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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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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Multiple Myeloma, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Multiple Myeloma provide recommendations for diagnosis, workup, treatment, follow-up, and supportive care for patients with monoclonal gammopathy of renal significance, solitary plasmacytoma, smoldering myeloma, and multiple myeloma. These NCCN Guidelines Insights highlight some of the important updates and changes in the 1.2020 version of the NCCN Guidelines for Multiple Myeloma.

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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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in 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 panel's discussion, including the literature reviewed.**

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The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

Overview

Multiple myeloma (MM) accounts approximately 1.8% of all cancers and slightly more than 17% of hematologic malignancies in the United States.[1] Myeloma is most frequently diagnosed in people aged 65 to 74 years, with the median age being 69 years.[2] The American Cancer Society has estimated 32,110 new myeloma cases will be diagnosed in the United States in 2019, with an estimated 12,960 deaths.[3]

The NCCN Multiple Myeloma Panel has developed guidelines for the management of patients with various plasma cell neoplasms, including solitary plasmacytoma, smoldering myeloma, multiple myeloma, systemic light chain amyloidosis, and Waldenström macroglobulinemia. These guidelines are updated annually, and sometimes more often if new high-quality clinical data become available.

Significant updates have been made to the 1.2020 version of the NCCN Guidelines for Multiple Myeloma. These NCCN Guidelines Insights focus only on the updates specific to imaging recommendations for MM; treatment options for newly diagnosed transplant-eligible and transplant-ineligible candidates, maintenance therapy, and previously treated MM; and management of renal disease in patients with MM. A complete list of updates to the 1.2020 version is available at NCCN.org.

Updates to Imaging Recommendations

Imaging for Initial Diagnostic Workup

A skeletal survey has been the standard for assessing bone disease in any individual with suspected myeloma for decades.[4] However, this technique has significant limitations related to lower sensitivity compared with advanced imaging.

CT alone or in combination with FDG-PET has been shown to be significantly superior regarding the sensitivity to detect osteolytic lesions in patients with monoclonal plasma cell disorders. A multicenter analysis by the International Myeloma Working Group (IMWG) comparing conventional skeletal survey with whole-body CT scans from 212 patients with monoclonal plasma cell disorders found that whole-body CT was positive in 25.5% of patients with a negative skeletal survey. The sensitivity of skeletal survey and whole-body low-dose CT in the long bones is not significantly different; the difference is mainly in detection of abnormalities in spine and pelvis.[5,6] In a study of 29 patients, CT showed osteolytic lesions in 5 patients (17%), whereas skeletal survey results were negative.[7] Studies have shown that whole-body low-dose CT is superior to skeletal survey radiographs in areas that are difficult to visualize using skeletal surveys, such as the skull and ribs.[8]

FDG-PET/CT also has been shown to identify more lesions than plain radiographs and to detect lesions in patients with negative skeletal surveys.[9–11] It is important to note that if PET/CT is selected instead of whole-body low-dose CT, the imaging quality of the CT part of the PET/CT should be equivalent to a whole-body low-dose CT. Usually the CT part is used only for attenuation correction, which is not sufficient to assess myeloma bone disease and stability of the spine.

MRI is useful for discerning smoldering myeloma from MM. Because the disease burden in patients with smoldering myeloma is lower than in those with MM, imaging techniques with high sensitivity must be used, and MRI is a sensitive technique for detecting marrow infiltration by myeloma.[12,13]

NCCN Recommendations

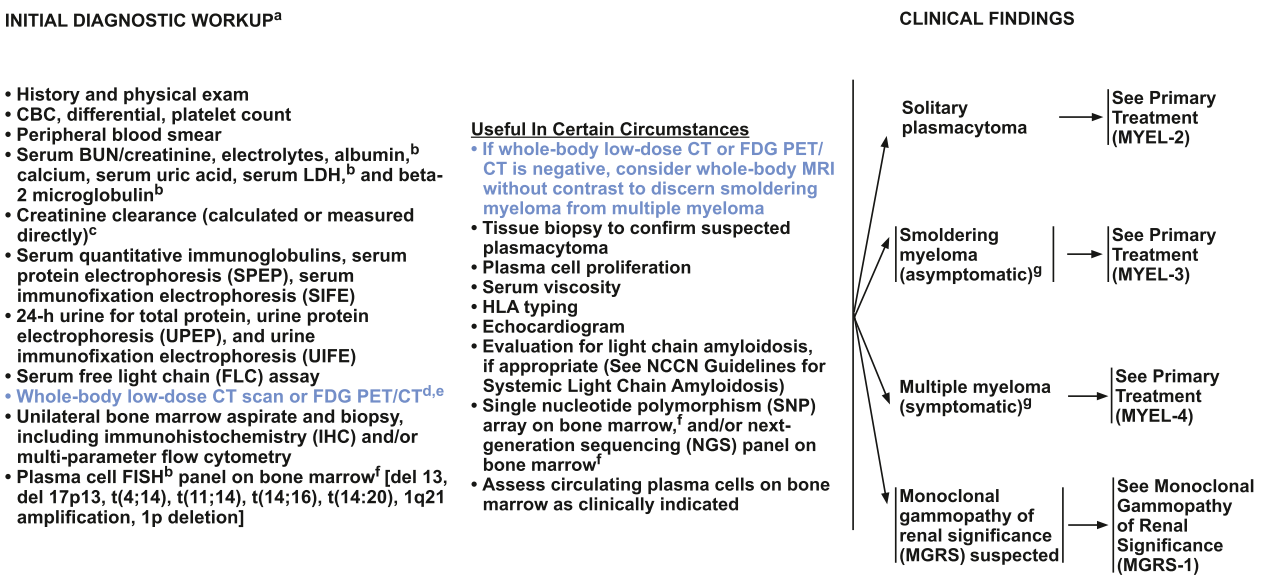
For initial diagnostic workup of patients with suspected MM, the NCCN panel recommends either whole-body low-dose CT or FDG-PET/CT (see MYEL-1, page opposite page). The panel also noted that skeletal survey is acceptable when advanced imaging is not available.

Imaging for Follow-up

Residual focal lesions detected by either FDG-PET/CT or MRI have been shown to be of adverse prognostic significance.[14–17] Zamagni et al[17] reported progression-free survival (PFS) of 44 months in patients with residual focal lesions on FDG-PET/CT versus 84 months for those with no residual focal lesions after systemic treatment (P=.0009). In the IMAJEM trial, both PFS (P=.011) and overall survival (OS; P=.033) were significantly better in patients with negative FDG-PET/CT results before initiation of maintenance therapy.[15] An analysis by Walker et al[16] showed that conventional MRI normalizes over a prolonged period of time, making FDG-PET/CT superior for follow-up. However, in small cohorts, functional imaging sequence for MRI called diffusion-weighted imaging was shown to have superior sensitivity to detect residual disease compared with FDG-PET/CT.[18–20] Furthermore, unlike FDG-PET/CT, MRI does not expose patients to radiation.

NCCN Recommendations

For follow-up of patients with MM after primary treatment (see MYEL-5, page 1158), the NCCN panel recommends advanced imaging (ie, whole-body FDG-PET/CT, low-dose CT scan, whole-body MRI without contrast) as clinically indicated, and using the same imaging modality used during the initial workup for the follow-up assessments.



[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] These tests are essential for R-ISS staging. See Staging Systems for Multiple Myeloma (MYEL-A).
[c] See Management of Renal Disease in Multiple Myeloma (MYEL-H).
[d] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If whole-body FDG PET/CT or low-dose CT has been performed, then skeletal survey is not needed.
[e] See Principles of Imaging (MYEL-B).
[f] CD138 positive selected sample is strongly recommended for optimized yield.
[g] See Definitions of Smoldering and Multiple Myeloma (MYEL-C).

MYEL-1

Updates to Treatment Options for Newly Diagnosed MM

The panel added new regimen options in the 1.2020 version for both transplant-eligible and transplant-ineligible patients with newly diagnosed MM.

Daratumumab/Lenalidomide/Dexamethasone

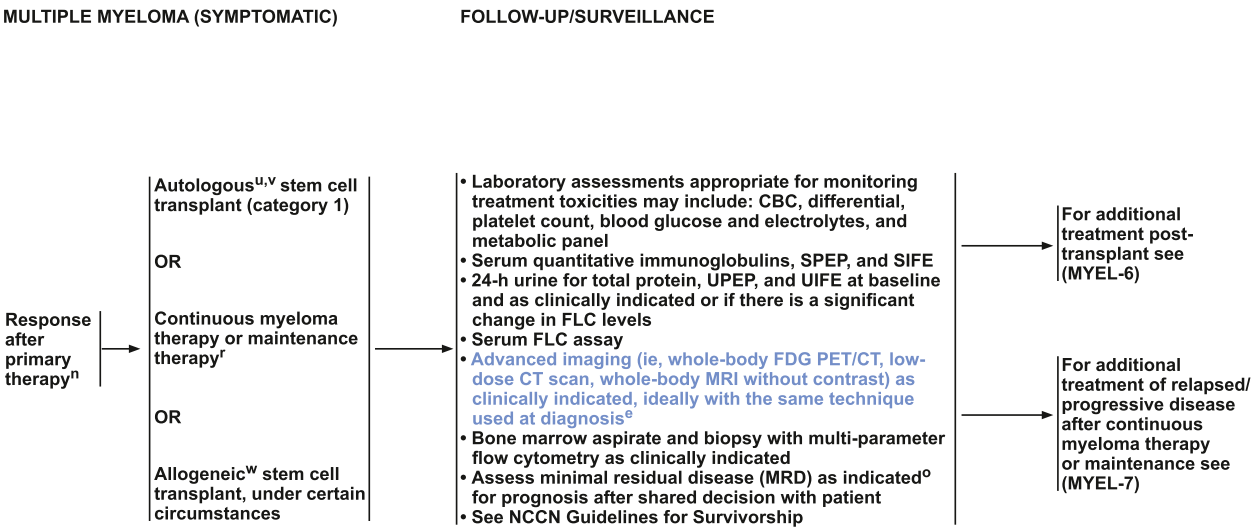
In transplant-ineligible patients with newly diagnosed MM, results of a recently reported phase III trial (MAIA) showed that daratumumab/lenalidomide/dexamethasone significantly reduced the risk of disease progression or death by 44% (hazard ratio [HR], 0.56; 95% CI, 0.43–0.73; $P<.001$).[21] The addition of daratumumab to lenalidomide/dexamethasone resulted in deeper responses compared with lenalidomide/dexamethasone, including increased rates of complete response or better (48% vs 25%), very good partial response (VGPR) or better (79% vs 53%), and overall response (93% vs 81%).[21] Rates of pneumonia, neutropenia, and leukopenia were higher in patients receiving daratumumab.[21] Based on the results of this study, the FDA approved the use of daratumumab/lenalidomide/dexamethasone in this setting.

Carfilzomib/Cyclophosphamide/Dexamethasone

The efficacy seen with bortezomib in combination with cyclophosphamide and dexamethasone in patients with MM led to studies of other proteasome inhibitors in combination with cyclophosphamide and dexamethasone.

The carfilzomib/cyclophosphamide/dexamethasone regimen has been studied in phase I/II trials of transplant-ineligible patients with newly diagnosed MM. Trials have investigated both once-weekly and twice-weekly carfilzomib dosing combined with a fixed dose of cyclophosphamide and dexamethasone.[22,23] A pooled analysis of 2 phase I and II studies comparing 2 alternative schedules of carfilzomib showed similar response rates in transplant-ineligible patients with newly diagnosed MM treated with once-weekly carfilzomib at 70 mg/m^2 and those treated with twice-weekly carfilzomib at 36 mg/m^2. The PFS and OS were also similar. Median PFS was 35.7 months in the once-weekly group and 35.5 months in the twice-weekly group (HR, 1.39; $P=.26$). The 3-year OS was 70% and 72%, respectively (HR, 1.27; $P=.5$).[24]

Consistent with these results, the more recent phase Ib CHAMPION-2 study evaluated the safety



[e] See Principles of Imaging (MYEL-B).
[n] See Response Criteria for Multiple Myeloma (MYEL-E).
[r] See Myeloma Therapy (MYEL-F).
[u] Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant. See Discussion.
[v] Renal dysfunction and advanced age are not contraindications to transplant.
[w] Allogeneic stem cell transplant in multiple myeloma should only be used in the setting of a clinical trial. Current data do not support miniallografting alone.

MYEL-5

and tolerability of twice-weekly carfilzomib (3 different doses) in combination with cyclophosphamide and dexamethasone for the treatment of patients with newly diagnosed MM. This study found that that 56 mg/m^2 of carfilzomib combined with weekly cyclophosphamide and dexamethasone was effective and had manageable toxicity.[25]

Ixazomib/Cyclophosphamide/Dexamethasone

In a phase I trial, ixazomib/cyclophosphamide/dexamethasone was shown to be a convenient, all-oral combination that is well tolerated and effective in patients with newly diagnosed MM.[26] Subsequently, a multicenter phase II trial investigated the efficacy and toxicity of weekly oral ixazomib, cyclophosphamide, and low-dose dexamethasone as induction, followed by single-agent ixazomib maintenance, in elderly (median age, 73 years) transplant-ineligible patients with newly diagnosed MM.[27] The overall response rate after initial therapy with ixazomib/cyclophosphamide/dexamethasone was 73%. After a median follow-up of 26.1 months, the PFS was 23.5 months.

NCCN Recommendations for Primary Myeloma Therapy

In the 1.2020 version of the NCCN Guidelines, the NCCN panel included carfilzomib/cyclophosphamide dexamethasone and ixazomib/cyclophosphamide/dexamethasone for both transplant and nontransplant settings as options useful in certain circumstances, such as in patients with renal insufficiency and/or peripheral neuropathy. The panel has also noted that carfilzomib can be given once or twice weekly at different doses (see MYEL-F, pages 1159–1161).

The NCCN panel also included daratumumab/lenalidomide/dexamethasone as a preferred category 1 option for patients with newly diagnosed MM who are transplant-ineligible (see MYEL-F, pages 1159–1161). Also, because regimens containing melphalan are rarely used in North America, daratumumab in combination with bortezomib/lenalidomide/dexamethasone has now been listed under "Other Recommended Regimens" in this setting.

The doublet regimens were removed from the page listing therapies for transplant candidates with the rationale that doublets would be recommended for patients

MYELOMA THERAPY[a-g,i,j]

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[h]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances[k] • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclosphosphamide/dexamethasone[l] • Ixazomib/cyclophosphamide/dexamethasone[l] • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[m] (VTD-PACE)

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[n] (category 1)
Other Recommended Regimens • Ixazomib (category 1) • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Therapy (MYEL-G).
[c] Subcutaneous bortezomib is the preferred method of administration.
[d] 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 transplant. Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[e] See Management of Renal Disease in Multiple Myeloma (MYEL-H).
[f] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[g] Both weekly and twice-weekly dosing schemas for bortezomib may be appropriate and acceptable.
[h] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[i] Carfilzomib can be used once or twice weekly and at different doses.
[j] Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[k] Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, patients who could not be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.
[l] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[m] Generally reserved for the treatment of aggressive multiple myeloma.
[n] 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.

Continued

MYEL-F
1 OF 3

who would not be considered for initial treatment with a 3-drug regimen, such as those not initially eligible for transplant. Therefore, for transplant-ineligible patients, the 2-drug regimens are still listed as options with a note stating that triplet regimens should be used as standard therapy for patients with MM, but that those who could not be considered for treatment initiation with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.

Updates to Maintenance Therapy Recommendations

In the 1.2020 version, the NCCN panel clarified the maintenance regimens appropriate for patients who received autologous hematopoietic cell transplant (AHCT) versus those who did not, and classified these regimens as either "Preferred," "Other Recommended," or "Useful in Certain Circumstances."

Lenalidomide

Multiple randomized phase III trials have shown a PFS benefit of lenalidomide maintenance after AHCT[28,29] and in transplant-ineligible patients after primary therapy.[30–32] Furthermore, a meta-analyses showed improved OS benefit with lenalidomide maintenance after AHCT,[33] with an OS at 7 years of 62% in the group receiving lenalidomide maintenance versus 50% in those receiving placebo.[33]

NCCN Recommendations for Lenalidomide Maintenance

Given the high-level data, the NCCN panel continues to list single-agent lenalidomide as a category 1 preferred maintenance regimen for both transplant-eligible and transplant-ineligible patients (see MYEL-F, pages 1159–1161).

Bortezomib

Maintenance with proteasome inhibitors has also been evaluated in randomized trials. The HOVON trial compared bortezomib versus thalidomide as maintenance therapy after AHCT for 2 years[34,35] and showed that bortezomib maintenance prolonged PFS; however, in a subset analysis, the benefit of bortezomib maintenance was primarily seen in patients with high-risk myeloma (median OS not reached at 54 vs 24 months; HR, 0.36, 95% CI, 0.18–0.74).[34]

MYELOMA THERAPY[a-c,e-g,i,j]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1)[o] • Daratumumab[p]/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[k,q] • Bortezomib/cyclophosphamide/dexamethasone[h]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab[p]/bortezomib/melphalan/prednisone (category 1)
Useful In Certain Circumstances • Bortezomib/dexamethasone[k] • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[l]

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[n] (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Therapy (MYEL-G).
[c] Subcutaneous bortezomib is the preferred method of administration.
[e] See Management of Renal Disease in Multiple Myeloma (MYEL-H).
[f] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[g] Both weekly and twice-weekly dosing schemas for bortezomib may be appropriate and acceptable.
[h] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[i] Carfilzomib can be used once or twice weekly and at different doses.
[j] Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[k] Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, patients who could not be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.
[l] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[n] 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.
[o] This is the only regimen shown to have overall survival benefit.
[p] Daratumumab may interfere with serologic testing and cause false-positive indirect Coombs test. Type and screen should be performed before using daratumumab.
[q] 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.

Continued

A multicenter phase III trial showed that consolidation with bortezomib after autologous stem cell transplant improved PFS only in patients not achieving at least VGPR.[36] Results of the phase III UPFRONT study also showed that maintenance with single-agent bortezomib was well-tolerated when administered after treatment with bortezomib-based primary therapy.[37]

NCCN Recommendations for Bortezomib Maintenance

Because none of the clinical trials discussed previously were designed to assess the contribution of bortezomib as maintenance therapy (bortezomib was given during induction and continued as maintenance,[34,36,37] or the control arm had a different induction therapy regimen plus maintenance therapy[34]), the panel included bortezomib as a category 2A "Other Recommended" maintenance option for both transplant-eligible and transplant-ineligible patients (see MYEL-F, pages 1159–1161). For high-risk patients, the panel considers bortezomib/lenalidomide an option for maintenance therapy, and therefore has included this combination as "Useful in Certain Circumstances."[38]

Ixazomib

The phase III trial TOURMALINE-MM3, which studied 2 years of maintenance with ixazomib versus placebo in patients who had achieved at least a partial response following induction therapy and a single AHCT, showed that ixazomib improved PFS (median, 26.5 months [95% CI, 23.7–33.8] vs 21.3 months [95% CI, 18.0–24.7]; HR, 0.72; 95% CI, 0.58–0.89).[39] The risk of developing secondary malignancies was similar in the control arm and in patients receiving maintenance ixazomib.

NCCN Recommendations for Ixazomib Maintenance

Based on the positive results of the TOURMALINE-MM3 trial, designed specifically to study the benefit of maintenance ixazomib, the NCCN panel included ixazomib as a category 1 "Other Recommended" maintenance option for transplant-eligible patients (see MYEL-F, pages 1159–1161).

Updates to Treatment Options for Previously Treated MM

A variety of therapies continue to be listed as options for previously treated MM. The choice of appropriate

MYELOMA THERAPY[a-c,f,g,i,j,r,s]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[r]	
Preferred Regimens	
• Bortezomib/lenalidomide/dexamethasone	• Daratumumab[p]/bortezomib/dexamethasone (category 1)
• Carfilzomib (twice weekly)/dexamethasone (category 1)[k]	• Daratumumab[p]/lenalidomide/dexamethasone (category 1)
• Carfilzomib (weekly)/dexamethasone[k]	• Elotuzumab[w]/lenalidomide/dexamethasone (category 1)[t]
• Carfilzomib/lenalidomide/dexamethasone (category 1)[t]	• Ixazomib/lenalidomide/dexamethasone (category 1)[t]
Other Recommended Regimens	
• Bendamustine/bortezomib/dexamethasone	• Elotuzumab/pomalidomide/dexamethasone[v]
• Bendamustine/lenalidomide/dexamethasone	• Ixazomib/cyclophosphamide/dexamethasone
• Bortezomib/liposomal doxorubicin/dexamethasone (category 1)	• Ixazomib/dexamethasone[k]
• Bortezomib/cyclophosphamide/dexamethasone	• Ixazomib/pomalidomide/dexamethasone
• Carfilzomib/cyclophosphamide/dexamethasone	• Lenalidomide/dexamethasone[y] (category 1)[k]
• Cyclophosphamide/lenalidomide/dexamethasone	• Panobinostat[z]/bortezomib/dexamethasone (category 1)
• Bortezomib/dexamethasone (category 1)[k]	• Panobinostat[z]/carfilzomib[k]
• Daratumumab[p,u]	• Panobinostat[z]/lenalidomide/dexamethasone
• Daratumumab[p]/carfilzomib/dexamethasone	• Pomalidomide[x]/cyclophosphamide/dexamethasone
• Daratumumab[p]/pomalidomide[v]/dexamethasone	• Pomalidomide[x]/dexamethasone[y] (category 1)[k]
• Elotuzumab/bortezomib/dexamethasone	• Pomalidomide[x]/bortezomib/dexamethasone (category 1)
	• Pomalidomide[x]/carfilzomib/dexamethasone
Useful In Certain Circumstances	
• Bendamustine	• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[m] ± bortezomib (VTD-PACE)[m]
• Carfilzomib/cyclophosphamide/thalidomide/dexamethasone	• High-dose cyclophosphamide
• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[m]	• Selinexor/dexamethasone[aa]

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Therapy (MYEL-G).
[c] Subcutaneous bortezomib is the preferred method of administration.
[f] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[g] Both weekly and twice-weekly dosing schemas bortezomib agent may be appropriate and acceptable.
[i] Carfilzomib can be used once or twice weekly and at different doses.
[j] Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[k] Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, patients who could not be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.
[m] Generally reserved for the treatment of aggressive multiple myeloma.
[p] Daratumumab may interfere with serologic testing and cause false-positive indirect Coombs test. Type and screen should be performed before using daratumumab.
[r] Consideration for appropriate regimen is based on the context of clinical relapse.
[s] If a regimen listed on this page was used as a primary induction therapy and relapse is >6 mo, the same regimen may be repeated.
[t] Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[u] 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.
[v] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor.
[w] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[x] 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.
[y] Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[z] Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[aa] Indicated for patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

MYEL-F
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therapy for a patient would depend on the context of clinical relapse, such as prior treatment and duration of response. New regimens were included as options for the treatment of relapsed/refractory MM in the 1.2020 version of the NCCN Guidelines (see MYEL-F, pages 1159–1161).

Daratumumab/Carfilzomib/Dexamethasone

Combination daratumumab/carfilzomib/dexamethasone was studied in a phase Ib, open-label, nonrandomized, multicenter study in patients (n=82) with relapsed/refractory MM. At a median follow-up of 16 months, the overall response rate was 84%. In the overall treatment population, although the median PFS was not reached, the 12- and 18-month PFS rates were 74% and 66%, respectively.[40] Based on these data, the NCCN panel included this regimen as an "Other Recommended" option for relapsed/refractory MM.

Ixazomib/Cyclophosphamide/Dexamethasone

Combination ixazomib/cyclophosphamide/dexamethasone has been shown to be tolerable and efficacious in patients with newly diagnosed MM.[26,27] A phase II study evaluating this regimen in the relapsed/refractory setting in patients with a median age of 63.5 years also found it to be well tolerated. At a median follow-up of 15.2 months, the median PFS was 14.2 months, with a trend toward better PFS in patients aged ≥65 versus <65 years (median, 18.7 vs 12.0 months; HR, 0.62; P=.14).[41] Therefore, the NCCN panel included this all-oral regimen as an "Other Recommended" option for relapsed/refractory MM.

Pomalidomide/Bortezomib/Dexamethasone

Results were recently published of the phase III, open-label, multicenter, randomized OPTIMISMM study that evaluated the safety and efficacy of pomalidomide/bortezomib/dexamethasone (n=281) versus bortezomib/dexamethasone (n=278) in patients with relapsed/refractory MM who previously received lenalidomide.[42] After a median follow-up of 15.9 months, significantly improved PFS was seen in the pomalidomide arm (median, 11.20 vs 7.10 months; HR, 0.61; 95% CI, 0.49–0.77; P<.0001). The most commonly reported grade 3/4 treatment-related adverse events in the pomalidomide arm were neutropenia, infections, and thrombocytopenia.[42]

MANAGEMENT OF RENAL DISEASE IN MULTIPLE MYELOMA[a]

Tests
- Serum creatinine, electrolytes, and uric acid
- Urinalysis, electrolytes, and sediment
- 24-h urine collection for protein and UPEP/UIFE
- SPEP/SIFE and serum FLCs
- Consider renal ultrasound, renal biopsy

Treatment Options
- Pulse dexamethasone
- Bortezomib-based regimen
- Consider third drug: cyclophosphamide, thalidomide, anthracycline, or daratumumab
- Can switch to other regimen once renal function has improved
- Use other plasma cell-directed therapy with caution
- See Response Criteria for Multiple Myeloma (MYEL-E)
- See Myeloma Therapy (MYEL-F)

Supportive Care
- Provide hydration to dilute tubular light chains; goal urine output is 100–150 cc/h
- Monitor fluid status
- Treat hypercalcemia, hyperuricemia, and other metabolic abnormalities
- Discontinue nephrotoxic medications
- Dialysis
  - Refractory electrolyte disturbances, uremia, and fluid overload
- Mechanical removal of serum FLCs; goal removal of 50%
  - High cutoff dialysis filters
  - Plasmapheresis
- Renal dosing of all medications

Recommendations for Lenalidomide Dosing in Patients with Multiple Myeloma Who Have Renal Impairment

Category	Renal Function (Cockcroft-Gault CL_{Cr})	Lenalidomide Dosing in Multiple Myeloma
Moderate renal impairment	CL_{Cr} ≥30 mL/min to <60 mL/min	10 mg every 24 h
Severe renal impairment	CL_{Cr} <30 mL/min (not requiring dialysis)	15 mg every 48 h
End-stage renal disease	CL_{Cr} <30 mL/min (requiring dialysis)	5 mg once daily; on dialysis days, dose should be administered after dialysis

CL_{Cr} = creatinine clearance

Pamidronate and Zoledronic Acid Dosing in Patients with Multiple Myeloma Who Have Renal Impairment

Degree of Renal Impairment	Pamidronate (focal segmental glomerulosclerosis)	Zoledronic Acid (tubular cell toxicity)
None	90 mg IV over >2 h every 3–4 wks	4 mg IV over >5 min every 3–4 wks
Mild/moderate renal impairment	Use standard dose	Reduce dose
Severe renal impairment	60–90 mg over 4–6 h	Not recommended

[a] Defined as serum creatinine >2 mg/dL or established glomerular filtration rate (eGFR) <60 mL/min/1.73 sqm.

MYEL-H

Based on these phase III trial results, the NCCN panel included pomalidomide/bortezomib/dexamethasone as a category 1 therapeutic option for patients who received at least 2 prior therapies, including an immunomodulatory agent (IMiD) and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Carfilzomib/Cyclophosphamide/Thalidomide/Dexamethasone

Results of the phase I/II CYCLONE trial showed that the 4-drug carfilzomib/cyclophosphamide/thalidomide/dexamethasone regimen is efficacious, with an overall response rate of 91%, and 76% of patients with MM achieving a VGPR or greater after 4 cycles.[43] This regimen has now been included under the list of regimens "Useful in Certain Circumstances" for relapsed/refractory MM.

Selinexor/Dexamethasone

Selinexor was recently approved for the treatment of myeloma. This agent induces apoptosis of MM cells by selectively inhibiting nuclear export compound that blocks exportin 1 (XPO1), forcing nuclear accumulation and activation of tumor suppressor proteins, and inhibiting nuclear factor κB and the translation of oncoprotein mRNAs, such as c-myc and cyclin-D. Selinexor in combination with dexamethasone was studied in the phase IIb STORM trial in patients with relapsed/refractory MM who had multiple prior therapies and were refractory to IMiDs (lenalidomide and pomalidomide), proteasome inhibitors (bortezomib and carfilzomib), and the CD38 antibody (daratumumab).[44] A total of 122 patients were included in the intent-to-treat population. Partial response or better was observed in 26% of patients (95% CI, 19%–35%).

The most common adverse events reported during treatment were thrombocytopenia in 73% of patients, fatigue in 73%, nausea in 72%, and anemia in 67%.

Based on these results, the NCCN panel included selinexor/dexamethasone in the list of regimens "Useful in Certain Circumstances" as an option for patients with relapsed/refractory MM who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 IMiD agents, and an anti-CD38 monoclonal antibody.

Management of Renal Disease in Patients With MM

In patients with MM and monoclonal gammopathies, renal disease usually results from the production of monoclonal immunoglobulin or light/heavy chains by a clonal proliferation of plasma cells or B cells. Renal disease is seen in 20% to 50% of patients with myeloma and has been observed to negatively affect outcomes.[45–47] In the 1.2020 version of the NCCN Guidelines, the panel added a new page outlining management of renal disease in MM (see MYEL-H, page 1162).

In patients with myeloma, renal insufficiency, defined as elevated serum creatinine level of >2 mg/dL or established glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, is usually due to light chain cast nephropathy, but other causes must be considered, including hypercalcemia, volume depletion, and hyperuricemia as well as nephrotoxic medications or intravenous contrast. In addition, concomitant amyloidosis and monoclonal immunoglobulin deposition should be suspected when renal insufficiency or albuminuria is present without high levels of light chains.

Diagnostic Tests

According to the NCCN panel, diagnostic workup of patients with symptomatic myeloma should include serum creatinine measurement, electrolytes assessment, eGFR, electrophoresis of a sample from a 24-hour urine collection, serum electrophoresis, and serum free light chain measurement. If proteinuria predominantly consists of light chains with high serum levels of free light chain, and the cause of renal insufficiency can be attributed to myeloma, a renal biopsy may not be necessary. However, patients without a clear and complete explanation for their renal insufficiency should undergo renal biopsy to assess for other pathophysiology, such as monoclonal immunoglobulin deposition disease or membranoproliferative glomerulonephritis.

Treatment Options

Initial treatment of cast nephropathy includes administering appropriate myeloma therapy and providing adequate supportive care.

Myeloma Therapy

Myeloma therapy using bortezomib-containing regimens should be initiated as soon as possible to decrease the production of nephrotoxic clonal immunoglobulin.[48] Bortezomib/dexamethasone containing regimens can be administered to patients with severe renal impairment and those on dialysis and do not require renal dose adjustment.[46] If the 2-drug bortezomib/dexamethasone regimen is used as initial treatment, a third drug that does not require dose adjustment can be added, including cyclophosphamide, thalidomide, an anthracycline, or daratumumab. Other agents available for myeloma therapy should be used with caution and with dose adjustments based on the degree of renal function impairment, as recommended by the IMWG.[49] A retrospective study evaluated lenalidomide and dexamethasone based on 2 phase III trials of lenalidomide/low-dose dexamethasone in patients with relapsed/refractory myeloma and a serum creatinine level of <2.5 mg/dL.[50] Patients grouped by creatinine clearance >60 mL/min (n=243), 30 to 60 mL/min (n=82), and <30 mL/min (n=16) showed no difference in response rates to lenalidomide/low-dose dexamethasone. Those with renal insufficiency had higher rates of thrombocytopenia and lenalidomide discontinuation than those without renal insufficiency. The NCCN panel outlined recommendations for lenalidomide dosing based on degree of renal function in patients with MM and renal impairment. Although prospective data to define optimal dosing are often lacking, pomalidomide has been studied in patients with relapsed myeloma in 3 different categories of renal insufficiency (eGFR 30–40 mL/min/1.73 m^2, eGFR <30 mL/min/1.73 m^2, and those requiring dialysis), and full-dose pomalidomide of 4 mg/d was found to be safe in all 3 groups.[51] High-dose chemotherapy and autologous stem cell transplantation can be safely performed in patients with renal insufficiency, including those on dialysis. Conditioning with reduced-dose melphalan has outcomes comparable to standard-dose melphalan and should be considered in those who are otherwise eligible for the procedure.[52,53]

Supportive Care

Intravenous fluids should be started promptly in patients with MM and renal disease to decrease the renal tubular light chain concentration, with a goal urine output of 100 to 150 mL/h. Careful assessment of fluid status is critical to avoid hypervolemia, especially in patients with oliguria renal failure.

In addition, nephrotoxic medications should be discontinued and other metabolic abnormalities corrected, such as hypercalcemia and hyperuricemia. Hydration, bisphosphonates, denosumab, and/or calcitonin are recommended to reduce calcium levels in the case of hypercalcemia. In patients with renal disease, pamidronate and zoledronic acid should be used with caution; the NCCN panel has provided recommended dosing of these agents (see MYEL-H, page 1162).

Dialysis may be required in selected patients, in addition to prompt institution of antimyeloma therapy. Mechanical removal of light chains may be considered on a case-by-case basis. Although the benefit of mechanical removal of free light chains has not been established, limited evidence supports the use of

plasmapheresis or high-cutoff dialysis to reduce pathogenic light chains.

Conclusions

These NCCN Guidelines Insights highlight important updates and changes specific to treatment options for MM in the 1.2020 version of the NCCN Guidelines. The NCCN Guidelines are in continuous evolution; they are updated annually, and sometimes more often if new high-quality clinical data become available in the interim. 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 in order to provide optimal care. The physician and patient have the 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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