Current Clinical Algorithms and Recent Therapeutic Advances in the Management of Multiple Myeloma and Related Blood Disorders

FACULTY
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MODERATOR
Neil Love, MD

CONTENTS
1 Audio CD

Bonus Audio: Access approximately 45 minutes of additional content available only on the web at ResearchToPractice.com/MMTT117
OVERVIEW OF ACTIVITY
Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 12% of all hematologic cancer and carries with it one of the worst death to new cases ratios. Although MM only represents 1.4% of all new cancer cases diagnosed in the United States, it would be difficult to identify another area of oncology in which the research database — and related treatment implications — has evolved more rapidly during the past decade. Featuring information on the latest research developments along with expert perspectives, this CME activity will deliver highly applicable, current clinical information delving into the individualized and multifaceted management of MM.

LEARNING OBJECTIVES
• Develop a risk-adapted treatment plan for patients with smoldering MM, considering the roles of observation and active treatment.
• Use patient- and disease-related factors, including cytogenetic profile, to customize the use of induction and maintenance therapeutic approaches in the transplant and nontransplant settings.
• Consider available research data and other clinical factors in the best-practice selection, sequencing and combining of current and recently approved novel agents in the nonresearch care of patients with relapsed/refractory MM.
• Design and implement a plan of care to recognize and manage side effects and toxicities associated with recently approved systemic therapies to support quality of life and continuation of treatment.
• Identify ongoing trials of investigational approaches in MM, and refer appropriate patients and obtain consent for study participation.

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Penn State College of Medicine and Research To Practice. Penn State College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT
Penn State College of Medicine designates this enduring material for a maximum of 2.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY
This CME activity contains an audio component. To receive credit, the participant should review the CME information, listen to the audio tracks, complete the Post-test with a score of 80% or better and fill out the Educational Assessment and Credit Form located in the back of this booklet or on our website at ResearchToPractice.com/MMTT117/CME.
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CME INFORMATION

FACULTY AFFILIATIONS

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MODERATOR

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CONTENT VALIDATION AND DISCLOSURES

It is the policy of Research To Practice and Penn State College of Medicine to ensure balance, independence, objectivity and scientific rigor in all their educational programs. All faculty, planners and managers participating in this activity are required to disclose any relevant financial relationship(s) they (or spouse/partner) have with a commercial interest that benefits the individual in any financial amount that has occurred within the past 12 months; and the opportunity to affect the content of CME about the products or services of the commercial interest. Research To Practice and Penn State College of Medicine ensured that any conflicts of interest were resolved before the educational activity occurred.

FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Fonseca — Consulting Agreements: Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Novartis, Sanofi Genzyme, Takeda Oncology. Dr Raje — Consulting Agreements: Amgen Inc, Celgene Corporation, Novartis; Contracted Research: AstraZeneca Pharmaceuticals LP, Lilly.


PENN STATE COLLEGE OF MEDICINE — Faculty and staff involved in the development and review of this activity have disclosed no relevant financial relationships.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice and Penn State College of Medicine do not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.
Case discussion: A 64-year-old woman with monoclonal gammopathy of undetermined significance (MGUS) is monitored over time and develops a slight increase in protein levels.

Ongoing trials for patients with smoldering myeloma.

Importance of quality control for FISH analysis.

QuiRedex: Results of a Phase III trial of lenalidomide/dexamethasone versus observation for high-risk smoldering myeloma.

Activity of daratumumab and elotuzumab in smoldering myeloma.

Case discussion: An 87-year-old man initially diagnosed with smoldering myeloma presents with progressive disease and receives RVD-lite → lenalidomide maintenance.

ELOQUENT-1: A Phase III trial of lenalidomide/dexamethasone with or without elotuzumab for previously untreated multiple myeloma (MM).

Duration of therapy and activity of RVD-lite in elderly patients with MM.

Emergence of ixazomib as a component of induction and maintenance therapy for MM.

Triplet versus doublet induction therapy for MM.

IFM/DFCI 2009: Results of a Phase III trial evaluating immediate versus delayed autologous stem cell transplant (ASCT) after induction therapy for MM.

Results of a meta-analysis of lenalidomide maintenance after high-dose melphalan and ASCT for patients with MM.

Case discussion: A 76-year-old man with relapsed/refractory MM receives pomalidomide and daratumumab.

Management of daratumumab-associated infusion reactions.

Efficacy of daratumumab in combination with an IMiD or a proteasome inhibitor for relapsed/refractory MM.

Activity of the anti-CD38 monoclonal antibody isatuximab (SAR650984) in relapsed/refractory MM.

Investigating predictors of response for IMiD sensitivity in MM.

The "Tao" of myeloma: Harnessing normal cell biology versus targeting cancer genetics.

Case discussion: A 45-year-old man with relapsed/refractory MM receives daratumumab and lenalidomide/dexamethasone.

Critical evaluation of new therapeutic options for relapsed/refractory MM.

Activity and tolerability of daratumumab-based regimens for relapsed/refractory MM.

Retreatment with IMiD-based regimens and/or addition of monoclonal antibodies for patients with IMiD-refractory disease.

Results of Phase III studies of daratumumab in combination with lenalidomide/dexamethasone (POLLUUX) or with bortezomib/dexamethasone (CASTOR) for relapsed/refractory MM.

Subcutaneous delivery of daratumumab for patients with relapsed/refractory MM.

Management of relapsed/refractory MM and renal impairment.

Results of the MYRE study comparing intensive hemodialysis with high-cutoff or standard high-flux dialyzer for patients with MM receiving a bortezomib-based regimen.

Activity of the Bcl-2 inhibitor venetoclax alone and in combination with bortezomib/dexamethasone for patients with MM and 11;14 translocation.

Off-label use of venetoclax for relapsed/refractory plasma cell leukemia.

Incidence of venetoclax-associated tumor lysis syndrome in MM.

Activity of the anti-PD-1 antibody pembrolizumab in combination with an IMiD for relapsed/refractory MM.
Track 31 **Case discussion:** A 66-year-old woman with relapsed/refractory Waldenström macroglobulinemia (WM) receives bendamustine/rituximab

Track 32 **Case discussion:** A 74-year-old man with newly diagnosed WM receives ibrutinib

Track 33 Emerging research with chimeric antigen receptor T-cell therapy

**Related Video Program**

Visit www.ResearchToPractice.com/MMTT117/Video to view video highlights of the discussion among (from left) Drs Fonseca, Raje and Love and earn additional *AMA PRA Category 1 Credit™*.  

**Topics covered include:**

- Distinguishing smoldering from active multiple myeloma (MM) and indications for treatment or observation
- Biologic rationale for targeting Bcl-2 in MM and activity of venetoclax in relapsed/refractory disease
- Efficacy and safety data with and ongoing evaluation of recently approved agents — daratumumab, elotuzumab, ixazomib — for MM
- Role of immune checkpoint inhibitors in MM
- Current role of autologous stem cell transplantation and the role of MRD (minimal residual disease)

**SELECT PUBLICATIONS**


Attal M et al. Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS). *Proc ASCO* 2016; Abstract 8001.

Avet-Loiseau H et al. Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial. *Proc ASH* 2015; Abstract 191.


Dimopoulos MA et al. ELOQUENT-1: A phase III, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in subjects with previously untreated multiple myeloma (CA204-006). Proc ASCO 2012;Abstract TPS8113.

Durie B et al. Bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): Results of the randomized Phase III trial SWOG S0777. Proc ASH 2015;Abstract 25.


ICARIA-MM: A Phase 3 randomized, open-label, multicenter study comparing isatuximab (SAR650984) in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma. NCT02990338


Ramasamy K et al. Safety of treatment (Tx) with pomalidomide (POM) and low-dose dexamethasone (loDEX) in patients (pts) with relapsed or refractory multiple myeloma (RRMM) and renal impairment (RI), including those on dialysis. Proc ASH 2015;Abstract 374.

Richter JR et al. Updated data from a phase II dose finding trial of single agent isatuximab (SAR650984, anti-CD38 mAb) in relapsed/refractory multiple myeloma (RRMM). Proc ASCO 2016;Abstract 8005.


Usmani SZ et al. Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma: An adjusted treatment comparison. Am J Hematol 2017;[Epub ahead of print].

Usmani SZ et al. Open-label, multicenter, dose escalation Phase 1b study to assess the subcutaneous delivery of daratumumab in patients (pts) with relapsed or refractory multiple myeloma (PAVO). Proc ASH 2016;Abstract 1149.
QUESTIONS (PLEASE CIRCLE ANSWER):

1. Analysis of the IFM/DFCI 2009 trial evaluating immediate or delayed ASCT after RVd induction therapy indicated both progression-free survival (PFS) and overall response rate benefits for patients who underwent treatment with ___________.
   a. RVd
   b. RVd and ASCT
   c. Neither a nor b (PFS and response rate were equivalent in the 2 study arms)

2. An analysis of the predictive value of minimal residual disease (MRD) in a subset of patients on the IFM/DFCI 2009 trial demonstrated that MRD negativity was highly predictive of PFS.
   a. True
   b. False

3. Results from the QuiRedex study indicated a benefit in progression-free survival in patients with ___________ who received lenalidomide/dexamethasone versus observation.
   a. Monoclonal gammopathy of undetermined significance
   b. Smoldering myeloma
   c. MM

4. The Phase III SWOG-S0777 trial evaluating RVd versus Rd for patients with previously untreated MM without an intent for immediate ASCT demonstrated ___________ with RVd.
   a. A significant improvement in PFS
   b. No improvement in PFS

5. A study presented by Usmani and colleagues at the 2016 ASH meeting demonstrated that daratumumab ___________ safely be administered via subcutaneous injection.
   a. Could
   b. Could not

6. Infusion reactions associated with administration of daratumumab tend to persist over the course of the patient's treatment.
   a. True
   b. False

7. The Phase III randomized CASTOR study evaluating daratumumab/bortezomib/dexamethasone versus bortezomib/dexamethasone ___________ a significant improvement in PFS with the addition of daratumumab for patients with relapsed or refractory MM.
   a. Demonstrated
   b. Did not demonstrate

8. Which of the following is the mechanism of action of isatuximab?
   a. Anti-CD38 monoclonal antibody
   b. Anti-PD-1/PD-L1 antibody
   c. Immunomodulatory drug
   d. Proteasome inhibitor

9. Sensitivity to venetoclax for MM has primarily been observed in patients with t(11;14) disease.
   a. True
   b. False

10. Recent studies have demonstrated that the addition of pembrolizumab ___________ successfully restore activity to either lenalidomide and/or pomalidomide in patients with IMiD-refractory MM.
    a. Can
    b. Cannot
Current Clinical Algorithms and Recent Therapeutic Advances in the Management of Multiple Myeloma and Related Blood Disorders

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>BEFORE</th>
<th>AFTER</th>
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<tbody>
<tr>
<td>Revised diagnostic criteria for identifying smoldering versus early symptomatic myeloma and implications for therapeutic approach</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>Activity of daratumumab in combination with lenalidomide/dexamethasone or with bortezomib/dexamethasone for relapsed/refractory MM</td>
<td>4 3 2 1</td>
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<td>Biologic rationales for the effectiveness of venetoclax in patients with MM and for the lower risk of treatment-associated tumor lysis syndrome seen in MM than in chronic lymphocytic leukemia</td>
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<td>Emerging research data with and nonresearch role, if any, of ixazomib as a component of induction and maintenance therapy for MM</td>
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Practice Setting:
- Academic center/medical school
- Community cancer center/hospital
- Group practice
- Solo practice
- Government (eg, VA)
- Other (please specify) .................................................................

Approximately how many new patients with multiple myeloma do you see per year? .................................................................

Was the activity evidence based, fair, balanced and free from commercial bias?
- Yes
- No
If no, please explain: ........................................................................................................

Please identify how you will change your practice as a result of completing this activity (select all that apply).
- This activity validated my current practice
- Create/revise protocols, policies and/or procedures
- Change the management and/or treatment of my patients
- Other (please explain): ..................................................................................................

If you intend to implement any changes in your practice, please provide 1 or more examples:
........................................................................................................................................................................................

The content of this activity matched my current (or potential) scope of practice.
- Yes
- No
If no, please explain: ........................................................................................................

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
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<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
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<tr>
<td>• Develop a risk-adapted treatment plan for patients with smoldering MM, considering the roles of observation and active treatment.</td>
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<td>N/M</td>
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EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

• Design and implement a plan of care to recognize and manage side effects and toxicities associated with recently approved systemic therapies to support quality of life and continuation of treatment. ................................................................. 4 3 2 1 N/M N/A

• Identify ongoing trials of investigational approaches in MM, and refer appropriate patients and obtain consent for study participation. ................................................................. 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

Would you recommend this activity to a colleague?
☐ Yes ☐ No
If no, please explain:

PART 2 — Please tell us about the faculty and moderator for this educational activity

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
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<tr>
<td>Rafael Fonseca, MD</td>
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<td>Noopur Raje, MD</td>
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Moderator

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<tr>
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<tr>
<td>Neil Love, MD</td>
<td>4 3 2 1</td>
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Please recommend additional faculty for future activities:

REQUEST FOR CREDIT — Please print clearly

Name: ............................................................. Specialty: .........................

Professional Designation:
☐ MD  ☐ DO  ☐ PharmD  ☐ NP  ☐ RN  ☐ PA  ☐ Other

Street Address: ................................................. Box/Suite: .........................

City, State, Zip: ........................................................................................................

Telephone: ................................................. Fax: ........................................

Email: .................................................................

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I certify my actual time spent to complete this educational activity to be _________ hour(s).

Signature: ................................................................. Date: ..........................

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