Multiple Myeloma: Updates on Diagnosis and Management

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Two- and 3-drug treatment regimens and autologous stem cell transplants provide opportunities for longer term disease remission, though most patients will still develop relapsed multiple myeloma.

Multiple myeloma (MM) is a disease that is primarily treated by hematologists; however, it is important for primary care providers (PCPs) to be aware of the presentation and diagnosis of this disease. Multiple myeloma often is seen in the veteran population, and VA providers should be familiar with its diagnosis and treatment so that an appropriate referral can be made. Often, the initial signs and symptoms of the disease are subtle and require an astute eye by the PCP to diagnose and initiate a workup.

Once a veteran has an established diagnosis of MM or one of its precursor syndromes, the PCP will invariably be alerted to an adverse event (AE) of treatment or complication of the disease and should be aware of such complications to assist in management or referral. Patients with MM may achieve long-term remission; therefore, it is likely that the PCP will see an evolution in their treatment and care. Last, PCPs and patients often have a close relationship, and patients expect the PCP to understand their diagnosis and treatment plan.

PRESENTATION

Multiple myeloma is a disease in which a neoplastic proliferation of plasma cells produces a monoclonal immunoglobulin. It is almost invariably preceded by premalignant stages of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM), although not all cases of MGUS will eventually progress to MM.[1] Common signs and symptoms include anemia, bone pain or lytic lesions on X-ray, kidney injury, fatigue, hypercalcemia, and weight loss.[2] Anemia is usually a normocytic, normochromic anemia and can be due to involvement of the bone marrow, secondary to renal disease, or it may be dilutional, related to a high monoclonal protein (M protein) level. There are several identifiable causes for renal disease in patients with MM, including light chain cast nephropathy, hypercalcemia, light chain amyloidosis, and light chain deposition disease. Without intervention, progressive renal damage may occur.[3]

DIAGNOSIS

All patients with a suspected diagnosis of MM should undergo a basic workup, including complete blood count; peripheral blood smear; complete chemistry panel, including calcium and albumin; serum free light chain analysis (FLC); serum protein electrophoresis (SPEP) and immunofixation; urinalysis; 24-hour urine collection for electrophoresis (UPEP) and immunofixation; serum B2-microglobulin; and lactate dehydrogenase.[4] A FLC analysis is particularly useful for the diagnosis and monitoring of MM, when only small amounts of M protein are secreted into the serum/urine or for nonsecretory myeloma, as well as for light-chain-only myeloma.[5]

A bone marrow biopsy and aspirate should be performed in the diagnosis of MM to evaluate the bone marrow involvement and genetic abnormality of myeloma cells with fluorescence in situ hybridization

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Table 1. Diagnostic Criteria

Monoclonal gammopathy of undetermined significance
- Serum monoclonal protein < 3 g/dL
- Clonal bone marrow plasma cells < 10%
- Absence of end organ damage attributed to the plasma cell disorder (hypercalcemia, renal failure, anemia, bone lesions)

Smoldering multiple myeloma
- Serum monoclonal protein (IgG or IgA) > 3 g/dL and/or clonal bone marrow plasma cells 10%-60%
- Absence of end organ damage attributable to plasma cell disorder

Multiple myeloma
- Clonal bone marrow plasma cells > 10% *or*
- Biopsy proven plasmacytoma *and*
  Evidence of end organ damage attributable to underlying plasma cell disorder:
  - Serum calcium > 11.5 mg/dL, *and/or*
  - Renal insufficiency: serum creatinine > 2 mg/dL, *and/or*
  - Anemia: hemoglobin < 10 g/dL or > 2 g/dL below lower limit of normal, *and/or*
  - Bone lesions: lytic lesions, severe osteopenia, or pathological fractures
- If no end organ damage, then clonal plasma cells > 60%

Table 2. Durie-Salmon Staging

Stage I	All of the following: • Hemoglobin > 10 g/dL • Serum calcium level normal (< 12 mg/dL) • No lytic bone lesions • Serum IgG < 5 g/dL • Serum IgA < 3 g/dL • Urine monoclonal protein < 4 g/d
Stage II	Does not fit stage I or stage III criteria
Stage III	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Lytic bone lesions • Serum IgG > 7g/dL • Serum IgA > 5 g/dL • Urine monoclonal protein >12 g/d

(FISH) and cytogenetics, both of which are very important in risk stratification and for treatment planning. A skeletal survey is also typically performed to look for bone lesions.[4] Magnetic resonance imaging (MRI) can also be useful to evaluate for possible soft tissue lesions when a bone survey is negative, or to evaluate for spinal cord compression.[5] Additionally, an MRI should be performed in patients with SMM at the initial assessment, because focal lesions in the setting of SMM are associated with an increased risk to progression.[6] Since plain radiographs are usually abnormal only after ≥ 30% of the bone is destroyed, an MRI offers a more sensitive image.

Two MM precursor syndromes are worth noting: MGUS and SMM. In evaluating a patient for possible MM, it is important to differentiate between MGUS, asymptomatic SMM, and MM that requires treatment.[4] Monoclonal gammopathy of undetermined significance is diagnosed when a patient has a serum M protein that is < 3 g/dL, clonal bone marrow plasma cells < 10%, and no identifiable end organ damage.[5] Smoldering MM is diagnosed when either the serum M protein is > 3 g/dL or bone marrow clonal plasma cells are > 10% in the absence of end organ damage.

Symptomatic MM is characterized by > 10% clonal bone marrow involvement with end organ damage that includes hypercalcemia, renal failure, anemia, or bone lesions. The diagnostic criteria are summarized in Table 1. The International Myeloma Working Group produced updated guidelines in 2014, which now include patients with > 60% bone marrow involvement of plasma cells, serum FLC ratio of > 100, and > 1 focal lesions on an MRI study as symptomatic MM.[5,6]

Most patients with MM will have a M protein produced by the malignant plasma cells detected on an SPEP or UPEP. The majority of immunoglobulins were IgG and IgA, whereas IgD and IgM were much less common.[2] A minority of patients will not have a detectable M protein on SPEP or UPEP. Some patients will produce only light chains and are designated as light-chain-only myeloma. For these patients, the FLC assay is useful for diagnosis and disease monitoring. Patients who have an absence of M protein on SPEP/UPEP and normal FLC assay ratios are considered to have nonsecretory myeloma.[7]

STAGING AND RISK STRATIFICATION
Two staging systems are used to evaluate a patient's prognosis: the Durie-Salmon staging system, which is based on tumor burden (Table 2); and the International Staging System (ISS), which uses a combination of serum beta 2 microglobulin (B2M) and serum albumin levels to pro-

duce a powerful and reproducible 3-stage classification and is more commonly used by hematologists due to its simplicity to use and reliable reproducibility (Table 3).

In the Durie-Salmon staging system, patients with stage I disease have a lower tumor burden, defined as hemoglobin > 10 g/dL, normal calcium level, no evidence of lytic bone lesions, and low amounts of protein produced (IgG < 5 g/dL; IgA < 3 g/dL; urine protein < 4 g/d). Patients are classified as stage III if they have any of the following: hemoglobin < 8.5 g/dL, hypercalcemia with level > 12 mg/dL, bony lytic lesions, or high amounts of protein produced (IgG > 7 g/dL; IgA > 5 g/dL; or urine protein > 12 g/d). Patients with stage II disease do not fall into either of these categories. Stage III disease can be further differentiated into stage IIIA or stage IIIB disease if renal involvement is present.[8]

In the ISS system, patients with stage I disease have B2M levels that are < 3.5 mg/dL and albumin levels > 3.5 g/dL and have a median overall survival (OS) of 62 months. In this classification, stage III patients have B2M levels that are > 5.5 mg/dL and median OS was 29 months. Stage II patients do not meet either of these criteria and OS was 44 months.[9] In a study by Mayo Clinic, OS has improved over the past decade, with OS for ISS stage III patients increasing to 4.2 years. Overall survival for both ISS stage I and stage III disease seems to have increased as well, although the end point has not been reached.[10]

All myeloma patients are risk stratified at initial diagnosis based on their cytogenetic abnormalities identified mainly by FISH studies and conventional cytogenetics, which can serve as an alternative if FISH is unavailable. Genetic abnormalities of MM are the major predictor for the outcome and will affect treatment choice. Three risk groups have been identified: high-risk, intermediate-risk, and standard-risk MM (Table 4).[11]

MANAGEMENT OF MGUS AND SMM

Patients with MGUS progress to malignant conditions at a rate of 1% per year.[12] Those individuals who are diagnosed with MGUS or SMM typically do not require therapy. According to the International Myeloma Working Group guidelines, patients should be monitored based on risk stratification. Those with low-risk MGUS (IgG M protein < 1.5 g/dL and no abnormal FLC ratio) can be monitored every 6 months for 2 to 3 years. Those who are intermediate to high risk need

Table 3. International Staging System

Stage I	Beta-2 microglobulins < 3.5 mg/L Serum albumin > 3.5 mg/dL
Stage II	Does not fit stage I or stage III criteria
Stage III	Beta-2 microglobulins > 5.5 mg/L

a baseline bone marrow biopsy in addition to skeletal survey and should check urine and serum levels for protein every 6 months for the first year and then annually thereafter.

Patients with SMM are at an increased risk of progression to symptomatic MM compared with patients with MGUS (10% per year for the first 5 years, 3% per year for the next 5 years).[13] Therefore, experts recommend physician visits and laboratory testing for M proteins every 2 to 3 months for the first year and then an evaluation every 6 to 12 months if the patient remains clinically stable.[14] Additionally, there are new data to suggest that early therapy with lenalidomide plus dexamethasone for SMM can prolong time to disease progression as well as increase OS in individuals with SMM at high risk for progression.[15]

Patients With MM

All patients with a diagnosis of MM require immediate treatment. Initial choice of therapy is driven by whether a patient is eligible for an autologous stem cell transplant (ASCT), because certain agents, such as alkylating agents, should typically be avoided in those who are transplant eligible. Initial therapy for patients with MM is also based on genetic risk stratification of the disease. Patients with high-risk disease require a complete response (CR) treatment for long-term OS and thus benefit from an aggressive treatment strategy. Standard-risk patients have similar OS regardless of whether or not CR is achieved and thus can either be treated with an aggressive approach or a sequential therapy approach.[16]

Transplant-Eligible Patients

All patients should be evaluated for transplant eligibility, because it results in superior progression-free survival (PFS) and OS in patients with MM compared with standard chemotherapy. Transplant eligibility requirements differ, depending on the transplant center. There is no strict age limit in the U.S. for determining

Table 4. Multiple Myeloma Risk Stratification

Standard risk
Hyperdiploidy
t(11;14)
t(6;14)

Intermediate risk
t(4;14)
Deletion 13
Hypodiploidy by conventional karyotyping

High risk
Deletion 17q13
t(14;16)
t(14;20)
High-risk gene expression profiling signature

transplant eligibility. Physiological age and factors such as functional status and liver function are often considered before making a transplant decision.

For VA patients, transplants are generally considered in those aged < 65 years, and patients are referred to 1 of 3 transplant centers: VA Puget Sound Healthcare System in Seattle, Washington; Tennessee Valley Healthcare System in Nashville; or South Texas Veterans Healthcare System in San Antonio.[17] All patients who are transplant eligible should receive induction therapy for 2 to 4 months before stem cell collection. This is to reduce tumor burden, for symptomatic management, as well as to lessen end organ damage. After stem cell collection, patients undergo either upfront ASCT or resume induction therapy and undergo a transplant after first relapse.

Bortezomib Regimens

Bortezomib is a proteasome inhibitor (PI) and has been used as upfront chemotherapy for transplant-eligible patients, traditionally to avoid alkylating agents that could affect stem cell harvest. It is highly efficacious in the treatment of patients with MM. Two- or 3-drug regimens have been used. Common regimens include bortezomib, cyclophosphamide, dexamethasone; bortezomib, thalidomide, dexamethasone (VTD); bortezomib, lenalidomide, dexamethasone (VRD); bortezomib, doxorubicin, dexamethasone; as well as bortezomib, dexamethasone.[18] Dexamethasone is less expensive than VTD or VRD, well tolerated, and efficacious. It is often used upfront for newly diagnosed MM.[19] Three-drug regimens have shown to be more efficacious than 2-drug regimens in clinical trials (Table 5).[20]

Of note, bortezomib is not cleared through the kidney, which makes it an ideal choice for patients with renal function impairment. A significant potential AE with bortezomib is the onset of peripheral neuropathy. Bortezomib can be administered once or twice weekly. Twice-weekly administration of bortezomib is preferred when rapid results are needed, such as light chain cast nephropathy causing acute renal failure.[21]

Lenalidomide Plus Dexamethasone

Lenalidomide is a second-generation immunomodulating agent that is being increasingly used as initial therapy for MM. There is currently no data showing superiority of bortezomib-based regimens to lenalidomide plus dexamethasone in reference to OS. Bortezomib-based regimens seem to overcome the poor prognosis associated with t(4;14) translocation and thus should be considered in choosing initial chemotherapy treatment.[22]

Lenalidomide can affect stem cell collection; therefore, it is important to collect stem cells in transplant-eligible patients who are aged < 65 years or for those who have received more than 4 cycles of treatment with this regimen.[23,24] A major AE to lenalidomide-containing regimens is the increased risk of thrombosis. All patients on lenalidomide require treatment with aspirin at a minimum; however, those at higher risk for thrombosis may require low-molecular weight heparin or warfarin.[25]

Carfilzomib Plus Lenalidomide Plus Dexamethasone

Carfilzomib is a recently approved PI that has shown promise in combination with lenalidomide and dexamethasone as initial therapy for MM. Several phase 2 trials have reported favorable results with carfilzomib in combination with lenalidomide and dexamethasone in MM.[26,27] More studies are needed to establish efficacy and safety before this regimen is routinely used as upfront therapy.[11]

Thalidomide Plus Dexamethasone

Although there are no randomized controlled trials comparing lenalidomide plus dexamethasone with thalidomide plus dexamethasone, these regimens have been compared in retrospective studies. In these studies, lenalidomide plus dexamethasone showed both a

higher response rate as well as an increased PFS and OS compared with thalidomide plus dexamethasone. Additionally, lenalidomide's AE profile was more favorable than that of thalidomide. In light of this, lenalidomide plus dexamethasone is preferred to thalidomide plus dexamethasone in the management of MM, although the latter can be considered when lenalidomide is not available or when a patient does not tolerate lenalidomide.[28]

VDT-PACE
A multidrug combination that should be considered in select populations is the VDT-PACE regimen, which includes bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide. This regimen can be considered in those patients who have aggressive disease, such as those with plasma cell leukemia or with multiple extramedullary plasmacytomas.[11]

Autologous Stem Cell Transplant
Previous data suggest that ASCT improves OS in MM by 12 months.[29] A more recent open-label, randomized trial comparing melphalan and ASCT to melphalan-prednisone-lenalidomide showed significant prolonged PFS and OS among patients with MM.[30] Although the role of ASCT may change as new drugs are integrated into initial therapy of MM, ASCT is still the preferred approach in transplant-eligible patients. As such, all patients who are eligible should be considered to receive a transplant.

There remains debate about whether ASCT should be performed early, after 2 to 4 cycles of induction therapy, or late after first relapse. Several randomized trials failed to show a difference in survival for early vs delayed ASCT approach.[31] Generally, transplant can be delayed for patients with standard-risk MM who have responded well to therapy.[11] Those patients who do not achieve a CR with their first ASCT may benefit from a second (tandem) ASCT.[32] An allogeneic transplant is occasionally used in select populations and is the only potentially curative therapy for these patients. However, its high mortality rate precludes its everyday use.

Transplant-Ineligible Patients
For patients with newly diagnosed MM who are ineligible for ASCT due to age or other comorbidities, chemotherapy is the only option. Many patients will benefit not only in survival, but also in quality of life. Immu-nomodulatory agents, such as lenalidomide and thalidomide, and PIs, such as bortezomib, are highly effective and well tolerated. There has been a general shift to using these agents upfront in transplant-ineligible patients.

All previously mentioned regimens can also be used in transplant-ineligible patients. Although no longer the preferred treatment, melphalan can be considered in resource-poor settings.[11] Patients who are not transplant eligible are treated for a fixed period of 9 to 18 months, although lenalidomide plus dexamethasone is often continued until relapse.[11,33]

Melphalan Plus Prednisone Plus Bortezomib
The addition of bortezomib to melphalan and prednisone results in improved OS compared with that of melphalan and dexamethasone alone.[34] Peripheral neuropathy is a significant AE and can be minimized by giving bortezomib once weekly.

Melphalan Plus Prednisone Plus Thalidomide
Melphalan plus prednisone plus thalidomide has shown an OS benefit compared with that of melphalan and prednisone alone. The regimen has a high toxicity rate (> 50%) and a deep vein thrombosis rate of 20%, so patients undergoing treatment with this regimen require thromboprophylaxis.[35,36]

Melphalan Plus Prednisone
Although melphalan plus prednisone has fallen out of favor due to the existence of more efficacious regimens, it may be useful in an elderly patient population who lack access to newer agents, such as lenalidomide, thalidomide, and bortezomib.

ASSESSING TREATMENT RESPONSE
The International Myeloma Working Group has established criteria for assessing disease response. Patient's response to therapy should be assessed with a FLC assay before each cycle with SPEP and UPEP and in those without measurable M protein levels. A bone marrow biopsy can be helpful in patients with immeasurable M protein levels and low FLC levels, as well as to establish that a CR is present.

A CR is defined as negative SPEP/UPEP, disappearance of soft tissue plamacytomas, and < 5% plasma cells in bone marrow. A very good partial response is defined as serum/urine M protein being present on

Table 5. Commonly Used Regimens

Regimen	Adverse Events
Bortezomib + cyclophosphamide + dexamethasone (VCD)	Cystitis Peripheral neuropathy Myelotoxicity
Bortezomib + thalidomide + dexamethasone (VTD)	Peripheral neuropathy Rash (including SJS/TEN) Thromboembolism
Bortezomib + lenalidomide + dexamethasone (VRD)	Myelotoxicity Neuropathy Thromboembolism
Bortezomib + doxorubicin + dexamethasone (PAD)	Peripheral neuropathy
Bortezomib + dexamethasone (VD)	Peripheral neuropathy
Lenalidomide + dexamethasone (RD)	Myelotoxicity Thromboembolism
Carfilzomib + lenalidomide + dexamethasone (KRD)	Myelotoxicity Thromboembolism
Melphalan + prednisone + bortezomib (VMP)	Myelotoxicity Peripheral neuropathy
Melphalan + prednisone + thalidomide (MPT)	Myelotoxicity Rash (including SJS/TEN) Thromboembolism
Thalidomide + dexamethasone (TD)	Myelotoxicity Peripheral neuropathy Rash (including SJS/TEN) Thromboembolism
Melphalan + prednisone (MP)	Myelotoxicity

Abbreviation: SJS/TEN, Stevens Johnson syndrome/toxic epidermal necrolysis.

immunofixation but not electrophoresis or reduction in serum M protein by 90% and urine M protein < 100 mg/d. For those without measurable M protein, a reduction in FLC ratio by 90% is required. A partial response is defined as > 50% reduction of the serum monoclonal protein and/or < 200 mg urinary M protein per 24 hours or > 90% reduction in urinary M protein. For those without M protein present, they should have > 50% decrease in FLC ratio.[5]

Maintenance Therapy

There is currently considerable debate about whether patients should be treated with maintenance therapy following induction chemotherapy or transplant. In patients treated with transplant, there have been several studies to investigate the use of maintenance therapy. Lenalidomide has been evaluated for maintenance therapy following stem cell transplant and has shown superior PFS with dexamethasone as post-ASCT maintenance; however, this is at the cost of increased secondary cancers.[37]

Thalidomide has also been studied as maintenance therapy and seems to have a modest improvement in PFS and OS but at the cost of increased toxicities, such as neuropathy and thromboembolism.[38,39] Still other studies compared bortezomib maintenance with thalidomide maintenance in posttransplant patients and was able to show improved OS. As a result, certain patients with intermediate- or high-risk disease may be eligible for bortezomib for maintenance following transplant.[11] For transplant-ineligible patients, there is no clear role for maintenance therapy.

REFRACTORY/RELAPSED DISEASE TREATMENTS

Nearly all patients with MM will relapse at some point in their disease. Relapse is usually detected during surveillance and should be considered when the patient develops new bone lesions, hypercalcemia, anemia, renal failure, or rapid rise in M protein levels. For these patients, treatment options that should be considered are an ASCT if one has not been done before; an additional ASCT, providing the patient has not relapsed within 12 months of the first; repeating the initial chemotherapy regimen; or choosing an alternative chemotherapy regimen.[5,11] For those who are not transplant candidates, chemotherapy remains the only option.

Single-agent bortezomib has shown promise in relapsed/refractory MM, with more than one-third of patients having partial response or CR.[40,41] A study of bortezomib combined with liposomal doxorubicin has also shown a modest improvement in time to progression compared with single-agent bortezomib and can also be considered for relapsed/refractory disease.[42] An additional option is an immunonomodulatory drug, such as

lenalidomide or thalidomide. Unfortunately, poorer outcomes have been reported for patients who are refractory to both lenalidomide or bortezomib.[43]

Pomalidomide is a thalidomide analog and has activity in MM that is relapsed or refractory with acceptable response rates when used with dexamethasone.[44] Carfilzomib is a PI approved for treatment of relapsed or refractory MM in patients who have failed lenalidomide and bortezomib.[45] The FDA recently approved panobinostat, a histone deacetylase inhibitor, for patients with MM who have failed 2 prior therapies, and it has shown improved PFS.[46] Patients should be treated in a clinical trial whenever possible, and emerging new options include second generation PIs, such as ixazomib, other histone deacetlyase inhibitors, AKT/P13K/mTOR inhibitors, heat-shock-protein inhibitors, and monoclonal antibodies.

CONCLUSIONS

Despite significant advances in the management of MM, the disease remains incurable. Virtually all patients will develop relapsed disease, although strides in the field have provided opportunities for longer term remissions. There are a multitude of strategies that are under investigation, and further studies are needed to establish their role in the treatment of patients with MM. ●

Author disclosures

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