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REVIEW

Initial Therapeutic Approaches to Patients with Multiple Myeloma

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ABSTRACT

Multiple Myeloma (MM) is part of a spectrum of plasma cell disorders that may result in end organ damage. MM is subclassified into high and standard risk based on cytogenetic and laboratory markers. The treatment of newly diagnosed multiple myeloma is constantly changing with the advent of novel therapies. Recent advances in therapies have resulted in longer time to remission and overall survival. the introduction of targeted therapy with monoclonal antibodies such as Daratumumab has improved stringent complete response to 39%. In this review, we outline the current approach to diagnosis, prognosis, and management of newly diagnosed multiple myeloma in both transplant eligible and ineligible patients

Keywords: Multiple myeloma; Therapeutic approaches

Key Summary Points

Diagnostic criteria and risk stratification for newly diagnosed MM has evolved in the recent years

Triplets with lenalidomide combined with a proteasome inhibitor or a monoclonal antibody has become the standard of care for newly diagnosed MM

Quadruplets with all these three classes appear to be highly effective

Stem cell transplant followed by maintenance is the current standard for newly diagnosed transplant eligible MM

High-risk MM requires a more individualized approach with MRD as a goal, with more intense and sustained treatment approaches

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14744313.

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INTRODUCTION

Multiple myeloma (MM) is part of a spectrum of plasma cell disorders which includes monoclonal gammopathy of undetermined significance (MGUS) and smoldering or asymptomatic MM [1]. MM accounts for 1% of all cancers and 10% of hematologic malignancies. The prevalence of MM is higher among men, those of African ancestry, and increases with age [2]. MGUS and smoldering MM can both transform to symptomatic MM. In this review, we provide a comprehensive review of recent advances in the initial management of symptomatic MM. MGUS has a low transformation rate at 1–2% per year, while smoldering MM has a 10% chance annually for the first 5 years with a subsequent reduction [3, 4]. This review was conducted in compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DIAGNOSIS OF MULTIPLE MYELOMA

Multiple myeloma (MM) is a disease caused by clonal proliferation of bone marrow plasma cells in the marrow with resulting end organ damage. Less frequently, extramedullary plasmacytoma, a collection of plasma cells, may be the only presenting feature of MM. The diagnosis of MM has been based on meeting the traditional "CRAB" criteria to include hypercalcemia, renal insufficiency, anemia, and bone disease. The International Multiple Myeloma Working Group (IMWG) added three additional criteria that can establish the diagnosis of MM by virtue of these conferring a very high risk of progression to MM in a short time: abnormal serum free light chain ratio ($\geq$100), $\geq$60% plasma cell infiltration in bone marrow, and the presence of $\geq$2 focal lesions in the bone or bone marrow [5].

MM is always preceded by monoclonal gammopathy of undetermined significance (MGUS), although it is recognized clinically in only a small proportion of patients prior to the diagnosis of MM. This asymptomatic disease state is characterized by low levels of serum M protein and the presence of monoclonal plasma cells without concomitant end organ damage. The rate of progression of MGUS to MM is roughly 1% per year, it remains constant over time, and most patients with MGUS can be managed by observation alone [6]. Some patients with MGUS may progress to an intermediate phase of smoldering MM (SMM) characterized by higher levels of M protein and monoclonal plasma cells when compared to MGUS. The yearly rate of progression from SMM to MM during the first 5 years of diagnosis is 10%, decreasing to $\sim$3% per year for the next 5 years, and approximating the same risk as MGUS after that. At this stage, it is important to identify patients at higher risk for progression to implement close follow-up and enrollment in clinical trials aimed at slowing the rate of progression to overt MM [7].

APPROACH TO INITIAL THERAPY

Currently, treatment is only indicated for patients with symptomatic MM. Patients with SMM are typically monitored closely, without treatment, for signs of progression to MM. Recent studies suggest a benefit for therapeutic intervention in patients with high-risk SMM. Patients in this stage of the disease can be reviewed for eligibility to be enrolled in clinical trials, especially if at higher risk for progression [7]. Upon the initial diagnosis of MM, patients are typically assessed for eligibility for autologous stem cell transplant given the benefit seen with this approach in eligible patients. Transplant eligibility may vary across healthcare settings. Generally, patients younger than 65 years of age with no significant comorbidities have been included in phase 3 trials evaluating the benefit of ASCT, but several studies have shown that older patients with good performance status may derive equivalent benefit. Other exclusion criteria include significant organ dysfunction or poor functional status. Historically, this approach has been driven by the potential impact on initial therapy, such as alkylating agents on the ability to collect stem

cells. Given that the newer therapies have less effect on the stem cell collection, this decision can potentially be delayed until after initial control of the disease, which may also lead to an improved performance status and improvement in renal function. This has led to a convergence of the initial approaches of myeloma irrespective of the transplant eligibility. Induction therapy is typically composed of multidrug regimens and is designed to rapidly reduce tumor burden. Specific regimen choice is guided by cytogenetic abnormalities, patient renal function, and functional status, among other characteristics [8]. For transplant-ineligible patients, the treatment regimen can be guided by clinical algorithms that factor in age, comorbidities, the activities of daily living, and instrumental activities of daily living to reliably predict survival and toxicity for various treatment regimens [9].

RISK STRATIFICATION

MM is a heterogenous disease with a spectrum of clinical behavior that ranges from an indolent course to an extremely aggressive malignancy associated with poor outcome, a pattern that is often driven by the complement of genetic abnormalities in any given patient. Although the prognosis of patients with MM is dependent on multiple factors, genetic abnormalities seem to be the primary driver of disease progression [10, 11]. With the advancement of available therapies, identification of genetic abnormalities increasingly allows for individualized and targeted therapy [12]. The three most widely used risk stratification models are the Mayo Stratification and Risk Adapted Therapy (mSMART), the IMWG, and the Intergroupe Francais Du Myleome (IFM) risk models. All three prognostic schemes utilize the presence of cytogenetic abnormalities for stratification. In addition to cytogenetics, the IMWG consensus utilizes the Revised International Staging System (RISS) as an additional prognostic schema outlined in Table 1 [13]. The RISS was created in response to criticisms due to the lack of incorporation of other known prognostic markers, such as cytogenetics and the lactate dehydrogenase level (LDH). mSMART, another

Table 1 Revised international staging system for myeloma

Stage I
All of the following:
Serum albumin $\geq$ 3.5 gm/dL
Serum β-2-microglobulin $<$ 3.5 mg/L
No high-risk cytogenetics
Normal serum LDH
Stage II
Not fitting into stages I or III
Stage III
Both of the following:
Serum β-2-microglobulin $>$ 5.5 mg/L
High-risk cytogenetics [*t*(4;14), *t*(14;16), or del(17p)] or elevated serum LDH

Table 2 mSMART risk stratification

Standard risk
Trisomies
t(11;14)
t(6;14)
Intermediate risk
t(4;14)
Gain(1q)
High risk
t(14;16)
t(14;20)
Del(17p)
TP53 mutation
High-risk GEP signature
R-ISS stage III
High plasma cell S-phase

prognosticator schema, is the outlier in that it does not utilize traditional non-genetic prognostic systems such as the RISS, but rather gene expression profiles (GEP) and plasma cell proliferative rate in addition to cytogenetics (Table 2) [8].

MM can be subdivided into two cytogenetic groups: hyperdiploid and non-hyperdiploid [14]. Hyperdiploid MM (H-MM) is characterized by trisomies of odd numbered chromosomes with the exception of 13. Roughly 50% of patients with MM present with H-MM when analyzed by fluorescence in situ hybridization. H-MM is associated with response durability to various treatments and longer overall survival (OS). Although H-MM is associated with better prognosis, there is heterogeneity within this group, with some molecular phenotypes conferring worse outcomes. A subgroup of H-MM has been shown to include high expression of cancer testis antigen (CTA) genes *CTAG, SSX, GAGE*, and *MAGE* families) and mitosis/proliferation-related genes (*TOP2A, NEK, ASPM*, and *CENPA*), with this subset having high proliferative rates and worse overall survival [14, 15]. The second cytogenetic group, non-hyperdiploid MM (NH-MM), is characterized by a high frequency of IgH translocations. These IgH translocations are frequently partnered with oncogenes, such as 11q13 (Cyclin D1), 12p13 (Cyclin D2), 6p21 (cyclin D3), 4p16 (MMSET/FGRF3), and 16p23, 20q12, and 8q24 (MAF, MAFB, and MAFA, respectively) [16, 17]. Classification of disease as NH-MM confers a worse prognosis and decreased OS when compared to H-MM. Additional poor prognostic cytogenetic abnormalities include deletion of chromosome 13, which is associated with NH-MM, but may also be a poor prognostic marker independent of this association [18]. Other poor prognostic factors include *t*(4;14), *t*(14;16), and del 17p [8]. Deletion of 17p occurs in roughly 10% of newly diagnosed MM (NDMM) and negatively impacts OS and progression-free survival likely due to the loss of the tumor suppressor gene *TP53* [19].

TREATMENT OF TRANSPLANT INELIGIBLE PATIENTS

Historically, non-ASCT candidates have been treated with melphalan-prednisone (MP) combined with thalidomide (MPT) or bortezomib (VMP). Several phase III clinical trials have supported the efficacy of triple regimens over MP therapy alone [20, 21]. Along with MPT and melphelan-prednisone-lenalidomide (MPR), continuous R-dexamethasone (Rd) has proven to be part of the standard of care. A phase III clinical trial comparing continuous Rd, Rd18 (72 weeks), and MPT for 72 weeks found a statistically significant difference between continuous Rd and MPT for PFS and OS. The continuous Rd treatment arm had a median PFS of 26.0 compared to 21.9 months for the MPT arm. PFS was similarly extended when comparing continuous Rd versus Rd18. Median OS was increased by 10 months in the continuous Rd arm versus MPT [22]. Addition of bortezomib (V) to continuous Rd in a phase III clinical trial has also shown a benefit in PFS and OS in newly diagnosed MM that were not considered for early transplant. VRd significantly improved median PFS (43 vs. 30 months in the Rd group) and median OS (75 vs. 64 months in the Rd group) [23]. Although this study shows promise for treatment of transplant ineligible NDMM, it is important to note that the majority of patients (57%) included in this trial were < 65 years old. The limited number of patients who were more than 65 years of age may limit the prognostic utility demonstrated in this trial for this age group. A recently published follow-up analysis of the SWOG SO777 trial has furthered solidified VRd as an effective treatment option for treatment ineligible NDMM. In this update, the median PFS and OS in the VRd cohort were significantly higher when compared to the Rd arm [24]. Recently, the CD38 monoclonal antibody, daratumumab, has shown efficacy in the treatment of transplant ineligible NDMM. A phase III clinical trial assessed the efficacy of nine cycles of VMP with daratumumab (D-VMP) versus VMP alone in patients who are deemed ineligible for stem cell transplantation. At the median follow-up of

16.5 months, the D-VMP had superior rates of 18 month PFS of 71.6% compared to the VMP group, which was at 50.2%. Secondary end points of this trial showed significant improvements in overall response rate, which was 90.9% in the D-VMP group compared to 73.9 with VMP alone ($p < 0.0010$). Complete response rate was also significantly improved in the D-VMP group at 42.6% versus 24.4% ($p < 0.001$). This response was maintained in patients greater than 75 years of age with poor organ function and higher ISS stage. Patients with high-risk cytogenetics benefited less than those with standard risk [25]. An updated analysis on this clinical trial showed continued responses in the D-VMP group. A higher rate of grade 3–4 infections was noted in the D-VMP group versus VMP alone (25.1 vs. 14.7). Although there was a higher rate of infection in the daratumumab group treatment, discontinuation was only seen in a small number of patients [26]. Since Rd has been a standard treatment for transplant ineligible NDMM, a phase III clinical trial (MAIA) evaluated the clinical efficacy of DRd compared to Rd among 737 patients with NDMM who were ineligible for ASCT. At a median follow-up of 30 months, the PFS rate was 70.6% in the daratumumab group versus 55.6% in the control group [hazard ratio (HR) of 0.56; 95% confidence interval (CI) 0.43–0.73; $P < 0.001$]. Complete response rates doubled, and patients negative for minimal residual disease were threefold higher in the daratumumab group. These results were only seen in the subgroup of patients with standard-risk cytogenetics. Progression-free survival was not as high in the subgroup of patients that had high risk cytogenetics [27]. A phase III Clarion study compared carfilzomib-melphalan-prednisone (KMP) with bortezomib-melphalan-prednisone (VMP) in transplant ineligible NDMM. No significant difference was found when comparing PFS (22.3 vs. 22.1 months) in the KMP and VMP groups, respectively (HR 0.906; 95% CI 0.746–1.101; $p = 0.159$). Median OS, ORR, and CRR were also not significantly altered [28]. Carfilzomib was also tested in combination with lenalidomide and dexamethase (KRd) in the phase III ENDURANCE trial. KRd was compared to VRd as initial therapy for NDMM. The trial was stopped early due to futility. Median PFS was 34.6 and 34.4 months in the KRd and VRd arms, respectively. The 3-year OS was also not significantly affected. Furthermore, KRd was associated with higher rates of cardio-pulmonary and renal toxicities [29]. Other drugs, such as ixazomib and elotuzumab, have also been studied in combination with Rd in the TOURMALINE-MM2 and ELOQUENT-1 phase III trials, respectively. Both trials failed to demonstrate statistical improvement in median PFS, therefore not reaching their primary end points [30, 31]. The results of the phase 3 trials in MM are summarized in Table 3.

TRANSPLANT ELIGIBLE—INITIAL THERAPY

The cornerstone of initial therapy over the past decade for patients with transplant-eligible NDMM has been regimens containing lenalidomide or bortezomib. The IFM 2005-01 phase III trial enrolled 482 patients to assess the efficacy of bortezomib plus dexamethasone compared with vincristine, doxorubicin, and dexamethasone (VAD) as induction therapy before stem cell transplantation. The bortezomib-containing group was found to have significantly higher CR/nCR (14.8 vs. 6.4%), VGPR, (37.7 vs. 15.1%), and overall response (78.5 vs. 62.8%) rates [32]. In a separate trial testing the efficacy of the bortezomib plus dexamethasone treatment regimen, cytogenetics appeared to play a role in the outcomes with treatment. Patients with $t(4;14)$ were found to have improved prognosis with bortezomib/dexamethasone versus VAD. Event-free survival (EFS) in the bortezomib/dexamethasone cohort was 28 months versus 16 months for VAD and 4-years OS was 63% versus 32%, respectively ($p < 0.001$). Del(17p) patients saw no difference between the treatment arms [33]. Addition of bortezomib to a chemotherapy regimen can further improve outcomes. In the Total Therapy 3 trial, VTD (bortezomib, thalidomide, and dexamethasone) was added to PACE (cisplatin, doxorubicin, cyclophosphamide, and etoposide). At 24 months, 83% patients undergoing

Table 3 Phase III randomized trials for transplant non-eligible NDMM[a]

Trial	Primary outcome	Enrolled patients	Treatment	Median PFS	Median OS	CR rate	Median follow-up
Facon 2018	PFS	1623	Continuous Rd	26.0	59.1	22%	67
FIRST trial				21.0	62.3	20%	
			Rd MPT	21.9	49.1	12%	
Durie 2017	PFS	525	VRd	43.0	75.0	16%	55
SWOG-SO777			Rd	30.0	64.0	8%	
Durie 2020	PFS	460	VRd	41.0	N/R	24.2%	84
SWOG-SO777			Rd	29.0	69.0	12.1%	
Mateos 2018	PFS	706	D-VMP	71.6%[b]	N/R	42.6%	16.5
ALCYONE			VMP	50.2%[b]	N/R	24.4%	
Dimopoulous 2018 Updated ALCYONE	PFS	706	D-VMP	N/R	N/R	45.1%	27.8
			VMP	19.1	N/R	25.3%	
Facon 2019	PFS	737	DRd	N/R	N/R	46.7%	28.0
MAIA			Rd	31.9	N/R	24.9%	
Facon 2019	PFS	955	KMP	22.3	N/R	25.9%	22
CLARION			VMP	22.1	N/R	23.1%	
Kumar 2020	PFS	1087	KRd	34.6	86%[c]	N/A	N/A
ENDURANCE			VRd	34.4	84%[c]	N/A	N/A

N/R not reached
[a] All time periods are listed in months
[b] 18 month PFS rate
[c] 3-year OS rate

the treatment regimen achieved nCR, while at a median follow-up of 20 months EFS and OS were 84% and 86%, respectively. Results of this study showed that bortezomib can be effectively incorporated into chemotherapy-containing treatments [34].

Lenalidomide/dexamethasone combinations have proven to be effective in this group as pre-transplant induction. Combination of lenalidomide and high-dose dexamethasone (HD) versus HD alone was shown to be efficacious in treating NDMM. In the SWOG Trial, Zonder et al. [35] showed that the double regimen of Len + HD is superior to HD in ORR (85.3 vs. 51.3%), PFS (77 vs. 55%), and major response rate. Similar to bortezomib, lenalidomide has been used in combination with cyclophosphamide (RCd) as initial therapy. In a phase II study, RCd treatment regimen showed an ORR of 85%, including a 32% VGPR. Myelosuppression was a significant toxicity which led to decreased doses of cyclophosphamide. This decreased dose did not seem to hinder the responses [36].

Table 4 Phase III randomized trials for treatment eligible NDMM

Trial	Primary outcome	Enrolled patients	Treatment	Median PFS	Median OS	CR rate	Median follow-up
Harousseau 2010	CR/nCR	482	VAD	29.7	N/R	6.4%[a]	32.2
IFM 2005–01			Rd	36.0	N/R	14.8%[a]	
Zonder 2010	PFS	198	RD	52%[b]	79%[c]	N/A	47.2
S0232			High dose Dex	32%[b]	73%[c]	N/A	
Cavo 2010	CR/nCR	480	VTD	68%[5]	86%[e]	19%	36
NCT01134484			TD	56%[5]	84%[e]	5%	
Moreau 2019	sCR after 100 days	1085	D-VTD	N/R	N/R	39%	18.8
CASSIOPEA			VTD	N/R	N/R	26%	
Voorhees 2020	sCR	207	D-RVd	95.8%[d]	N/R	79.8%	22.1
GRIFFIN			RVd	89.8%[d]	N/R	60.8%	

[a] Post-induction CR/nCR rates
[b] 3-year PFS rate
[c] 3-year OS rate
[d] 2-year PFS rate
[e] Estimated 3-year rate of PFS or OS

Based on this evidence, triple drug regimens have been developed and are the current standard of care for ASCT-eligible NDMM. A phase III study enrolled 480 patients to test the efficacy and safety of bortezomib in addition to thalidomide/dexamethasone (VTD) compared to TD alone. CR or nCR was recorded in 31% of VTD patients versus 11% of TD ($p < 0.0001$). The VTD treatment arm also saw significantly increased grade 3 or 4 adverse events (56% vs. 33%; respectively) with peripherally neuropathy having a higher occurrence in VTD patients [37]. Bortezomib + lenalidomide + dexamethasone (VRd) in phase III trials has shown a CR of 33.4% in the standard-risk population and 34.8% in those with high-risk cytogenetics. VGPR also significantly increased by 66.6% and 70.7% in the standard- and high-risk cytogenetics, respectively, after induction therapy was finished. Minimal residual disease (MRD) after induction therapy was 28.8%. Depth of responses deepened over time, with greater efficacy being shown over induction cycles, ASCT, and consolidation. VRD was well tolerated with a low frequency of grade 3 (3.7%) or grade 4 (0.2) events. The most common grade 3 events noted were neutropenia (2.9%) and infection (9.2). These treatment-emergent adverse events led to discontinuation in 3.1% of enrolled patients [38]. VRd therapy, when compared to other commonly used triplet therapies, provides superior response rates. Kumar et al. [39], compared the efficacy of VRd to bortezomib, cyclophosphamide, and dexamethasone (VCd). Greater CR (35.4 vs. 18.3%) and VGPR rates (61.5 vs. 48.3%) were seen in VRd patients when compared to VCd with no significant differences in peripheral neuropathy and hematologic toxicity ratio (HR 0.906; 95% CI 0.746–1.101; $p = 0.159$). Median OS, ORR, and CRR were also not significantly altered.

The introduction of the monoclonal antibody, daratumumab, targeted against CD38 on the myeloma cell opened up the possibility of adding yet another class of drug to the upfront combinations. It has been tested in addition to VTd (D-VTd) as a quadruplet therapy in the phase III CASSIOPEIA clinical trial. DVT-d was compared to VTd alone with a primary end point of stringent CR (sCR) at 100 days post-transplantation. At 100 days, the D-VTd group showed increased rates of sCR compared to VTd alone, 29 vs, 20%, respectively [odds ratio (OR): 1.60, 1.21–2.12; $p = 0.0010$]. CR, VGPR, and MRD rates were all superior in the DVT-d cohort ($p < 0.0001$). Although high-risk and standard-risk patients both demonstrated benefit in MRD and median PFS, D-VTd patients with high-risk cytogenetics showed lower odds of achieving sCR compared to their standard-risk counterparts [40]. D-VRd has shown initial safety and efficacy reports in the randomized phase II GRIFFIN study. Sixteen patients participated in this trial and all achieved VGPR and 63% reached CR after consolidation. At median follow-up of 15.6 months, 15 patients had not seen disease progression. Furthermore, adverse effects did not lead to any deaths or treatment discontinuations [41]. Updated results from the GRIFFIN trial ($n = 207$) showed increased rates of sCR in the D-RVd versus RVd (42.4 vs. 32.0%, respectively) at the end of post-ASCT consolidation. The depth of the response was also increased at the median follow-up of 22.1 months. sCR at follow-up was 62.6% in the D-RVd group and 45.4% in the RVd group [42]. These results show promise for other ongoing trials, such as the PERSEUS phase III trial that is also testing the efficacy of D-VRd compared to VRd alone in NDMM [43]. Summary of the trials mentioned within this section are outlined in Table 4.

AUTOLOGOUS STEM CELL TRANSPLANTATION

With the advent of highly efficacious regimens for NDMM, the use of ASCT as initial treatment modality has been the subject of debate mainly due to its significant associated toxicities. Several phase III clinical trials have confirmed that treatment regimens that include ASCT demonstrated greater PFS and OS versus patients who do not receive this modality. Survival benefit is seen when ASCT is added to chemotherapy or more contemporary regimens [44]. Furthermore, the safety of ASCT, particularly at experienced centers, has been vastly improved with treatment-related mortality being less than 1% [45]. Given the proven efficacy of ASCT, as well as advancements in treatment safety, ASCT is considered as a primary therapeutic modality for NDMM for patients eligible to undergo the procedure. The debate regarding ASCT has shifted to the optimal timing of this intervention. ASCT can be performed as part of initial therapy or at the time of the first relapse. Various trials have been conducted to assess the optimal timing of ASCT. Multiple well-conducted trials have shown that OS is unaffected by the timing of ASCT therapy. Although OS did not show a significant difference between immediate or delayed ASCT, PFS was longer if ASCT was part of initial therapy as well as increased rates of MRD negativity [46, 47].

Whether ASCT has been chosen to be done upfront or at the time of relapse, mobilization of hematopoietic stem cells is essential. Currently, the two widely used regimens are steady-state mobilization with use of plerixafor or high-dose cyclophosphamide plus granulocyte colony stimulating factor (G-CSF). One retrospective study showed that the use chemotherapy in addition to G-CSF produced a greater mobilizing effect than either chemotherapy or G-CSF alone [48]. The most common chemotherapy plus G-CSF combination is cyclophosphamide in addition to filgrastim or lenograstim [49]. The advent of lenalidomide and its increasing use as part of induction therapy has proven to negatively affect stem cell mobilization success rates. The myelosuppressive effects of lenalidomide are thought to act through the upregulation of chemokine receptor 4 (CXCR4) and the increase of the binding of stem cells to the stroma [50, 51]. A randomized phase II clinical trial compared low-dose cyclophosphamide plus G-CSF versus G-CSF alone as mobilization regimens in patients pre-

treated with regimens containing lenalidomide. The results showed that combination treatment of chemotherapy with G-CSF was superior to G-CSF alone. The yield of 3×10^6 kg CD34 + cells in 1–2 apheresis was 94% with chemotherapy with G-CSF and 77% with G-CSF alone [52]. Plerixafor, a CXCR4 antagonist, has also shown efficacy in improving success of mobilization in both patients who have received lenalidomide pre-treatment and those who had not when used in combination of G-CSF. A phase III clinical trial compared the efficacy of plerixafor plus G-CSF or placebo pulse G-CSF. The primary end point was set to be collection of 6×10^6 CD34 + cells/kg in 2 or less apheresis. As many as 71.6% of the plerixafor group reached this primary end point, while 34.4% of the placebo group met the criteria ($p < 0.001$) [53]. In patients treated with lenalidomide, a retrospective study found that the minimum number of CD34 + cells necessary for collection (2×10^6 cells/kg) were collected in 86.7% of patients in a median of 1 day when treated with plerixafor plus G-CSF [54]. A second study, confirming the beneficial impact of plerixafor plus G-CSF, demonstrated that 69% of patients previously treated with lenalidomide underwent successful mobilization and reached the minimum of 2.0×10^6 cells/kg in a median time of 2 days [55].

CONDITIONING REGIMEN

Intravenous high-dose melphalan (HIM) at a dose of 200 mg/m^2 has been the most widely used conditioning regimen prior to ASCT. Various clinical trials that have assessed the added value of increased doses of melphalan or used HDM in combination with bortezomib have not shown improved OS rates [56]. Ongoing studies are currently investigating the benefit of adding bendamustine in conditioning regimens. A phase II clinical trial enrolling 18 patients with NDMM and 17 patients with relapsed or refractory MM (RRMM) evaluated a primary end point of CR at 100 days and found that 51% of patients met the design criteria. Median PFS was also measured with the NDMM and RRMM, averaging 48 and 45 months, respectively [57]. Bendamustine and HIM has shown promising outcomes in the depth of response and PFS, and further studies are warranted.

Busulfan plus melphalan have offered additional benefit when compared to melphalan alone. A phase III clinical trial that enrolled 205 patients found that those who were placed on a busulfan plus melphalan conditioning regiment prior to ASCT had a longer PFS when compared to melphalan alone. Median PFS for the busulfan plus melphalan was 64.7 months versus 43.5 months in the melphalan-only group. OS was not significantly affected between the two groups [58]. This study confirmed the findings of a previous trial that looked at the efficacy of oral busulfan plus melphalan versus melphalan alone in patients enrolled in the GEM2000 study undergoing ASCT. In addition, median PFS was increased in the busulfan plus melphalan group when compared to melphalan alone (41 vs. 31 months, respectively). Although the median PFS was increased in the busulfan plus melphalan group, there was no difference in OS in this study. This may be in part due to the increased risk of veno-occlusive disease seen in patients receiving busulfan plus melphalan [59].

CONSOLIDATION THERAPY

In patients with positive outcomes after ASCT, consolidation therapy has been shown to increase the CR rates and molecular remission (MR). Achievement of MR is associated with increased PFS [60]. A randomized phase III GIMEMA-MMY-3006 study evaluated the response to VTD versus TD as induction therapy and consolidation therapy after double ASCT. The initial analysis done at a median of 36 months showed VTD has superior CR/nCR and longer median PFS than TD. An updated analysis done at a median of 59 months maintained the improvement in CR/nCR and PFS seen in the VTD arm. It is important to note that the benefits were sustained through both standard- and high-risk subgroups [61]. Studies have also shown that VRD is an effective consolidation regimen. The IFM conducted a study testing two cycles of VRD as consolidation after

receiving induction using VRD and ASCT. VGPR after induction, transplantation, and consolidation were 58%,70%, and 87%, respectively. 58% of patients achieved CR and 68% were MRD negative. None of the patients that achieved MRD negativity had relapsed at the median follow-up of 39 months [62]. Phase III EMN02/HO95 trial's second randomization phase tested the effects of two cycles of VRD consolidation plus lenalidomide maintenance versus lenalidomide maintenance alone. The VRD arm showed significant advantages in prolonging PFS in those with low-risk cytogenetics. The benefits of consolidation therapy were not retained in patients with high-risk cytogenetics (del(17p) and/or *t*(4;14) and/or *t*(14;16) [56]. More recently, the BMT CTN 0702 trial, showed that consolidation with a second ASCT or RVD does not improve PFS or OS when compared to ASCT plus lenalidomide maintenance. No significant differences were noted in PFS, OS, or CR between the ASCT plus lenalidomide, tandem ASCT plus lenalidomide, and ASCT plus VRD and lenalidomide maintenance [63].

MAINTENANCE THERAPY

Although MM is well managed with upfront multidrug therapy and ASCT, these interventions are not curative, and the disease is likely to progress and relapse. Thus, ideal maintenance therapy should be added to prolong PFS and OS with the safest toxicity profile. A meta-analysis that included three RCTs (Cancer and Leukemia Group B 100104, Gruppo Italiano Malattie Ematologiche dell'Adulto RV-MM-PI-209, and Intergroupe Francophone du Myélome 2005-02) studied the effects of lenalidomide maintenance post-ASCT versus placebo or observation in NDMM. The study found that median PFS in the lenalidomide arm was increased compared with the control group, 52.8 versus 23.5 months. respectively (HR 0.48; 95% CI 0.41–0.55). OS was also beneficially impacted with addition of lenalidomide. Median OS was not reached in the lenalidomide group and was 86 months in the placebo or observation groups [64]. The OS benefit was less pronounced in patients greater than 60 years of age and in women. Of important note, PFS but not OS was impacted by lenalidomide maintenance in those with high-risk cytogenetics, although this may be due to the small number of patients presenting with the high-risk cytogenetics [64]. A separate phase III myeloma XI found that all cytogenetic subgroups demonstrated improved PFS when given lenalidomide maintenance [65]. The major concern with lenalidomide maintenance is the increased likelihood of secondary primary malignancy (SPM) [64, 65]. Analysis of the 2732 patients enrolled in the Myeloma XI trial found SPM to be present in 3.8% of patients after 3 years. Age was strongly correlated as a predisposing risk factor for developing SPM. In transplant non-eligible patients greater than 74 years old, the lenalidomide group had a 17.3% cumulative incidence after 3 years compared to 6.5% in the observation only group. Although SPM incidence was increased, death as a consequence was very low and survival benefit outweighed the risk [66].

Unlike lenalidomide, bortezomib has not been shown to improve PFS compared to observation in prospective phase 3 trials, but has been suggested to benefit those with high-risk cytogenetics, in whom bortezomib increased PFS from 16 to 27 months when compared to observation in a retrospective study. One possible benefit to bortezomib over lenalidomide was that discontinuation due to toxicity was 7% and 17%, respectively [67]. A phase III HOVON-65/GMMG-HD4 trial investigated the efficacy of bortezomib during induction and maintenance. Participants were split into two groups and received induction therapy with VAD or bortezomib, doxorubicin, and dexamethasone (PAD). ASCT was performed for both groups followed by maintenance in which the VAD group was given thalidomide and the PAD group was given bortezomib. Patients receiving bortezomib as part of induction and maintenance demonstrated better OS, PFS, and CR. Bortezomib-included regimens were again seen to provide survival benefit to those with high-risk cytogenetics [68]. Although bortezomib has shown promise as a post-ASCT therapy, parenteral administration provides an

obstacle for many. An oral proteasome inhibitor, ixazomib, has been tested as a maintenance therapy in a phase III TOURMALINE-MM3 trial for those with NDMM. Ixazomib when compared to placebo showed a 39% improvement in PFS and a 28% reduction in risk of progression/death. Deeper responses and greater conversion to MRD negativity were seen in the ixazomib arm versus placebo. These benefits were maintained over all subgroups of patients. Furthermore, the rate of SPM was not increased between treatment arms (3% in both) [69]. Ixazomib has also been tested in phase I/II trials as maintenance therapy for transplant-ineligible MM. Ixazomib has demonstrated deepening of response as well as positive safety profiles in this cohort of patients [70].

TREATMENT APPROACH—HIGH-RISK CYTOGENETICS

Patients with high-risk cytogenetics have a worse prognosis with shorter PFS and OS. The data seem to support that combining proteasome inhibitors and lenalidomide improves the outcomes among those with high risk (HR) cytogenetics. Bortezomib-based induction regimens have gained popularity due to multiple studies supporting the benefits to PFS, OS, and CR rates in transplant-eligible patients. A meta-analysis of four randomized clinical trials found that CR and nCR post-transplantation in bortezomib-treated patients was the same for both high- (del(17p) and *t*(4;14) and standard-risk (SR) cytogenetics [38]. More recently, the PETHEMA/GEM2012 trial found that patients with HR cytogenetics treated with 6 cycles of VRD followed by ASCT had CR similar to those with SR cytogenetics (34.8% and 33.4%, respectively). Median PFS was not reached in both HR and SR subgroups at the time of follow-up [38]. In a study comparing VTD to TD as induction therapy prior to double ASCT patients with *t*(14;4) had a much greater increase in OS when placed on VTD. OS in the HR group was 69% when on VTD versus 37% when placed on TD [37]. For non-transplant-eligible patients there are very few data. One phase III study, conducted by the GIMEMA group, suggests that VMP may restore PFS for those with HR cytogenetics, while other groups, such as IFM and PETHNA, have found no benefit to bortezomib-based regimens [71–73].

In transplant-eligible patients, HDT + ASCT contributes to improved outcomes across cytogenetic groups. Those with HR MM may gain further benefit from a second ASCT. A meta-analysis of four European trials found that double ASCT following bortezomib-based induction was able to partially mitigate poor PFS with patients who have multiple adverse variables. Additionally, this trial found that double ASCT may be most beneficial to those who failed CR after exposure to induction therapy with bortezomib [74].

Maintenance/and or consolidation therapy with bortezomib has been found to reduce the risk associated with both HR cytogenetics del(17p) and *t*(4;14). The HOVON-65/GMMG-HD4 trial patients with *t*(14;4) who received bortezomib therapy post-tandem ASCT had prolonged PFS and OS compared to the group who received thalidomide maintenance. Five-year PFS was 16% in the bortezomib group and 8% in the thalidomide group. Similarly, 5-year OS was 52% and 33% in the bortezomib and thalidomide cohorts, respectively. Patients with del(17p) also saw a benefit to 5 years OS. In this cohort, the bortezomib group had a 5-year OS of 65% versus 18% for the thalidomide arm [75]. The GIMEMA MM-BO2005 trial supported the use of bortezomib as consolidation/maintenance in HR MM. In this phase III trial, patients were randomized to receive either VTD or TD as consolidation therapy post-tandem ASCT. In the VTD group, the 3-year PFS was similar (69 vs. 74%) between patients with and without the *t*(4;14) cytogenetic abnormality. The TD group did not see the increase in PFS for those with HR MM. The 3-year PFS for those on TD with t(4;14) was 37% versus 63% for SR patients [76]. Ixazomib, an oral PI, has also shown promise in prolonging PFS in those with HR MM. A phase II study tested the efficacy of lenalidomide plus ixazomib as maintenance therapy post-ASCT. Both SR and HR patients had not reached median PFS at median follow-up of 37.8 months [77]. The phase III TOURMALINE-MM3 trial confirmed the benefit of ixazomib as

maintenance therapy for HR MM. For patients with high cytogenetic risk the percentage of patients reaching PFS at 24 months was significantly higher at 46% vs. 24% in the placebo group [78]. Future maintenance therapies involving ixazomib should be investigated, particularly for its utility for patients with high-risk cytogenetics.

TREATMENT APPROACH—FRAIL PATIENTS

With MM being a disease predominantly seen in older individuals, it is important to assess the frailty of the patient, as this may significantly affect treatment strategy and toxicities. Assessment tools, such as the IMWG geriatric assessment, the Initial Myeloma Comorbidity Index, and the Revised Myeloma Comorbidity Index, are imperative to use throughout the course of treatment to continue to gauge risk and to tailor treatment for high-risk patients [79]. A major factor in the treatment of MM patients that affects frailty is drug toxicity. A meta-analysis by Brighen et al. [80] found that drug discontinuation due to toxicity or adverse events (AEs) was associated with a shorter survival, highlighting the need for a reduced dose intensity treatment strategy in this subset of patients at risk for drug toxicity [81]. With this in mind, minimizing the dose and the number of drugs may increase the duration of treatment. Treatment using triplet lenalidomide drug regimens, MPR and cyclophosphamide-prednisone-lenalidomide was compared to doublet therapy using Rd for transplant-ineligible NDMM. Rd therapy was non-inferior to the alkylator-including regimens when looking at median PFS and 4-year OS, while boasting decreased toxicity [82]. Doublet therapy using bortezomib also showed non-inferiority when compared to bortezomib-based triplet therapies. The phase IIIB UPRONT trial compared VD, VTD, and VMP and found non-significant differences in the median PFS which were 14.7, 15.4, and 17.3 months, respectively. Differences in median OS were also non-significant with VD, VTD, and VMP, being 49.8, 51.5, and 53.5 months, respectively. VD and VMP were also found to have less AEs than treatment with VTD. Although the UPFRONT trial did not specifically target frail patients, it showed that bortezomib-containing doublet therapy is a non-inferior treatment option compared to bortezomib-containing triplet regimens. Additional benefit to doublet therapy includes increased patient quality of life scores, which is of importance in frail patients. Single-agent bortezomib was additionally used as maintenance with limited additional toxicity and maintained responses in 89% of patients [83]. Drug regimens used in younger, fitter patients may also be modified to be used in older, more frail patients. An RVD drug regimen (RVD-lite) was designed to maintain efficacy while decreasing toxicities. A phase II trial tested the efficacy of RVD-lite in transplant-ineligible NDMM and found robust benefits to PFS (41.9 months) and median OS not reached at median follow-up at 61.9 months. More importantly, the rate of discontinuation due to drug toxicity was 4% [84]. Bortezomib-based regimens may also be able to overcome adverse prognosis in patients with *t*(4;14) and del(17p) [85]. It is also important to note that older patients tend to have worse outcomes and greater toxicity when given high-dose dexamethasone. Low-dose dexamethasone or prednisone should be considered if appropriate [86, 87]

SUPPORTIVE CARE

Risk of venous thromboembolism (VTE) is known to be increased due to certain disease- and treatment-related factors. Both immunomodulators and high-dose dexamethasone have shown thrombotic potential in MM [88]. VTE risk assessment has long been used to guide treatment for thromboprophylaxis. The IMWG guidelines advise the use of aspirin in low VTE-risk patients and low molecular weight heparin (LMWH) if multiple risk factors are present [89]. Both aspirin and LMWH have been shown to decrease VTE rates in those with MM, with the latter being more efficacious [89]. Direct oral anti coagulants (DOAC) are now being tested as thromboprophylaxis and are looked upon favorably due to

oral administration and no required blood monitoring. A phase II study was conducted to test the efficacy of apixaban in MM patients treated with immunomodulatory compounds. Of the 104 enrolled patients, there were two recorded venous or arterial thrombotic events in addition to one major and eleven clinically-relevant non-major bleeds [90]. More studies are necessary to further test the efficacy of DOACs, especially compared to the standard of care (LMWH).

MM patients are at an increased risk for both bacterial and viral infections, a major cause mortality in this patient population. Patients diagnosed with MM have a sevenfold increase in developing an infection compared to matched controls. Furthermore, infection was the underlying cause in 22% of MM deaths at 1 year follow-up in a single retrospective study [91]. A phase III trial enrolling 977 patients aimed to assess the efficacy of antibiotic prophylaxis to prevent infection in NDMM. One group received 500 mg levofloxacin daily for 12 weeks, while the other received placebo. In the levofloxacin group, 19% of patients had a first febrile episode or death versus 27% in the placebo group (HR 0·66, 95% CI 0·51–0·86). Furthermore, there was no increase in health care-associated infections [92]. These findings suggest that levofloxacin may be an effective prophylactic strategy which is associated with a reduced risk of bacterial infections in patients undergoing anti-myeloma therapy. Antiviral prophylactic therapy may also be beneficial in patients receiving VAD therapy, high-dose dexamethasone, or bortezomib-based regimens due to increased risk of reactivation or newly acquired herpetic infection [93]. Acyclovir has shown a beneficial effect in the mitigation of herpes zoster infections during the course of treatment. Two separate studies have shown that, with the use of acyclovir and the adherence to the drug schedule, the risk of herpes infection was significantly reduced [91, 94].

A vast majority of MM patients develop osteolytic lesions during the course of the disease, and these may produce significant pain and decreased quality of life. Intravenous bisphosphate therapy (BPT) therapy such as pamidronate or zoledronic acid (ZA) are recommended during symptomatic disease due to their efficacy in various randomized trials, which demonstrated a decrease in skeletal-related events, less bone pain, and increased quality of life when patients were placed on BPT [95]. The monoclonal antibody denosumab, a RANK-L inhibitor, has been tested in a phase III trial to test its efficacy in comparison to ZA for the treatment of bone disease in NDMM. The study found denosumab to be non-inferior to ZA in time to first skeletal related event (hazard ratio 0·98, 95% CI 0·85–1·14; $p_{\text{non-inferiority}} = 0{\cdot}010$) [96]. Denosumab may be preferred to ZA in patients with renal toxicity or hypercalcemia of malignancy [97]. Surgical intervention also plays a role in the management of bone disease in MM. For individuals with vertebral compression fractures, vertebroplasty has been shown to provide pain reduction and improvements in mobility. Surgical measures may also be used in long bone fractures and cord compression, and after failed control with non-surgical measures [98].

CONCLUSION

Management of MM has been rapidly evolving with multitude of clinical trials testing novel agents or regimens. The introduction of novel multidrug regimens has brought into the question the necessity of ASCT as the initial treatment modality. At this time, it continues to be recommended and provides survival benefit. Currently, proteasome inhibitors and immunomodulatory drugs comprise the backbone of most modern treatment regimens. The development of daratumumab and its efficacy in NDMM has also highlighted the therapeutic use of monoclonal antibodies in upfront therapy. The development of these new drugs has prolonged OS and PFS, and has done so while minimizing toxicities. Although the field of MM treatment is rapidly progressing, the treatment of this disease remains complex and rapidly changing.

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