rate of skeletal-related event (SRE) within 2 years of randomization. The 12-weekly schedule was found to be non-inferior to the 4-weekly schedule in terms of the proportion of SREs. The toxicity profile was similar between the two schedules. There was no difference in the time to SRE in the subset of patients with the diagnosis of MM [111]. Although this study was not specifically powered to analyze the subset

Table 2 Selected randomized clinical trials for novel regimens in relapsed/refractory MM with emphasis on elderly population

Study	Median age (age) and % elderly patients	Regimen	ORR (%)	SAE (%)	Median PFS (months)	Median OS (months)
ASPIRE [90, 107]	64 years (31–91); 49.6% patients ≥ 65 years; 29% were ≥ 70 years	KRd vs Rd. (*n*=	87 vs 67 Age ≥ 70 years: 90 vs 66	60 vs 54	26.7 m vs 17.3 m (HR 0.69; $p = 0.0001$) Age ≥ 70 years: 23.6 m vs 16 m (HR 0.7)	48.3 m vs 40.4 m (HR 0.79, $p = 0.0045$)
ENDEAVOR [108, 109]	65 years (17% and 14% ≥ 75 years in Kd and Vd arms respectively)	Kd vs Vd ($n = 929$)	77 vs 63	59 vs 40	18.7 m vs 9.4 m (HR 0.53, $p < 0.001$) Age 65–74 years: HR = 0·53 (0·38–0·73) Age ≥ 75 years: HR =0·38 (0·23–0·65)	47.6 m vs 40 m (HR 0.9; $p = 0.010$) Age 65–74: HR 0·71 (0·51–0·98) Age ≥ 75 years: HR 0·84 (0·52–1·36)
TOURMALINE MM1 [93]	66 years (30–91) with 52% patients in the study > 65 years of age	IRd Vs Rd.($n = 722$)	78 vs 72	47 Vs 49	20.6 m vs 14.7 m (HR 0.74; $p = 0.01$) Age 66–75 years: 17.5 m vs 17.6 m (HR 0.83; p = NS) Age > 75 years: 18.5 m vs 13.1 m (HR 0.87; p = NS)	Median OS not reached in either arm
ELOQUENT-2 [101]	67 years (37–91)	ERD vs RD ($n = 646$)	79 vs 66	65 Vs 57	19.4 m vs 14.9 m (HR 0.70, $p < 0.001$)	43.7 m vs 39.7 m ($p = 0.025$, NS)
POLLUX [100]	65 years (34–89) with 54% and 50% patients ≥ 65 years in DRd and Rd., respectively	DRd vs Rd. ($n = 569$)	93 vs 76	49 vs 42	NR vs 17.5 m (HR 0.37, $p < 0.0001$)	1-year OS 92 vs 86% Median OS not reached in either arm;

AE, adverse event; *ERD*, elotuzumab-lenalidomide-dexamethasone; *IRd*, Ixazomib-lenalidomide-dexamethasone; *Kd*, Carfilzomib-dexamethasone; *KRD*, carfilzomib-lenalidomide-dexamethasone; *ORR*, overall response rate; *PI*, proteasome inhibitor; *R*, lenalidomide; *RD*, lenalidomide-dexamethasone; *SAE*, serious adverse effects; *Vd*, Bortezomib-dexamethasone; *VGPR*, very good partial response

of MM patients, reducing the frequency of ZA to 12 weekly is a reasonable approach, particularly for the elderly. A randomized phase 3 trial comparing 30 mg ($n = 156$) versus 90 mg ($n = 157$) monthly dose of intravenous pamidronate for prophylaxis of SREs in MM found no additional benefit of the higher dose pamidronate on the time-to-first SRE or physical activity. Furthermore, there was a higher rate of osteonecrosis (8 patients in 90 mg arm vs 2 in 30 mg arm) with the higher dose [112]. Denosumab, a RANK ligand inhibitor, has also been recently approved in the USA for treating myeloma bone disease. In a randomized phase III non-inferiority study comparing denosumab and ZA for the time to first on-study SRE, denosumab was found to be non-inferior to ZA. Also, the rate of renal adverse events was lower in the denosumab arm (10 vs 17.1%, $p < 0.001$). There was evidence of superior PFS with the denosumab arm but this did not translate into an overall survival benefit [113•].

Elderly patients are at higher risk of hematologic toxicities and persistent neutropenia can reduce the time on treatment for these patients due to frequent treatment discontinuations [2, 114]. To prevent the occurrence of febrile neutropenia and increase the tolerability of therapy, dose modifications and the use of granulocyte-colony stimulating factor should be considered [115]. Use of erythropoietin stimulating agents may be an option to improve hemoglobin levels during therapy, especially in patients with renal insufficiency and hemoglobin levels less than 10 g/dL [116, 117]. Given their propensity for infections, influenza vaccination is especially important in patients with MM. A recent double-blind, randomized trial compared two doses of the Fluzone® high-dose influenza vaccination (separated by 30 days) to the standard practice of a single dose (standard-dose in age < 65 years and high-dose in age ≥ 65 years) vaccine. The study demonstrated an improvement in the rate of seroprotection against the three influenza vaccine strains to 58% with the 2-dose strategy compared to 33% with the single dose strategy ($p < 0.05$) at the end of the flu season [118]. Prophylactic antibiotic use with levofloxacin has also been studied in an effort to reduce early infection-related mortality in MM. In a large randomized double-blinded study (TEAMM trial) with 977 MM patients, the patients were randomized to receive 500 mg levofloxacin daily for 12 weeks versus placebo. The primary endpoint of the study was number of febrile episodes (≥ 38 °C treated with anti-infectives) or death due to any cause within the first 12 weeks. Patients in the placebo arm showed significantly higher events (27% vs 19%; HR 1.52. 95% CI 1.1701.97; $p = 0.002$) compared to the levofloxacin arm. Additionally, there was no significant difference in the carriage of resistant organism like *C. difficile*, methicillin-resistant Staphylococcus aureus or gram-negative extended spectrum beta-lactamase

producing bacteria. However, the 1-year OS was comparable in the two arms [119]. Thus, prophylactic antibiotic use may represent a potential strategy for reducing early mortality and febrile episodes in patients with MM.

Conclusion

The management of multiple myeloma in the elderly and frail patient population is associated with various challenges. A critical component of the initial evaluation on which the subsequent management rests is perhaps a detailed assessment of the fitness and frailty status of the patient. While the goals of therapy in the elderly are similar to the younger population, the treatment strategies used in younger, fit patients cannot be extrapolated to the elderly population. There is urgent need for clinical trials specifically evaluating older and less fit population of patients with MM.

Compliance with Ethical Standards

Conflict of Interest Prashant Kapoor reports grants from GSK, grants from TAKEDA, grants from SANOFI, grants from AMGEN, and grants from JANNSEN, outside the submitted work. Saurabh Zanwar and Jithma Prasad Abeykoon declare that they have no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2013, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/archive/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. SEER Website 2015.
2. Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Bladé J, Mateos MV, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). Blood. 2011;118(17):4519–29. https://doi.org/10.1182/blood-2011-06-358812.
3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3–9. https://doi.org/10.1038/leu.2008.291.
4. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–e48. https://doi.org/10.1016/S1470-2045(14)70442-5.
5. Kastritis E, Terpos E, Moulopoulos L, Spyropoulou-Vlachou M, Kanellias N, Eleftherakis-Papaiakovou E, et al. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. Leukemia. 2013;27(4):947–53. https://doi.org/10.1038/leu.2012.309.
6. Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood. 2008;111(2):785–9. https://doi.org/10.1182/blood-2007-08-108357.
7. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. N Engl J Med. 2011;365(5):474–5. https://doi.org/10.1056/NEJMc1106428.
8. Dimopoulos MA, Kastritis E, Delimpasi S, Katodritou E, Hatzimichael E, Kyrtsonis M-C, et al. Multiple myeloma in octogenarians: clinical features and outcome in the novel agent era. Eur J Haematol. 2012;89(1):10–5. https://doi.org/10.1111/j.1600-0609.2012.01784.x.
9. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the international myeloma working group. J Clin Oncol. 2010;28(33):4976–84. https://doi.org/10.1200/jco.2010.30.8791.
10. Bredella MA, Essary B, Torriani M, Ouellette HA, Palmer WE. Use of FDG-PET in differentiating benign from malignant compression fractures. Skelet Radiol. 2008;37(5):405–13. https://doi.org/10.1007/s00256-008-0452-5.
11. Aggarwal A, Salunke P, Shekhar BR, Chhabra R, Singh P, Bhattacharya A, et al. The role of magnetic resonance imaging and positron emission tomography-computed tomography combined in differentiating benign from malignant lesions contributing to vertebral compression fractures. Surg Neurol Int. 2013;4(Suppl 5):S323–6. https://doi.org/10.4103/2152-7806.112619.
12. Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol. 2012;13(4):353–65. https://doi.org/10.1016/S1470-2045(12)70041-4.
13. Howell DA, Smith AG, Jack A, Patmore R, Macleod U, Mironska E, et al. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. BMC Blood Disord. 2013;13:9. https://doi.org/10.1186/2052-1839-13-9.
14. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516–20. https://doi.org/10.1182/blood-2007-10-116129.
15. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122–8. https://doi.org/10.1038/leu.2013.313.
16. Schaapveld M, Visser O, Siesling S, Schaar CG, Zweegman S, Vellenga E. Improved survival among younger but not among older patients with multiple myeloma in the Netherlands, a population-based study since 1989. Eur J Cancer. 2010;46(1):160–9. https://doi.org/10.1016/j.ejca.2009.07.006.
17. Verelst S, Karim-Kos H, Blommestein H, Sonneveld P. Are we making progress? Survival in plasma cell malignancies in the era of novel treatments. A population based study of 17790 patients in the Netherlands [abstract]. Haematologica. 2012;97:242.

18. Palumbo A, Anderson K. Multiple Myeloma. N Engl J Med. 2011;364(11):1046–60. https://doi.org/10.1056/NEJMra1011442.
19. Costa LJ, Zhang M-J, Zhong X, Dispenzieri A, Lonial S, Krishnan A, et al. Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma. Biol Blood Marrow Transplant. 2013;19(11):1615–24. https://doi.org/10.1016/j.bbmt.2013.08.002.
20. Ludwig H, Durie BGM, Bolejack V, Turesson I, Kyle RA, Blade J, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. Blood. 2008;111(8):4039–47. https://doi.org/10.1182/blood-2007-03-081018.
21. Palumbo A, Waage A, Hulin C, Beksac M, Zweegman S, Gay F, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica. 2013;98(1):87–94. https://doi.org/10.3324/haematol.2012.067058.
22. Bringhen S, Mateos MV, Zweegman S, Larocca A, Falcone AP, Oriol A, et al. Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013;98(6):980–7. https://doi.org/10.3324/haematol.2012.075051.
23. Kleber M, Ihorst G, Terhorst M, Koch B, Deschler B, Wäsch R, et al. Comorbidity as a prognostic variable in multiple myeloma: comparative evaluation of common comorbidity scores and use of a novel MM–comorbidity score. Blood Cancer J. 2011;1(9):e35. https://doi.org/10.1038/bcj.2011.34.
24. Mateos M-V, Ocio EM, Paiva B, Rosiñol L, Martínez-López J, Bladé J, et al. Treatment for patients with newly diagnosed multiple myeloma in 2015. Blood Rev. 2015;29(6):387–403. https://doi.org/10.1016/j.blre.2015.06.001.
25. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. Blood. 2015;125(20):3076–84. https://doi.org/10.1182/blood-2014-09-568915.
26. Kumar S. Treatment of newly diagnosed multiple myeloma in transplant-eligible patients. Curr Hematol Malig Rep. 2011;6(2):104–12. https://doi.org/10.1007/s11899-011-0083-0.
27. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341(27):2061–7. https://doi.org/10.1056/NEJM199912303412706.
28. Mateos M-V, Oriol A, Martínez-López J, Gutiérrez N, Teruel A-I, Paz Rd et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010;11(10):934–941. doi:https://doi.org/10.1016/S1470-2045(10)70187-X.
29. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan- prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010;28(34):5101–9. https://doi.org/10.1200/JCO.2010.29.8216.
30. Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, Buadi F, Dingli D, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. J Clin Oncol. 2013;31(36):4529–35. https://doi.org/10.1200/JCO.2013.49.0086.
31. Lahuerta JJ, Mateos MV, Martínez-López J, Rosiñol L, Sureda A, de la Rubia J, et al. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. J Clin Oncol. 2008;26(35):5775–82. https://doi.org/10.1200/JCO.2008.17.9721.
32. Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood. 2011;117(11):3025–31. https://doi.org/10.1182/blood-2010-09-307645.
33. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002;20(2):494–502. https://doi.org/10.1200/JCO.2002.20.2.494.
34. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz J-P, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients:: Recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol. 2005;55(3):241–52. https://doi.org/10.1016/j.critrevonc.2005.06.003.
35. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115(19):4547–53. https://doi.org/10.1002/cncr.24490.
36. Kuo H-K, Scandrett KG, Dave J, Mitchell SL. The influence of outpatient comprehensive geriatric assessment on survival: a meta-analysis. Arch Gerontol Geriatr. 2004;39(3):245–54. https://doi.org/10.1016/j.archger.2004.03.009.
37.•• Palumbo A, Bringhen S, Mateos M-V, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an international myeloma working group report. Blood. 2015;125(13):2068–74. https://doi.org/10.1182/blood-2014-12-615187 **Landmark study demonstrating role of incorpation of a frailty index in tailoring therapy of elderly patients with multiple myeloma**.
38. Kleber M, Ihorst G, Gross B, Koch B, Reinhardt H, Wäsch R, et al. Validation of the Freiburg Comorbidity Index in 466 multiple myeloma patients and combination with the international staging system are highly predictive for outcome. Clin Lymphoma Myeloma Leuk. 2013;13(5):541–51. https://doi.org/10.1016/j.clml.2013.03.013.
39. Nooka AK, Lonial S. Death by a thousand cuts: the slow demise of chemotherapy. Cancer. 2016;122(13):1971–3. https://doi.org/10.1002/cncr.30024.
40. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008;112(8):3107–14. https://doi.org/10.1182/blood-2008-04-149427.
41. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial. Lancet. 2007;370(9594):1209–18. https://doi.org/10.1016/S0140-6736(07)61537-2.
42. Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116(9):1405–12. https://doi.org/10.1182/blood-2009-08-237974.
43. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 study. J

Clin Oncol. 2010;28(19):3160–6. https://doi.org/10.1200/JCO.2009.26.1610.

44. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009;27(22):3664–70. https://doi.org/10.1200/JCO.2008.21.0948.
45. Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol. 2011;86(1):16–22. https://doi.org/10.1111/j.1600-0609.2010.01524.x.
46. Sacchi S, Marcheselli R, Lazzaro A, Morabito F, Fragasso A, Di Renzo N, et al. A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant. Leuk Lymphoma. 2011;52(10):1942–8. https://doi.org/10.3109/10428194.2011.584006.
47. Kapoor P, Rajkumar SV, Dispenzieri A, Gertz MA, Lacy MQ, Dingli D, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis. Leukemia. 2011;25(4):689–96. https://doi.org/10.1038/leu.2010.313.
48.• Fayers PM, Palumbo A, Hulin C, Waage A, Wijermans P, Beksaç M et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from six randomized clinical trials. Blood. 2011:blood-2011-03-341669. https://doi.org/10.1182/blood-2011-03-341669. **Individual patient data meta-analysis demonstrating superiority of MPT vs MP in transplant-ineligible multiplemyeloma.**
49. Palumbo A, Facon T, Sonneveld P, Bladè J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008;111(8):3968–77. https://doi.org/10.1182/blood-2007-10-117457.
50. Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. Blood. 2010;115(7):1343–50. https://doi.org/10.1182/blood-2009-08-239046.
51. Zou Y, Sheng Z, Niu S, Wang H, Yu J, Xu J. Lenalidomide versus thalidomide based regimens as first-line therapy for patients with multiple myeloma. Leuk Lymphoma. 2013;54(10):2219–25. https://doi.org/10.3109/10428194.2013.774393.
52. Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan-Khan AA, et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood. 2015;126(11):1294–301. https://doi.org/10.1182/blood-2014-12-613927.
53.•• Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759–69. https://doi.org/10.1056/NEJMoa1112704 **Landmark phase III study establishing continuous lenalidomide-based therapy as a standard of care for transplant ineligible MM**.
54.•• Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17. https://doi.org/10.1056/NEJMoa1402551 **Landmark phase III trial supporting continuous lenalidomide-based therapy as a standard of care for transplant ineligible MM**.
55. Delforge M, Minuk L, Eisenmann J-C, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. Haematologica. 2015;100(6):826–33. https://doi.org/10.3324/haematol.2014.120121.
56. Palumbo A, Gay F, Cavallo F, Di Raimondo F, Larocca A, Hardan I, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. J Clin Oncol. 2015;33(30):3459–66. https://doi.org/10.1200/JCO.2014.60.2466.
57. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906–17. https://doi.org/10.1056/NEJMoa0801479.
58. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol. 2013;31(4):448–55. https://doi.org/10.1200/jco.2012.41.6180.
59.• Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Community-based phase IIIB trial of three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015;33(33):3921–9. https://doi.org/10.1200/JCO.2014.58.7618 **Phase III study of bortezomib-thalidomide combination as upfront therapy in elderly MM**.
60. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679–86. https://doi.org/10.1182/blood-2010-02-268862.
61.•• Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2016. https://doi.org/10.1016/S0140-6736(16)31594-X **Large phase III trial establishing bortezomib-lenalidomide-dexamethasone (VRd) therapy as the current standard of care for transplant ineligible MM in the US**.
62. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011;12(5):431–40. https://doi.org/10.1016/s1470-2045(11)70081-x.
63. Merz M, Salwender H, Haenel M, Mai EK, Bertsch U, Kunz C, et al. Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial. Haematologica. 2015;100(7):964–9. https://doi.org/10.3324/haematol.2015.124347.
64. O'Donnell E, Laubach JP, Yee AJ, Huff CA, Basile F, Wade PM, et al. A phase II study of modified lenalidomide, bortezomib, and dexamethasone (RVD lite) for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2014;124(21):3454.
65. Kortuem KM, Stewart AK. Carfilzomib. Blood. 2013;121(6):893–7. https://doi.org/10.1182/blood-2012-10-459883.
66. Facon T, Lee J, Moreau P, Niesvizky R, Dimopoulos M, Hajek R, et al. Phase 3 study (CLARION) of carfilzomib, melphalan, prednisone (KMP) v bortezomib, melphalan, prednisone (VMP) in newly diagnosed multiple myeloma (NDMM). Clin Lymphoma Myeloma Leuk. 2017;17(1 Suppl 1):e26–e7.
67.•• Mateos M-V, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378(6):518–28. https://doi.org/10.1056/NEJMoa1714678 **Recent phase**

III study establishing the efficacy and safety of daratumumab-based therapy in transplant ineligible MM, making it one of the accepted frontline treatment options in this setting.

68. Mateos M-V, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28(13):2259–66. https://doi.org/10.1200/JCO.2009.26.0638.
69. Magarotto V, Bringhen S, Offidani M, Benevolo G, Patriarca F, Mina R, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood. 2016;127(9):1102–8. https://doi.org/10.1182/blood-2015-08-662627.
70.•• Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Blood. 2018; 132(Suppl 1):LBA-2-LBA. doi:https://doi.org/10.1182/blood-2018-120737. **Recent randomized phase III study (late-breaking abstract at ASH 2018) demonstrating improvement in PFS with daratumumab in combination with Rd in transplant ineligible MM in the frontline setting.**
71.•• Larocca A, Salvini M, De Paoli L, Cascavilla N, Benevolo G, Galli M, et al. Efficacy and feasibility of dose/schedule-adjusted Rd-R Vs. continuous rd in elderly and intermediate- fit newly diagnosed multiple myeloma (NDMM) patients: RV-MM-PI-0752 Phase III Randomized Study. Blood. 2018;132(Suppl 1):305. https://doi.org/10.1182/blood-2018-99-111796 **Recent randomized study focusing exclusively on intermediate fit (frailty score=1) newly diagnosed elderly MM demonstrating (Rd) followed by reduced dose lenalidomide maintenance being the more feasible therapy comared to continued Rd**.
72. Attal M, Lauwers-Cances V, Hulin C, Facon T, Caillot D, Escoffre M, et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). Blood. 2015;126(23):391.
73. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? Hematology. 2012;2012(1):335–41. https://doi.org/10.1182/asheducation-2012.1.335.
74. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014;32(6):587–600. https://doi.org/10.1200/jco.2013.48.7934.
75. Mehta J, Cavo M, Singhal S. How I treat elderly patients with myeloma. Blood. 2010;116(13):2215–23. https://doi.org/10.1182/blood-2009-10-163329.
76.• Sharma M, Zhang M-J, Zhong X, Abidi MH, Akpek G, Bacher U, et al. Older patients with myeloma derive similar benefit from autologous transplantation. Biol Blood Marrow Transplant. 2014;20(11):1796–803. https://doi.org/10.1016/j.bbmt.2014.07.013 **Large CIBMTR study demonstrating safety and efficacy of autologous stem cell transplant in elderly myeloma**.
77. Merz M, Jansen L, Castro FA, Hillengass J, Salwender H, Weisel K, et al. Survival of elderly patients with multiple myeloma-effect of upfront autologous stem cell transplantation. Eur J Cancer. 2016;62:1–8. https://doi.org/10.1016/j.ejca.2016.04.004.
78. Gertz MA, Buadi FK, Hayman SR, Lacy MQ, Dispenzieri A, Dingli D, et al. Safety outcomes for autologous stem cell transplant in multiple myeloma. Mayo Clin Proc. 2018;93(1):56–8. https://doi.org/10.1016/j.mayocp.2017.09.012.
79. Kumar SK, Dingli D, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, et al. Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: results from a matched pair analysis. Am J Hematol. 2008;83(8):614–7. https://doi.org/10.1002/ajh.21191.
80. Jantunen E, Kuittinen T, Penttilä K, Lehtonen P, Mahlamäki E, Nousiainen T. High-dose melphalan (200 mg/m2) supported by autologous stem cell transplantation is safe and effective in elderly (⩾65 years) myeloma patients: comparison with younger patients treated on the same protocol. Bone Marrow Transplant. 2006;37(10):917–22. https://doi.org/10.1038/sj.bmt.1705360.
81. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, Nunzi M, et al. Intermediate- dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood. 2004;104(10):3052–7. https://doi.org/10.1182/blood-2004-02-0408.
82. Garderet L, Beohou E, Caillot D, Stoppa AM, Touzeau C, Chretien ML, et al. Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: a prospective multicenter study. Haematologica. 2016;101(11):1390–7. https://doi.org/10.3324/haematol.2016.150334.
83. Larocca A, Palumbo A. How I treat fragile myeloma patients. Blood. 2015;126(19):2179–85. https://doi.org/10.1182/blood-2015-05-612960.
84. Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood. 2015;125(20):3085–99. https://doi.org/10.1182/blood-2014-11-568923.
85. Knopf KB, Duh MS, Lafeuille M-H, Gravel J, Lefebvre P, Niculescu L, et al. Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk. 2014;14(5):380–8. https://doi.org/10.1016/j.clml.2014.03.005.
86. Ahn J-S, Jung S-H, Lee S-S, Ahn S-Y, Yang D-H, Kim Y-K, et al. Clinical outcome of bortezomib retreatment in patients with relapsed or refractory multiple myeloma. Biomed Res Int. 2014;2014:145843–7. https://doi.org/10.1155/2014/145843.
87. Jakubowiak AJ, Siegel DS, Martin T, Wang M, Vij R, Lonial S, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. Leukemia. 2013;27(12):2351–6. https://doi.org/10.1038/leu.2013.152.
88. Kumar S, Vij R, Kaufman JL, Mikhael J, Facon T, Pegourie B, et al. Venetoclax monotherapy for relapsed/refractory multiple myeloma: safety and efficacy results from a phase I study. Blood. 2016;128(22):488.
89. Badros AZ, Vij R, Martin T, Zonder JA, Wong AF, Woo T, et al. Phase II study of carfilzomib in patients with relapsed/refractory multiple myeloma and renal insufficiency. J Clin Oncol. 2010;28(15_suppl):8128. https://doi.org/10.1200/jco.2010.28.15_suppl.8128.
90. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142–52. https://doi.org/10.1056/NEJMoa1411321.
91. Kolb B, Hulin C, Caillot D, Benboubker L, Tiab M, Blin N, et al. Phase I/II study of carfilzomib plus melphalan-prednisone (CMP) in elderly patients with de novo multiple myeloma. J Clin Oncol. 2012;30(15_suppl):8009. https://doi.org/10.1200/jco.2012.30.15_suppl.8009.
92. Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol. 2014;15(13):1503–12. https://doi.org/10.1016/s1470-2045(14)71125-8.

93. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621–34. https://doi.org/10.1056/NEJMoa1516282.
94. Zanwar S, Abeykoon JP, Kapoor P. Ixazomib: a novel drug for multiple myeloma. Expert Rev Hematol. 2018;11(10):761–71. https://doi.org/10.1080/17474086.2018.1518129.
95. Lacy MQ, McCurdy AR. Pomalidomide. Blood. 2013;122(14):2305–9. https://doi.org/10.1182/blood-2013-05-484782.
96. Shah JJ, Stadtmauer EA, Abonour R, Cohen AD, Bensinger WI, Gasparetto C et al. Carfilzomib, pomalidomide, and dexamethasone (CPD) in patients with relapsed and/or refractory multiple myeloma. Blood. 2015:blood-2015-05-643320. doi:https://doi.org/10.1182/blood-2015-05-643320.
97. Richardson PGG, Hofmeister CC, Siegel DSD, Lonial S, Laubach J, Efebera YA et al. MM- 005: A phase I trial of pomalidomide, bortezomib, and low-dose dexamethasone (PVD) in relapsed and/or refractory multiple myeloma (RRMM). J Clin Oncol. 2013;31(suppl; abstr 8584).
98. Leleu X, Karlin L, Macro M, Hulin C, Garderet L, Roussel M, et al. Pomalidomide plus low- dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results. Blood. 2015;125(9):1411–7. https://doi.org/10.1182/blood-2014-11-612069.
99. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open- label, randomised, phase 2 trial. Lancet. 2016;387(10027):1551–60. https://doi.org/10.1016/S0140-6736(15)01120-4.
100. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319–31. https://doi.org/10.1056/NEJMoa1607751.
101. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373(7):621–31. https://doi.org/10.1056/NEJMoa1505654.
102. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med. 2018;379(19):1811–22. https://doi.org/10.1056/NEJMoa1805762.
103. van de Donk NW, Moreau P, Plesner T, Palumbo A, Gay F, Laubach JP, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. Blood. 2016;127(6):681–95. https://doi.org/10.1182/blood-2015-10-646810.
104. Sanchez L, Wang Y, Siegel DS, Wang ML. Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. J Hematol Oncol. 2016;9:51. https://doi.org/10.1186/s13045-016-0283-0.
105. Raje NS, Berdeja J, Lin Y, Munshi NC, Siegel David, Liedtke M et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. J Clin Oncol. 2018; 36(suppl; abstr 8007).
106. Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, et al. Deep and durable responses in patients (pts) with relapsed/refractory multiple myeloma (MM) treated with monotherapy GSK2857916, an antibody drug conjugate against B-cell maturation antigen (BCMA): preliminary results from part 2 of study BMA117159. Blood. 2017;130(Suppl 1):741.
107. Dimopoulos MA, Stewart AK, Masszi T, Špička I, Oriol A, Hájek R, et al. Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age: secondary analysis from the phase 3 ASPIRE study. Br J Haematol. 2017;177(3):404–13. https://doi.org/10.1111/bjh.14549.
108. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng W-J, Oriol A, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(10):1327–37. https://doi.org/10.1016/S1470-2045(17)30578-8.
109. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17(1):27–38. https://doi.org/10.1016/S1470-2045(15)00464-7.
110. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC myeloma IX): a randomised controlled trial. Lancet. 2010;376(9757):1989–99. https://doi.org/10.1016/S0140-6736(10)62051-X.
111. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases. JAMA. 2017;317(1):48–58. https://doi.org/10.1001/jama.2016.19425.
112. Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A, et al. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study group): a double-blind, randomised controlled trial. Lancet Oncol. 2010;11(10):973–82. https://doi.org/10.1016/s1470-2045(10)70198-4.
113.• Raje NS, Roodman GD, Willenbacher W, Shimizu K, Garcia-Sanz R, Durie BG, et al. Impact of denosumab (DMB) compared with zoledronic acid (ZA) on renal function in the treatment of myeloma bone disease. J Clin Oncol. 2017;35(15_suppl):8005. https://doi.org/10.1200/JCO.2017.35.15_suppl.8005 **Recent large randomized phase III study demonstrating comparable efficacy of zoledronic acid and denosumab in preventing skeletal related events in MM**.
114. Mateos M-V. Management of treatment-related adverse events in patients with multiple myeloma. Cancer Treat Rev. 2010;36(Suppl 2):S24–32. https://doi.org/10.1016/S0305-7372(10)70009-8.
115. Palumbo A, Bladé J, Boccadoro M, Palladino C, Davies F, Dimopoulos M, et al. How to manage neutropenia in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2012;12(1):5–11. https://doi.org/10.1016/j.clml.2011.11.001.
116. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S. American society of clinical oncology/american society of hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Oncol Pract. 2010;6(6):317–20. https://doi.org/10.1200/JOP.2010.000132.
117. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer—meta-analysis based on individual patient data. Cochrane Database Syst Rev. 2009;3:CD007303. https://doi.org/10.1002/14651858.CD007303.pub2.
118. Branagan A, Duffy E, Foster C, Verma R, Zhang L, Gan G, et al. Two dose series of high- dose influenza vaccine is associated with longer duration of serologic immunity in patients with plasma cell disorders. Blood. 2017;130(Suppl 1):438.
119. Drayson MT, Bowcock S, Planche T, Iqbal G, Wood J, Raynes K, et al. Tackling Early Morbidity and Mortality in Myeloma (TEAMM): assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections in 977 patients. Blood. 2017;130(Suppl 1):903.