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Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management

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Abstract

Multiple myeloma accounts for approximately 10% of hematologic malignancies. The diagnosis requires $\geq 10\%$ clonal bone marrow plasma cells or a biopsy proven plasmacytoma *plus* evidence of one or more multiple myeloma defining events: CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features felt related to the plasma cell disorder, bone marrow clonal plasmacytosis $\geq 60\%$, serum involved/uninvolved free light chain (FLC) ratio ≥ 100 (provided involved FLC is ≥ 100 mg/L), or >1 focal lesion on magnetic resonance imaging. Patients with del(17p), t(14;16), and t(14;20) have high-risk multiple myeloma. Patients with t(4;14) translocation and gain(1q) have intermediate-risk. All others are considered standard-risk. Initial treatment consists of bortezomib, lenalidomide, dexamethasone (VRd). In high-risk patients, carfilzomib, lenalidomide, dexamethasone (KRd) is an alternative to VRd. In eligible patients, initial therapy is given for approximately 3–4 cycles followed by autologous stem cell transplantation (ASCT). Standard risk patients can opt for delayed ASCT at first relapse. Patients not candidates for transplant are treated with VRd for approximately 8–12 cycles followed by lenalidomide or lenalidomide plus dexamethasone. After ASCT, lenalidomide maintenance is recommended for standard risk patients, while maintenance with a bortezomib-based regimen is needed for patients with intermediate or high-risk disease. Most patients require a triplet regimen at relapse, with the choice of regimen varying with each successive relapse. Aggressive relapse with extramedullary plasmacytomas or plasma cell leukemia may require anthracycline containing combination chemotherapy regimens.

1 | DISEASE OVERVIEW

Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic malignancies.¹ Each year over 30 000 new cases are diagnosed in the United States, and over 12 000 patients die of the disease.² The annual age-adjusted incidence in the United States has remained stable for decades at approximately 4 per 100 000.³ Multiple myeloma is slightly more common in men than in women, and is twice as common in African-Americans compared with Caucasians.⁴ The median age of patients at the time of diagnosis is about 65 years.⁵

Unlike other malignancies that metastasize to bone, the osteolytic bone lesions in multiple myeloma exhibit no new bone formation.⁶ Bone disease is the main cause of morbidity and can be detected on routine skeletal radiographs, low-dose whole body computed tomography (WB-CT), magnetic resonance imaging (MRI), or fluorodeoxyglucose positron emission tomography/computed tomographic

scans (PET/CT).^{7,8} Other major clinical manifestations are anemia, hypercalcemia, renal failure, and an increased risk of infections. Approximately, 1% to 2% of patients have extramedullary disease (EMD) at the time of initial diagnosis, while 8% develop EMD later on in the disease course.⁹

Almost all patients with multiple myeloma evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS).^{10,11} MGUS is present in over 3% of the population above the age of 50,^{12,13} and the prevalence is approximately 2-fold higher in blacks compared with whites.^{14,15} MGUS progresses to multiple myeloma or related malignancy a rate of 1% per year.^{16,17} Since MGUS is asymptomatic, over 50% of individuals who are diagnosed with MGUS have had the condition for over 10 years prior to the clinical diagnosis.¹⁸ In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically.¹⁹ SMM progresses to multiple myeloma at a rate of

TABLE 1 International myeloma working group diagnostic criteria for multiple myeloma and related plasma cell disorders

Disorder	Disease definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	All 3 criteria must be met: <ul style="list-style-type: none"> • Serum monoclonal protein (non-IgM type) <3 gm/dL • Clonal bone marrow plasma cells <10%^a • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma	Both criteria must be met: <ul style="list-style-type: none"> • Serum monoclonal protein (IgG or IgA) ≥3 g/dL, or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10%-60% • Absence of myeloma defining events or amyloidosis
Multiple myeloma	Both criteria must be met: <ul style="list-style-type: none"> • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma • Any one or more of the following myeloma defining events: <ul style="list-style-type: none"> • Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: <ul style="list-style-type: none"> • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) • Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 μmol/L (>2 mg/dL) • Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL • Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) • Clonal bone marrow plasma cell percentage ≥60% • Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L) • >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)
IgM Monoclonal gammopathy of undetermined significance (IgM MGUS)	All 3 criteria must be met: <ul style="list-style-type: none"> • Serum IgM monoclonal protein <3 g/dL • Bone marrow lymphoplasmacytic infiltration <10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.
Light Chain MGUS	All criteria must be met: <ul style="list-style-type: none"> • Abnormal FLC ratio (<0.26 or >1.65) • Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) • No immunoglobulin heavy chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells <10% • Urinary monoclonal protein <500 mg/24 hours
Solitary Plasmacytoma	All 4 criteria must be met <ul style="list-style-type: none"> • Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal bone marrow with no evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

(Continues)

approximately 10% per year over the first 5 years following diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter. This rate of progression is influenced by the underlying cytogenetic

type of disease; patients with t(4;14) translocation, del(17p), and gain (1q) are at a higher risk of progression from MGUS or SMM to multiple myeloma.²⁰⁻²²

TABLE 1 (Continued)

Disorder	Disease definition
Solitary Plasmacytoma with minimal marrow involvement ^b	<p>All 4 criteria must be met</p> <ul style="list-style-type: none"> • Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Clonal bone marrow plasma cells <10% • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

Reproduced from Rajkumar et al.¹

^aA bone marrow can be deferred in patients with low risk MGUS (IgG type, M protein <15 gm/L, normal free light chain ratio) in whom there are no clinical features concerning for myeloma.

^bSolitary plasmacytoma with 10% or more clonal plasma cells is considered as multiple myeloma.

2 | DIAGNOSIS

The revised International Myeloma Working Group criteria for the diagnosis of multiple myeloma and related disorders are shown on Table 1.¹ The diagnosis of multiple myeloma requires the presence of one or more myeloma defining events (MDE) in addition to evidence of either 10% or more clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma. MDE consists of established CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features as well as 3 specific biomarkers: clonal bone marrow plasma cells $\geq 60\%$, serum free light chain (FLC) ratio ≥ 100 (provided involved FLC level is ≥ 100 mg/L), and more than one focal lesion on MRI. Each of the new biomarkers is associated with an approximately 80% risk of progression to symptomatic end-organ damage in two or more independent studies. The updated criteria represent a paradigm shift since they allow early diagnosis and initiation of therapy before end-organ damage.

When multiple myeloma is suspected clinically, patients should be tested for the presence of M proteins using a combination of tests that should include a serum protein electrophoresis (SPEP), serum immunofixation, and the serum FLC assay.²³ Approximately, 2% of patients with multiple myeloma have true nonsecretory disease and have no evidence of an M protein on any of the above studies.^{5,24} Bone marrow studies at the time of initial diagnosis should include fluorescent in situ hybridization (FISH) probes designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), trisomies, and del(17p) (see Risk-Stratification below).²⁵ Conventional karyotyping to detect hypodiploidy and deletion 13 has value, but if FISH studies are done, additional value in initial risk-stratification is limited. Gene expression profiling if available can provide additional prognostic value.²⁶ Serum CrossLaps to measure carboxy-terminal collagen crosslinks (CTX) may be useful in assessing bone turnover and to determine adequacy of bisphosphonate therapy.^{27,28} The extent of bone disease is best assessed by low-dose WB-CT or PET/CT imaging.⁸ MRI scans are useful in patients with suspected SMM to rule out focal bone marrow lesions that can be seen before true osteolytic disease occurs. MRI imaging is also useful in assessing EMD, suspected cord compression, or when detailed imaging

of a specific symptomatic area is needed. Conventional skeletal survey is less sensitive than low-dose WB-CT and PET/CT and recommended only if resources for more advanced imaging are not available.

The M protein is considered to be measurable if it is ≥ 1 g/dL in the serum and or ≥ 200 mg/day in the urine. The M protein level is monitored by SPEP and serum FLC assay to assess treatment response every month while on therapy, and every 3–4 months when off-therapy. The serum FLC assay is particularly useful in patients who lack a measurable M protein, provided the FLC ratio is abnormal and the involved FLC level is ≥ 100 mg/L.²⁹ Urine protein electrophoresis is recommended at least once every 3–6 months, to follow the urine M protein level as well as to detect other renal complications that may result in albuminuria. Response to therapy assessment and minimal residual disease (MRD) evaluation is based on the revised International Myeloma Working Group uniform response criteria.³⁰

3 | MOLECULAR CLASSIFICATION

Although multiple myeloma is still considered a single disease, it is in reality a collection of several different cytogenetically distinct plasma cell malignancies (Table 2).^{31,32} On FISH studies of the bone marrow, approximately 40% of multiple myeloma is characterized by the presence of trisomies in the neoplastic plasma cells (trisomic multiple myeloma), while most of the rest have a translocation involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 (IgH translocated multiple myeloma).^{33–36} A small proportion of patients have both trisomies and IgH translocations. Trisomies and IgH translocations are considered primary cytogenetic abnormalities and occur at the time of establishment of MGUS. In addition, other cytogenetic changes termed secondary cytogenetic abnormalities arise along the disease course of multiple myeloma, including gain(1q), del(1p), del(17p), del(13), RAS mutations, and secondary translocations involving MYC. Both primary and secondary cytogenetic abnormalities can influence disease course, response to therapy, and prognosis. Importantly, the interpretation and impact of cytogenetic abnormalities in multiple myeloma vary depending on the disease phase in which they are detected (Table 3).³⁷

TABLE 2 Primary molecular cytogenetic classification of multiple myeloma

Subtype	Gene(s)/chromosomes affected ^a	Percentage of myeloma patients
Trisomic multiple myeloma	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21	42
IgH translocated multiple myeloma		30
t(11;14) (q13;q32)	<i>CCND1</i> (cyclin D1)	15
t(4;14) (p16;q32)	<i>FGFR-3</i> and <i>MMSET</i>	6
t(14;16) (q32;q23)	<i>C-MAF</i>	4
t(14;20) (q32;q11)	<i>MAFB</i>	<1
Other IgH translocations ^a	<i>CCND3</i> (cyclin D3) in t(6;14) multiple myeloma	5
Combined IgH translocated/trisomic multiple myeloma	Presence of trisomies and any one of the recurrent IgH translocations in the same patient	15
Isolated Monosomy 14	Few cases may represent 14q32 translocations involving unknown partner chromosomes	4.5
Other cytogenetic abnormalities in absence of IgH translocations or trisomy or monosomy 14		5.5
Normal		3

Modified from Kumar et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood* 2012; 119:2100. © American Society of Hematology.

^aIncludes the t(6;14)(p21;q32) translocation, and rarely, other IgH translocations involving uncommon partner chromosome.

4 | PROGNOSIS AND RISK STRATIFICATION

Survival estimates in multiple myeloma vary based on the source of the data. Data from randomized controlled trials using modern therapy show that the median survival in multiple myeloma is approximately 6 years.³⁸ In the subset of patients eligible for ASCT, 4-year survival rates are more than 80%³⁹; the median overall survival (OS) among these patients is approximately 8 years.⁴⁰ Among elderly patients (age >75 years), median OS is lower, and is approximately 5 years.³⁸ These numbers likely underestimate current survival probabilities since they predate the arrival of monoclonal antibodies and several other new agents that have been introduced in the last 3 to 5 years. Conversely, they may be overestimates of the true population-based survival since they are derived from randomized controlled trials where patients with poor performance status and comorbidities are typically excluded. Nevertheless, these estimates are valuable benchmarks, and appear generalizable to newly diagnosed myeloma patients in good performance status.⁴¹

More precise estimation of prognosis requires an assessment of multiple factors. As in other cancers, OS in multiple myeloma is affected by host characteristics, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy.^{42,43} Tumor burden in multiple myeloma has traditionally been assessed using the Durie-Salmon Staging⁴⁴ and the International staging system (ISS).^{45,46} Disease biology best reflected based on the molecular subtype of multiple myeloma (Table 2), the presence or absence of secondary cytogenetic abnormalities such as del(17p), gain(1q), or del(1p).^{25,32} In addition to cytogenetic risk factors, two other markers that are associated with aggressive disease biology are elevated serum lactate dehydrogenase

and evidence of circulating plasma cells on routine peripheral smear examination (plasma cell leukemia). The Revised International Staging System (RISS) combines elements of tumor burden (ISS) and disease biology (presence of high risk cytogenetic abnormalities or elevated lactate dehydrogenase level) to create a unified prognostic index that helps in clinical care as well as in comparison of clinical trial data (Table 4).⁴⁷ To ensure uniform availability, only 3 widely available cytogenetic markers are used in the RISS; the Mayo Clinic mSMART risk stratification (www.msmaart.org) (Table 5) has additional detail that is valuable in formulating a therapeutic strategy.⁴⁸

Treated appropriately, the survival of patients with certain high risk categories can approach that of patients with standard risk disease. In a large trial using bortezomib-based induction, early tandem ASCT, and bortezomib maintenance, the median OS of patients with del(17p) was approximately 8 years (8-year survival rate of 52%), and was identical to patients with standard risk multiple myeloma. In contrast, survival was lower for patients with t(4;14) translocation (8-year survival rate, 33%) and for patients with gain(1q) abnormality (8-year survival rate, 36%). These findings underscore the limitations of current risk stratification models in the context of modern therapy and highlight the need to stratify multiple myeloma based on individual cytogenetic groups rather than arbitrary heterogeneous risk categories.³¹

5 | INDICATIONS FOR THERAPY

To initiate therapy, patients must meet criteria for multiple myeloma as outlined in Table 1. In earlier trials, treatment of asymptomatic patients with SMM was associated with a benefit in progression free survival

TABLE 3 Cytogenetic abnormalities on clinical course and prognosis in multiple myeloma

Cytogenetic abnormality	Clinical setting in which abnormality is detected	
	Smoldering multiple myeloma	Multiple myeloma
Trisomies	Intermediate-risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7–10 years Most have myeloma bone disease at diagnosis Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(6;14) (p21;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(4;14) (p16;q32)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years Needs bortezomib-based initial therapy, early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
t(14;16) (q32;q23)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
Gain(1q21)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
Del(17p)	High-risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard-risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high risk IgH translocations, and del 17p
Isolated Monosomy 13, or Isolated Monosomy 14	Standard-risk of progression, median TTP of 5 years	Effect on prognosis is not clear
Normal	Low-risk of progression, median TTP of 7–10 years	Good prognosis, probably reflecting low tumor burden, median OS >7–10 years

ASCT, autologous stem cell transplantation; FISH, fluorescent in situ hybridization; MM, multiple myeloma; OS, overall survival; TTP, time to progression; SMM, Smoldering multiple myeloma.
Reproduced from Rajan and Rajkumar.³⁷

(PFS) but not OS.⁴⁹ However, a recent randomized trial found that early therapy with lenalidomide and dexamethasone in patients with high risk SMM can prolong PFS and OS.⁵⁰ Although these results need further confirmation, they indicate the potential benefit of early intervention in selected asymptomatic patients.

6 | TREATMENT OF NEWLY DIAGNOSED MYELOMA

Survival in multiple myeloma has improved significantly in the last 15 years.⁵¹ The initial impact came from the introduction of thalidomide,⁵² bortezomib,⁵³ and lenalidomide.^{54,55} In the last 5 years, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab have been approved by the Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma, and promise to improve outcomes further. Numerous combinations have been developed using drugs that have shown activity in multiple myeloma, and the most commonly used regimens are listed in Table 6.^{56–75} These drugs work through a variety of mechanisms, some of which are not fully understood. Thalidomide, lenalidomide, and pomalidomide are termed immunomodulatory agents (IMiDs). IMiDs bind to cereblon and activate cereblon E3 ligase activity, resulting in the rapid ubiquitination and degradation of two specific B cell

transcription factors, Ikaros family zinc finger proteins Ikaros (IKZF 1) and Aiolos (IKZF3).^{76–78} They may cause direct cytotoxicity by inducing free radical mediated DNA damage.⁷⁹ They also have anti-angiogenic, immunomodulatory, and tumor necrosis factor alpha inhibitory properties. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors.^{80–82} Elotuzumab and daratumumab are monoclonal antibodies targeting SLAMF7 and CD38 respectively.^{73,83,84} Panobinostat is a deacetylase inhibitor.^{75,85}

The approach to treatment of symptomatic newly diagnosed multiple myeloma is outlined in Figure 1 and is dictated by eligibility for ASCT and risk-stratification. The data to support their use from recent randomized trials using new active agents for multiple myeloma are provided in Table 7.^{38,39,60,86–88} There is an ongoing “cure versus control” debate on whether we should treat multiple myeloma with an aggressive multi-drug strategy targeting complete response (CR) or a sequential disease control approach that emphasizes quality of life as well as OS.^{89,90}

Recent data show that MRD negative status (as estimated by next generation molecular methods or flow cytometry) has favorable prognostic value.³⁰ However, additional trials are needed to determine if changes in treatment need to be made based on MRD status. At present, MRD results are recommended mainly as a prognostic metric and not for used in making treatment decisions. We

TABLE 4 Revised international staging system for myeloma⁴⁷

Stage
Stage I All of the following: <ul style="list-style-type: none"> • Serum albumin ≥ 3.5 gm/dL • Serum beta-2-microglobulin < 3.5 mg/L • No high risk cytogenetics • Normal serum lactate dehydrogenase level
Stage II <ul style="list-style-type: none"> • Not fitting Stage I or III
Stage III Both of the following: <ul style="list-style-type: none"> • Serum beta-2-microglobulin > 5.5 mg/L • High risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated serum lactate dehydrogenase level

Derived from: Palumbo et al.⁴⁷

also need additional data to determine if MRD negativity can be used as a surrogate endpoint for regulatory approval, and if sustained MRD negativity may be a marker of cure in at least a subset of patients.⁹¹

6.1 | Initial treatment in patients eligible for ASCT

Typically, patients are treated with approximately 3–4 cycles of induction therapy prior to stem cell harvest. After harvest, patients can either undergo frontline ASCT or resume induction therapy delaying ASCT until first relapse. There are many options for initial therapy, and the most common treatment regimens are discussed below. These regimens can also be used at the time of relapse. In general, the low-dose dexamethasone regimen (40 mg once a week) is preferred in all regimens to minimize toxicity. In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG), the low-dose dexamethasone approach was associated with superior OS and significantly lower toxicity.⁵⁸

TABLE 5 Mayo clinic risk stratification for multiple myeloma (mSMART)

Risk group	Percentage of newly diagnosed patients with the abnormality
Standard Risk	75%
Trisomies	
t(11;14)	
t(6;14)	
Intermediate Risk	10%
t(4;14)	
Gain(1q)	
High Risk	15%
t(14;16)	
t(14;20)	
del(17p)	

6.1.1 | Bortezomib-containing regimens

Bortezomib, lenalidomide, dexamethasone (VRd) is the current standard of care for newly diagnosed multiple myeloma. In a recent randomized trial conducted by the Southwest Oncology Group (SWOG), response rates, PFS, and OS were significantly superior with VRd compared with Rd (Table 7).³⁸ If lenalidomide is not available for use as initial therapy or in the presence of acute renal failure, other bortezomib-containing regimens such as bortezomib-thalidomide-dexamethasone (VTd) or bortezomib-cyclophosphamide-dexamethasone (VCd) can be used instead of VRd. A recent randomized trial found that VTd results in superior response rates compared with VCd, but impact on long-term outcomes is not known.⁸⁸ Therefore both are reasonable alternatives to VRd.

In initial studies, peripheral neuropathy was a major concern with bortezomib therapy. Neuropathy with bortezomib can occur abruptly, and can be significantly painful and debilitating. However, the neurotoxicity of bortezomib can be greatly diminished by administering bortezomib once a week instead of twice-weekly,^{61,62} and by administering the drug subcutaneously instead of the intravenous route.⁹² The once-weekly subcutaneous bortezomib schedule (Table 6) has made serious neuropathy an uncommon problem, and has made regimens such as VRd, VCd, and VTd much more tolerable. Bortezomib does not appear to have any adverse effect on stem cell mobilization.⁹³

6.1.2 | Lenalidomide-low dose dexamethasone (Rd)

Rd which combines lenalidomide with a lower dose of dexamethasone (40 mg once weekly) is an active regimen in newly diagnosed multiple myeloma, and has less toxicity and better OS than lenalidomide plus high dose dexamethasone or MPT.^{58,87} Currently Rd is recommended mainly for patients who are unable to tolerate a triplet regimen due to advanced age, poor performance status, or comorbidities. Stem cell collection with granulocyte stimulating factor (G-CSF) alone may be impaired when Rd is used as induction therapy.⁹⁴ Thus, patients over the age of 65 and those who have received more than 4 cycles of Rd stem cells must be mobilized with either cyclophosphamide plus G-CSF or with plerixafor.^{95,96} All patients treated with Rd require anti-thrombosis prophylaxis. Aspirin is adequate for most patients, but in patients who are at higher risk of thrombosis, either low-molecular weight heparin or warfarin is needed.^{97–99}

6.1.3 | Carfilzomib-lenalidomide-dexamethasone (KRd)

Two phase II trials have reported excellent results with the newly approved proteasome inhibitor carfilzomib when used in combination with lenalidomide and dexamethasone for newly diagnosed multiple myeloma.^{100,101} However, more data on safety and efficacy of KRd are needed before this regimen can be recommended in newly diagnosed multiple myeloma, except in young patients with high risk cytogenetics. A randomized trial in the United States (referred to as the Endurance trial) is currently ongoing comparing VRd versus KRd as initial therapy.

6.1.4 | Multi-drug combinations

Besides the regimens discussed above, other options include anthracycline-containing regimens such as bortezomib, doxorubicin,

TABLE 6 Major treatment regimens in multiple myeloma

Regimen	Usual Dosing Schedule ^a
Thalidomide-dexamethasone (Td) ^{b 56,57}	Thalidomide 200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Lenalidomide-dexamethasone (Rd) ⁵⁸	Lenalidomide 25 mg oral days 1–21 every 28 days Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days Repeated every 4 weeks
Pomalidomide-dexamethasone (Pom/Dex) ⁵⁹	Pomalidomide 4 mg days 1–21 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Bortezomib-melphalan-prednisone (VMP) ^{b 60–62}	Bortezomib 1.3 mg/m ² subcutaneous days 1, 8, 15, 22 Melphalan 9 mg/m ² oral days 1–4 Prednisone 60 mg/m ² oral days 1 to 4 Repeated every 35 days
Bortezomib-thalidomide-dexamethasone (VTd) ^{b 63}	Bortezomib 1.3 mg/m ² subcutaneous days 1, 8, 15, 22 Thalidomide 100–200 mg oral days 1–21 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks × 4 cycles as pretransplant induction therapy
Bortezomib- Cyclophosphamide-Dexamethasone ^b (VCd or CyBord) ^{64,65}	Cyclophosphamide 300 mg/m ² orally on days 1, 8, 15, and 22 Bortezomib 1.3 mg/m ² subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks ^c
Bortezomib-Lenalidomide-Dexamethasone (VRd) ^{b 65,66}	Bortezomib 1.3 mg/m ² subcutaneous days 1, 8, 15 Lenalidomide 25 mg oral days 1–14 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 weeks ^d
Carfilzomib- Cyclophosphamide-Dexamethasone (KCd) ^{e 67}	Carfilzomib 20 mg/m ² (days 1 and 2 of Cycle 1) and 27 mg/ m ² (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m ² orally on days 1, 8, 15 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Carfilzomib-Lenalidomide-Dexamethasone (KRd) ^{e 68}	Carfilzomib 20 mg/m ² (days 1 and 2 of Cycle 1) and 27 mg/ m ² (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Carfilzomib-Pomalidomide-Dexamethasone (KPd) ^{e 69}	Carfilzomib 20 mg/m ² (days 1 and 2 of Cycle 1) and 27 mg/ m ² (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Daratumumab-Lenalidomide-Dexamethasone (DRd) ⁷⁰	Daratumumab 16 mg/ kg intravenously weekly x 8 weeks, and then every 2 weeks for 4 months, and then once monthly Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Daratumumab-Bortezomib-Dexamethasone (DVd) ^{b 71}	Daratumumab 16 mg/ kg intravenously weekly x 8 weeks, and then every 2 weeks for 4 months, and then once monthly Bortezomib 1.3 mg/m ² subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Bortezomib-Dexamethasone repeated in usual schedule every 4 weeks
Daratumumab-Pomalidomide-Dexamethasone (DPd) ⁷²	Daratumumab 16 mg/kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Repeated every 4 weeks

(Continues)

TABLE 6 (Continued)

Regimen	Usual Dosing Schedule ^a
Elotuzumab-Lenalidomide-Dexamethasone (ERd) ⁷³	10 mg/ kg intravenously weekly x 8 weeks, and then every 2 weeks Lenalidomide 25 mg oral days 1–21 Dexamethasone per prescribing information Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Ixazomib-Lenalidomide-Dexamethasone (IRd) ⁷⁴	Ixazomib 4 mg oral days 1, 8, 15 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Panobinostat-Bortezomib ⁷⁵	Panobinostat 20 mg oral three times a week × 2 weeks Bortezomib 1.3 mg/m ² subcutaneous days 1, 8, 15 Repeated every 3 weeks

^aAll doses need to be adjusted for performance status, renal function, blood counts, and other toxicities.

^bDoses of dexamethasone and/or bortezomib reduced based on other data showing lower toxicity and similar efficacy with reduced doses; subcutaneous route of administration of bortezomib preferred based on data showing lower toxicity and similar efficacy compared to intravenous administration.

^cThe day 22 dose of all 3 drugs is omitted if counts are low, or after initial response to improve tolerability, or when the regimen is used as maintenance therapy; When used as maintenance therapy for high risk patients, further delays can be instituted between cycles.

^dOmit day 15 dose if counts are low or when the regimen is used as maintenance therapy; When used as maintenance therapy for high risk patients, lenalidomide dose may be decreased to 10–15 mg per day, and delays can be instituted between cycles as done in total therapy protocols.

^eCarfilzomib can also be considered in a once a week schedule of 56 mg/m² on days 1, 8 and 15 every 28 days (cycle 1, day 1 should be 20 mg/m²); Day 8, 9 doses of carfilzomib can be omitted in maintenance phase of therapy after a good response to improve tolerability; KCd dosing lowered from that used in the initial trial which was conducted in newly diagnosed patients.

dexamethasone (PAD)⁴⁰ or multi-agent combination chemotherapy regimens such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide).^{102,103}

These regimens are particularly useful in patients with aggressive disease such as plasma cell leukemia or multiple extramedullary plasmacytomas. Several other regimens have been tested in newly diagnosed

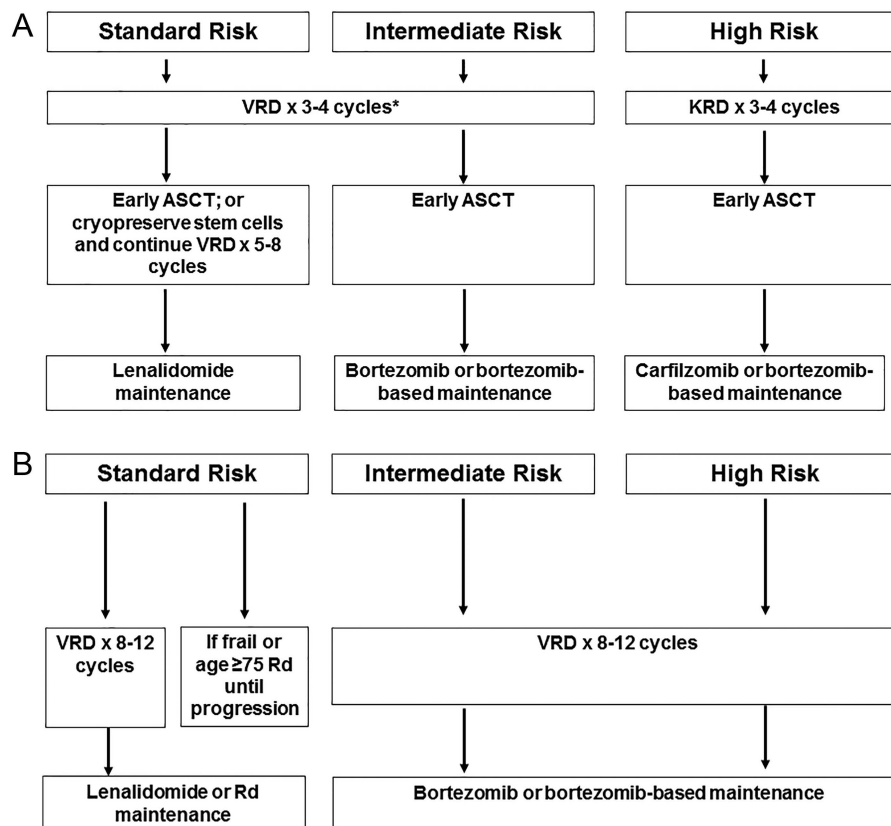


FIGURE 1 Approach to the treatment of newly diagnosed multiple myeloma in transplant eligible (A) and transplant ineligible (B) patients. ASCT, autologous stem cell transplantation; CR, complete response; KRd, carfilzomib, lenalidomide, dexamethasone; Rd, lenalidomide plus dexamethasone; VGPR, very good partial response; VRD, bortezomib, lenalidomide, dexamethasone

TABLE 7 Results of recent randomized studies in newly diagnosed myeloma

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (Median in months)	P value for progression free survival	Overall survival (Median in months) ^a	P value for overall survival
San Miguel et al; Mateos et al ^{b 60,86}	MP	331	35	8	17		43	
	VMP	337	71	41	24	<0.001	NR	<.001
Benboubker et al ⁸⁷	MPT	547	62	28	21	<0.001	48	.016 ^c
	Rd x 18 months	541	73	43	21		53	
	Rd till progression	535	75	44	26		56	
Durie et al ³⁸	Rd	229	72	32	31	0.002	64	.025
	VRd	242	82	43	43		75	
Moreau et al ⁸⁸	VCd	169	83	56	N/A		N/A	N/A
	VTd	169	92	66	N/A	N/A	N/A	
Attal et al ³⁹	VRd	350	97	77	36		NR; 82% at 4 years	.87
	VRd-ASCT	350	98	88	50	<0.001	NR; 81% at 4 years	

^aEstimated from survival curves when not reported.

^bProgression free survival not reported, numbers indicate time to progression.

^cRd until progression versus MPT.

CR, complete response; MP, melphalan plus prednisone; MPT, melphalan plus prednisone plus thalidomide; N/A, not available; NS, not significant; Rd, lenalidomide plus dexamethasone; VMP, bortezomib plus melphalan plus prednisone; VTd, bortezomib, thalidomide, dexamethasone; VRd, bortezomib, lenalidomide plus dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

multiple myeloma, but there are no clear data from randomized controlled trials that they have an effect on long-term endpoints compared with the regimens discussed earlier.

Recommendations

- In standard-risk and intermediate-risk patients eligible for ASCT, I favor VRd as initial therapy for 3–4 cycles, followed by ASCT and lenalidomide maintenance therapy. In patients who are tolerating therapy and responding well, an alternative is VRd for 8 to 12 cycles followed by lenalidomide maintenance therapy; in such patients stem cells must be collected for cryopreservation after the first 3–4 cycles of VRd, and ASCT must be considered at first relapse.
- In high-risk patients, I favor KRd as initial therapy for 3–4 cycles followed by ASCT and then maintenance with a proteasome inhibitor-based regimen.
- In patients presenting with acute renal failure suspected to be secondary to light-chain cast nephropathy, I prefer VCd or VTd as initial therapy in conjunction with plasma exchange (or dialysis with high-cut-off filter). Plasma exchange is continued daily until the serum FLC levels are less than 50 mg/dL and then repeated as needed till chemotherapy is fully effective.
- In patients presenting with plasma cell leukemia or multiple extramedullary plasmacytomas, I prefer VDT-PACE as initial therapy followed by ASCT and then maintenance with a bortezomib-based regimen.

- Once weekly subcutaneous bortezomib is preferred in most patients for initial therapy, unless there is felt to be an urgent need for rapid disease control.
- Dexamethasone 40 mg once a week (low-dose dexamethasone) is preferred in most patients for initial therapy, unless there is felt to be an urgent need for rapid disease control.

6.2 | Initial treatment in patients not eligible for ASCT

In patients with newly diagnosed multiple myeloma who are not candidates for ASCT due to age or other comorbidities, the major options for initial therapy are the same as those discussed earlier for patients eligible for ASCT. Typically treatment is given with a bortezomib-based regimen for approximately 8–12 cycles followed by maintenance. Although melphalan-based regimens have been extensively tested in these patients, they are not recommended due to concerns about stem cell damage and secondary myelodysplastic syndrome and leukemia. In the United States transplant eligibility is not determined by a strict age cut-off, and many patients enrolled in the melphalan-based clinical trials would be considered candidates for ASCT.

6.2.1 | Bortezomib-based regimens

VRd has shown a survival benefit compared with Rd, and is the preferred choice for initial therapy in patients who are not candidates for ASCT (Table 7).³⁸ VRd is administered for approximately 8–12 cycles,

followed by maintenance therapy. Alternatives to VRd include VCd and VTd as discussed earlier. In patients in whom initial therapy with VRd is not possible mainly for logistical reasons (such as problems with compliance due to need for parenteral administration), ixazomib can be considered in place of bortezomib.

6.2.2 | Lenalidomide plus dexamethasone (Rd)

Rd is an option for the treatment of elderly patients with newly diagnosed multiple myeloma who are unable to tolerate triplet therapy due to advanced age, poor performance status, or co-morbidities. An international phase III trial compared MPT versus Rd for 18 cycles versus Rd until progression in 1623 patients.⁸⁷ PFS was superior with Rd until progression compared with the other two arms; OS was superior with Rd until progression compared with MPT. This trial provided the first evidence that OS can be improved in patients who are not eligible for transplant using a regimen that does not contain melphalan.

6.2.3 | Melphalan-based regimens

VMP is a bortezomib-based regimen that has shown better OS compared with MP.^{60,86} Substituting melphalan with thalidomide in the VMP regimen has not shown a benefit.⁶¹ Melphalan-based regimens are considered only if there is problems with access to lenalidomide. Even in these situations, the risks of melphalan can be reduced by using cyclophosphamide instead, and studies show this substitution does not alter efficacy.¹⁰⁴ Thus, the VCd regimen can be considered as a minor modification of the VMP regimen, in which cyclophosphamide is used as the alkylating agent in place of melphalan. This variation has the advantage of not affecting stem cell mobilization, and dosing is more predictable. Randomized trials have found superior PFS and OS with 4-drug regimens such as daratumumab-VMP and VMPT compared with VMP, but the contribution of the fourth drug to the induction component cannot be ascertained from these trials and more data on overall survival are needed.⁶²

Recommendations

- In standard-risk patients, I prefer VRd as initial therapy administered for approximately 8–12 cycles, followed by lenalidomide maintenance
- In frail elderly patients, I prefer Rd as initial therapy, administered until progression. Dexamethasone may be started at 20 mg once a week, then reduced as much as possible after the first 4–6 cycles, and possibly discontinued after the first year.
- In intermediate- and high-risk patients, I favor VRd as initial therapy for approximately 8–12 cycles followed if possible by a lower intensity (one dose every two weeks) maintenance schedule of bortezomib.

6.3 | Hematopoietic stem cell transplantation

6.3.1 | Autologous stem cell transplantation (ASCT)

ASCT improves median OS in multiple myeloma by approximately 12 months.^{105–108} However, randomized trials found similar OS with early

ASCT (immediately following 4 cycles of induction therapy) versus delayed ASCT (at the time of relapse as salvage therapy).^{109–111} A recent trial by the Intergroupe Francophone du Myelome (IFM) compared early versus delayed ASCT in patients treated with VRd followed by lenalidomide maintenance.³⁹ Patients were randomized to receive either VRd (3 cycles) followed by ASCT and then VRd consolidation (2 cycles) versus VRd × 8 cycles with ASCT reserved for relapse. Both arms received lenalidomide maintenance for one year. A significant improvement in PFS was seen as expected with early ASCT, but this has so far not translated into a difference in OS (Table 7). Based on these results, it is reasonable to consider a delayed ASCT in patients with standard-risk multiple myeloma who prefer such an approach for personal and logistic reasons.

The role of tandem (double) ASCT is unclear. In earlier randomized trials, an improvement in OS was seen in two studies,^{112,113} but other studies failed to show such an improvement.^{114,115} More recent data are available from two other randomized trials are also inconclusive. In a trial conducted in Europe, an improvement in PFS and OS was seen with tandem ASCT in both standard and high risk patients.¹¹⁶ However, no survival benefit was seen in a randomized trial conducted in the United States by the Bone Marrow Transplantation Clinical Trials Network (BMT-CTN) in standard or high risk multiple myeloma (BMT-CTN 0702 trial).¹¹⁷ The US trial more likely reflects the impact of tandem ASCT in the context of modern therapy when most new options for salvage are available. Thus routine tandem ASCT is not recommended outside of a clinical trial setting except in selected young patients with high risk multiple myeloma.

6.3.2 | Post-transplant consolidation

Consolidation therapy is a term used for the administration of a short course of therapy, usually with 2 or more drugs, prior to the start of long-term maintenance. The BMT-CTN 0702 trial had an arm that investigated the benefit of post-transplant consolidation therapy followed by lenalidomide maintenance versus lenalidomide maintenance alone. In this trial, additional cycles of VRd chemotherapy administered as consolidation after ASCT did not result in significant benefit. Unlike earlier trials, the BMT-CTN 0702 trial specifically isolated the effect of consolidation and is therefore more compelling than trials where one could not ascertain the precise added value of consolidation therapy on PFS and OS. Consolidation therapy after ASCT is not recommended and patients should proceed to standard low-intensity maintenance therapy.

6.3.3 | Allogeneic transplantation

The role of allogeneic and nonmyeloablative-allogeneic transplantation in multiple myeloma is controversial with studies showing conflicting results.^{118,119} The treatment related mortality (TRM) rate (10%–20%) and GVHD rates are fairly high.¹²⁰ Although allogeneic transplantation should still be considered as investigational, it may be a consideration for young patients with high-risk disease who are willing to accept a high TRM and the unproven nature of this therapy for a chance at better long-term survival.

Recommendations

- ASCT should be considered in all eligible patients. But in standard-risk patients responding well to therapy, ASCT can be delayed until first relapse provided stem cells are harvested early in the disease course.
- Tandem ASCT is not recommended outside of clinical trials except in selected young patients with high risk multiple myeloma.
- At present, allogeneic transplantation as frontline therapy should largely be considered investigational.

6.4 | Maintenance therapy

Maintenance therapy is indicated following ASCT. Maintenance therapy should also be considered in following completion of 8–12 cycles of initial therapy in patients treated without ASCT. Lenalidomide is the standard of care for maintenance therapy for most patients.^{87,121–125} In a meta-analysis of randomized trials, a significant improvement in PFS and OS was seen with lenalidomide maintenance compared with placebo or no therapy.¹²⁶ Lenalidomide maintenance is associated with a 2–3-fold increase in the risk of second cancers and patients must be counseled in this regard and monitored.

The impact of lenalidomide maintenance in patients with intermediate- and high risk multiple myeloma is unclear. In the meta-analysis, no significant OS benefit was seen in these subsets of high risk patients.¹²⁶ In contrast, bortezomib administered every other week has been shown to improve OS, particularly in patients with del(17p).¹²⁴ Bortezomib-based maintenance may thus be preferable for intermediate- and high-risk patients.

The benefit of maintenance therapy in patients who did not undergo upfront ASCT is less clear. Based on the results of the SWOG trial, maintenance therapy with lenalidomide or Rd should be considered in patients who are in good performance status after completion of initial 8–12 cycles of triplet therapy. Patients who are treated with double therapy with Rd due to frailty or performance status are usually treated with this regimen until disease progression. After the first 18 cycles, the dose of dexamethasone can be lowered to minimize side effects. In some patients dexamethasone may need to be discontinued.

Although the benefit of maintenance is now established, data on optimal duration are lacking. We also need to consider the cost, toxicity, and inconvenience of long-term indefinite maintenance therapy. Many patients seek a drug-free interval. An ECOG trial is comparing lenalidomide maintenance given until progression versus a limited duration of 2 years. Trials are also examining if the duration of maintenance can be modified based on MRD results.

Recommendations

- I recommend lenalidomide maintenance for standard-risk patients following ASCT. I also recommend lenalidomide or Rd maintenance following 8–12 cycles of initial therapy among patients who did not receive ASCT as part of initial therapy.

- I recommend maintenance with bortezomib (or an alternative proteasome inhibitor) for patients with intermediate- and high-risk multiple myeloma

7 | TREATMENT OF RELAPSED MULTIPLE MYELOMA

Almost all patients with multiple myeloma eventually relapse. The remission duration in relapsed multiple myeloma decreases with each regimen.¹²⁷ The median PFS and OS in patients with relapsed multiple myeloma refractory to lenalidomide and bortezomib is poor, with median times of 5 months and 9 months, respectively.¹²⁸ The choice of a treatment regimen at relapse is complicated and is affected by many factors including the timing of the relapse, response to prior therapy, aggressiveness of the relapse, and performance status (TRAP). Patients are eligible for an ASCT should be considered for the procedure if they have never had one before, or if they have had an excellent remission duration with the first ASCT defined as a remission of at least 36 months or longer with maintenance. In terms of drug therapy, a triplet regimen containing at least two new drugs that the patient is not refractory to should be considered. An approach to the treatment of relapsed multiple myeloma is given in Figure 2. Major regimens used in the treatment of multiple myeloma, including relapsed disease are listed in Table 6. Recent advances in the treatment of relapsed multiple myeloma, including new active agents and results of major randomized trials are discussed below (Table 8).^{68,70,71,73–75,130–134} One important consideration is that the lenalidomide-containing regimens listed in Table 8 were tested mainly in patient populations who were not previously exposed to lenalidomide. In contrast, current clinical practice typically consists of patients who have been treated with lenalidomide and are often relapsing while on a lenalidomide-containing regimen. In patients who are considered refractory to lenalidomide, one option is to consider pomalidomide-based regimens.

7.1 | Bortezomib-based regimens

These regimens are appropriate for patients who received a bortezomib-based triplet for a period of time, and then stopped therapy. In these patients if relapse occurs after a reasonable period of remission off all therapy, then restarting the same (or similar) bortezomib-based triplet is reasonable and also carries lower cost and risk. As in newly diagnosed multiple myeloma, VRd, VCd, and VTd are active regimens in relapsed disease.^{136,137}

7.2 | Daratumumab

Daratumumab targeting CD38 has shown promise in relapsed, refractory multiple myeloma.⁸³ In a phase II trial, daratumumab as a single-agent was produced a response rate of approximately 30% in heavily pretreated patients.⁸⁴ Based on these findings, daratumumab was first granted accelerated approval by the FDA in 2015 for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an

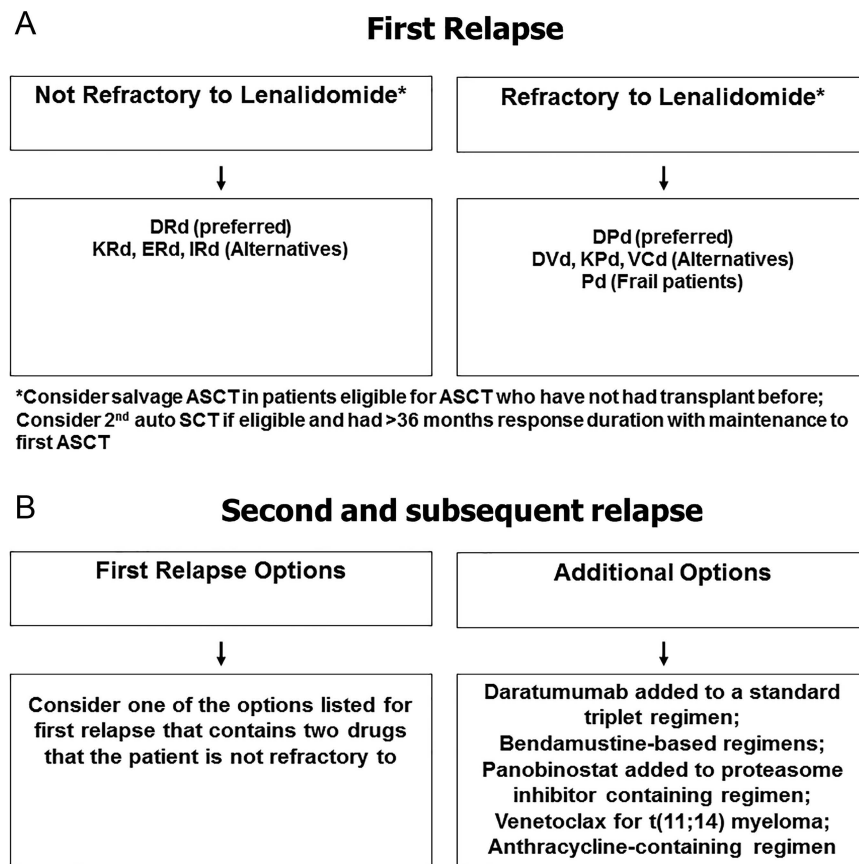


FIGURE 2 Suggested options for the treatment of relapsed multiple myeloma in first relapse (A) and second or higher relapse (B). ASCT, autologous stem cell transplantation; DRd, daratumumab, lenalidomide, dexamethasone; DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; Elo-Rd, Elotuzumab, lenalidomide, dexamethasone; IRd, ixazomib, lenalidomide, dexamethasone; KPd, carfilzomib, pomalidomide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; Pd, pomalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone

immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent. Subsequently 3 other daratumumab-based combinations have shown efficacy and have been approved by the FDA. These include daratumumab, lenalidomide, dexamethasone (DRd), daratumumab, bortezomib, dexamethasone (DVd), and daratumumab, pomalidomide, dexamethasone (DPd) (Table 8). The various triplets available for use in relapsed disease have not been compared head-to-head, but daratumumab-based regimens appear to have the greatest reduction in risk of progression, and may be preferred for first relapse subject to availability and cost considerations.¹³⁸

7.3 | Carfilzomib

Carfilzomib is a novel keto-epoxide tetrapeptide proteasome inhibitor initially approved in 2013 for the treatment of relapsed refractory multiple myeloma in patients who have been previously treated with lenalidomide and bortezomib. In a phase 2 study (PX-171-003-A1), of 266 patients (80% of patients whom were refractory or intolerant to both bortezomib and lenalidomide), single-agent carfilzomib resulted in a response rate of 24% for a median duration of approximately 8 months.¹³⁹ KRd has been subsequently shown to be effective in a randomized trial, and is a major option for the treatment of relapsed disease (Table 8).⁶⁸ In another

randomized trial carfilzomib plus dexamethasone was associated with an improvement in PFS and OS compared with bortezomib plus dexamethasone in relapsed multiple myeloma.^{133,134} However, the dose of carfilzomib used in this trial (56 mg/m²) is twice the standard dose, and carries a much higher cost compared with bortezomib. Carfilzomib is typically administered twice-weekly at a dose of 27 mg/m² (refer to Table 6), but a once-weekly schedule of 70 mg/m² may be equally effective and safe, and more convenient. Carfilzomib carries a lower risk of neurotoxicity than bortezomib, but a small proportion (5%) of patients can experience serious cardiac side effects. Carfilzomib-based regimens are important options at relapse, and can work well even in patients who are refractory to a bortezomib-containing regimen.

7.4 | Pomalidomide

Pomalidomide is an analog of lenalidomide and thalidomide initially approved in 2013 for the treatment of relapsed refractory multiple myeloma. It has significant activity in relapsed refractory multiple myeloma, even in patients failing lenalidomide.^{140,141} Response rate with pomalidomide plus dexamethasone (Pd) in patients refractory to lenalidomide and bortezomib is approximately 30%.^{59,142} In a randomized trial, Pd was found superior to high-dose dexamethasone

TABLE 8 Results of recent randomized studies in relapsed myeloma

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (Median in months)	P value for progression free survival	Overall survival ^a (Median in months)	P value for overall survival
Lonial et al ^{73,129}	Rd	325	66	28	15		40	N/A
	Elo-Rd	321	79	33	19	<.001	44	0.03
Stewart et al ^{68,130}	Rd	396	67	14	18		40	0.04
	KRd	396	87	32	26	.0001	48	
Moreau et al ⁷⁴	Rd	362	72	7	15		N/A	N/A
	IRd	360	78	12	21	.012	N/A	
Dimopoulos et al ⁷⁰	Rd	283	76	44	18.4	<.001	N/A; 87% at 1 year	NS
	DRd	286	93	76	NR		N/A; 92% at 1 year	
Palumbo et al ⁷¹	Vd	247	63	29	7.2	<.001	N/A; 70% at 1 year	0.30
	DVd	251	83	59	NR		N/A; 80% at 1 year	
San Miguel et al ^{75,131}	Vd	381	55	6	8.1		36	0.54
	Pano-Vd	387	61	11	12	<.0001	40	
San Miguel et al ¹³²	Dex	153	10	0	1.9		8	NS
	Pd	302	31	1	4.0	<.0001	13	
Dimopoulos et al ^{133,134}	Vd	465	63	6	9		40	0.01
	Kd	464	77	13	19	<.0001	48	

^aEstimated from updated publication when available; estimated from survival curves when not reported.

CR, complete response; Dex, high dose dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; Elo-Rd, Elotuzumab, lenalidomide, dexamethasone; IRd, ixazomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; N/A, not available; NS, not significant; Pano-Vd, Panobinostat, bortezomib, dexamethasone; Pd, pomalidomide, dexamethasone; Rd, lenalidomide plus dexamethasone; Vd, bortezomib, dexamethasone.

in patients refractory to other forms of therapy for multiple myeloma (Table 8).¹³² Pomalidomide-containing triplet regimens such as daratumumab, pomalidomide, dexamethasone (DPd) and carfilzomib, pomalidomide, dexamethasone (KPd) are active and are important options at relapse for patients who are considered lenalidomide-refractory. In frail patients and in those with indolent relapse, the doublet regimen of Pd is a reasonable option for patients with indolent relapse.

7.5 | Elotuzumab

Elotuzumab, a monoclonal antibody targeting the signaling lymphocytic activation molecule F7 (SLAMF7).⁷³ Unlike daratumumab, elotuzumab does not have single-agent activity but shows synergistic activity when combined with Rd. In a phase III trial of 646 patients, elotuzumab, lenalidomide, dexamethasone (ERd) was superior to Rd (Table 8).⁷³ Elotuzumab is well tolerated, and was initially approved in 2015 by the FDA to be given in combination with Rd for the treatment of patients with multiple myeloma who have received one to three prior therapies.

7.6 | Ixazomib

Ixazomib is an oral proteasome inhibitor that is active in both the relapsed refractory setting and in newly diagnosed multiple myeloma.^{74,143} It has the advantage of once-weekly oral administration. Compared with bortezomib it has more gastrointestinal adverse events, but lower risk of neurotoxicity. In a randomized controlled trial in relapsed multiple myeloma, ixazomib, lenalidomide, dexamethasone (IRd) was found to improve PFS compared with Rd (Table 8).⁷⁴ Based on these results ixazomib was initially approved by the FDA in 2015 to be given in combination with Rd for the treatment of patients with multiple myeloma who have received at least one prior therapy.

7.7 | Doxorubicin and liposomal doxorubicin

Anthracyclines have marginal single-agent activity in multiple myeloma. A phase III randomized trial found that median time to progression (TTP) was superior with bortezomib plus pegylated liposomal

doxorubicin compared with bortezomib alone, 9.3 months versus 6.5 months, respectively, $P < 0.001$.¹⁴⁴ OS at 15 months was also superior, 76% compared with 65%, respectively, $P = 0.03$. Despite this study, liposomal doxorubicin is infrequently used in the treatment of relapsed multiple myeloma given availability of other active agents. Doxorubicin-containing regimens such as PAD or VDT-PACE may be useful in the treatment of patients with aggressive multiple myeloma refractory to other standard myeloma agents.

7.8 | Panobinostat

Panobinostat is a pan-deacetylase inhibitor initially approved by the FDA in 2015 for the treatment of patients with multiple myeloma who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent.⁷⁵ Its putative mechanism of action is blockade of the aggresome pathway, an alternative route for cells to bypass the lethal effects of proteasome inhibition. By combining bortezomib and panobinostat, there is simultaneous blockade of both proteasome and aggresome pathways.^{145,146} In a randomized trial of 768 patients, bortezomib/dexamethasone plus panobinostat was associated with superior PFS compared with bortezomib/dexamethasone plus placebo.⁷⁵ However, panobinostat therapy is associated with grade 3 diarrhea in approximately 25% of patients, and care should be exercised when using this drug. I recommend a lower initial dose of panobinostat than the approved starting dose, and that bortezomib be used in the once-weekly subcutaneous schedule rather than the twice weekly regimen used in the pivotal trial (Table 6)

7.9 | Other options

Despite the multiple option available, more patients eventually become refractory to all drug classes. Some additional options to consider for relapsed disease in refractory multiple myeloma include bendamustine-containing regimens such as bendamustine, lenalidomide, dexamethasone or bendamustine, bortezomib, dexamethasone.^{147,148} Other options include the addition of panobinostat to a proteasome-inhibitor containing regimen, or the use of quadruplet regimen in which daratumumab is added to a standard triplet regimen. Venetoclax is not approved for use in multiple myeloma, but is commercially available, and appears to have single-agent activity in patients with t(11;14) subtype of multiple myeloma.¹⁴⁹ For young high-risk patients with a suitable donor, allogeneic transplantation is an option as well.

7.10 | Emerging options

There are several investigational approaches that are promising and patients should be considered for clinical trials investigating these approaches. Two of the most exciting options include antigen receptor T cells (CAR-T) targeting B cell maturation antigen (BCMA) such as bb2121,¹⁵⁰ and GSK2857916 (a humanized anti-BCMA antibody that is conjugated to monomethyl auristatin-F, a microtubule disrupting agent).¹⁵¹ Other agents with single-agent activity that are promising include isatuximab (a CD38 monoclonal antibody), marizomib (a new proteasome inhibitor), oprozomib, (an oral proteasome inhibitor related

to carfilzomib), filanesib (a kinesin spindle protein inhibitor), dinaciclib (a cyclin dependent kinase inhibitor), and LGH-447 (a pan PIM kinase inhibitor).

Recommendations

- Patients who are eligible for ASCT should consider ASCT as salvage therapy at first relapse if they have never had a transplant before, or if they have had a prolonged remission with the first ASCT.
- If relapse occurs more than 6 months after stopping therapy, the initial treatment regimen that successfully controlled the multiple myeloma initially can be re-instituted when possible.
- At first relapse, for patients who are not refractory to lenalidomide, my preferred option is DRd. Alternatives include KRd, IRd, and ERd.
- At first relapse, for patients who are refractory to lenalidomide, my preferred option is DPd. Alternatives include DVd, KPd, and VCd
- Patients who have an indolent relapse or who are frail can be treated with oral regimens such as IRd or Pd.
- At second or higher relapse, I switch to a triplet regimen that contains at least 2 new drugs that the patient is not refractory to.
- Additional options to consider in patients with multiple relapses and disease that is refractory to conventional regimens include bendamustine-based regimens, the addition of panobinostat to a proteasome-inhibitor containing regimen, quadruplet daratumumab-containing regimens, multi-drug chemotherapy regimens, allogeneic transplantation in young high risk patients with a suitable donor, and venetoclax in patients with t(11;14) multiple myeloma.
- Patients with more aggressive relapse with plasma cell leukemia or extramedullary plasmacytomas often require therapy with a multi-drug anthracycline containing regimen such as VDT-PACE.
- The duration of therapy has not been well addressed in relapsed multiple myeloma, and in some regimens such as those employing parenteral proteasome inhibitors it may be reasonable to stop therapy once a stable plateau has been reached to limit minimize risks of serious toxicity.

8 | SMOLDERING MULTIPLE MYELOMA

SMM is a stage that is clinically positioned between MGUS and multiple myeloma.¹³⁵ It comprises of a heterogeneous group of patients, some of whom have multiple myeloma which has not yet manifested with MDEs, and some who have premalignant MGUS. Patients with SMM have a risk of progression of approximately 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year thereafter.¹⁹ Patients with the highest risk of progression (ultra-high risk) have now been reclassified as having multiple myeloma by the new IMWG criteria.¹ Within the current definition of SMM (Table 1), there are two groups of patients: high risk (25% per year risk of progression in the first 2 years) and low risk (~ 5% per year risk of progression).¹³⁵ Criteria for high risk SMM are given on Table 9.

TABLE 9 Criteria for high risk smoldering multiple myeloma^a

Bone marrow clonal plasma cells $\geq 10\%$ and any one or more of the following:
Serum M protein ≥ 30 g/L
IgA SMM
Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
Serum involved/uninvolved free light chain ratio ≥ 8 (but less than 100)
Progressive increase in M protein level (Evolving type of SMM) ^b
Bone marrow clonal plasma cells 50%-60%
Abnormal plasma cell immunophenotype ($\geq 95\%$ of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
t (4;14) or del 17p or 1q gain
Increased circulating plasma cells
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

M, monoclonal; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SMM, smoldering multiple myeloma.

^aNote that the term smoldering multiple myeloma excludes patients without end-organ damage who meet revised definition of multiple myeloma, namely clonal bone marrow plasma cells $\geq 60\%$ or serum free light chain (FLC) ratio ≥ 100 (plus measurable involved FLC level ≥ 100 mg/L), or more than one focal lesion on magnetic resonance imaging. The risk factors listed in this Table are not meant to be indications for therapy; they are variables associated with a high risk of progression of SMM, and identify patients who need close follow up and consideration for clinical trials.

^bIncrease in serum monoclonal protein by $\geq 25\%$ on two successive evaluations within a 6 month period.

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Presence of one or more of these factors is associated with a median TTP to multiple myeloma of approximately 2 years. Early studies in SMM failed to show an advantage to early intervention, but were limited by lack of power, safe and effective drugs, and a risk-adapted strategy.^{152,153} A recent randomized trial conducted in Spain found that patients with high risk SMM had significant prolongation of PFS and OS with Rd compared with observation.^{50,154} These are very promising results, and further confirmatory studies are ongoing. Observation is still the standard of care for SMM; however, selected high risk SMM patients with multiple risk factors can be considered for therapy. They are also candidates for clinical trials testing early intervention, some of which are testing intensive therapy with curative intent.¹⁵⁵

Recommendations

- I recommend observation for most patients with SMM.
- Consideration of multiple myeloma therapy can be given to the small subset of patients with SMM who have multiple high risk factors especially if there is progressive rise in monoclonal protein levels.

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AUTHORS' CONTRIBUTION

SVR conceived of the article, researched the literature, and wrote the manuscript.

CONFLICT OF INTERESTS

SVR declares no conflict of interest.

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