

Multiple Myeloma: Diagnosis and Treatment Options

MULTIPLE MYELOMA (MM), the second most commonly diagnosed hematologic cancer in the United States, is the uncontrolled proliferation of malignant monoclonal plasma cells in the bone marrow.^{1,2} MM is most frequently diagnosed among people aged 65 to 74 years (the median age at diagnosis is 69), men, and people of African American descent (2013-2017).² It is estimated that there were 32,270 new cases and 12,830 deaths from MM in 2020. The 5-year relative survival rate of MM (2010-2016) is 53.9%, with the median age at death being 75 years.²

To diagnose MM, practitioners must distinguish it from other plasma cell neoplasms/dyscrasias.³ In addition to the patient's history and physical examination, numerous studies are needed.³ To determine whether the patient's MM is symptomatic or asymptomatic, the National Comprehensive Cancer Network (NCCN) recommends a complete blood count, a peripheral blood smear, blood urea nitrogen and creatinine, creatinine clearance, serum electrolytes, liver function tests, serum calcium, albumin, lactate dehydrogenase, and β_2 -microglobulin.³

Along with these studies, the NCCN also recommends additional serum and urine analyses. The serum is analyzed to determine immunoglobulin levels, how much monoclonal protein is present (through serum protein electrophoresis), and the type of M protein involved (through serum immunofixation electrophoresis). This information enables practitioners to monitor disease progression and treatment response.³ Urine analyses include 24-hour total protein, urine immunofixation electrophoresis, and urine protein electrophoresis.³

Together with the previous studies, the NCCN also recommends the following studies:

- **BONE MARROW EVALUATION:** A bone marrow evaluation is necessary because a major criterion for diagnosing MM is whether the percentage of clonal bone marrow plasma cells is at least 10%.³
- **SERUM FREE LIGHT-CHAIN ASSAY:** The serum free light-chain assay is a sensitive way to screen for MM. It informs prognosis and is necessary to demonstrate stringent complete response according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.³
- **CYTOGENETIC STUDIES:** Cytogenetic studies can identify certain MM disease subtypes. Specific amplifications, deletions, and translocations have occurred in patients with MM.³
- **IMAGING:** Imaging detects bone disease. For the initial diagnostic work-up, the NCCN recommends fluorodeoxyglucose-positron emission tomography/computed tomography (CT) or whole-body low-dose CT. When preferred imaging is unavailable, a skeletal survey may be used.³

These study results can then be used to see whether the patient fulfills the criteria for MM (symptomatic). The diagnosis requires “clonal bone marrow plasma cells at least 10% or biopsy-proven bony or extramedullary plasmacytoma” and any CRAB criteria or SLiM biomarkers.³ CRAB criteria include calcium greater than 11 mg/dL; renal insufficiency (creatinine > 2 mg/dL or creatinine

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clearance less than 40 mL/min); anemia (hemoglobin < 10 g/dL or 2 g/dL < normal); and bone lesions.³ SLiM biomarker criteria include 60% or more clonal plasma cells in the bone marrow; involved/uninvolved free light chain (FLC) ratio at least 100 with the involved FLC being at least 100 mg/L; and MRI with “more than 1 focal marrow (nonosteolytic) lesion.”³

Fortunately, newer agents have demonstrated improved clinical outcomes or are under investigation for treating RRMM.

After a patient receives a diagnosis of symptomatic MM, they will first receive primary therapy.³ The NCCN’s preferred primary therapy options for transplant candidates include bortezomib/lenalidomide/dexamethasone and bortezomib/cyclophosphamide/dexamethasone.³ Nontransplant candidates are also eligible for many of the same regimens as transplant candidates.³ The NCCN prefers 3-drug regimens for their higher response rates and depth of response, but 2-drug regimens may be appropriate for patients who are elderly and/or frail.³

Those eligible for a transplant then receive high-dose chemotherapy and autologous hematopoietic cell transplant (HCT).³ Every patient should be evaluated for HCT. Depending on the setting, any of the following 3 types of HCT may be appropriate: single autologous HCT, tandem HCT (when a second course of high-dose therapy and HCT is given within 6 months of the first course), or an allogeneic HCT.³

Following primary therapy, patients begin maintenance. Under the maintenance therapy discussion, the NCCN highlights lenalidomide, bortezomib, and ixazomib. Single-agent lenalidomide is a preferred regimen.³ Although lenalidomide does not have the same neurologic toxicity as thalidomide, it does increase the risk of certain toxicities, including the rate of severe neutropenia and the risk of secondary cancer.³ Bortezomib is notable as an option for both transplant-eligible and -ineligible patients.³ Ixazomib is a category 1 “other recommended” therapy for those who are transplant eligible.³

MM almost invariably progresses or relapses, generally while patients are receiving therapy.⁴ The IMWG defines 3 types of relapse: clinical relapse, relapse from complete response (only if the end point is disease-free survival), and relapse from minimal residual disease (MRD) negative (only if the end point is disease-free survival).⁵

Each type of relapse is indicated by 1 or more of the specified criteria. Clinical relapse criteria include a hypercalcemia that is greater than 11 mg/dL; a decrease in hemoglobin of at least 2 g/dL that is not related to therapy or other nonmyeloma-related conditions; an increase in serum creatinine by 2 mg/dL or more from the start of the therapy that is attributable to myeloma; hyperviscosity related to serum paraprotein; a definite increase, which is defined as a 50% (and at least 1-cm) increase as measured serially by the sum of the products of the maximal perpendicular diameters of measured lesions in the size of existing plasmacytomas or bone lesions; development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); and direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder.⁵

Complete response criteria include the development of at least 5% plasma cells in the bone marrow; the reappearance of serum or urine M protein by immunofixation or electrophoresis; and the appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).⁵

Relapse from MRD-negative criteria include development of at least 5% clonal plasma cells in the bone marrow; loss of the MRD-negative state by evidence of clonal plasma cells on next-generation flow or next-generation sequencing, or positive imaging study for recurrence of myeloma; reappearance of serum or urine M protein by immunofixation or electrophoresis; and appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).⁵

Fortunately, newer agents including immunomodulators (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies (mAbs), histone deacetylase inhibitors (HDACis), chimeric antigen receptor (CAR) T-cell therapy, nuclear export inhibitors/selective inhibitors of nuclear export (SINEs), and bispecific monoclonal antibodies (BsMAbs) have demonstrated improved clinical outcomes or are under investigation for treating RRMM.⁶

Immunomodulators

The mechanism(s) of action for IMiDs are incompletely understood, but it is believed that they (1) break down intrinsic proteins by binding to cereblon; (2) promote myeloma cell cycle arrest and apoptosis by inhibiting oncogenes and increasing expression of tumor suppressor

genes; (3) inhibit angiogenesis, growth factor production, and the differentiation of osteoclasts; and (4) enhance natural killer (NK) cell activity and other immune effects.⁶ Thalidomide, lenalidomide, and pomalidomide are 3 IMiDs used to treat certain patients with MM.⁶

Thalidomide was initially approved in 1998 and has a black box warning for embryo-fetal toxicity and venous thromboembolism. It is indicated in combination with dexamethasone to treat patients with a new diagnosis of MM.⁷ It is the predecessor to lenalidomide and pomalidomide.⁶

Lenalidomide was initially approved in 2005 and has a black box warning for embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism. Its indications are less restrictive than those of other myeloma agents. For MM, it is indicated in combination with dexamethasone to treat adults. It is also indicated as a maintenance therapy for those who have received autologous hematopoietic stem cell transplantation.⁸

Pomalidomide was approved in 2013 and has a black box warning for embryo-fetal toxicity and venous and arterial thromboembolism. It is indicated in combination with dexamethasone for the treatment of MM in adult patients who have been treated with 2 or more therapies including lenalidomide and a PI but whose disease progressed within 60 days of completing their last therapy.⁹ Even in disease that is refractory or resistant to lenalidomide, pomalidomide can potentially elicit a response.⁶

Proteasome Inhibitors

Another class of agents used to treat patients with MM is the PIs. PIs work by interfering with the ubiquitin proteasome system to prevent protein recycling, eventually resulting in apoptosis.⁶ PIs are generally thought of as being “critical components of any regimen that is used to treat patients with high-risk myeloma or patients with renal failure.”⁴ The PIs used to treat MM include bortezomib, carfilzomib, and ixazomib, with marizomib under development.⁶

Bortezomib was the first PI approved in 2003.^{6,10} It is given parenterally, is reversible,⁴ and is indicated for the treatment of patients with MM and mantle cell lymphoma.¹⁰

Carfilzomib is a second-generation PI approved in 2012; it is not reversible and is given intravenously.^{4,6} It is indicated in combination with (1) lenalidomide and dexamethasone, (2) dexamethasone, or (3) daratumumab and dexamethasone for the treatment of RRMM in people who have already been treated with 1 to 3 lines of therapy.¹¹ It is also indicated as a single-agent treatment in people with RRMM who have been treated with at least 1 line of therapy.¹¹

Ixazomib is the first oral PI.⁶ It was approved in 2015 and is indicated in combination with lenalidomide and

dexamethasone to treat myeloma in patients who have been treated with at least 1 therapy.¹²

Marizomib is a PI in clinical development, with the latest trial in myeloma—a phase 1 trial—completed in 2016.^{6,13}

Monoclonal Antibodies

The development of mAbs has affected survival in both the up-front and relapse settings.⁶ The mAbs used to treat patients with MM include elotuzumab and daratumumab.⁶

Elotuzumab is an anti-SLAMF7 mAb whose Fc portion binds to CD16 receptors of NK cells, activating them to kill myeloma cells.¹⁴ Approved in 2015, it was the first mAb approved for RRMM; compared with other drugs, it has demonstrated modest improvements in overall survival (OS).^{6,15} It is not indicated as a monotherapy. Instead, it has approval for adult patients with MM in 2 combinations: (1) with lenalidomide and dexamethasone in those who have already been treated with 1 to 3 therapies and (2) with pomalidomide and dexamethasone in those who have already been treated with at least 2 therapies including a PI and lenalidomide.¹⁵

Daratumumab—an anti-CD38 IgG1 humanized mAb—kills tumor cells by targeting CD38 on myeloma plasma cells and modulating the immune system.⁶ It was approved in 2015 and is indicated for the treatment of MM both as a monotherapy and in multiple combinations.¹⁶ As a monotherapy, it is indicated in patients who have previously been treated with at least 3 lines of therapy including a PI and an IMiD or in those double-refractory to both a PI and an IMiD. Its 6 approved combinations vary not only by the agents with which daratumumab is combined but also by the patient populations in which they are indicated.¹⁶

Histone Deacetylase Inhibitor

Panobinostat is an HDACi that regulates intracellular protein homeostasis, the cell cycle, and apoptosis. HDACis may be synergistic with PIs given that they both lead to protein accumulation.⁶ Approved in 2015, panobinostat is indicated in combination with bortezomib and dexamethasone for the treatment of MM in patients who have previously been treated with at least 2 regimens including bortezomib and an IMiD.¹⁷ Panobinostat also has a black box warning for serious and fatal toxicities that include cardiac toxicities and severe diarrhea.¹⁷

CAR T-Cell Therapy

CAR T cell is a cellular therapy in which the patient's own T cells are removed and genetically modified to produce CARs, which are receptors that do not exist naturally and are able to attach to a tumor antigen. Once modified to have the specific CAR, the modified T cells are multiplied in a lab and then infused back into the patient.¹⁸

Idecabtagene vicleucel is the first B-cell maturation antigen–directed CAR T-cell therapy for patients with relapsed/refractory MM after 4 or more prior lines of therapy, including an immunomodulatory agent, a PI, and an anti-CD38 mAb.¹⁹ Approval followed the phase 2 KarMMA trial (NCT03361748) in which idecabtagene vicleucel had an overall response rate of 72% (95% CI, 62%-81%) and a stringent complete response rate of 28% (95% CI, 19%-38%) in patients with RRMM who had previously been treated with at least 4 lines of therapy.¹⁹ Idecabtagene vicleucel is given as a 1-time infusion and has a boxed warning for cytokine release syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, neurologic toxicities, and prolonged cytopenia.¹⁹

Nuclear Export Inhibitor/Selective Inhibitor of Nuclear Export

Selinexor is a first-in-class SINE that works by blocking XPO1, a protein that is often overexpressed in MM.²⁰ Selinexor was initially approved in 2019 and is now indicated in combination with bortezomib and dexamethasone to treat MM in adults who have previously been treated with at least 1 therapy; it is also indicated for use in combination with dexamethasone to treat RRMM in adults who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 immunomodulatory agents, and an anti-CD38 mAb.²¹

Bispecific Monoclonal Antibodies

BsMAbs are under investigation in MM; they bind to 2 different antigens at the same time, usually one on a T cell and the other on the tumor cell. In a way, BsMAbs are like CAR T-cell therapy in that they both use the host's own cells to target the neoplastic cells. However, BsMAbs can be available faster because they do not require the processing of CAR T-cell therapy.¹⁴ Three BsMAb platforms of note in clinical trials are the BiTE platform, DuoBody platform, and DART platform.¹⁴ The BiTE platform is made up of 2 single-chain variable fragments; one binds to CD3 on T cells, and the other binds to tumor.¹⁴ The DuoBody platform is used to develop bispecific antibodies able to connect with 2 different targets.^{14,22} The DART platform has diabodies reinforced with a C-peptide disulfide bond.¹⁴

Even though this discussion of agents is not exhaustive, a multitude of treatment options exist, with more agents in development. Nevertheless, PIs are considered a crucial component of regimens used to treat high-risk myeloma.⁶ And, along with PIs, IMiDs have significantly advanced and are fundamental to MM treatment.⁶ The introduction of PIs and IMiDs increased OS in patients with MM and changed how patients are treated.²³

For patients who are fit and younger, a PI and an IMiD are usually used in the first-line setting for induction, and

most patients with RRMM have been treated with drug combinations including a PI and/or an IMiD.⁶ Perhaps the more challenging question is regarding what to do next as patients relapse. As new agents are developed, treatment choices and potential combinations increase, bringing not only opportunity but also complexity.²⁴ Practitioners have not only doublets but also triplets, quadruplets, and other combinations from which to choose, often with more than 1 option within each of those categories.^{24,25}

Another part of treatment choice rests on sequencing, which is the order in which the patient receives treatments.²⁶ Trials have not compared most regimens head-to-head in MM, and determining ideal treatment sequence is an unmet need.²⁵

Although treatment guidelines provide recommendations, multiple choices remain. To facilitate navigating treatment choices, stakeholders can evaluate disease-related, patient-related, and treatment-related factors.

Finally, timing is one of the biggest challenges in treating RRMM, and it is also of critical importance.⁶ Research suggests that patients do better when treated in clinical trials or at specialty treatment centers. This may be due to regular monitoring, which enables prompt identification of biochemical relapse. Superior outcomes may be demonstrated when patients are treated earlier at the biochemical stage rather than later at the symptomatic stage.²⁷

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The Patient

Age can influence treatment choice but should not be the only factor taken into consideration. An older patient who is fit may be appropriate for the same treatment as a younger patient.²⁵ Instead of using age alone, the IMWG developed an assessment tool to determine patient frailty/fitness. The geriatric assessment tool incorporates 4 parts: age, activities of daily living, instrumental activities of daily

living, and the Charlson comorbidity index.²⁵ It provides a patient score from 0 to 5 with 0 indicating fit, 1 indicating intermediate fitness, and 2 or higher indicating frail.^{25,28} Able to predict both the risk of toxicity and death in elderly patients with myeloma, the tool can inform the feasibility of a treatment regimen.²⁸

In addition to their inclusion in the IMWG assessment tool, comorbidities/organ function also need to be evaluated independently against a potential treatment regimen's possible toxicity.²⁵ The risk of cytopenias, for instance, is increased with certain PIs and IMiDs, but many elderly patients already suffer from cytopenias.²⁵ Therefore, practitioners need to be prepared to manage cytopenias, perhaps through dose reduction or interruption or with granulocyte colony-stimulating factor if febrile neutropenia is an issue.²⁵

Finally, the more subjective parameters of preference and quality of life also need to be considered.²⁵ Patients want to be able to continue their regular activities. When daily activities are compromised, patients tend to do worse, whereas preservation of routine is associated with less fatigue, fewer adverse effects (AEs), and better quality of life. Alternatively, when quality of life is compromised, treatment may be cut short.²⁷

The Disease

Treatment choices also hinge on disease qualities such as whether the patient experienced early or late relapse, for instance. Early relapse is considered that which occurs in patients who have received 1 to 3 lines of therapy, whereas late relapse is that which occurs in patients who have received more than 3 lines.²⁵ For early relapse, practitioners can start by determining whether the patient is refractory or sensitive to lenalidomide and/or bortezomib.²⁵ For late relapse, the main considerations are whether the patient is refractory to 3 or more agents and, if so, which ones.²⁵

Length of response to previous treatments also matters when determining later treatment. For instance, if the patient relapsed many months after being off therapy (therapy de-escalation is encouraged to minimize toxicity once patients have been stable long enough), then that same therapy can potentially be tried again.²⁵

Lastly, the risk status of the current disease needs to be determined.²⁵ The relapse could be a potentially less aggressive biochemical relapse, or patients who relapse may have developed genetic abnormalities they did not have earlier such as a *MYC* rearrangement, 1p deletion, 1q amplification, or 17p deletion, for instance. Genetic changes such as these can alter the patient's prognosis.⁴

Treatment

Pivotal to treatment selection in RRMM is what treatment the patient has already received. If the patient has never

had an autologous stem cell transplant (ASCT) or if the patient had a greater than 18-month-long progression-free survival (PFS) with a first ASCT, then practitioners should consider ASCT for those who are eligible.²⁵ Patients with an indolent relapse who responded well to ASCT before are candidates for salvage ASCT.⁴

Which treatment(s) the patient has already received is also critical because many of the agents' FDA-approved indications are defined by previous treatment. Pomalidomide, for instance, is indicated in patients who have already undergone at least 2 lines of therapy including lenalidomide and a PI.⁹ Idecabtagene vicleucel's label is even more stringent: It is indicated in patients with RRMM after 4 or more lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.¹⁹

When deciding which treatment to use next, providers should also consider how the patient tolerated earlier therapy and the length of response.⁴ Toxicities and comorbidities that have developed as a result of earlier treatment can complicate treatment at relapse.⁴

Lastly, availability can be an issue for patients. Patients may not be able to access a particular agent because of costs, inability to travel, or other issues.²⁷ On a related note, how the treatment is administered (eg, orally, intravenously, subcutaneously) is also an important consideration. Even if time without progression is shorter with an oral regimen or if the oral regimen has more potential AEs, patients may still prefer the convenience of this route, particularly if they cannot or do not want to go to a health care facility for infusions.²⁷

As new agents become available, treatment becomes more promising but also more complex.²⁵ Practitioners need to analyze patient, treatment, and disease factors to choose the treatment that is best for the individual patient.²⁵ Triplet regimens are generally preferable to doublets, but practitioners need to balance maximizing the potential for PFS and OS with minimizing toxicity and maintaining quality of life.²⁵ ♦

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