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Multiple Myeloma: Every Year a New Standard?

S. Vincent Rajkumar, M.D.

Division of Hematology, Mayo Clinic, Rochester, Minnesota.

Multiple myeloma (MM) accounts for about 10% of all hematologic malignancies. The revised International Myeloma Working Group criteria for the diagnosis of MM and related disorders are shown on Table 1.[1] The diagnosis of MM 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 features (hypercalcemia, renal failure, anemia, or lytic bone lesions) and 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.

Although MM is still considered a single disease, it is in reality a collection of several different cytogenetically distinct plasma cell malignancies. Trisomies and IgH translocations are considered primary cytogenetic abnormalities and occur at the time of establishment of MGUS. Other cytogenetic changes termed secondary cytogenetic abnormalities occur disease course such as gain(1q), del(1p), del(17p), del(13), *RAS* mutations, and secondary translocations involving *MYC*. The presence of del(17p), gain(1q), t(4;14), t(14;16), and t914;20) are considered to reflect high risk disease.

Survival of MM has improved significantly in the last 15 years.[2] There are many active drugs to treat MM in addition to alkylators and corticosteroids. Thalidomide, lenalidomide, and pomalidomide are termed immunomodulatory agents (IMiDs). Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors. Elotuzumab and daratumumab are monoclonal antibodies targeting SLAMF7 and CD38 respectively. Panobinostat is a deacetylase inhibitor.

Numerous regimens have been developed with these new drugs, and each year additional new regimens are being developed. Recent data show that MRD negative status (as estimated by next generation molecular methods or flow cytometry) has favorable prognostic value.[3] However, additional trials are needed to determine if changes in treatment need to be

Corresponding Author: S. Vincent Rajkumar, MD, Professor of Medicine, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905 USA Phone: 507 284 2511; Fax: 507 266 4972, rajkumar.vincent@mayo.edu.

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

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made based on MRD status. At present, MRD results are recommended mainly as a prognostic metric and not for used in making treatment decisions.

Initial Treatment in Patients Eligible for Transplantation

Typically, patients are treated with approximately 3–4 cycles of induction therapy with bortezomib, lenalidomide, dexamethasone (VRd) prior to stem cell harvest.[4] If lenalidomide is not available for use as initial therapy or in the presence of acute renal failure, other bortezomib-containing regimens such as bortezomib-thalidomide-dexamethasone (VTd) or bortezomib-cyclophosphamide-dexamethasone (VCd) can be used instead of VRd. After harvest, patients can either undergo frontline autologous stem cell transplantation (ASCT) or resume induction therapy delaying ASCT until first relapse. In general, the low-dose dexamethasone regimen (40 mg once a week) is preferred in all regimens to minimize toxicity. In a randomized trial, low-dose dexamethasone approach was associated with superior survival and significantly lower toxicity.[5] Similarly, the neurotoxicity of bortezomib can be greatly diminished by administering bortezomib once a week instead of twice-weekly, and by administering the drug subcutaneously instead of the intravenous route.

New options for initial therapy in younger patients include carfilzomib-lenalidomide-dexamethasone (KRd, daratumumab, lenalidomide, dexamethasone (DRd), and daratumumab plus VRd. But additional data on impact of these regimens compared to VRd are needed. A randomized trial in the United States (referred to as the Endurance trial) is currently ongoing comparing VRd versus KRd as initial therapy.

Initial Treatment in Patients Not Eligible for Transplantation

In patients with newly diagnosed MM who are not candidates for ASCT due to age or other comorbidities, initial therapy is with VRd is administered for approximately 8–12 cycles, followed by maintenance therapy with lenalidomide. Alternatives to VRd include VCd and VTd as discussed earlier.

Stem Cell Transplantation

A recent trial by the Intergroupe Francophone du Myelome compared early versus delayed ASCT in patients treated with VRd followed by lenalidomide maintenance.[6] 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 overall survival. Allogenic transplantation is still investigational, but can be considered for young patients with high-risk disease in first relapse.

Maintenance Therapy

Maintenance with lenalidomide is the standard of care for most patients after initial therapy. In a meta-analysis of randomized trials, a significant improvement in PFS and OS was seen

with lenalidomide maintenance compared with placebo or no therapy.[7] For high-risk patients, bortezomib-based maintenance should be considered.

Relapsed MM

Almost all patients with MM eventually relapse. The choice of a treatment regimen at relapse is complicated and is affected by many factors including the *t*iming of the relapse, *r*esponse to prior therapy, *a*ggressiveness of the relapse, and *p*erformance status (TRAP). Patients are eligible transplant should be considered for the procedure if they have never had one before, or if they have had an excellent remission duration with the first transplant. As in newly diagnosed MM, VRd, VCd, and VTd are active regimens in relapsed disease.

Three daratumumab-based combinations have shown efficacy: daratumumab, lenalidomide, dexamethasone (DRd), daratumumab, bortezomib, dexamethasone (DVd), and daratumumab, pomalidomide, dexamethasone (DPd).[8] Other options include KRd, ixazomib, lenalidomide, dexamethasone (IRd), elotuzumab, lenalidomide, dexamethasone (ERd), and various pomalidomide-based regimens such as daratumumab, pomalidomide, dexamethasone (DPd) and carfilzomib, pomalidomide, dexamethasone (KPd). For aggressive relapses, anthracycline-containing regimens may be useful.

Other drugs to consider for relapse include panobinostat, a pan-deacetylase inhibitor; and bendamustine-containing regimens such as bendamustine, lenalidomide, dexamethasone or bendamustine, bortezomib, dexamethasone. Venetoclax appears to have single-agent activity in patients with t(11;14) subtype of MM.

Two of the most exciting investigational options are chimeric antigen receptor T cells (CAR-T) targeting B cell maturation antigen (BCMA) such as bb2121,[9] and GSK2857916 (a humanized anti-BCMA antibody that is conjugated to monomethyl auristatin-F, a microtubule disrupting agent).[10] Other agents with single-agent activity that are promising include isatuximab, selinexor, and and LGH-447 (a pan PIM kinase inhibitor).

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Table 1.

International Myeloma Working Group Diagnostic Criteria for MM 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 MM	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
MM	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
Solitary Plasmacytoma	All 4 criteria must be met

Disorder	Disease Definition
	• 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 hypercealcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

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*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 MM