NCCN Guidelines® Insights

Multiple Myeloma, Version 3.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Multiple Myeloma provide recommendations for diagnosis, evaluation, treatment, including supportive-care, and follow-up for patients with myeloma. These NCCN Guidelines Insights highlight the important updates/changes specific to the myeloma therapy options in the 2018 version of the NCCN Guidelines.

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Multiple Myeloma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Multiple Myeloma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:
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MYELOMA THERAPY[1-4]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens

- **Bortezomib/lenalidomide[5]/dexamethasone (category 1)**
- **Bortezomib/cyclophosphamide/dexamethasone[6]**

Other Recommended Regimens

- **Bortezomib/doxorubicin/dexamethasone (category 1)**
- **Carfilzomib[7,8]/lenalidomide[5]/dexamethasone**
- **Ixazomib/lenalidomide[5]/dexamethasone (category 2B)**

Useful In Certain Circumstances

- **Bortezomib/dexamethasone (category 1)[9]**
- **Bortezomib/thalidomide/dexamethasone (category 1)**
- **Lenalidomide[5]/dexamethasone (category 1)[9]**
- **Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)**

[1]Selected, but not inclusive of all regimens.
[2]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[3]Subcutaneous bortezomib is the preferred method of administration.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[5]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[6]Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[7]Optimal dosing in this regimen has not been defined.
[8]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[9]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

MYEL-D (1 OF 3)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cell clones that produce monoclonal immunoglobulin. These plasma cell clones proliferate in the bone marrow causing skeletal damage, a hallmark of MM. Other disease-related complications include hypercalcemia, renal insufficiency, anemia, and infections. MM accounts for approximately 1.8% of all cancers and slightly more than 17% of hematologic malignancies in the United States.[1] The American Cancer Society has estimated that 30,280 new MM cases will occur in the United States in 2017, with an estimated 12,590 deaths.[1]

The NCCN MM Panel has developed guidelines for the management of patients with various plasma cell neoplasms, including solitary plasmacytoma, smoldering myeloma, MM, systemic light-chain amyloidosis, and Waldenström's macroglobulinemia. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are updated annually,

MYELOMA THERAPY[1-4]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens
- **Bortezomib/lenalidomide/dexamethasone (category 1)**
- **Lenalidomide/low-dose dexamethasone (category 1)[9,10]**
- **Bortezomib/cyclophosphamide/dexamethasone[6]**

Other Recommended Regimens
- **Carfilzomib[8]/lenalidomide/dexamethasone**
- **Carfilzomib[8]/cyclophosphamide/dexamethasone**
- **Ixazomib/lenalidomide/dexamethasone**

Useful In Certain Circumstances
- **Bortezomib/dexamethasone[9]**

MAINTENANCE THERAPY

Preferred Regimens
- **Lenalidomide[11] (category 1)**

Other Recommended Regimens
- **Bortezomib**

[1]Selected, but not inclusive of all regimens.
[2]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[3]Subcutaneous bortezomib is the preferred method of administration.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[6]Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[8]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[9]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[10]Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.
[11]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

MYEL-D (2 OF 3)

and sometimes more often if new high-quality clinical data that impact the care of affected individuals become available.

These NCCN Guidelines Insights focus on updates to the 2018 version of the NCCN Guidelines for MM, including those regarding therapy options for both newly diagnosed and relapsed/refractory (R/R) MM.

There are several classes of agents used for the treatment of MM, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), histone deacetylase inhibitors, monoclonal antibodies, alkylators, and steroids. These drugs are combined as doublets, triplets, and/or multiple drug regimens for treating MM, thus making the choice of optimal therapy at diagnosis and relapse quite challenging. In the 2018 version, the NCCN panel has categorized all MM therapy regimens as "preferred," "other recommended," or "useful under certain circumstances." The purpose of classifying regimens is to provide guidance on treatment selection considering the evidence, relative efficacy, toxicity, and other factors, such as preexisting comorbidities (eg, peripheral neuropathy [PN], renal insufficiency), nature of the disease, and, in some cases, access to agents.

The guidelines list regimens recommended by the NCCN MM Panel for newly diagnosed transplant-eligible and non–transplant-eligible candidates, maintenance therapy, and previously treated myeloma (MYEL-D, 1–3; pages 13–15). The panel notes that this list is a selected one and not inclusive of all regimens used for the management of MM.

Updates to Treatment Options for Newly Diagnosed MM

For treatment of newly diagnosed transplant-eligible patients, bortezomib-based triple-drug regimens listed as preferred options include bortezomib/lenalidomide/dexamethasone (VRd) and bortezomib/cyclophosphamide/dexamethasone (VCd). After VRd demonstrated tolerability and efficacy in patients

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MYELOMA THERAPY[1-4,12]

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[8]/dexamethasone (category 1)[9]
- Carfilzomib[8]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[13]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[8]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[8]/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

[1]Selected, but not inclusive of all regimens.
[2]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[3]Subcutaneous bortezomib is the preferred method of administration.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[8]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[9]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[12]Consideration for appropriate regimen is based on the context of clinical relapse.
[13]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[14]May interfere with serological testing and cause false-positive indirect Coombs test.(See MYEL-E)
[15]Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[16]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[17]Indicated for the treatment of patients who have received at least one prior therapy.
[18]Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[19]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[20]Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[21]Generally reserved for the treatment of aggressive multiple myeloma.

MYEL-D (3 OF 3)

with newly diagnosed MM in phase II studies,[2–4] the pivotal phase III multicenter SWOG S0777[5] trial compared it with lenalidomide/dexamethasone. In this trial, newly diagnosed patients with MM were randomly assigned to receive 6 months of primary therapy with either VRd or lenalidomide/dexamethasone, each followed by maintenance therapy with lenalidomide/dexamethasone until progression or unacceptable toxicity. The group treated with VRd showed a significantly longer progression-free survival (PFS) of 43 versus 30 months (hazard ratio [HR], 0.712; 95% CI, 0.56–0.906) and improved median overall survival (OS) of 75 versus 64 months (HR, 0.709; 95% CI, 0.524–0.959).[5] Based on the significant improvement in PFS and OS seen with VRd, the NCCN panel included this regimen as a category 1, preferred option for the primary treatment of transplant-eligible and non–transplant-eligible patients with newly diagnosed MM (MYEL-D, 1 of 3; page 13).

For patients receiving lenalidomide-based regimens, the panel recommends harvesting peripheral blood stem cells before prolonged exposure to lenalidomide. Full-dose aspirin is recommended as thromboprophylaxis, and therapeutic anticoagulation is recommended for those at high risk for thrombosis. The NCCN panel recommends herpes prophylaxis in patients receiving bortezomib therapy (or other PIs) and those receiving anti-CD38 or elotuzumab monoclonal antibody therapy. Subcutaneous administration is the preferred route for bortezomib, based on the findings of the MMY-3021 trial showing that subcutaneous single-agent bortezomib had noninferior efficacy to intravenous bortezomib with regard to overall response rate (ORR) after 4 cycles.[6] Although time to progression and OS were similar in both groups,[6,7] patients receiving bortezomib subcutaneously experienced a significant reduction in PN (MYEL-D, 1 and 2 of 3; pages 13 and 14).

Data from phase II studies have demonstrated the tolerability and efficacy of VCd in the manage-

ment of patients with newly diagnosed MM.[3,8–11] The NCCN MM Panel has included combination VCd in the list of primary treatments for both transplant-eligible and non–transplant-eligible patients with newly diagnosed MM; this is a preferred option, especially in patients with acute renal insufficiency. According to the panel, patients can consider switching to VRd after renal function improves (MYEL-D, 1 and 2 of 3; pages 13 and 14).

In addition to these bortezomib-based regimens, lenalidomide/low-dose dexamethasone is included as a category 1, preferred regimen for non–transplant-eligible patients. The international multicenter FIRST trial compared the efficacy and safety of lenalidomide/dexamethasone given continuously or for a fixed duration (72 weeks) with melphalan/prednisone/thalidomide (MPT) in elderly non–transplant-eligible patients with newly diagnosed MM (n=1,623).[12] After a median follow-up of 37 months, risk of progression or death was reduced by 28% in patients receiving continuous lenalidomide/dexamethasone versus MPT (HR, 0.72; 95% CI, 0.61–0.85; *P*<.001).[12] An OS benefit was also seen in the lenalidomide/dexamethasone arm versus MPT (HR, 0.78; CI, 0.64–0.96; *P*=.02).[12] Continuous lenalidomide/dexamethasone also reduced the risk of progression or death compared with 18 cycles of lenalidomide/dexamethasone (HR, 0.70; 95% CI, 0.89–1.20; *P*=.70), and demonstrated longer median OS.[13]

Results of the ECOG E4A03 trial,[14] which included elderly patients with MM, also demonstrated that lenalidomide/low-dose dexamethasone is a well-tolerated and effective regimen for transplant-eligible and non–transplant-eligible patients. In this study, the OS rate was significantly higher with lenalidomide/low-dose dexamethasone compared with lenalidomide/high-dose dexamethasone.[15] The inferior survival outcome observed with high-dose dexamethasone was greatest in patients aged ≥65 years. Patients who did not proceed to autologous stem cell transplant (autoSCT) had an OS rate of 91% with lenalidomide/low-dose dexamethasone at the end of 2 years.[15] The 3-year OS of patients who received 4 cycles of primary treatment with either dose followed by autoSCT was 92%, suggesting that lenalidomide and dexamethasone is a reasonable choice for primary therapy before SCT.[15] However, it should be noted that the choice to proceed to SCT was not randomized, but rather based on physician and patient preference.

Based on the this evidence, lenalidomide/low-dose dexamethasone is listed as a category 1, preferred option in the NCCN Guidelines for non–transplant-eligible patients, especially those who are frail or elderly with standard-risk features. For transplant-eligible patients, lenalidomide/dexamethasone is listed as a category 1 option in the category "useful in certain circumstances," with a note that triple-drug regimens are preferred as primary therapy for transplant-eligible patients, although elderly or frail patients may be treated with doublet regimens (MYEL-D, 2 of 3; page 14).

The full list of recommended regimens for transplant-eligible and non–transplant-eligible candidates with newly diagnosed MM can be found on pages 13 and 14 (MYEL-D, 1 and 2 of 3).

Updates to Maintenance Therapy Recommendations

In transplant-eligible patients, multiple phase III randomized trials have evaluated maintenance therapy with lenalidomide after autoSCT.[16,17] A recent meta-analysis of 1,208 patients randomized to lenalidomide maintenance or placebo showed improved median PFS associated with lenalidomide maintenance (52.8 vs 23.5 months; HR, 0.48; 95% CI, 0.41–0.55).[18] At 7 years, OS was 62% in the lenalidomide maintenance group versus 50% for placebo or observation. In those with high-risk cytogenetics and International Staging System (ISS) stage III disease, a PFS benefit was seen with lenalidomide maintenance versus placebo, but not an OS benefit.

In non–transplant-eligible patients, several randomized trials have explored the benefit of maintenance therapy with lenalidomide after completion of primary therapy. Data from the phase III MM015 study show that lenalidomide maintenance after melphalan/prednisone/lenalidomide primary therapy significantly reduced the risk of disease progression and increased PFS.[19] In the FIRST trial, use of lenalidomide until disease progression was associated with superior PFS compared with a fixed duration of lenalidomide.[13] Updated survival analysis from the CALGB 100104 (Alliance) study at a median follow-up of 91 months reported a median time to progression of 57.3 months (95% CI, 44.2–73.3)

with lenalidomide and 28.9 months (95% CI, 23.0–36.3) with placebo (HR, 0.57; 95% CI, 0.46–0.71; *P*<.0001).[20]

Several reports show higher incidences of secondary malignancies when lenalidomide is used as maintenance therapy post-SCT or in a melphalan-containing regimen.[16,17,20–22] However, there seems to be an increased risk for secondary cancers, especially post-SCT[16,17,23] or after treatment with melphalan-containing regimens.[22] According to the results of the FIRST trial, in the continuous lenalidomide/dexamethasone arm, absence of the alkylator melphalan is associated with a lower incidence of second malignancies.[12] In the recent meta-analysis,[18] at a median follow-up of 79.5 months before disease progression on lenalidomide maintenance, the rates of second primary hematologic and solid tumor malignancies were 5.3% and 5.8%, respectively. The benefits of improved PFS with lenalidomide maintenance must be weighed against the increased rate of severe (grade 3 and 4) neutropenia, risk of second cancers, and other toxicities, including cost.[24] The NCCN panel notes that the benefits and risks of maintenance therapy with lenalidomide, including the risk secondary cancers, should be discussed with patients (MYEL-D, 2 of 3; page 14).

Given the significant improvement in PFS and the OS benefit, the NCCN panel now lists single-agent lenalidomide as a category 1, preferred maintenance regimen (MYEL-D, 2 of 3; page 14).

Maintenance with bortezomib has also been evaluated in randomized trials. Results from the HOVON study show that maintenance with single-agent bortezomib after autoSCT is well tolerated and associated with improvement in ORR.[25] A multicenter phase III trial showed that consolidation with bortezomib after autoSCT improved PFS only in patients not achieving at least a very good partial response (VGPR) after autoSCT; there was no difference in PFS in patients with a VGPR or better (≥VGPR) after autoSCT.[26] Preliminary results of the phase III UPFRONT study also show that maintenance with single-agent bortezomib is well tolerated when administered after treatment with bortezomibbased primary therapy.[27] Results show that the response rates, including complete response and ≥VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of PN.[27] Bortezomib is listed as an "Other Recommended" maintenance regimen in the NCCN Guidelines (MYEL-D, 2 of 3; page 14).

Updates to Treatment Options for Previously Treated MM

A variety of therapies are available as options for patients with previously treated MM. Choice of therapy depends on the context of clinical relapse, such as prior treatment and duration of response, with options including systemic therapy, autoSCT for eligible patients who did not receive autoSCT as part of their initial treatment, or consideration for a clinical trial. For those who received autoSCT as part of initial treatment and achieved a durable response or stable disease, consideration should be given to a second SCT on or off clinical trial at the time of relapse/disease progression. If relapse occurs >6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen. Several new regimens were included as options for the treatment of R/R MM in the 2018 version of the NCCN Guidelines (MYEL-D, 3 of 3; page 15).

Triple-drug regimens remain standard therapy options for patients with MM; however, the NCCN panel notes that selected patients, such as those who are elderly or frail, may be treated with doublet regimens, and a third drug could be added if/when the patient's condition improves. Results of the phase III ENDEAVOR trial in patients with R/R MM treated with multiple prior lines of therapy showed improved ORR with carfilzomib (twice weekly)/dexamethasone compared with bortezomib/dexamethasone (77% vs 63%). Further, a 2-fold improvement was observed in median PFS with carfilzomib/dexamethasone versus bortezomib/dexamethasone (18.7 vs 9.4 months; HR, 0.53; *P*<.0001).[28] Additionally, a lower incidence of PN but an increased frequency of heart failure, acute renal failure, and hypertension was seen in the carfilzomib group. OS analysis showed that the carfilzomib/dexamethasone group lived 7.6 months longer (median OS, 47.6 months for carfilzomib vs 40 for bortezomib; HR, 0.791; 95% CI, 0.648–0.964; *P*=.010).[29]

A phase II study in patients with R/R MM (n=104) evaluated safety and efficacy of weekly dosing[30] of carfilzomib (70 mg/m^2) with dexamethasone.[31] The observed ORR was 77% (95% CI, 68–

85). At 13.6 months, median PFS was 16.2 months (95% CI, 10.2–21.0).[31] Based on the data from the ENDEAVOR trial, the NCCN MM Panel included the combination of carfilzomib (twice weekly) and dexamethasone as a category 1, preferred option for patients with R/R MM. Carfilzomib (weekly) with dexamethasone is included under "Other Recommended Regimens" for patients with previously treated MM (MYEL-D, 3 of 3; page 15).

A phase II trial comparing the safety and toxicity of carfilzomib/cyclophosphamide/dexamethasone versus VCd in patients who received one prior regimen for R/R MM showed that carfilzomib/cyclophosphamide/dexamethasone is well tolerated, with carfilzomib having a similar toxicity profile to that seen in other trials.[32] Considering these data, the panel included carfilzomib/cyclophosphamide/dexamethasone under "Other Recommended Option" for patients with previously treated MM (MYEL-D, 3 of 3; page 15).

For patients with R/R MM who have received at least one prior therapy, 3 regimens were added as category 1: ixazomib/lenalidomide/dexamethasone for those who have received at least one prior therapy, and daratumumab/lenalidomide/dexamethasone and daratumumab/bortezomib/dexamethasone based on the results of the multicenter, randomized, phase III POLLUX and CASTOR trials, respectively.[33,34]

For patients with R/R MM who have received ≥2 prior therapies, including an IMiD and a PI, and who have demonstrated disease progression on or within 60 days of completion of the last therapy, 2 new regimens were added as options in the updated guidelines: ixazomib/pomalidomide/dexamethasone and daratumumab/pomalidomide/dexamethasone. The inclusion of ixazomib/pomalidomide/dexamethasone was based on the results of recently reported phase I/II studies.[32,35] The inclusion of daratumumab/pomalidomide/dexamethasone was based on the results of a phase Ib multicenter study that included >100 patients who had received ≥2 prior lines of therapy (excluding daratumumab or pomalidomide).[36] At a median follow-up of 13.1 months, the ORR was 60%, and median PFS and OS were 8.8 and 17.5 months, respectively; the estimated survival at 1 year was 66%.[36] Phase III studies of daratumumab/pomalidomide/dexamethasone compared with pomalidomide/dexamethasone are ongoing. The addition of IMiDs to daratumumab in patients with refractory MM may overcome refractoriness in both agents.[37]

Daratumumab can interfere with cross-matching and red blood cell antibody screening; therefore, the NCCN panel recommends performing a type and screen before administering this agent to inform future matching. Daratumumab can also interfere with immunofixation assays used to determine response to therapy if the dominant myeloma clone is IGG kappa, because daratumumab is itself an IGG monoclonal antibody.

Patients with an aggressive relapse may need multidrug combinations for effective disease control; VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)[38–40] is one such regimen that is now an option listed under "Useful in Certain Circumstances" for treating previously treated aggressive MM (MYEL-D, 3 of 3; page 15).

The full list of recommended regimens for previously treated MM can be found on page 15 (MYEL-D, 3 of 3).

Conclusions

These NCCN Guidelines Insights highlight important updates/changes specific to treatment options for newly diagnosed and R/R MM in the 2018 version of the NCCN Guidelines for MM. The NCCN Guidelines are in continuous evolution, and are updated annually or more often if new, high-quality clinical data become available. The recommendations in the NCCN Guidelines, with few exceptions, are based on evidence from clinical trials. Expert medical clinical judgment is required when applying these guidelines in the context of individual clinical circumstances to provide optimal care. Both physicians and patients have a responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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Posttest Questions

1. Based on the significant improvements in PFS and OS seen in the phase III (SWOG S0777) trial, which of the following regimens is included in the NCCN Guidelines as a category 1, preferred option for the primary treatment of both transplant-eligible and non–transplant-eligible patients with newly diagnosed MM?
   a. Bortezomib, lenalidomide, and dexamethasone
   b. Bortezomib, cyclophosphamide, and dexamethasone
   c. Lenalidomide and low-dose dexamethasone

2. Which of the following statements is not true?
   a. Daratumumab can interfere with cross-matching and red blood cell antibody screening.
   b. Full-dose aspirin is recommended in the NCCN Guidelines as thromboprophylaxis for patients receiving lenalidomide.
   c. Subcutaneous and intravenous infusion are "preferred" methods of administration of bortezomib in the NCCN Guidelines.

3. True or False: The 2 new regimens added to the NCCN Guidelines as options for patients with R/R MM who have received at least 2 prior therapies, including an IMiD and a PI, and who have demonstrated disease progression on or within 60 days of completion of the last therapy are: ixazomib/pomalidomide/dexamethasone and daratumumab/pomalidomide/dexamethasone.