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The pharmacologic management of multiple myeloma in older adults

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Abstract

Introduction: Multiple myeloma is a disease predominately affecting older adults. Pivotal to treating older adults is understanding their physiologic differences compared to younger subjects and how the complexity of therapies has an impact upon this patient population.

Areas covered: Herein, the authors address the efficacy of chemotherapy regimens, decision-making for older adults, chemotherapy-associated toxicity and the approach to management. This review focuses on the complex treatment of older multiple myeloma patients and management of treatment-related adverse events.

Expert opinion: Balancing efficacy and managing toxicity is a challenge for older myeloma patients. This group is more susceptible to treatment toxicities due to a higher incidence of pre-existing comorbidities and underlying diminished physiologic reserve. Intensive therapies such as autologous hematopoietic cell transplant (AHCT), however, still should be considered for all multiple myeloma patients, including older adults. The continued development of novel therapies and increased use of multi-drug regimens has changed the treatment paradigms yet understanding the complexity of the aging adult in the context of various drugs is warranted.

Keywords

Multiple myeloma; older adult; toxicity; novel agents; hematopoietic cell transplant; hematology

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Declaration of interest

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1. Introduction

Multiple myeloma is a hematologic malignancy predominately affecting older adults. Despite significant treatment advances in recent years, this disorder still remains incurable [1]. The National Cancer Institute (NCI) Surveillance, Epidemiology and End Results Program (SEER) estimates the diagnosis of 30,770 new cases in the United States in 2018 at a median age at diagnosis of 69 years [2]. Treatment of a neoplastic disease affecting the older adult presents a unique set of challenges including the management of comorbid conditions, age-related physiologic factors, and underlying health, as well as the increased risk of adverse events from treatment (Table 1) [3].

With the advent of novel therapies such as thalidomide, lenalidomide, and bortezomib, overall survival in myeloma patients has significantly improved [9]. Unfortunately, however, this improvement was predominantly found in patients under 60–75 years of age [10]. Cohorts of patients at the Mayo Clinic demonstrated a median overall survival of 28 months for patients over 65 years vs 42 months for patients under 65 years at the time of diagnosis [9]. This lack of survival improvement in older adults may be due to several factors.

1.1. Chronologic versus physiologic age assessment

The concept of chronologic versus physiologic age in management decisions for older adult myeloma patients has increasingly been recognized as playing a key role. *Chronologic age* refers to the number of years a person has been living; while it is easy to define this value objectively for any patient, it is often not a complete or accurate representation of overall health status. The concept of *physiologic age* encompasses individual patient characteristics including medical comorbidities, functional status and independence in the activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and cognitive function [11,12]. In approaching older adults with myeloma, it is imperative to estimate the patient's underlying health status and perceived ability to tolerate chemotherapy and/or autologous hematopoietic cell transplant (AHCT). Historically, performance status tools such as Karnofsky Performance Status and ECOG performance status have been used to gauge overall health but have significant limitations in estimating underlying physiologic reserve and moreover, are incredibly subjective [13]. One potential solution is to borrow from the discipline of Geriatric Oncology as these specialists have developed many tools that can better assess underlying health status independent of aging.

1.2. Geriatric assessment

Evaluating overall health status in the older cancer patient is recognized as increasingly valuable and is a particularly important part of the treatment decision process in the myeloma patient. The American Society of Clinical Oncology (ASCO) recommends that all older adults greater than age 65 years undergo a Geriatric Assessment to identify vulnerabilities not routinely captured in a standard oncologic assessment [14]. A Comprehensive Geriatric Assessment (CGA) is defined as a process implementing a multidisciplinary approach to both identify and intervene on medical, psychosocial and functional limitations. This exercise can result in a coordinated plan to optimize overall health as a patient undergoes aging [15]; it is central in assessing risk of toxicity, mitigating

age-related functional decline, treatment decision stratification, survivorship and prognosis [16]. CGA programs are implemented in concert with geriatric care or primary care, but many interdisciplinary clinics and programs are emerging specifically in the context of cancer care [17,18].

Clinicians inherently recognize that, independent of age, a patient can be considered fit, vulnerable, or fragile. The later, the syndrome of fragility, is described, especially in the older adult, as increased vulnerability and decreased physiologic reserve leading to adverse health outcomes [19]. Classically described by Fried and colleagues [20], this phenotype is associated with three or more of the following criteria: weakness (decreased hand grip); low physical activity; slow walk speed; self-report of exhaustion; or weight loss. Unfortunately, describing frailty in the myeloma population is extremely challenging due to various frailty metrics and inconsistent use of geriatric assessment variables in clinical trial design (Table 2). Particularly in multiple myeloma, many patient populations are pre-designated for treatment and/or hematopoietic cell transplant based upon chronologic age alone (e.g. 65 years and older deemed non-transplant eligible). Moreover, several of the oncology frailty models include age in the frailty assessments, making it difficult to eliminate age-based decisions when gaging vulnerability [21].

Evaluating frailty has been explored in several different myeloma populations, both in those patients newly diagnosed and also in subjects prior to undergoing AHCT. One of the best established tools is the International Myeloma Working Group (IMWG) GA tool based on age, comorbidities (Charlson Comorbidity Index), ADL and IADL for newly diagnosed myeloma patients enrolled into non-transplant clinical trials [25]. Engelhardt et al. [26] demonstrated the utility of a revised-Myeloma Comorbidity Index as a valid prognostic tool which evaluates frailty. Using renal and lung function, Karnofsky Performance Status impairment, frailty and age as significant risks for overall survival, they developed a weighted revised Myeloma Comorbidity Index. This metric allowed for the identification of subject who were fit (revised Myeloma Comorbidity Index ≤ 3 [n = 247, 30.8%]); intermediate-fit (revised Myeloma Comorbidity Index 4–6 [n = 446, 55.7%]); and frail patients (revised Myeloma Comorbidity Index >6 [n = 108, 13.5%]); median overall survival rates for these subgroups were 10.1, 4.4 and 1.2 years, respectively. Fiala and colleagues [27] validated a frailty index using a Medicare database that had greater prognostic value in non-cancer patients than in a myeloma patient population. Moreover, geriatric assessment variables also have been analyzed to predict treatment decisions [28] and assess risk of adverse consequences [29], e.g. prolonged hospitalization and hospital readmission. The disparate use of various frailty tools and models make it difficult to apply uniform assessments of frailty in treatment and transplant decisions. Nonetheless, the myeloma community continues to explore how to best optimize treatment for older adults understanding that frailty is both quantifiable yet dynamic [30,31]. Clinicians still continue to rely upon clinical judgement and choose therapies they believe will provide maximum benefit while minimizing harm. Even in the older adult group, most fit and many intermediate-fit (or vulnerable) patients usually can benefit from and tolerate therapy. Caution, however, must continue to be used in those likely to fall into the frail group. Until an assessment tool generally has been universally validated and accepted in the older adult, clinicians should consider early and ongoing referral to a geriatric specialist and utilize the

assessment tools available to identify frailty; all the while, the treating physician must be extremely familiar with the optimal approaches to the various phases of myeloma and pick regimens accordingly, as presented below.

2. Induction regimen considerations

The initial or induction therapy for older myeloma subjects in the United States is highly variable and is dependent upon many factors. This group is vulnerable to adverse events associated with multi-drug combinations, which can lead to dose reductions or cessation of therapy; these factors, in turn, lead to poorer outcomes [25]. Corticosteroids were the first class of agents that possessed significant anti-myeloma activity and nearly all regimens utilize either dexamethasone or prednisone as part of therapy. Older individuals are prone to more corticosteroid-related adverse events including metabolic derangements, atrial fibrillation, thrombo-embolic phenomenon, and neurologic dysfunction. Hence, this group of agents is given for shorter periods and at reduced doses [32]. For example, the standard oral 40 mg/week dexamethasone dose should be lowered to 20 mg/week in patients >75 years.

Strategies for selecting 2-drug therapy vs. 3-drug therapy is aimed at disease control while balancing for treatment-related toxicity and accounting for factors related to aging. Below we will address the efficacy of chemotherapy and targeted agents, as well as their toxicity and management. Induction treatment for myeloma classically has been strategized for transplant-eligible patients vs. transplant-ineligible patients, although this approach is antiquated. Historically, oral melphalan was avoided in patients who potentially were AHCT candidates due to the association of poor hematopoietic progenitor cell mobilization [33]. Due to a similar risk of impaired progenitor cell mobilization, long-term use of lenalidomide was avoided [34]. In the modern era, for both eligible and ineligible patients for transplant, the most common regimens incorporate varying schedules and doses of bortezomib, lenalidomide with dexamethasone [35].

3. Chemotherapeutic agent review

3.1. Melphalan

Historically, for many years the combination of melphalan and prednisone (MP) was the standard of care for older adults with myeloma. Use of this regimen resulted in an overall response rate of about 65% with an overall survival (OS) of almost 30 months, but it was associated with hematologic and gastro-intestinal toxicity [36]. Adding thalidomide to this combination (MPT) provided a higher but not statistically significant survival advantage over MP in randomized trials for older adults, i.e. 3 year survival rates were 80% for MPT and 64% for MP (HR for MPT 0.68, 95% CI 0.38–1.22, $p = 0.19$) [37]. Thalidomide use, however, was associated with significant adverse events including somnolence, neuropathy, and thrombo-embolic phenomenon. Subsequently, with the advent of novel agents, both bortezomib (Velcade[®], Takeda Oncology, V) and lenalidomide (Revlimid[®], Celgene Corporation, R) have been examined to replace thalidomide in combination with melphalan, referred to as VMP and RMP. These new 3-drug combinations have been considered as one of the frontline regimens for aging adults [38]. Table 3 shows improved outcomes without

increasing adverse events. More recently, the addition of newer agents such as the monoclonal antibody, daratumumab, has been added, i.e. a four drug combination. While the daratumumab-VMP combination conferred a lower risk of disease progression, a subgroup analysis in subjects ≥ 75 years of age showed that they experienced a higher rate of infection (pneumonia) in the daratumumab-containing group [39]. Despite these relatively effective combinations, the myelosuppressive nature of melphalan precludes it from routine use in the U.S.. With evidence supporting the use of modified schedules and doses of bortezomib, lenalidomide and corticosteroids in the older myeloma patient, the use of oral melphalan as first line treatment is less common in the U.S..

3.2. Immunomodulatory drugs (IMiD)

The first clinical immunomodulatory drug, thalidomide, was attractive because of its anti-myeloma effects yet lack of marrow suppressive properties. Its addition to MP resulted in improved response rates, depth of response, progression-free survival (PFS) and OS. However, as discussed above, the non-hematologic toxicities of somnolence, peripheral neuropathy and thrombo-embolic phenomenon roughly doubled with the addition of thalidomide to MP [48]. Although efficacious, thalidomide use has fallen out of favor to other agents such as lenalidomide [37,49].

3.2.1. Lenalidomide—Lenalidomide is a second generation IMiD developed as a more potent, less toxic analog of thalidomide. Lenalidomide has been studied alone and as part of combination therapy. Lenalidomide predominately is eliminated via the kidney and this agent must be dose-reduced in renal insufficiency, a common issue in older patients [50]. Studies have demonstrated that melphalan, lenalidomide and prednisone (MPR) with or without lenalidomide maintenance therapy, prolongs PFS and OS in comparison to MP. This toxicity profile compares similarly with MPT [51,52]. The two-drug option using lenalidomide and dexamethasone (Rd) also gives favorable results. In comparison with MPT, this regimen, as shown in Table 3, is associated with a survival advantage and less toxicity [53].

Lenalidomide has been combined with bortezomib in both the up-front setting as well as in combination with daratumumab, carfilzomib and elotuzumab for patients who have relapsed, refractory disease [54–57]. Significant data also support its use in the maintenance setting after AHCT; however, this approach is not without toxicity [58]. Compared to placebo, lenalidomide therapy was associated with more myelosuppression and report of secondary malignancies [58]. Lenalidomide use is associated with mild myelosuppression as part of its adverse event profile, whereas thalidomide's effects of severe peripheral neuropathy (10% incidence), fatigue and constipation can be taxing, particularly for older adults [52]. The use of lenalidomide also is associated with an increased risk of secondary primary malignancies. A meta-analysis identified this cumulative risk at 6.9% in patients who received lenalidomide vs 4.8% in those who did not [59]. Thromboembolic phenomenon also is seen when dexamethasone is added to lenalidomide [60]. Table 4 addresses various risk factors and appropriate prophylaxis.

3.2.2. Pomalidomide—Pomalidomide, another IMiD approved in 2013 for use in the relapsed, refractory myeloma setting, possesses a more potent anti-myeloma effect than either thalidomide or lenalidomide. Efficacy was established in several studies (MM-002 and MM-003) in combination with low-dose dexamethasone (40 mg/week, or 20 mg/week if age 75 years) [61–63]. Pomalidomide, similar to lenalidomide, is associated with mild myelosuppression, peripheral neuropathy (17.9% all grades) and a low risk of venous thromboembolism [63]. Unlike lenalidomide, the body's main method of eliminating pomalidomide is via the hepatic route, and this agent can be administered in renal dysfunction, with a reduced starting dose of 3 mg even in patients receiving hemodialysis [64]. Pomalidomide carries the similar risk of thrombo-embolic phenomenon; however, the incidence of secondary malignancies was found to be less than lenalidomide at an incidence of 1.3% in patients receiving the pomalidomide-dexamethasone combination [62].

The immunomodulatory drugs have demonstrated significant efficacy in the treatment of both newly diagnosed and relapsed, refractory myeloma. Lenalidomide should be the first choice IMiD for newly diagnosed myeloma based on tolerability and efficacy with pomalidomide reserved for treatment in the relapsed, refractory setting. The use of thalidomide should be avoided due to intolerability compared to lenalidomide and pomalidomide.

3.3. Proteasome inhibitors

Proteasome inhibitors have changed the treatment paradigm of multiple myeloma dramatically and have become the standard of care as a backbone in regimens for induction, maintenance and as salvage therapy for patients with relapsed/refractory disease [65]. The three currently FDA-approved proteasome inhibitors offer flexibility in dosing, route of administration schedule, and toxicity profiles. These differences can be tailored for patient-specific characteristics such as comorbidities, compliance, and previous treatments making them an attractive option for older patients.

3.3.1. Bortezomib—Bortezomib, first approved in 2003 in the United States, is a first-in-class reversible proteasome inhibitor that has shown efficacy in various multi-drug combinations in the newly diagnosed, maintenance and relapsed, refractory multiple myeloma treatment settings [54,66–70]. For a variety of reasons, myeloma patients often experience impaired kidney function. Bortezomib is the preferred agent in those individuals who have renal failure; bortezomib therapy can result in prompt disease control and provides the potential for recovery of kidney function. Complete renal response with resolution of renal insufficiency is more common with treatment regimens containing bortezomib (71%) than with conventional chemotherapy (41%) or with immunomodulatory therapy (45%) [71]. Bortezomib causes a mild, reversible thrombocytopenia, and can be associated with peripheral sensory neuropathy. Patients may also experience diarrhea, nausea, fatigue and constipation [70]. Most toxicities may be managed with dose and/or frequency reductions. Appropriate dose level reductions to 1.0 mg/m² and 0.7 mg/m² may be effective in managing toxicity as well as changing the frequency to once week from twice weekly administration.

The APEX trial first compared high-dose dexamethasone as a single agent versus the addition of twice-weekly bortezomib in the relapsed, refractory setting; superior response rates and one year survival and tolerability were noted [70]. Subsequently, in the phase 3 VISTA trial, bortezomib was added to the previous standard-of-care melphalan-prednisone (VMP vs MP) regimen in newly diagnosed patients ineligible for high-dose AHCT therapy [69]. Highlighting a subgroup analysis of patients 75 years or older, the median time to progression was equivalent to that of a younger patient population; however, the rates of complete response were slightly lower. Initially, OS in patients 75 years old was less than a younger subgroup but at a 5 year follow-up point, an OS benefit was maintained. These data helped to establish bortezomib as a standard of care drug for the initial treatment of patients 65 years of age or older [69,72].

Bortezomib plus dexamethasone (VD) and in combination with thalidomide or melphalan (VTD, VMP) have been evaluated in older adults ineligible for AHCT. Table 3 shows that the response rates, PFS and OS were similar, yet toxicities were more common with VTD. Other combination regimens that substitute conventional melphalan treatment with the alternative alkylating agent, cyclophosphamide (VCD, CyBorD), also have been evaluated and show excellent responses compared to Rd or CRD and are well tolerated [73,74]. With an acceptable safety profile, the three drug regimen of bortezomib, lenalidomide and dexamethasone for eight cycles has become the current standard of care induction regimen for newly diagnosed, transplant ineligible multiple myeloma patients and established the superiority of a three-drug vs two-drug regimen [54]. In older adult patients, a three-drug regimen is safe and with appropriate dosing modifications. Utilizing a once weekly bortezomib dosing schedule in conjunction with reduced-doses of lenalidomide and dexamethasone should be strongly considered for the older myeloma patient.

3.3.2. Bortezomib maintenance therapy—Bortezomib administration in the maintenance setting has been shown to improve PFS. First established in combination with thalidomide (VMPT-VT) and with prednisone (VMP-VP) in older adult patients unable to undergo AHCT, bortezomib administration after completing VMPT or VMP provided superior PFS and response rates [66,75]. Bortezomib administration for two years after AHCT significantly improved PFS and highlighted a benefit in patients whose disease was harboring the chromosomal deletion 17p13 [76]. It should be noted the median age in this study was only 57 years, so tolerability may not be fully extrapolated to an older population. Unlike lenalidomide, bortezomib did not have any reported secondary malignancies. The route of subcutaneous administration and risk of peripheral neuropathy, however, eventually could limit its long-term utility [77].

3.3.3. Carfilzomib—Carfilzomib, an irreversible proteasome inhibitor, was approved in the United States in 2012 for the treatment of relapsed and refractory multiple myeloma. Administered parenterally twice weekly, efficacy has been established alone with dexamethasone and in combination with lenalidomide, pomalidomide or cyclophosphamide [55,78–80]. With a decreased incidence of peripheral neuropathy compared to bortezomib, the side effect profile of carfilzomib remains favorable with the most frequent adverse events being myelosuppression and fatigue. Pre-treatment cardiovascular evaluation and close

blood pressure monitoring is recommended for patients receiving carfilzomib as cardiovascular toxicities have been observed [78]. Patients receiving carfilzomib should be monitored closely for pulmonary symptoms as well as both new-onset and decompensated heart failure, and rarely pulmonary toxicity with acute respiratory distress syndrome (ARDS), may occur [81,82]. Once weekly carfilzomib has been evaluated and deemed tolerable for patients who may be unable to travel to clinic or tolerate twice weekly administration [83].

3.3.4. Ixazomib—Ixazomib, the first oral proteasome inhibitor, has demonstrated efficacy when administered in combination with lenalidomide and dexamethasone. The recommended starting dose is 4 mg once weekly on days 1, 8 and 15 of a 28 day cycle. Ixazomib should be taken on an empty stomach, at least one hour before or two hours after food [84]. Consideration should be given to administration time as taking it at bedtime may help to avoid nausea. With a tolerable safety profile, myelosuppression, rash and diarrhea were the most commonly reported adverse events [85]. The starting dose of ixazomib should be reduced to 3 mg in patients with impaired renal function (creatinine clearance <30 mL/min) or end-stage renal disease. While providing a successful treatment option for those older patients unable to travel, administration of an all oral regimen may be difficult for patients who struggle with compliance. Although not yet FDA-approved, ixazomib is currently being explored in the maintenance setting [NCT02312258]. Recently, the randomized phase 3 TOURMALINE-MM3 [86], trial reported ixazomib maintenance resulted in improved PFS vs placebo in the post-transplant setting.

4. Role of hematopoietic cell transplantation

4.1. Autologous hematopoietic cell transplant (AHCT)

Induction therapy followed by high-dose melphalan with AHCT is the standard of care for patients <65 years old [87]. Eligibility for transplant is subjective, but dependent on age related factors, comorbidities, and underlying health status. Older adults with myeloma may have dynamic changes in their health and with disease control can become ‘eligible’ for more intensive therapies. Alternatively, others may develop adverse sequelae where AHCT is no longer indicated. Paramount to transplant decision-making is recognizing the shared-decision model where AHCT is a discussion among the individual, caregivers, and treating physician to optimize a treatment trajectory that is congruent with patient goals.

4.2. AHCT in the older adult

Despite the establishment of AHCT in the treatment of myeloma, under-utilization of AHCT in the older patient has been a significant contributing factor to the decreased survival in this population [88]. Recently, AHCT utilization has improved, and consequently, OS for older adults is improving. Large registry studies from the European Group for Blood and Marrow Transplantation (EBMT) have shown the proportion of AHCT recipients 65 years old is increasing where over 50% of autologous transplants are older than 60 years of age as of 2016 [89,90].

Under-utilization for transplant may be a result of conflicting data in older adult AHCT studies. The largest older adult AHCT study was the Intergroupe Francophone due Myélome (IFM) 99–06 study where 447 patients were randomized to receive either melphalan-prednisone; melphalan-thalidomide-prednisone; or tandem AHCTs using a reduced dose of melphalan at 100 mg/m² (MEL100). Early death was reported in 7% of patients in the MP group, 2% in the MPT group, and 9% in the MEL100 group. MPT was associated with a significant OS benefit compared with both MP and MEL100 [91].

In contrast to these results, more recent, prospective evaluations, registry studies, and multiple single-center retrospective analyses have yielded more favorable results in the older adult undergoing AHCT [92–99]. The Mayo Clinic evaluated outcomes of AHCT patients above and below 65 years of age. Older patients were more likely to receive a reduced dose of melphalan (30% vs. 5%), experience similar overall response rates (97% vs. 98%), have similar times to disease progression (29 months vs. 18 months), and show no differences in OS (not reached vs. 53 months) [98]. Likewise, the German Myeloma Study group reported on 202 patients aged ≥60 years who underwent AHCT; 97% of patients received melphalan 200 mg/m² (MEL200), with 21% receiving tandem transplants. There was no significant difference in mortality by day 100, and age was not a risk factor for adverse outcome [99].

4.3. Melphalan dosing

The feasibility of MEL200 in selected older adult patients is further supported by retrospective studies, where advancing age was not predictive of worse PFS post-AHCT [100,101]. The optimal dosing strategy of high-dose melphalan in older adults undergoing AHCT is unclear. Many studies have reported MEL200 without significant differences in treatment toxicity compared to younger patients. Furthermore, higher dosages of melphalan may partially explain improved outcomes, compared to other studies using lower doses of melphalan [87]. Nonetheless, melphalan 140 mg/m² is commonly used in older adults (>70 years) in an effort to preemptively reduce risk of transplant toxicity [93,101].

5. Novel therapies

Therapy selection for older adults is evolving, and questions remain on how to sequence newer agents such as the monoclonal antibodies; daratumumab and elotuzumab.

5.1. Daratumumab

Daratumumab is a CD38-targeted monoclonal antibody that causes myeloma cell death through a variety of immune-mediated mechanisms [102]. As previously discussed, daratumumab recently was approved to be administered in combination with VMP in the frontline setting in patients unable to receive an AHCT [39]. It is difficult to identify how approval of this will effect treatment decisions in the United States as VMP is not common as an initial treatment in older adult patients. In the relapsed, refractory disease setting, daratumumab currently is approved to be administered as monotherapy with dexamethasone or in combination with bortezomib, lenalidomide or pomalidomide [56,103,104]. Daratumumab is well-tolerated with infusion-related reactions during the first infusion being the most significant toxicity. Daratumumab may interfere with identification of antibodies

during the blood product crossmatch process. Thus, clear communication between the provider and blood bank are crucial so proper steps to account for this interference, such as treatment of patient blood samples with dithiothreitol can be under-taken [105].

5.2. Elotuzumab

Elotuzumab is a first-in-class humanized immunostimulatory monoclonal antibody targeted against the signaling lymphocytic activation molecule F7 (SLAMF7, formerly called CS1) and is approved for relapsed disease, in combination with lenalidomide and dexamethasone [57]. While no specific risks or toxicities have been identified for older adult patients receiving elotuzumab, a dose reduction of concomitant lenalidomide and dexamethasone may be warranted in the older patient. Older myeloma patients also should be made aware of the increased risk of herpes zoster reactivation and receive appropriate prophylaxis.

Studies are ongoing to explore how monoclonal antibodies can best be incorporated into myeloma therapies across the board.

5.3. Venetoclax

Venetoclax is an oral BCL-2 inhibitor that induces cell death in myeloma cells, especially those cells with the t (11;14) abnormality. Administered slowly step-wise over weeks to reach doses up to 1,200 mg daily and with or without dexamethasone, venetoclax is well-tolerated with nausea, diarrhea and thrombocytopenia being the most frequently reported toxicities [106]. Venetoclax also has been combined with bortezomib and dexamethasone and has shown promising results. With an overall response rate of 67%, the combination is safe with similar toxicities as monotherapy administration [107]. Older adult patients should be apprised to the side effects of nausea, diarrhea, and vomiting to mitigate the risk of dehydration. Review of concomitant medications should be performed to screen for potential drug interactions.

6. Managing expectant toxicities

Therapeutic options for myeloma continue to expand and personalizing therapy for the individual subject remains a challenge. Therapeutic decisions are based on individual patient characteristics as well as expected therapeutic toxicities.

6.1. Venous thromboembolism

The risk of venous thromboembolism (VTE) is a reflection of drug class effect with varying incidence (0–33%), obviously higher with IMiDs compared to other agents. The addition of dexamethasone further increases that risk and has been reported as being as high as 75% if administered without thrombo-embolic prophylaxis [60]. Given this risk, it is recommended that thrombo-embolic prophylaxis be administered to all patients receiving combination regimens (Table 4). Care must be taken to reduce the risk of VTE yet minimize the risk of bleeding, which can be a concern in older adult patients who are at high risk of falls.

6.2. Peripheral neuropathy

Although bortezomib efficacy and tolerability has been long established in older patients, bortezomib is not without toxicity [108]. Peripheral neuropathy (PN) is one of the most frequently reported adverse events with bortezomib administration often leading to dose modification and therapy discontinuation [109]. The development of peripheral neuropathy seems to be dependent on treatment, dose exposure and route of administration (intravenous versus subcutaneous), with symptom improvement or stabilization after stopping or dose reduction [110]. In addition to dose reductions from 1.0 mg/m² and 0.7 mg/m², an Italian study demonstrated a once-weekly bortezomib administration schedule produced a significant reduction in PN while maintaining response rates and overall survival [110]. Modified RVD or 'RVD-lite' also may be considered for patients older than 75 years [111]. The phase 3 study by Moreau, et al confirmed that subcutaneous administration of bortezomib can reduce the incidence of all grade peripheral neuropathy (35% vs 53%) without compromising efficacy as compared to intravenous administration [112]. Adverse events should be closely assessed prior to each dose and both administration schedule and route modification should be strongly considered to avoid severe neurotoxicity in older adult patients or those with preexisting PN.

6.3. Cardiovascular toxicity

Carfilzomib is associated with a low incidence (20%) of unpredictable cardiovascular toxicities including hypertension, congestive heart failure and coronary artery disease [113]. There are conflicting data regarding the complications associated with carfilzomib with some literature suggesting no effect with cumulative dose and other reports suggesting an increased incidence with doses >45 mg/m² [113,114]. Although attention to cardiovascular sequelae throughout therapy is recommended, cardiovascular disease risk factors do not preclude its use. Close monitoring is recommended; however, serial echocardiograms have not been shown to predict events [113,114].

6.4. Gastrointestinal toxicities

Several drugs used in myeloma treatment regimens are associated with minor gastrointestinal toxicities. Bortezomib may cause nausea, diarrhea, constipation and vomiting with an incidence of 48%, 46%, 37% and 33% respectively [70]. Carfilzomib has a decreased incidence of nausea, diarrhea and constipation compared to bortezomib [78]. Lenalidomide and thalidomide also may cause constipation or diarrhea.

Nausea may be managed with anti-emetic premedication if warranted and rescue anti-emetics for home use. Avoidance of dehydration and weight loss due to lack of appetite, especially in the older adult population is of great concern. Care must be taken to avoid anti-emetic medications that can cause drowsiness or sedation in an older population at risk for falls and confusion. Diarrhea may be managed with anti-diarrheal medications and hydration while constipation should be addressed with hydration, fiber-rich foods and stool softeners or laxatives, if warranted. A modified schedule of bortezomib once weekly may attenuate the GI toxicity and dose reductions or treatment breaks may be helpful for lenalidomide and thalidomide [75].

7. Supportive care approaches

7.1. Antiviral prophylaxis

All patients receiving proteasome inhibitors and monoclonal antibodies routinely should receive antiviral prophylaxis. The administration of bortezomib in the APEX trial above was associated with a significantly higher incidence of reactivation herpes zoster, a common problem in the older adult population, compared to dexamethasone alone [115]. Elotuzumab also is associated with an increased risk of reactivation herpes zoster infection when compared to a control group of lenalidomide-dexamethasone therapy [57]. Either acyclovir or valacyclovir may be administered but both should be adjusted for decreased renal dysfunction, common in older adults.

7.2. Antibacterial prophylaxis

The predisposition of multiple myeloma patients to infection is likely multi-factorial from effects of targeted agents and chemotherapy, the immune modulation of myeloma itself as well as pre-existing comorbid conditions [116]. Levofloxacin has been shown to be beneficial in preventing severe infections in patients receiving bortezomib therapy [117]. The TEAMM trial recently evaluated the use of levofloxacin prophylaxis in newly diagnosed myeloma patients receiving induction therapy. Patients were permitted to continue sulfamethoxazole-trimethoprim. They reported a decreased incidence in febrile episodes and death in the first 12 weeks of treatment with the use of levofloxacin; however, at one year there was no survival benefit compared to the placebo group [118]. There was no increased incidence of healthcare associated infections however toxicity and QTc prolongation were not reported. The administration of levofloxacin is not entirely benign. Patients' medication lists should be thoroughly reviewed for potential drug-drug interactions prior to initiation and institutions must discuss the potential risk of anti-biotic resistance.

7.3. Immunoglobulin therapy

Myeloma patients often for a variety of reasons have functional hypogammaglobulinemia that can lead to infection and morbidity and mortality. Some studies have shown that intravenous immunoglobulin (IVIG) replacement or prophylaxis may be useful in hypogammaglobulinemic myeloma patients who have experienced more than one severe infection, especially in subjects who have low serum antibody concentrations after immunization against diphtheria, tetanus and pneumococcus [119]. IVIG has been shown to decrease occurrences of major infections but is not associated with a survival benefit [120]. Practitioners, however, must use caution as the increased risk of thrombosis due to thalidomide, lenalidomide and pomalidomide may be increased by IVIG therapy.

7.4. Bone modifying agents

Multiple myeloma patients who have lytic bone disease, osteoporosis, or osteopenia should be treated for up to 2 years with a bone-modifying agent to reduce the risk of pathologic or compression fractures. Additionally, there is some evidence of anti-myeloma activity of these agents. While bisphosphonates are traditionally considered the first-line bone modifying agents for myeloma patients, due largely to lower cost, denosumab a (RANK-

ligand inhibitor) may be considered a favorable agent for older adults. Denosumab carries no risk of nephrotoxicity [121], and acute side effects such as arthralgia are less common than with bisphosphonates. For patients with renal impairment, pamidronate is the preferred bisphosphonate. All patients receiving bone-modifying agents require dental examination prior to initiation of these agents due to the risk of osteonecrosis of the jaw; this issue may be especially important in older adult patients who are more likely to have baseline dental disease (Table 5) [122].

7.5. Potential drug interactions

With the increasing use of oral anti-myeloma agents and risk for polypharmacy, care must be taken to thoroughly evaluate patients' medication lists for drug-drug, drug-herbal, and drug-food interactions. Several anti-myeloma drugs undergo hepatic metabolism and should be evaluated when prescribing a moderate or strong CYP inducer or inhibitor. Examples include St. John's Wort, a known CYP3A4 inducer, leading to decreased efficacy of both ixazomib and venetoclax. Patients should also be educated on avoiding the ingestion of grapefruit, grapefruit juice and Seville oranges as well due to the CYP3A4 inhibition [124]. Interactions with a CYP inhibitor are likely to lead to increased toxicities which may be problematic in a more fragile older adult patient. Although seemingly benign, both ascorbic acid and green tea have both been shown to inhibit the effect of bortezomib when administered concomitantly and should be avoided [125,126].

8. Therapies in development

8.1. CAR-T therapy

CAR-T cells are T cells that have been genetically modified to express a chimeric antigen receptor directed toward a specific extracellular protein expressed by malignant cells. Specific protein targets of promise in myeloma have included the B-cell maturation antigen (BCMA), CD38, CD138, SLAMF7, and CD44v6 [127]. The exploration of CAR-T therapy may provide additional effective and durable treatment options for myeloma; however, their use in the treatment of older adults remains unknown [128,129].

9. Diagnostics and other considerations

9.1. Questions in diagnostics

9.1.1. PET/CT scans—F-fluoro-deoxy-glucose positron emission tomography/computed tomography, i.e. PET/CT scanning, has become a useful tool for imaging and for prognostication in hematologic malignancies. This tool, however, has been used less frequently in myeloma, in part, because simple and reproducible reporting criteria are lacking. Several groups recently have reported improved harmonization and this test can be a valuable tool for the work-up of patients with both newly diagnosed and relapsed or refractory myeloma [130,131]. PET/CT scans can selectively assess bone damage as well as extra-medullary disease and also have great utility to distinguish smoldering from active myeloma as well as monitor response to therapy.

9.1.2. Minimal residual disease (MRD) testing—Sophisticated new immunophenotypic and molecular techniques, including multiparameter flow cytometry, polymerase chain reaction and next-generation sequencing, are more sensitive tools than bone marrow morphology and serologic tests to detect the presence of a very low concentration of residual myeloma, termed minimal residual disease (MRD). A number of investigators have begun to incorporate MRD into clinical management to predict significantly inferior survival among patients clinically thought to be in complete remission [132,133]. As we have discussed above, the newer treatment approaches can better reduce tumor burden and now require utilization of more sensitive strategies to detect MRD and act as a more potent surrogate biomarker than the standard complete remission definition. Further, ‘not all complete remissions are created equal’, i.e. complete remission may be transient in some subjects while sustained in others. A full discussion of MRD in myeloma is beyond the scope of this review but some investigators suggest that these techniques routinely should be incorporated to assess the efficacy of treatment, aid in therapeutic decision-making and predict for OS. Unfortunately, however, at present, the role of MRD remains a subject of considerable debate, in part due to limited data and patient-, disease- and treatment-heterogeneity as well as the pros and cons of the different MRD techniques.

9.2. Cost considerations

As previously discussed, with the advent and incorporation of immunomodulators, proteasome inhibitors and monoclonal antibodies, the treatment paradigm for myeloma has evolved. As such, drug acquisition costs have also significantly increased and can be a large burden, especially on older adult patients who rely on fixed incomes. As patients progress through multiple lines of treatment, data have shown that drug costs also increase [134]. Care should be taken to ensure that all available resources i.e., manufacturer and patient assistance programs, are utilized to support the patient.

9.3. Future directions

Despite advances in the development of successful treatments of multiple myeloma, significant deficits remain in the treatment of relapsed refractory disease. Selinexor, an oral selective inhibitor of nuclear export (SINE) compound, has shown to be effective in heavily pretreated, relapsed refractory multiple myeloma with an overall response rate of 26.2% [135]. B cell maturation antigen (BCMA), which is exclusively expressed on the surface of plasmablasts and plasma cells, is a promising target for the recent development of new immunotherapies, antidrug conjugates and CD3 bi- and tri-specific molecules [136]. Although not yet approved, several anti-BCMA molecules show clinical efficacy with acceptable safety profiles. Checkpoint inhibitors have been effective in prolonging survival in solid tumors and lymphomas; however, they have not yet demonstrated efficacy in myeloma [137]. Unfortunately, the combination of a checkpoint inhibitor with an IMiD showed an increased risk of death in myeloma highlighting the need for increased understanding of checkpoint inhibition in myeloma [138].

10. Conclusion

Novel therapeutics and routine use of AHCT have led to substantial improvements in overall response rates and durable remissions in myeloma [139–141]. Herein we have addressed the pharmacologic management of older myeloma subjects; addressed unique considerations associated with disease management, and discussed select supportive care measures. Several effective strategies now have been established that enable relatively safe treatment of myeloma in older adults. Underlying age-related health factors should be considered but not pre-empt treatment in the older adult. The practitioner must be experienced with common toxicities of the various regimens and how best to mitigate adverse events unique to the individual. Awareness of age-related comorbidities, functional trajectory, infection prophylaxis and avoiding adverse consequences such as skeletal-related events or thrombosis are vital to optimize the best treatment for the older myeloma patient. Balancing efficacy with toxicity is especially imperative for older adults. This population is more susceptible to treatment toxicities due to a higher incidence of pre-existing comorbidities and variable physiologic reserve. Intensive therapies such as AHCT should be considered for all multiple myeloma patients, including older adults. The pharmacologic management of myeloma is increasingly complex and understanding the nuances of myeloma management, as it relates to the older adult physiology, is an area that is understudied and requires ongoing research.

11. Expert opinion

Balancing efficacy and managing toxicity is a challenge for older adults with myeloma. Recent studies suggest that three-drug regimens may be superior to two-drug regimens (SWOG S0777), in terms of disease response and survival [142]. Other groups are investigating dosage-attenuation of standard regimens (VCD-lite and RVD-lite) to be used in frail, older adults in order to reduce toxicity while maintaining efficacy [111]. Studies such as these may help to better define the optimal induction regimens for seniors who will not undergo AHCT. Therapy selection for older adults continues to evolve, and questions remain on how to sequence newer agents and how to best embrace novel therapies for older adults.

Importantly, some of the key findings when managing older adult myeloma patients is to recognize that health becomes highly heterogeneous with aging; only by understanding the unique and dynamic aspects of frailty can the clinician design a rationale treatment decision. Several available tools to quantify frailty in the older adult myeloma population can predict toxicity, drug discontinuation and overall survival (e.g. IMWG GA, Revised-MCI).

These therapeutic strategies are aimed to maximize benefit and minimize under-treatment while balancing for toxicity. Delineated in Table 6, for untreated, fit patients, standard triple drug VRd induction therapy with appropriate dose modifications for lenalidomide and dexamethasone should be offered. For untreated, unfit older adult patients, a two drug regimen consisting of lenalidomide plus dexamethasone (Rd) for patients with normal renal function or bortezomib plus dexamethasone (Vd) for patients with poor renal function should be considered.

AHCT should be considered for all older adults using a shared decision model reviewing patient expectations in terms of toxicities and quality of life. Lowering the dose of the high-dose melphalan AHCT preparative regimen is well-established in the older adult population and supportive care has improved considerably allowing for optimized recovery post-transplant. Maintenance therapy for older adults is recommended both for transplant-eligible and transplant-ineligible subjects; and should be continued until progression or toxicity [143].

At time of relapse, most second generation proteasome inhibitors and IMiDs are well-studied in older adults and are used commonly. The toxicity profiles are unique to the drugs and frail, older adults will have higher rates of hematologic and non-hematologic adverse event; drug discontinuation and subsequent relapsed may ensue if treatment is not carefully considered and monitored. Daratumumab remains an attractive treatment option as it is well tolerated and may be given in combination with other anti-myeloma drugs. As previously discussed, once-weekly carfilzomib may be beneficial for patients with transportation issues or a history of peripheral neuropathy; however, the risk of hypertension and heart failure must be acknowledged. Re-assessment of vulnerabilities both at diagnosis and throughout the continuum of treatment is required for the older myeloma patient. On-going and frequent reassessment is imperative in order to modify therapy to achieve the best response while mitigating adverse events. Previously stable comorbidities may be amplified with particular myeloma drug selection (i.e. neuropathy, cardiovascular decompensation); therefore, a careful review of all medical conditions is warranted.

Supportive care measures such as VTE prophylaxis, bone-strengthening agents and infection prophylaxis is indicated for all older adults to prevent unwanted sequelae such as thrombosis, skeletal-related events and infections, and should be implemented according to drug class and clinical context. Care should be taken to dose supportive care medications appropriately for renal dysfunction and other comorbidities.

In the future, the sequencing of therapy for myeloma patients will be more clear and personalized based upon genetic risk and underlying health status. One of the biggest and persisting challenges in the myeloma patient population is to consistently identify those patients suitable for intense therapy using standardized frailty tools and eliminating chronologic age bias in treatment decisions. To achieve this goal, clinicians must utilize the tools and resources available such as consulting geriatricians and utilizing online frailty assessment tools to provide the best care for these older adults. Moreover, future clinical trials embedding frailty assessments will standardize the approach to the older adult myeloma subject and more clearly identify patients at-risk of untoward toxicity.

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Article highlights

- Older adults with myeloma are more susceptible to treatment toxicities due to a higher incidence of pre-existing comorbidities and underlying diminished physiologic reserve
- Intensive therapies, including autologous hematopoietic cell transplant, should be considered for all myeloma patients, including older adults
- With an acceptable safety profile, the three drug regimen of bortezomib, lenalidomide, and dexamethasone (VRd) has become the current standard of care induction regimen for newly diagnosed multiple myeloma patients and established the superiority of a three-drug vs two-drug regimen
- VRd may successfully be given to older adults with appropriate dose and schedule modifications such weekly bortezomib administration combined with dose reductions in lenalidomide and dexamethasone
- Although the sequencing of use of novel agents remains unknown, daratumumab, elotuzumab, and venetoclax are effective and tolerable therapeutic options for older adults with myeloma

This box summarizes key points contained in the article.

Table 1.

Special risks associated with disease and treatment in older adult patients with myeloma.

Category	Considerations
Biologic	<ul style="list-style-type: none"> • Decreased bone marrow reserve requiring more apheresis sessions prior to AHCT may be mitigated by plerixafor [12] • Serum creatinine alone does not accurately reflect renal function; use of formulae to estimate creatinine clearance or 24-hour urine collection is preferred • Age-related cardiac remodeling and deposition of immunoglobulin light chains and amyloid proteins predisposes to cardiac dysfunction and arrhythmias [4] • Risk of venous thromboembolism increases with age • Older adult patients with myeloma are more likely to have advanced stage disease however high risk cytogenetics are less common with age [5]
Comorbidities	<ul style="list-style-type: none"> • Patients with pre-existing CAD requiring use of antiplatelet therapy are at increased bleeding risk with development of thrombocytopenia [4] • Adrenergic stress and high volumes of IV fluids associated with AHCT pose increased risks to older adult patients with pre-existing cardiac dysfunction
Toxicities	<ul style="list-style-type: none"> • Mood disturbances and muscle weakness associated with corticosteroids can be particularly debilitating to older adult patients [6] • Opioid analgesics may be required for management of treatment-related mucositis or pain related to lytic bone lesions, but may be poorly tolerated by older adult patients [7] • Myelosuppressive effects of treatment regimens such as high-dose melphalan may be prolonged in older adult patients, increasing risk of infections • Therapy and disease-associated thrombocytopenia predisposes older adults to bleeding while on anticoagulation [4] • Increased cardiac arrhythmias and GI toxicities with AHCT [12]
Functional	<ul style="list-style-type: none"> • Frail older adults have higher rates of non-hematologic AEs and therapy discontinuation [12] • Relative intolerance to treatment-related AEs [8] • Lower physical function and weight loss is associated with longer AHCT stay [29] • Poor performance status alone not predictive of decreased overall survival, but advanced age, decline in ability to perform ADLs and IADLs associated with worsened overall survival regardless of disease stage and treatment [6] • Increased fall risk in older adults carries bleeding risk that is augmented by thrombocytopenia and VTE prophylaxis

AHCT: autologous hematopoietic stem cell transplant; **ISS:** International Staging System; **CAD:** coronary artery disease; **IV:** intravenous; **GI:** gastrointestinal; **AEs:** adverse events; **ADLs:** activities of daily living; **IADLs:** instrumental activities of daily living.

Table 2.

Summary of frailty assessment tools.

Author	N of patients included	Median Age (range)	Frailty Assessment Tool	Outcome
Palumbo, et al. [25]	N = 869	74 years	IMWG Frailty Score Fit Intermediately Fit Frail	Simplified tool based on age, comorbidities (Charlson Comorbidity Index), activities of daily living (ADL) and instrumental activities of daily living (IADL) 3-yr OS: 84% in fit 76% in intermediate-fitness 57% in frail
Engelhardt et al. [26]	N = 801	63 years (21–93)	Revised Myeloma Comorbidity Index	Frail: Index >6 Median OS 1.2 years Intermediate Fit: Index 4–6 Median OS 4.4 years Fit: Index 3 Median OS 10.1 years
Fiala et al. [27]	N = 340	75 years	Frailty index (FI)	Lowest tertile of FI 48 month median OS vs. 23 month median OS for the highest tertile of FI
Li et al. [22]	N = 12,547	[All patients 66 years]	Frailty defined as poor claims – based disability status (PDS)	PDS frail vs fit: 3-year OS: 34% vs 61% (P = 0.01) who began first line therapy
Nathwani et al. [23]	N = 210	72 years (65–87)	Modified GA including Palumbo frailty score	Frailty score influences provider decision-making 50% of the time
Schutz et al. [24]	N = 150	77 years	Edmonton frailty score	Frailty status: OR 8.2 [1.9, 34]
Rosko et al. [29]	N = 100	59.5 years (36–75)	Geriatric Assessment (mixed metrics)	Pre-transplant physical function predicative of hospital length of stay. For each one-unit increase in physical function score, the average LOS decreased by 0.52 days (95% CI, –1.03–0.02); p = 0.04). Deficits in activity, anxiety/depression, handgrip, falls and weight loss associated with higher hospital readmission.
Wildes et al. [28]	N = 39	Myeloma 69.5 years	Geriatric Assessment (mixed metrics)	Age (P = 0.047), slow time on TUG (P = 0.048), CCI 1 (P = 0.002), poor baseline QOL (P = 0.006) all associated with ineligibility for autologous HCT

Table modified from Koll, et al [30] with permission of Springer Nature.

Table 3.

Select management considerations in older adults with multiple myeloma.

Drug	Topic	Study	Summary
Bortezomib	Rd vs. RVD	SWOG S0777 Durie BG [54]	<ul style="list-style-type: none"> Addition of bortezomib to lenalidomide-dexamethasone significantly improved PFS and OS Established superiority of three-drug regimen over two-drug regimen
		O'Donnell EK [111]	<ul style="list-style-type: none"> Once weekly bortezomib, dexamethasone with reduced lenalidomide dose of 15 mg in patients >75 years Acceptable tolerability profile
	IV vs. SQ bortezomib	Moreau P [112]	<ul style="list-style-type: none"> SQ administration of bortezomib reduces peripheral neuropathy with non-inferior efficacy
Carfilzomib	VD vs. VTD vs. VMP followed by maintenance bortezomib	UPFRONT Niesvizky [40]	<ul style="list-style-type: none"> Similar PFS and OS for all 3 regimens; VTD and VMP do not offer survival advantage over VD Adverse events most common with VTD
		CHAMPION-1 Berenson JR [41]	<ul style="list-style-type: none"> Weekly dosing schedule of carfilzomib 20 mg/m² and 70 mg/m² is safe and effective Decreases travel burden for treatment
	Once-weekly administration	ARROW Moreau P [42]	<ul style="list-style-type: none"> Once-weekly carfilzomib 70 mg/m² prolonged PFS vs twice weekly carfilzomib 27 mg/m² Toxicities equivalent May help avoid PN of bortezomib while maintaining treatment adherence
		Waxman AJ [113]	<ul style="list-style-type: none"> Incidence of all events 18.1% Incidence of grade 3 events: 8.2% Risk increased with doses 45 mg/m²
		Dimopoulos MA [114]	<ul style="list-style-type: none"> Presence of known cardiovascular disease associated with increased incidence of cardiac events No association with dose or duration of infusion
Patients with preexisting PN		Mikhael J [43]	<ul style="list-style-type: none"> Routine echocardiogram monitoring not recommended Minimize fluid administration Hold treatment in development of cardiac event, consider resuming at a lower dose
		Jakubowiak AJ [44]	<ul style="list-style-type: none"> Maximum dose of 36 mg/m² Initial treatment option for patients with preexisting PN that precludes VRd

Drug	Topic	Study	Summary
Dexamethasone	High-dose vs. low-dose	Rajkumar SV [45]	<ul style="list-style-type: none"> Lenalidomide with low-dose dexamethasone (40 mg weekly) had superior one-year survival vs. high-dose dexamethasone (160 mg weekly)
Lenalidomide	Lenalidomide at reduced dose	O'Donnell EK [111]	<ul style="list-style-type: none"> Reduced dose of 15 mg in patients >75 years old is very active Acceptable tolerability profile
	Safety in older adults	Touzeau C [46]	<ul style="list-style-type: none"> Lenalidomide is safe in patients 75 years old 50% of patients were started at a reduced dose due to poor performance status, renal dysfunction and previous cytopenias 29% required dose reduction during treatment due to cytopenias and poor performance status May be advantageous to initiate lenalidomide at a reduced dose in older adult patients
Pomalidomide	Safety in older adults	Leleu X [47]	<ul style="list-style-type: none"> ORR similar in patients >65 years old however survival slightly decreased Increased incidence of pneumonia in patients >65 years old 92% of patients >65 years old experienced a grade 3 or 4 adverse event May initiate at a reduced dose to avoid toxicity

PFS: progression-free survival; **OS:** overall survival; **VRd:** bortezomib, lenalidomide, dexamethasone; **IV:** intravenous; **SQ:** subcutaneous; **VD:** bortezomib, dexamethasone; **VTD:** bortezomib, thalidomide, dexamethasone; **VMP:** bortezomib, melphalan, prednisone; **PN:** peripheral neuropathy; **ORR:** overall response rate.

Table 4.

Stratification of venous thromboembolism risk in myeloma (modified from Palumbo, et al [60] with permission of Springer Nature).

Risk level	Risk factors	Recommended prophylaxis
Low	One or none of the following: <ul style="list-style-type: none"> • Obesity (BMI ≥ 30 kg/m²) • Previous VTE • CVC or pacemaker • Cardiac disease • Chronic renal disease • General surgery • Any anesthesia • Trauma • Use of EPO agonist • Hypercoagulable disorder • Hyperviscosity 	Aspirin 81–325 mg daily
Moderate	Two or more of the risk factors listed above	
High	<ul style="list-style-type: none"> • Administration of dexamethasone at doses ≥ 480 mg per month • Treatment with doxorubicin • Use of multiple chemotherapy agents (including dexamethasone) with or without an IMiD 	At least aspirin 81–325 mg daily; strongly consider enoxaparin 40 mg daily (or equivalent LMWH) or warfarin with INR goal 2–3 Enoxaparin 40 mg daily (or equivalent LMWH) or warfarin with INR goal 2–3

BMI: body mass index; **VTE:** venous thromboembolism; **EPO:** erythropoietin; **LMWH:** low molecular weight heparin; **INR:** international normalized ratio; **IMiD:** immunomodulatory drug (thalidomide, pomalidomide, or lenalidomide).

Table 5.

Select supportive care measures.

Prevention	Drug(s)	Outcome
Bacterial infections	Levofloxacin prophylaxis	<ul style="list-style-type: none"> Decreased febrile neutropenia [118] No increased incidence in <i>C. difficile</i>, MRSA or ESBL GmB
Antiviral prophylaxis	Acyclovir prophylaxis	<ul style="list-style-type: none"> Proteasome inhibitors associated with herpes zoster infections Administration of antiviral prophylaxis reduced risk of herpes zoster infections from 13% to 3%
	Recombinant herpes zoster vaccine	<ul style="list-style-type: none"> Immunogenicity achieved when administered 50–70 days after AHCT [123] Acceptable safety profile Applicability to practice remains unknown
Skeletal related events	Zoledronic acid Pamidronate Denosumab	<ul style="list-style-type: none"> Calcium + vitamin D may be warranted in patients with bone disease but without hypercalcemia [121] Pamidronate recommended for those with renal dysfunction (preferred bisphosphonate for patients with serum creatinine 3.0 mg/dL or estimated creatinine clearance <30 mL/min) [122] Denosumab may be considered in patients with severe renal dysfunction (may be used without dose reductions, regardless of renal function) Ensure routine dental care prior to initiation of bisphosphonates
Bleeding and thrombosis	Aspirin	<ul style="list-style-type: none"> Aspirin 81 mg–325 mg recommended for low risk patients [60] Prophylactic LMWH or full-dose warfarin with INR goal 2–3 for high risk patients Screen for and avoid any herbal supplement or medication that increases risk of bleeding (i.e. fish oil, NSAIDs) Role of DOACs unknown

MRSA: methicillin-resistant Staph. aureus; **ESBL GmB:** extended-spectrum beta-lactamase producing gram-negative bacilli; **MM:** multiple myeloma; **AHCT:** autologous hematopoietic stem-cell transplant; **LMWH:** low molecular weight heparin; **INR:** international normalized ratio; **NSAID:** non-steroidal anti-inflammatory drug; **DOAC:** direct oral anticoagulant.

Table 6.

Treatment strategies.

Patient Population	Treatment
Untreated fit but older adult	VRd-lite x4 cycles followed by AHCT and lenalidomide maintenance
Relapsed older adult but fit patient	Daratumumab based triplet regimen
Untreated older adult frail patient	Lenalidomide plus weekly dexamethasone
Relapsed vulnerable patient	Daratumumab and dexamethasone