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Multiple Myeloma, Version 1.2013

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NCCN Guidelines® Insights

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Featured Updates to the NCCN Guidelines

Kenneth C. Anderson, MD¹; Melissa Alsina, MD²; William Bensinger, MD³; J. Sybil Biermann, MD⁴; Adam D. Cohen, MD⁵; Steven Devine, MD⁶; Benjamin Djulbegovic, MD, PhD²; Edward A. Faber Jr, DO⁷; Cristina Gasparetto, MD⁸; Francisco Hernandez-Illizaliturri, MD⁹; Carol Ann Huff, MD¹⁰; Adetola Kassim, MD¹¹; Amrita Y. Krishnan, MD¹²; Michael Liedtke, MD¹³; Ruby Meredith, MD, PhD¹⁴; Noopur Raje, MD¹⁵; Jeffrey Schriber, MD¹⁶; Seema Singhal, MD¹⁷; George Somlo, MD¹²; Keith Stockerl-Goldstein, MD¹⁸; Steven P. Treon, MD, PhD¹; Donna Weber, MD¹⁶; Joachim Yahalom, MD¹⁹; Furhan Yunus, MD²⁰; Dorothy A. Shead, MS²¹; and Rashmi Kumar, PhD²¹

Abstract

These NCCN Guidelines Insights highlight the important updates/changes specific to the management of relapsed or progressive disease in the 2013 version of the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma. These changes include the addition of new regimens as options for salvage therapy and strategies to mitigate the adverse effects and risks associated with newer regimens for the treatment of multiple myeloma. (*JNCCN* 2013;11:11–17)

From ¹Dana-Farber Cancer Institute/Brigham and Women's Cancer Center; ²Moffitt Cancer Center; ³Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; ⁴University of Michigan Comprehensive Cancer Center; ⁵Fox Chase Cancer Center; ⁶The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; ⁷UNMC Eppley Cancer Center at The Nebraska Medical Center; ⁸Duke Cancer Institute; ⁹Roswell Park Cancer Institute; ¹⁰The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; ¹¹Vanderbilt-Ingram Cancer Center; ¹²City of Hope Comprehensive Cancer Center; ¹³Stanford Cancer Institute; ¹⁴University of Alabama at Birmingham Comprehensive Cancer Center; ¹⁵Massachusetts General Hospital Cancer Center; ¹⁶The University of Texas MD Anderson Cancer Center; ¹⁷Robert H. Lurie Comprehensive Cancer Center of Northwestern University; ¹⁸Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; ¹⁹Memorial Sloan-Kettering Cancer Center; ²⁰St. Jude Children's Research Hospital/University of Tennessee Cancer Institute; and ²¹National Comprehensive Cancer Network.

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Individual disclosures of potential conflicts of interest for the NCCN Multiple Myeloma Panel can be found on page 12.

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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 in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's 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 NCCN Guidelines for Multiple Myeloma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Multiple Myeloma

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CE AUTHORS: Nicole B. Fair, BS, Manager, Continuing Education and Grants, has disclosed that she has no relevant financial relationships. Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships. James Prazak, RPh, Director, Continuing Education and Grants, has disclosed the following relationships with commercial interests: Bristol-Myers Squibb Company: Pension; Pfizer, Inc: Stockholder; United Healthcare Group: Stockholder; Johnson & Johnson: Stockholder. Dorothy Shead, MS, Director, Patient and Clinical Information Operations, has disclosed that she has no relevant financial relationships. Rashmi Kumar, PhD, Oncology Scientist/Senior Medical Writer, has disclosed that she has no relevant financial relationships.

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Dr. Alsina: Clinical research support from Celgene Corporation and Millennium Pharmaceuticals, Inc. Consultant for Celgene Corporation. Advisory board member for Millennium Pharmaceuticals, Inc. Speaker bureau member for Ortho Biotech Products, L.P.

Dr. Anderson: Advisory board member for Bristol-Myers Squibb Company; Celgene Corporation; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; and Onyx Pharmaceuticals, Inc. Founder of acetylon and oncopep.

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Dr. Cohen: Advisory board member for Bristol-Myers Squibb Company; and Celgene Corporation. Independent response adjudication committee member for Celgene Corporation.

Dr. Devine: Investigator for Genzyme Corporation. Speaker bureau member for Novartis Pharmaceuticals Corporation.

Dr. Djulbegovic: Clinical research support from Millennium Pharmaceuticals, Inc.

Dr. Faber: Advisory board member for sanofi-aventis U.S.

Dr. Gasparetto: Advisory board member for Celgene Corporation. Speaker bureau member for Celgene Corporation and Millennium Pharmaceuticals, Inc.

Dr. Hernandez-Ilizaliturri: Advisory board member for Amgen Inc. and Celgene Corporation.

Dr. Huff: Principal investigator for Bristol-Myers Squibb Company and Geron. Advisory board member for Celgene Corporation and Millennium Pharmaceuticals, Inc.

Dr. Kassim: Advisory board member for Celgene Corporation.

Dr. Krishnan: Speaker bureau member for Celgene Corporation; Genentech, Inc.; and Millennium Pharmaceuticals, Inc. Advisory board member for Merck & Co., Inc.

Dr. Liedtke: Lecturer for Celgene Corporation.

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Dr. Schriber: Speaker bureau member for Celgene Corporation; Enzon Pharmaceuticals; Genzyme Corporation; Millennium Pharmaceuticals, Inc.; and Novartis Pharmaceuticals Corporation. Stock owner of Amgen Inc.; Celgene Corporation; and Onyx Pharmaceuticals, Inc.

Dr. Singhal: Clinical research support from Millennium Pharmaceuticals, Inc. and Onyx Pharmaceuticals, Inc. Speaker bureau member for Celgene Corporation. Advisory board member for Celgene Corporation and Millennium Pharmaceuticals, Inc.

Dr. Somlo: Principal investigator for AstraZeneca Pharmaceuticals LP; Celgene Corporation; and National Cancer Institute. Advisory board member for Abraxane; Celgene Corporation; Genentech, Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Roche Laboratories, Inc.; and Veridex, LLC. Speaker bureau member for Abraxane; Genentech, Inc.; and Roche Laboratories, Inc. Consultant for Abraxane; Genentech, Inc.; and Roche Laboratories, Inc.

Dr. Stockerl-Goldstein: Speaker bureau member for Celgene Corporation and Millennium Pharmaceuticals, Inc.

Dr. Treon: Advisor for Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Onyx Pharmaceuticals, Inc. Speaker bureau member for Millennium Pharmaceuticals, Inc.

Dr. Weber: Principal investigator for Merck & Co., Inc. Investigator for Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Ortho Biotech Products, L.P. Advisory board member for Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and proteolix.

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MYELOMA THERAPY^{1,2,3,6}

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.

Salvage Therapy	Preferred Regimens	Other Regimens
	• Repeat primary induction therapy (if relapse at > 6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib⁷ • Cyclophosphamide/bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone⁸ (category 1) • Thalidomide/dexamethasone⁸	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone

¹Selected, but not inclusive of all regimens.

²Recommend herpes zoster prophylaxis for patients treated with bortezomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.

³Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.

⁶Consideration for appropriate regimen is based on the context of clinical relapse.

⁷Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

⁸Consider single agent lenalidomide or thalidomide for steroid-intolerant individuals.

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MYEL-D
(2 of 2)

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

Overview

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. The American Cancer Society has estimated that 21,700 new cancer cases of MM will be diagnosed in the United States in 2012, and an estimated 10,710 deaths from the disease will occur.¹ The mean age of affected individuals is 62 years for men (75% >70 years) and 61 years for women (79% >70 years).

Understanding of the key pathways responsible for MM has led to the development of novel agents. The availability of many novel evidence-based options for the treatment of MM has led to significant improvements in response and survival.

Most patients with MM experience relapse or become refractory to treatment, partly because of the changing tumor biology. The agents and regimens used as initial therapy have shown significant activity and improved outcomes in patients with relapsed

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or refractory MM. These NCCN Guidelines Insights highlight the important updates/changes specific to the management of relapsed or progressive disease in the 2013 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MM. These include the addition of new agents and regimens as options for salvage therapy and strategies to mitigate the adverse effects and risks associated with newer regimens for the treatment of MM.

Treatment of Progressive or Relapsed Myeloma

Salvage therapy is considered for progressive or relapsed MM in patients with relapsed disease after autologous or allogeneic stem cell transplant (SCT); primary progressive disease after initial autologous or allogeneic SCT; and those ineligible for SCT with progressive or relapsing disease after initial primary therapy.

A variety of therapies are available as options for salvage therapy. The choice of therapy for relapsed/refractory MM is influenced by patient characteristics, comorbidities (eg, presence of significant peripheral neuropathy), and response to and time to relapse with previous therapies. If the relapse occurs more than 6 months after completion of the initial primary therapy, patients may be re-treated with the same primary regimen.

The NCCN Multiple Myeloma Panel members have classified the salvage regimens options either as “preferred regimens” or “other regimens” (see MY-EL-D 2 of 2, on page 13) based on evidence and a balance of efficacy and toxicity.

Preferred Salvage Therapy Regimens

Carfilzomib: In patients who have become resistant to bortezomib, the use of a new proteasome inhibitor, such as carfilzomib, with a different chemical backbone has been shown to overcome this resistance.^{2,3}

Carfilzomib is a second-generation proteasome inhibitor that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. Preclinical studies with carfilzomib show lack of neurodegeneration *in vitro*⁴ and less neurotoxicity in animal studies.⁵ The FDA granted accelerated approval of carfilzomib for the treatment of patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have shown disease progression on or within

60 days of completion of the last therapy. The FDA approval was based on the results of the open-label, single-arm phase II study in which 266 patients received single-agent carfilzomib intravenously twice weekly for 3 of 4 weeks.⁶ Of the evaluable patients in this study, 95% were refractory to their last therapy, and 80% were refractory to both bortezomib and lenalidomide. Patients had a median of 5 prior lines of therapy, including bortezomib, lenalidomide, and thalidomide. The primary end point of this trial was overall response rate (ORR), and secondary end points included duration of response, clinical benefit response rate ($\geq$ minimal response), progression-free survival (PFS), overall survival (OS), and safety. The ORR seen in the trial was 23.7%, median duration of response was 7.8 months, and median OS was 15.6 months.⁶ No cumulative toxicities were reported. Common adverse events reported were fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Treatment-related peripheral neuropathy occurred in 12.4% of patients overall. This is substantially lower than the incidence of peripheral neuropathy seen in the study evaluating subcutaneous bortezomib.^{7,8} The rate of cardiac events observed in this study was within the expected range for this population and also was not greater than previously reported with bortezomib.^{9,10} The safety and efficacy data of carfilzomib seen in this trial are comparable to those reported by other phase II trials.^{11,12} The available data indicate that carfilzomib produces durable responses with an acceptable tolerability profile in heavily pretreated patients with myeloma.

The results of the ongoing phase III studies should provide insight into the optimal use of carfilzomib in all patients with MM. The international, randomized, multicenter phase III trial known as ASPIRE has completed enrollment and is comparing lenalidomide plus low-dose dexamethasone with or without carfilzomib in patients who have received 1 to 3 prior therapies for relapsed MM (ClinicalTrials.gov identifier: NCT01080391). Other phase III trials currently recruiting patients include an international phase III trial, known as the ENDEAVOR trial, which will evaluate the combination of carfilzomib and low-dose dexamethasone versus the combination of bortezomib and low-dose dexamethasone (ClinicalTrials.gov identifier: NCT01568866). A phase III clinical trial, known as the FOCUS trial, will evaluate single-agent carfilzomib versus best sup-

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portive care in patients with relapsed and refractory MM who have received 3 or more prior therapies (ClinicalTrials.gov identifier: NCT01302392).

In the recently updated version of the NCCN Guidelines for MM, the panel included single-agent carfilzomib as a salvage therapy option in patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have shown disease progression on or within 60 days of completion of the last therapy (category 2A).

Bortezomib in Combination With Thalidomide and Dexamethasone: An international open-label study randomized 269 patients with progressive or relapsed MM after at least 1 autologous SCT to receive bortezomib with thalidomide and dexamethasone or thalidomide and dexamethasone.¹³ Patients receiving the triple-drug combination of bortezomib with thalidomide and dexamethasone had significantly better outcomes. Median time to progression was longer (19.5 vs. 13.8 months) and PFS was also significantly longer (18.3 vs. 13.6 months) compared with thalidomide and dexamethasone. The complete response (CR) and near-CR rate was higher in patients receiving bortezomib, thalidomide, and dexamethasone compared to thalidomide and dexamethasone (45% vs. 25%; $P=.001$). No significant difference was observed in OS between the arms over a median follow-up of 30 months. The most clinically significant adverse event seen was grade 3 peripheral neuropathy in 29% of patients on the triple-drug combination versus 12% of those on thalidomide and dexamethasone.¹³

The panel included bortezomib in combination with thalidomide and dexamethasone as an option for relapsed/refractory myeloma (category 2A).

Other Salvage Therapy Regimens

Lenalidomide in Combination With Bendamustine and Dexamethasone: A multicenter phase I/II trial investigated treatment with the combination of bendamustine, lenalidomide, and dexamethasone for patients ($n=29$) with relapsed refractory MM.¹⁴ A partial response was seen in 52% ($n=13$) of patients, and a very good partial response was seen in 24% ($n=6$). The median PFS was 6.1 months (95% CI, 3.7–9.4 months), and the 1-year PFS rate was 20% (95% CI, 6%–41%).¹⁴

The panel included lenalidomide in combination with bendamustine and dexamethasone as an option for relapsed/refractory myeloma (category 2A).

Vorinostat in Combination With Bortezomib: Vorinostat is an oral inhibitor of histone deacetylase (HDAC) class I and II proteins. It regulates genes and proteins involved in tumor growth and survival. It is FDA approved for the treatment of patients with cutaneous T-cell lymphoma. The synergistic effects of vorinostat and bortezomib have been shown in preclinical studies and were confirmed in independent phase I trials in patients with relapsed/refractory MM, showing an ORR of up to 42%.¹⁵ An international, multicentered, open-label, single-arm phase IIB trial called Vantage 095 studied combination vorinostat and bortezomib in patients who were bortezomib-refractory and in those considered refractory, intolerant, or ineligible for immunomodulatory drug-based regimens. The combination of vorinostat and bortezomib was active and well tolerated in these patients. The ORR in the Vantage 095 study was 17%.¹⁶ The median OS observed was 11.2 months, with a 2-year OS rate of 32%.¹⁹ Another international multicenter, randomized, double-blind phase II trial compared vorinostat and bortezomib with bortezomib and placebo in patients with relapsed/refractory MM.¹⁷ The ORR in patients treated with vorinostat and bortezomib was 56% versus 41% in those treated with bortezomib and placebo.¹⁷ The median PFS was 7.63 for vorinostat and bortezomib versus 6.83 months for bortezomib and placebo-treated patients.

Based on these data, the panel has included vorinostat in combination with bortezomib as a treatment option for relapsed/refractory myeloma (category 2A).

Management of Peripheral Neuropathy in MM

Peripheral neuropathy is a common complication seen in patients with MM. It can be caused by MM itself or by certain therapies, such as bortezomib, thalidomide, vinca alkaloids, and cisplatin. Bortezomib-induced neuropathy occurs in nearly 70% of patients.^{18–20} Although the neuropathy does improve with time in most patients, it has a significant impact on quality of life, especially in the elderly population.

Effective management of treatment-emergent peripheral neuropathy is critical to minimize the incidence and severity of this complication, while

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maintaining therapeutic efficacy. A randomized trial, MMY-3021, compared single-agent bortezomib administered through the conventional intravenous route versus the subcutaneous route in 222 patients.⁷ The findings from the phase III MMY-3021 study show noninferior efficacy with subcutaneous versus intravenous bortezomib with regard to the primary end point (ORR after 4 cycles of single-agent bortezomib). Consistent results were shown with regard to secondary end points.⁷ The results showed no significant differences between the groups in terms of time to progression or 1-year OS.^{7,8} However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy, and significantly less grade 3/4 neuropathy (6% vs. 16%).⁷ Based on these data, the updated US Prescribing Information notes that “starting bortezomib subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy.” The FDA-recommended dose of bortezomib is 1.3 mg/m² administered as either a 3- to 5-second bolus intravenous injection or a subcutaneous injection.

The panel has noted in a footnote that subcutaneous bortezomib may be considered for patients with preexisting or high-risk peripheral neuropathy (see MYEL-D 2 of 2, on page 13).

Conclusions

These NCCN Guidelines Insights highlight the important updates/changes specific to the management of recurrent or progressive disease in the most recent version of the NCCN Guidelines for MM. The NCCN Guidelines are in continuous evolution. They are updated annually, or sometimes more often if new high-quality clinical data become available in the interim. 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. 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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Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 70% minimum passing score and complete the evaluation at <http://education.nccn.org/node/8799>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

Posttest Questions

1. True or False: In the recently updated version of the NCCN Guidelines for Multiple Myeloma, the panel included single-agent carfilzomib as a salvage therapy option in patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have shown disease progression on or within 60 days of completion of the last therapy (category 2A).
2. True or False: The NCCN Guidelines for Multiple Myeloma

panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory myeloma (category 2A).

3. True or False: The NCCN Multiple Myeloma Panel members have classified the salvage regimens options either as “preferred regimens” or “other regimens” based on evidence and a balance of efficacy and toxicity.

