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Multiple Myeloma: 2016 update on Diagnosis, Risk-stratification and Management

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Abstract

Disease overview—Multiple myeloma accounts for approximately 10% of hematologic malignancies.

Diagnosis—The diagnosis requires ≥10% clonal bone marrow plasma cells or a biopsy proven plasmacytoma *plus* evidence of one or more multiple myeloma defining events (MDE): CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features felt related to the plasma cell disorder, bone marrow clonal plasmacytosis ≥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.

Risk stratification—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.

Risk-adapted initial therapy—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 months 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 Rd until progression, or alternatively, a triplet regimen such as VRD for approximately 12–18 months.

Maintenance therapy—After ASCT, lenalidomide maintenance is considered for standard risk patients who are not in very good partial response or better, while maintenance with a bortezomib-based regimen is needed for patients with intermediate or high-risk disease.

Management of refractory disease—Patients with indolent relapse can be treated with 2-drug or 3-drug combinations. Patients with more aggressive relapse require a triplet regimen or a combination of multiple active agents.

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Authorship Contribution Statement

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

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SVR declares no conflict of interest.

DISEASE OVERVIEW

Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic malignancies.[1,2] Each year over 20,000 new cases are diagnosed in the United States.[3] The annual *age-adjusted* incidence in the United States has remained stable for decades at approximately 4 per 100,000.[4] Multiple myeloma is slightly more common in men than in women, and is twice as common in African-Americans compared with Caucasians.[5] The median age of patients at the time of diagnosis is about 65 years.[6]

Unlike other malignancies that metastasize to bone, the osteolytic bone lesions in multiple myeloma exhibit no new bone formation.[7] Bone disease is the main cause of morbidity and can be detected on routine skeletal radiographs, magnetic resonance imaging (MRI), or fluoro-deoxyglucose (FDG) positron emission tomography/computed tomographic scans (PET/CT).[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 pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS).[10,11] MGUS is present in over 3% of the population above the age of 50, and progresses to multiple myeloma or related malignancy a rate of 1% per year.[12–15] 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.[16] In some patients, an intermediate asymptomatic but more advanced pre-malignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically.[17] SMM progresses to multiple myeloma at a rate of 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 SMM to multiple myeloma.[18,19]

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 ≥60%, serum free light chain (FLC) ratio ≥100 (provided involved FLC level is ≥100 mg/L), and more than one focal lesion on magnetic resonance imaging (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 (SIFE), and the serum free light chain (FLC) assay.[20] Approximately 2% of patients with multiple myeloma have true non-secretory disease and have no evidence of an M protein on any of the above studies.[6] 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).[21] 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 (GEP) if available can provide additional prognostic value.[22] Serum CrossLaps to measure carboxy-terminal collagen crosslinks (CTX) may be useful in assessing bone turnover and to determine adequacy of bisphosphonate therapy.[23,24] Although plain radiographs of the skeleton are typically required to assess the extent of bone disease, low dose whole body CT, PET/CT and MRI scans are more sensitive and one or more of them are indicated when symptomatic areas show no abnormality on routine radiographs, when there is doubt about the true extent of bone disease on plain radiographs alone, and when solitary plasmacytoma or SMM are suspected.[8,25]

The M protein is considered to be measurable if it is ≥1gm/dL in the serum and or ≥200 mg/day in the urine. The M protein level is monitored by serum and urine protein electrophoresis to assess treatment response every month while on therapy, and every 3–4 months when off-therapy. The serum free light chain assay is used to monitor patients with multiple myeloma who lack a measurable M protein, provided the FLC ratio is abnormal and the involved FLC level is ≥100 mg/L.[26] Response to therapy is assessed using the International Myeloma Working Group uniform response criteria.[27,28]

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).[29,30] On fluorescent in situ hybridization (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).[31–34] 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.[30]

PROGNOSIS AND RISK STRATIFICATION

The median survival is approximately 6–7 years; in patients eligible for ASCT 4 year survival rates exceed 80%. However, there is major variation in survival depending on host

factors, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy.[35,36] Tumor burden in multiple myeloma has traditionally been assessed using the Durie-Salmon Staging (DSS)[37] and the International Staging System (ISS).[38,39] Disease biology best reflected based on the molecular subtype of multiple myeloma (Table 2), and the presence or absence of secondary cytogenetic abnormalities such as del(17p), gain(1q), or del(1p).[21,29] It must be however noted that the interpretation and impact of cytogenetic abnormalities in multiple myeloma vary depending on the disease phase (Table 3).[30] 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 and helps in clinical care as well as in comparison of clinical trial data (Table 4).[40]

It is important to note that in order to ensure uniform availability, only 3 widely available cytogenetic markers are used in the RISS; the Mayo Clinic mSMART risk stratification (www.msmart.org) (Table 5) has additional detail that is valuable in formulating a therapeutic strategy.[41] Patients with standard risk multiple myeloma have a median overall survival (OS) of >7 years while those with high risk disease have a median OS of approximately 3 years despite tandem autologous stem cell transplantation (ASCT).[42] In addition to cytogenetic risk factors, two other markers that are associated with disease aggressiveness and high risk disease are elevated serum lactate dehydrogenase and plasma cell leukemia with evidence of circulating plasma cells on routine peripheral smear examination.

INDICATIONS FOR THERAPY

In order 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 (PFS) but not OS.[43] However, a recent randomized trial found that early therapy with lenalidomide and dexamethasone in patients with high risk SMM can prolong OS.[44] Although these results need further confirmation, they indicate the potential benefit of early intervention in selected asymptomatic patients.

TREATMENT OF NEWLY DIAGNOSED MYELOMA

OS in multiple myeloma has improved significantly in the last 15 years[45] with the emergence of thalidomide,[46] bortezomib,[47] and lenalidomide.[48,49] More recently, 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.[50–70] 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).[71–73] They may cause direct cytotoxicity by inducing free radical

mediated DNA damage.[74] They also have anti-angiogenic, immunomodulatory, and tumor necrosis factor alpha inhibitory properties. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors.[75–77] Elotuzumab and daratumumab are monoclonal antibodies targeting SLAMF7 and CD38 respectively.[68,69,78] Panobinostat is a deacetylase inhibitor.[70,79]

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.[42] The data to support their use from recent randomized trials using new active agents for multiple myeloma are provided in Table 7.[53,58,80–84] 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.[85,86] Recent data show that MRD negative status (as estimated by next generation molecular methods or flow cytometry) has favorable prognostic value. However, additional trials are needed to determine if changes in treatment need to be made based on MRD status.[84,87–89] At present, no specific changes in therapy are recommended based on MRD status.

Options for 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 (Rd, VRD, VTD, VCD, etc) 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.[53]

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.[53] Stem cell collection with granulocyte stimulating factor (G-CSF) alone may be impaired when Rd is used as induction therapy.[90] 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.[91,92] 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.[93–95]

Bortezomib-containing regimens—Three-drug regimens containing bortezomib such as bortezomib-cyclophosphamide-dexamethasone (VCD), bortezomib-thalidomide-dexamethasone (VTD), and bortezomib-lenalidomide-dexamethasone (VRD) are highly active in newly diagnosed multiple myeloma.[64] In a recent randomized trial conducted by the Southwest Oncology Group (SWOG), PFS and OS were significantly superior with

VRD compared with Rd (Table 7).[82] Other studies have shown superior response rates and PFS with VTD compared with other doublet regimens.[61,96] A recent randomized trial also found that the triplet regimen of VTD which contains a proteasome inhibitor (bortezomib) and an immunomodulatory agent (thalidomide) is superior to VCD.[83] Bortezomib-containing regimens also appear to partially overcome the poor prognosis associated with the t(4;14) translocation, del(17p) and certain other cytogenetic abnormalities.[61,97–99] Based on these data VRD or VTD are the preferred regimens for initial therapy in transplant eligible patients, and in fit transplant ineligible patients (Figure 1).

In initial studies, one of the main problems with bortezomib-containing regimens was the incidence of peripheral neuropathy. Neuropathy with bortezomib can occur abruptly, and can be significantly painful and debilitating. However, recent studies show that the neurotoxicity of bortezomib can be greatly diminished by administering bortezomib once a week instead of twice-weekly,[59,60] and by administering the drug subcutaneously instead of the intravenous route.[100] The once-weekly subcutaneous bortezomib schedule (see Table 6) has made serious neuropathy an uncommon problem, and has made regimens such as VCD and VRD much more tolerable. Unlike lenalidomide, bortezomib does not appear to have any adverse effect on stem cell mobilization.[101]

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.[102,103] 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.

Multi-drug combinations—Besides the regimens discussed above, another option is multi-agent combination chemotherapy, such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide).[97,98] VDT-PACE is 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 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, I favor VRD as initial therapy for 3–4 months, followed by stem cell harvest and ASCT. In patients who are tolerating therapy and responding well, it is equally reasonable to continue initial therapy after stem cell collection, reserving ASCT for first relapse; with such a strategy, therapy is usually stopped after 12–18 months.*
- *In high-risk patients, I favor KRD as initial therapy for 4 cycles followed by ASCT and then maintenance with a proteasome inhibitor-based regimen for at least 2 years.*

- *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. Plasma exchange is continued daily until the serum free light chain 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.*

Options for 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.[42]

Although the melphalan-based regimens discussed below have been extensively tested in these patients, they are falling out of favor 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. In general, initial therapy in patients who are not candidates for transplant is given until progression if Rd is used, and for a fixed duration of time (12–18 months) with triplet regimens. Maintenance therapy is considered for intermediate and high-risk patients.

Melphalan, prednisone, thalidomide (MPT)—Six randomized studies have compared melphalan, prednisone, thalidomide (MPT) with MP.[56,57,104–107] An OS advantage has been observed in three trials.[56,57,106] Two metaanalyses show a clear superiority of MPT over melphalan, prednisone (MP).[108,109] MPT is associated with a grade 3–4 toxicity rate of over 50%, and a DVT risk of 20%.[104]

Lenalidomide plus dexamethasone (Rd)—Rd is an attractive option for the treatment of elderly patients with newly diagnosed multiple myeloma because of its excellent tolerability, convenience, and efficacy. An international phase III trial compared MPT versus Rd for 18 months versus Rd until progression in 1623 patients.[81] 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 provides the first evidence that OS can be improved in patients ineligible for transplant using a regimen that does not contain melphalan.

Bortezomib-based regimens—VMP is a bortezomib-based regimen that has shown better OS compared with MP.[58,80] Substituting melphalan with thalidomide in the VMP regimen has not shown an advantage; in a randomized trial, bortezomib, thalidomide, prednisone (VTP) was not superior to VMP.[59] The risks of melphalan can be reduced by using cyclophosphamide instead, and studies show this substitution does not alter efficacy.[110] 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. A randomized trial found superior PFS and OS with a 4-drug regimen of VMPT compared with VMP in a randomized phase III trial.[60] However, melphalan-based regimens have fallen out of favor. VRD has shown a survival benefit compared with Rd, and is the preferred choice for a bortezomib-based regimen.[82] Other alternatives include VCD and VTD discussed earlier.

Other regimens—MP is not recommended unless there is lack of availability of other options.[111,112] TD is inferior to MP, and is not recommended in elderly patients.[113] The addition of lenalidomide to MP (MPR) does not improve PFS or OS compared with MP alone.[114] An ECOG randomized trial (E1A06) did not find any major benefit of MPR over MPT.[115]

Recommendations

- *In standard-risk patients, I prefer VRD as initial therapy administered for approximately 12 months. Rd given until progression is an alternative*.
- *In frail elderly patients, I prefer Rd as initial therapy, administered until progression. Dexamethasone may be started at 20 mg once a week as much as possible after the first 4–6 months, and possibly discontinued after the first year*.
- *In intermediate-risk patients, I favor VRD as initial therapy for approximately one year followed if possible by a lower intensity (one dose every two weeks) maintenance schedule of bortezomib for 2 years*.
- *In high-risk patients, I favor KRD as initial therapy for approximately one year followed by a lower intensity maintenance schedule of a proteasome inhibitor-based regimen*.

Role of Hematopoietic Stem Cell Transplantation

Autologous stem cell transplantation (ASCT)—ASCT improves median OS in multiple myeloma by approximately 12 months.[116–119] However, 3 randomized trials show that OS is similar whether ASCT is done early (immediately following 4 cycles of induction therapy) or delayed (at the time of relapse as salvage therapy).[120–122] A more recent trial by the Intergroupe Francophone du Myelome (IFM) and the Dana-Farber Cancer Institute (DFCI) compared early versus delayed ASCT in patients treated with VRD followed by lenalidomide maintenance.[84] Patients were randomized to receive either VRD (3 cycles) followed by ASCT and then VRD consolidation (2 cycles) versus VRD x 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). Two randomized trials have found benefit with tandem (double) versus single ASCT, with the benefit primarily seen in patients failing to achieve CR or VGPR with the first ASCT.[123,124] Two other randomized trials, however, have yet to show significant improvement in OS with double ASCT.[125,126] Tandem ASCT may be of value in eligible patients with del(17p) at diagnosis.[127]

Allogeneic Transplantation—The role of allogeneic and nonmyeloablative-allogeneic transplantation in multiple myeloma is controversial.[128,129] The TRM (10–20%) and high GVHD rates even with non-myeloablative allogeneic transplantation are fairly high.[130] Although allogenic 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 considered only if patients fail to achieve a VGPR with the first ASCT, or in selected patients with del(17p).*
- *At present, allogeneic transplantation as frontline therapy should largely be considered investigational.*

Post-transplant maintenance therapy

There is confusion about whether post-transplant strategies should be referred to as “consolidation” or “maintenance,” but these distinctions are semantic and do not distract from the main questions: Should we administer post-transplant therapy? Who should receive such therapy? Thalidomide has shown modest PFS and OS benefit as maintenance therapy in two randomized trials, but has drawbacks of significant non-hematologic toxicity.[131,132] Two randomized trials have shown better PFS with lenalidomide as post ASCT maintenance therapy.[133,134] However, patients in the control arm of these trials lacked uniform access to the active drug (thalidomide or lenalidomide) at relapse, and it is not clear whether the PFS improvement will be neutralized since patients in the control arm can always initiate the same therapy at the time of first relapse.[86] There is also a clear increased risk of second cancers with lenalidomide maintenance in both trials. Further, although one of the two trials is showing an OS benefit with lenalidomide maintenance, the benefit seems to be restricted to patients who received lenalidomide as induction therapy (and hence were likely known to be responsive). We need more confirmatory results on the survival benefit to determine patients who most benefit from maintenance, and to determine the optimal duration of maintenance.[135]

In one study, bortezomib administered every other week post-transplant produced better OS than thalidomide maintenance.[127] Although more studies are needed, bortezomib-based maintenance may be important for intermediate- and high-risk patients.

Recommendations

- *At this point it is not clear whether all patients should receive maintenance therapy post ASCT, but results of the maintenance trials must be discussed with the patient, along with the pros and cons of maintenance versus therapy at first relapse.*
- I recommend lenalidomide maintenance for standard-risk patients who fail to achieve VGPR after ASCT
- I recommend maintenance with a proteasome inhibitor such as bortezomib for patients with intermediate- and high-risk multiple myeloma

TREATMENT OF RELAPSED MULTIPLE MYELOMA

Almost all patients with multiple myeloma eventually relapse. The remission duration in relapsed multiple myeloma decreases with each regimen.[136] 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.[137] The choice of a treatment regimen at relapse is complicated and is affected by many factors including the type of prior regimen, number of prior lines of therapy, aggressiveness of the relapse. For example, a patient relapsing on VRD may need a regimen that contains at least one or more drugs with a unique mechanism of action, such as an alkylating agent or a monoclonal antibody. 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).[69,70,138–141]

Bortezomib and Lenalidomide based regimens

Approximately one-third of patients with relapsed refractory multiple myeloma respond to bortezomib when used as a single agent.[47] Two large phase III trials have shown superior TTP and OS with lenalidomide (25 mg oral days 1–21 every 28 days) plus dexamethasone compared to placebo plus dexamethasone in relapsed multiple myeloma.[142,143] As in newly diagnosed multiple myeloma, bortezomib can be combined with other active agents to produce highly active triplet regimens such as VCD, VTD, and VRD, representing some of the most active regimens in relapsed disease. For example, in a study of 85 patients with refractory multiple myeloma treated with VTD, 63% achieved PR including 22% near CR.[144] Similarly, VRD has also shown significant activity in relapsed, refractory multiple myeloma.[145]

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, $P<0.001$.[146] 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.

Carfilzomib

Carfilzomib is a novel keto-epoxide tetrapeptide proteasome inhibitor 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), 266 patients were treated with single-agent carfilzomib, including 80% of patients who were refractory or intolerant to both bortezomib and lenalidomide.[65] The overall response rate was 24%, and the median duration of response was 7.8 months. The most common side effects were fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%).[65] In a phase III trial of 792 patients, KRD was associated with better response rates, PFS, and OS compared with Rd.[139] In another randomized trial carfilzomib/dexamethasone demonstrated a doubling of PFS compared with bortezomib/dexamethasone in relapsed multiple myeloma; PFS 18.7 months versus 9.4 months, respectively, P<0.001.[140] However, the dose of carfilzomib used in this trial (56mg/m^2) was twice the approved dose, and carries a much higher cost compared with bortezomib. Further the dosing of bortezomib used in this trial was suboptimal (twice-weekly schedule) making it difficult to make definitive conclusions. Carfilzomib does have lower risk of neurotoxicity than bortezomib, but a small proportion (5%) of patients may experience serious cardiac side effects.

Pomalidomide

Pomalidomide is an analog of lenalidomide and thalidomide 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.[147,148] Response rate in patients refractory to lenalidomide and bortezomib is approximately 30%.[54,149] In a randomized trial, pomalidomide plus low dose dexamethasone was found superior to high-dose dexamethasone in patients refractory to other forms of therapy for multiple myeloma.[138] Pomalidomide is an analog of lenalidomide and thalidomide approved for the treatment of relapsed refractory multiple myeloma. It has significant activity in relapsed refractory multiple myeloma, even in patients failing lenalidomide,[147,148] or lenalidomide and bortezomib.[54,149] In a randomized trial of 302 patients with refractory multiple myeloma, Pd was found superior to high-dose dexamethasone, median PFS 4.0 months versus 1.9 months, respectively, P<0.0001).[138] As with Rd, the doublet regimen of Pd is a reasonable option for patients with indolent relapse. But more often, pomalidomide needs to be administered in combinations such as pomalidomide, cyclophosphamide, prednisone (PCP), pomalidomide, bortezomib, dexamethasone (PVD), or carfilzomib, pomalidomide, dexamethasone (KPD).

Panobinostat

Panobinostat is a pan-deacetylase inhibitor 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.[70] It is the first agent from a new class of drugs with meaningful clinical activity in multiple myeloma in nearly 15 years. Its putative mechanism of action is to block 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.[150,151] In a randomized trial of 768 patients, bortezomib/dexamethasone plus panobinostat was associated with superior PFS compared with bortezomib/dexamethasone plus placebo; median PFS 12 months versus 8.1months, respectively, P<0·0001).[70] However, panobinostat therapy was 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.[79]

Daratumumab

Daratumumab targeting CD38 has shown promise in relapsed, refractory multiple myeloma.[78] In a phase II trial, daratumumab as a single-agent was produced a response rate of approximately 30% in heavily pre-treated patients.[68] Based on these findings, daratumumab was 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 immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent. It is likely that in clinical practice, daratumumab will be used in combinations with other active regiments, since patients who will benefit from the drug will be relapsing from triplet combinations, and a higher response rate is needed in a timely manner.

Elotuzumab

Elotuzumab, a monoclonal antibody targeting the signaling lymphocytic activation molecule F7 (SLAMF7), has also shown activity in relapsed multiple myeloma.[69] Unlike daratumumab, elotuzumab does not appear to have any single-agent activity. However, it has shown synergistic activity when combined with Rd. In a phase III trial of 646 patients, elotuzumab plus Rd was superior to Rd in terms of PFS, median PFS 19.4 months versus 14.9 months, respectively, P<0.001.[69] Elotuzumab is well tolerated, and was 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.

Ixazomib

Ixazomib is an oral proteasome inhibitor that is active in both the relapsed refractory setting and in newly diagnosed multiple myeloma. 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.[141] Based on these results ixazomib was 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.

Other Emerging Options

Other promising agents include isatuximab (a CD38 monoclonal antibody), marizomib, a new proteasome inhibitor, oprozmib, an oral proteasome inhibitor related to carfilzomib; filanesib, a kinesin spindle protein inhibitor; dinaciclib, a cyclin dependent kinase inhibitor; venetoclax, a selective BCL-2 inhibitor, and LGH-447, a pan PIM kinase inhibitor. Each of these has shown single agent activity in relapsed multiple myeloma.

Recommendations

- *Patients who have cryopreserved stem cells early in the disease course should consider ASCT as salvage therapy at first relapse.*
- *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.*
- *Patients who have an indolent relapse or who are frail can be treated with Ixazomib-Rd, Elotuzumab-Rd, or pomalidomide-dexamethasone.*
- Patients with symptomatic or aggressive relapse can be treated with KRD or KPD
- *Options for patients with disease refractory to lenalidomide and bortezomib include daratumumab-based regimens such as daratumumab-pomalidomide-dexamethasone; or the addition of panobinostat to a proteasome-inhibitor; and regimens containing doxorubicin or liposomal doxorubicin.*
- *Patients with more aggressive relapse with plasma cell leukemia or extramedullary plasmacytomas often require therapy with a combination of active agents, eg., 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 in order to limit minimize risks of serious toxicity.*

SMOLDERING MULTIPLE MYELOMA

SMM is a stage that is clinically positioned between MGUS and multiple myeloma.[152] It comprises of a heterogenous 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.[17] 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).[152] Criteria for high risk SMM are given on Table 9. 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.[153,154] A recent randomized trial conducted in Spain found that patients with high risk SMM had an OS benefit when treated with Rd compared with observation; 3-year survival rate 94% versus 80%, respectively, P=0.03.[44] 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.

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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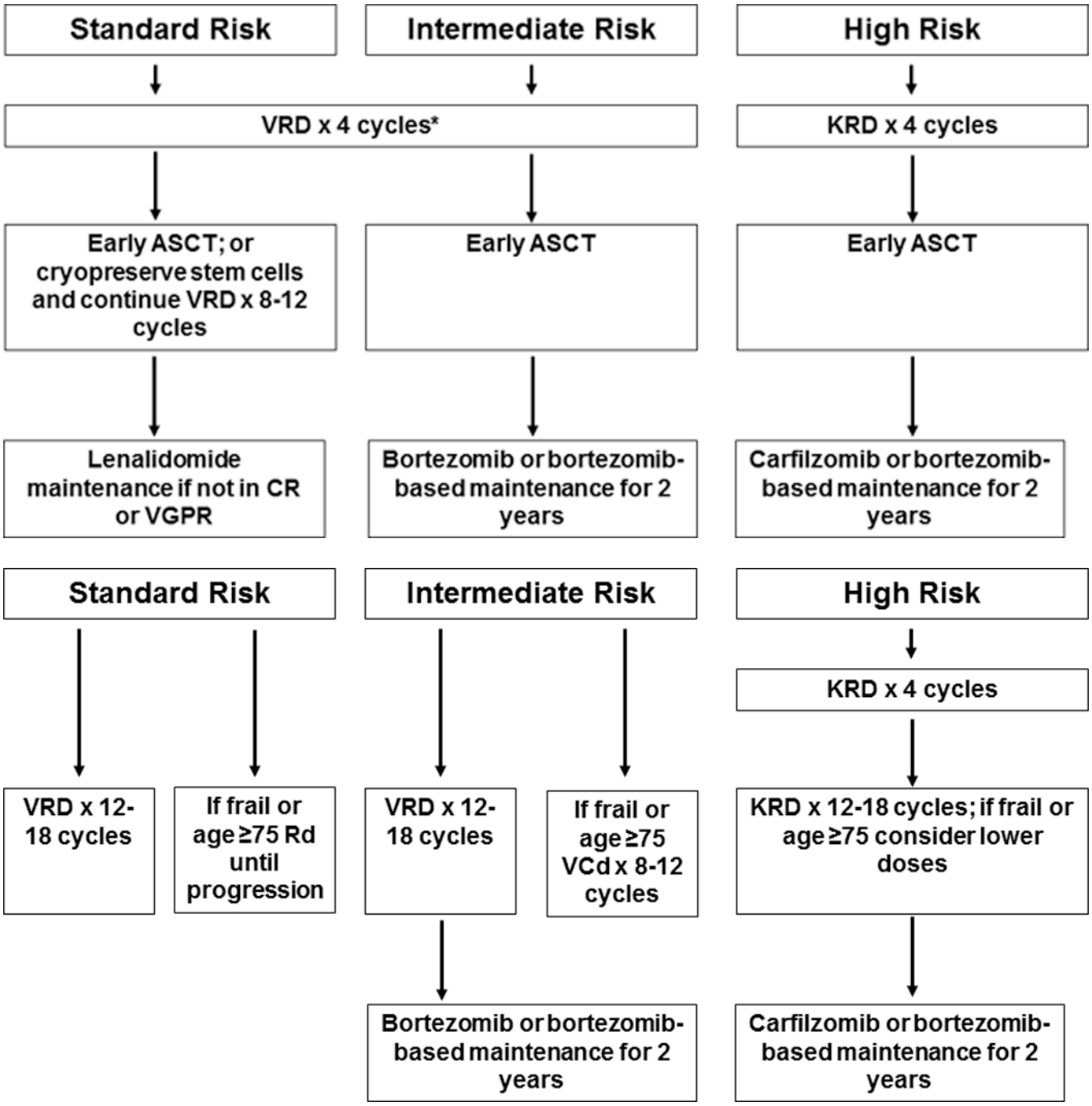
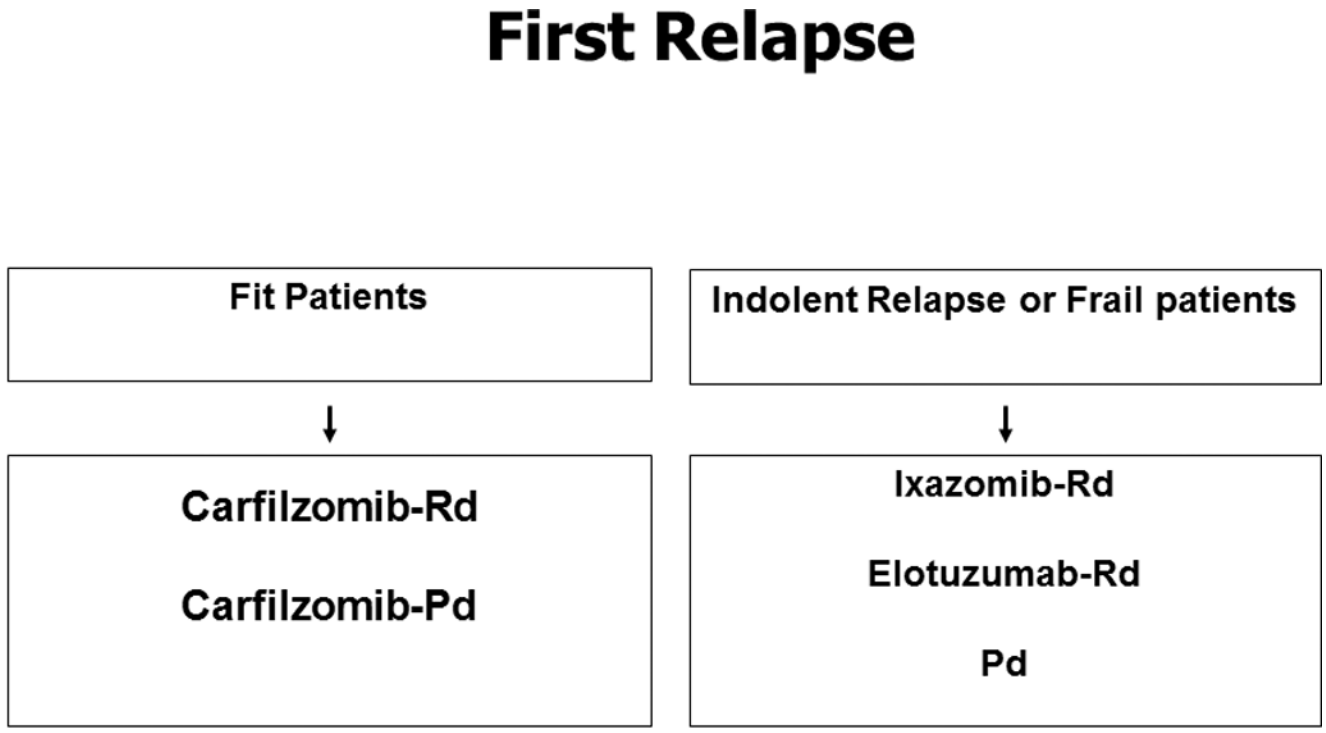


Figure 1.

Approach to the treatment of newly diagnosed multiple myeloma in transplant eligible (**A**) and transplant ineligible (**B**) patients

Abbreviations: VRD, bortezomib, lenalidomide, dexamethasone; KRD, carfilzomib, lenalidomide, dexamethasone; Rd, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; ASCT, autologous stem cell transplantation; CR, complete response; VGPR, very good partial response

Reproduced from: Rajkumar SV. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. Am J Hematol 2014;89:998–1009.



*Consider salvage ASCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first ASCT;

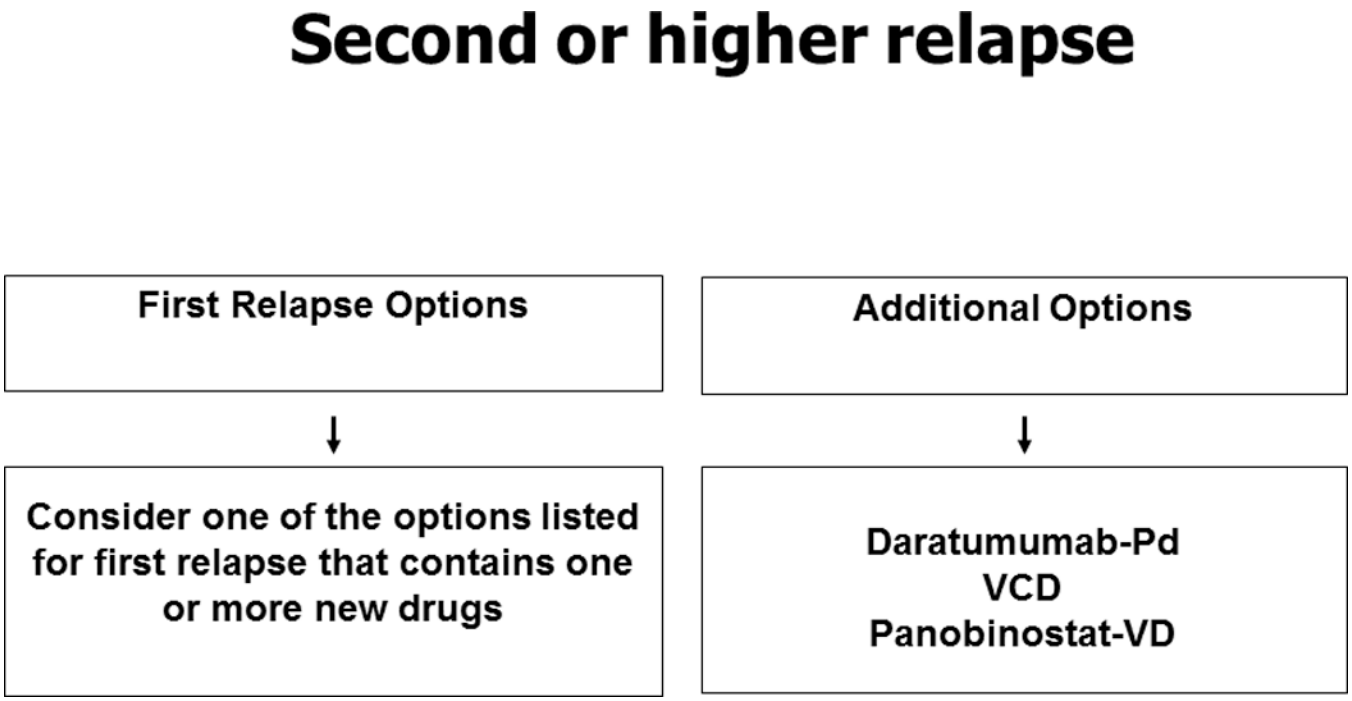


Figure 2.

Suggested options for the treatment of relapsed multiple myeloma in first relapse (**A**) and second or higher relapse (**B**)

Abbreviations: Rd, lenalidomide, dexamethasone; PD, pomalidomide, dexamethasone; Rd, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, dexamethasone; ASCT, autologous stem cell transplantation

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: • Serum monoclonal protein (non-IgM type) <3gm/dL • Clonal bone marrow plasma cells <10% * • 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: • Serum monoclonal protein (IgG or IgA) ≥3gm/dL, or urinary monoclonal protein ≥500 mg per 24h and/or clonal bone marrow plasma cells 10–60% • Absence of myeloma defining events or amyloidosis
Multiple Myeloma	Both criteria must be met: • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma • Any one or more of the following myeloma defining events: – Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: ♦ 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 5mm in size)
IgM Monoclonal gammopathy of undetermined significance (IgM MGUS)	All 3 criteria must be met: • Serum IgM monoclonal protein <3gm/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: • 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/24h

Disorder	Disease Definition
Solitary Plasmacytoma	All 4 criteria must be met • 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
Solitary Plasmacytoma with minimal marrow involvement **	All 4 criteria must be met • 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 SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-e548.

* A 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

** Solitary plasmacytoma with 10% or more clonal plasma cells is considered as multiple myeloma

Table 2

Primary Molecular Cytogenetic Classification of Multiple Myeloma

Subtype	Gene(s)/chromosomes affected*	Percentage of myeloma patients
Trisomic MM	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21	***42***
IgH translocated MM		***30***
t(11;14) (q13;q32)	*CCND1* (cyclin D1)	15
t(4;14) (p16;q32)	*FGFR-3* and MMSET	6
t(14;16) (q32;q23)	*C-MAF*	4
t(14;20) (q32;q11)	*MAFB*	<1
Other IgH translocations *	*CCND3* (cyclin D3) in t(6;14) MM	5
Combined IgH translocated/trisomic MM	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 S et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. Blood 2012; 119:2100. © American Society of Hematology.

* Includes the t(6;14)(p21;q32) translocation, and rarely, other IgH translocations involving uncommon partner chromosomes

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

FISH, fluorescent in situ hybridization; TTP, time to progression; OS, overall survival; SMM, Smoldering multiple myeloma, MM, multiple myeloma; ASCT, autologous stem cell transplantation

Reproduced from Rajan AM, Rajkumar SV. Blood Cancer J. 2015;5: e365

Table 4

Revised International Staging System for Myeloma[40]

Stage
Stage 1 All of the following: • 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 • Not fitting Stage I or III
Stage III Both of the following: • 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 A, et al. J Clin Oncol;2015;33:2863–2869.

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)	

Am J Hematol. Author manuscript; available in PMC 2017 July 01.

Table 6

Major Treatment Regimens in Multiple Myeloma

Regimen	Usual Dosing Schedule*
Melphalan-Prednisone (MP) (7-day schedule)[50]	Melphalan 8–10 mg oral days 1–7 Prednisone 60 mg/day oral days 1–7 Repeated every 6 weeks
Thalidomide-Dexamethasone (TD) **[51,52]	Thalidomide 200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Lenalidomide-Dexamethasone (Rd)[53]	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)[54]	Pomalidomide 4 mg days 1–21 Dexamethasone 40 mg orally on days on days 1, 8, 15, 22 Repeated every 4 weeks
Bortezomib-Dex (VD) **[55]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks‡
Melphalan-Prednisone-Thalidomide (MPT)[56,57]	Melphalan 0.25 mg/kg oral days 1–4 (use 0.20 mg/kg/day oral days 1–4 in patients over the age of 75) Prednisone 2 mg/kg oral days 1–4 Thalidomide 100–200 mg oral days 1–28 (use 100 mg dose in patients >75) Repeated every 6 weeks
Bortezomib-Melphalan-Prednisone (VMP) **[58–60]	Bortezomib 1.3 mg/m^2 intravenous 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) **[61]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22 Thalidomide 100–200 mg oral days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks x 4 cycles as pre-transplant induction therapy
Bortezomib- Cyclophosphamide-Dexamethasone ** (VCD or CyBorD)[62,63]	Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 and 22 Bortezomib 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Dexamethasone 40 mg orally on days on days 1, 8, 15, 22 Repeated every 4 weeks†
Bortezomib-Lenalidomide-Dexamethasone (VRD) **[63,64]	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15 Lenalidomide 25 mg oral days 1–14 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 weeks†
Carfilzomib[65]	Carfilzomib 20 mg/m^2 (Cycle 1) and 27 mg/ m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Repeated every 4 weeks†

Regimen	Usual Dosing Schedule*
Carfilzomib- Cyclophosphamide-Dexamethasone (CCyD) ‡‡[66]	Carfilzomib 20 mg/m^2 (Cycle 1) and 36 mg/ m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 Dexamethasone 40 mg orally on days on days 1, 8, 15 Repeated every 4 weeks†
Carfilzomib-Lenalidomide-Dexamethasone (KRD)[67]	Carfilzomib 20 mg/m^2 (Cycle 1) and 27 mg/ m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg oral days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks
Daratumumab[68]	16 mg/kg intravenously weekly x 8 weeks, every 2 weeks x 16 weeks, then once monthly
Elotuzumab-Lenalidomide-Dexamethasone[69]	10 mg/ kg intravenously weekly x 8 weeks, and then every 2 weeks Lenalidomide 25 mg oral days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Lenalidomide-Dexamethasone repeated in usual schedule every 4weeks
Panobinostat-Bortezomib **[70]	Panobinostat 20 mg orally three times a week x 2 weeks Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15 Repeated every 3weeks

*All doses need to be adjusted for performance status, renal function, blood counts, and other toxicities

**Doses of dexamethasone and/or bortezomib reduced based on subsequent data showing lower toxicity and similar efficacy with reduced doses.

†The 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.

‡Omit 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.

‡‡Dosing based on trial in newly diagnosed patients; in relapsed patients cycle 2 Carfilzomib dose is 27 mg/m2 consistent with approval summary

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	3 year Overall Survival rate (%)*	Overall survival (Median in months)*	P value for overall survival
Rajkumar et al[53]	RD	223	81	50	19.1		75	NR	
	Rd	222	70	40	25.3	0.026	74	NR	0.47
San Miguel et al; Mateos et al **[58,80]	MP	331	35	8	16.6		54	43	
	VMP	337	71	41	24	<0.001	69	NR	<0.001
Benboubker et al[81]	MPT	547	62	28	21.2	<0.001	63	48	0.016†
	Rd × 18 months	541	73	43	20.7		68	53	
	Rd till progression	535	75	44	25.5		72	56	
Durie et al[82]	Rd	232	N/A	N/A	31.0	0.007	75	63	0.011
	VRd	242	N/A	N/A	43.0		85	NR	
Moreau et al[83]	VCD	170	84	66	N/A		N/A	N/A	N/A
	VTD	170	92	77	N/A	N/A	N/A	N/A	
Attal et al[84]	VRD	350	N/A	46% CR	NR; 48% @3 years		88% at 3 years	NR	0.25
	VRD-ASCT	350	N/A	58% CR	NR; 61% at 3 years	<0.001	88% at 3 years	NR	

*Estimated from survival curves when not reported

**Progression free survival not reported, numbers indicate time to progression

†Rd until progression versus MPT

Abbreviations: MP, melphalan plus prednisone; MPT, melphalan plus prednisone plus thalidomide; VMP, bortezomib plus melphalan plus prednisone; Rd, lenalidomide plus dexamethasone; TD, thalidomide plus dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; VRD, bortezomib, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; N/A, not available; NS, not significant; CR, complete response; VGPR, very good partial response.

Reproduced from Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc 2016;91:101–119

Table 8

Results of Recent Randomized Studies in Relapsed Myeloma

Trial	Regimen	No. of patients	Overall Response rate (%)	CR (%)	Progression-free survival (Median in months)	P value for Progression free survival	Overall survival*	P value for Overall survival
Lonial et al[69]	Rd	325	66	7	14.9		N/A	N/A
	Elo-Rd	321	79	4	19.4	<0.001	N/A	
San Miguel et al[70]	Vd	381	55	6	8.1		30.4 (median in months)	0.26
	Pano-Vd	387	61	11	12	<0.0001	33.7 (median in months)	
San Miguel et al[138]	Dex	153	10	0	1.9		8 (median in months)	NS
	Pd	302	31	1	4.0	<0.0001	12.7 (median in months)	
Stewart et al[139]	Rd	396	67	14	17.6		2-year survival 65%	0.04
	KRd	396	87	32	26.3	0.0001	2-year survival 73.3%	
Dimopoulos et al[140]	Vd	465	63	6	9.4		2-year survival 65%	0.06
	Kd	464	77	13	18.7	<0.0001	2-year survival 72%	
Moreau et al[141]	Rd	362	75	7	14.7		N/A	N/A
	IRd	360	78	12	20.6	0.012	N/A	

*Estimated from survival curves when not reported

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

Reproduced from: Rajkumar SV. Myeloma today: disease definitions and treatment advances. Am J Hematol 2016;91;90–100.

Table 9

Criteria for High Risk Smoldering Multiple Myeloma *

Bone marrow clonal plasma cells ≥10% and any one or more of the following:
Serum M protein ≥30g/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) †
Bone marrow clonal plasma cells 50–60%
Abnormal plasma cell immunophenotype (≥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

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

* Note 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 ≥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

† Increase in serum monoclonal protein by ≥25% on two successive evaluations within a 6 month period

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