From Quandary to Clarity in Relapsed/Refractory Multiple Myeloma: Optimizing Treatment and Empowering Patients

A Three-Part Educational Series for Oncology Advanced Practitioners

HARBORSIDE
Medical Education

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Activity 2

Therapy for Relapsed/Refractory Multiple Myeloma (RRMM)—Preparing for Novel Agents

Learning objectives

- Interpret the clinical significance of findings from clinical trials supporting the efficacy and safety of approved and/or emerging therapeutic regimens and strategies for RRMM
- Identify potential adverse events (AEs) associated with approved and/or novel agents used to treat RRMM
- Devise strategies for mitigating AEs associated with therapies for RRMM

Unless otherwise specified, the treatments and interventions discussed are based on best available evidence, including published data and guidelines.

Phase 3 CASTOR Trial

- Anti-CD38 monoclonal antibody (mAb) daratumumab, bortezomib, dexamethasone (D-Vd) vs. Vd in patients with RRMM[1]
  - Longer progression-free survival (PFS) vs. Vd
- Subgroup analysis of patients ≥ 1 lines of therapy based on standard-risk vs. high-risk cytogenetics[2]
  - Prolonged PFS at 40-month follow-up across all cytogenetic risk groups in first and second relapse in D-Vd arm vs. Vd arm
  - Higher overall response and minimal residual disease negativity and sustained negativity in D-Vd group

1. Palumbo A, et al. *N Engl J Med.* 2016;375:754-66.
2. Weisel K, et al. *J Clin Oncol.* 2019;37 (suppl; abstr 8040).

Phase 3 COLUMBA Trial

- Subcutaneous (SC) vs. intravenous (IV) daratumumab in patients with RRMM[1]
  - No difference in efficacy
  - Significant reduction in infusion-related reactions (12.7% vs. 34.5%; $p < .0001$) and administration time (5 minutes vs. 421/255/205 minutes for first, second, and subsequent IV infusions) in SC arm vs. IV arm

1. Mateos M-V, et al. *J Clin Oncol.* 2019;37 (suppl; abstr 8005).

IV Daratumumab in RRMM

- Increased risk of infusion-related reactions
- Prolonged infusion time (8 weekly doses lasting multiple hours)
- Premedicate patients with antihistamines, acetaminophen, mast cell stabilizer montelukast
- Educate patients on symptoms of infusion-related reactions

Phase 3 OPTIMISMM Trial

- Immunomodulatory drug (IMiD) pomalidomide plus Vd (PVd) vs. Vd in patients with RRMM[1]
  - Longer median PFS in PVd arm vs. Vd arm (11.2 vs. 7.1 months; HR 0.61; $p < .0001$)
  - Among 391 patients refractory to lenalidomide: HR 0.65 favoring PVd
- Grade >3 adverse events (AEs) PVd vs. Vd
  - Overall serious AEs: 57% vs. 42%
  - Neutropenia: 42% vs. 9%
  - Thrombocytopenia: 27% vs. 29%

1. Richardson PG, et al. *Lancet Oncol.* 2019;20:781-94.

Phase 2 ELOQUENT-3 Trial

- Anti-SLAMF7 IMiD elotuzumab plus pomalidomide and dexamethasone (EPd) vs. Pd in patients with RRMM[1]
  - Overall response rate (ORR): 53% vs. 26% in Pd arm
  - Median PFS: 10.3 vs. 4.7 months in Pd arm
  - Overall survival, very good partial response, median time to response, and median duration of response also favored EPd
- Grade > 3 toxicity comparable between both groups

1. Dimopoulos MA, et al. *N Engl J Med.* 2018;379:1811-22.

IMiDs and mAbs in RRMM

- Pomalidomide (IMiD)
  - Useful for patients with lenalidomide-resistant MM
  - Efficacy demonstrated when combined with other novel agents
- Elotuzumab (mAb)
  - Must be combined with an IMiD for efficacy
  - More research necessary on most effective treatment sequencing

Phase 3 ICARIA-MM Trial

- Anti-CD38 mAb isatuximab plus Pd vs. Pd in patients with RRMM[1]
  - 92% lenalidomide refractory; 75.9% proteasome inhibitor refractory
  - Median PFS: 11.5 vs. 6.5 months in Pd arm (HR 0.596; *p* = .001)
  - ORR and depth of response also superior in isatuximab arm
- Grade > 3 AEs comparable in both arms

1. Richardson PG, et al. *J Clin Oncol.* 2019;37 (suppl; abstr 8004).

Dosing With Isatuximab

- Reduced number of weekly doses and increased number of every-other-week doses (vs. daratumumab)
- Discuss dosing model with patients and potential impact on quality of life
- No SC version of isatuximab yet

Selinexor

- Selective inhibitor of nuclear export (SINE)
- Penta-exposed/triple class disease: refractory to IMiD, PI, and anti-CD38 mAb
- Phase 2 STORM trial: Selinexor plus low-dose dexamethasone (Sd) in penta-refractory patients with RRMM (ORR: 26.2%)[1]
- Retrospective cohort review[2]
  - Median OS better in patients who received Sd as first therapy after disease became penta-refractory vs. patients who did not receive Sd (10.4 vs. 5.2 months; HR 0.49; *p* = .0241)

1. Chari A, et al. *Blood.* 2018;132:598.
2. Richardson PG, et al. *J Clin Oncol.* 2019;37 (suppl; abstr 8014).

Selinexor

- July 2019: FDA granted accelerated approval for selinexor in combination with dexamethasone for treatment of adults with RRMM after > 4 lines of therapy and refractory to > 2 PIs, > 2 IMiDs, and anti-CD38 mAb[1]
- Ongoing phase 3 BOSTON trial: selinexor, bortezomib, dexamethasone (SVd) vs. Vd in patients with RRMM[2]

1. FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-selinexor-multiple-myeloma.
2. ClinicalTrials.gov. NCT03110562.

CAR T-Cell Therapy in RRMM

- bb2121: chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen
- Phase 1 trial in 33 patients who had received > 3 lines of therapy, including IMiD and PI, for RRMM[1]
  - ORR: 85%
  - Complete response: 45% (relapse in 40% achieving a CR)
  - Median duration of response: 10.9 months
  - Median PFS: 11.8 months
- APs need to be educated about AEs associated with CAR T-cell therapy, including cytopenia, cytokine release syndrome, neurologic issues

1. Raje N, et al. *N Engl J Med.* 2019;380:1726-37.

Phase 2 and 3 BELLINI Trials

- Some malignant plasma cells express high BCL2 levels and are sensitive to BCL2 inhibition, particularly in t(11;14) disease[1]
- Phase 2: BCL2 inhibitor venetoclax plus Vd (Vd-Ven) or placebo in patients with RRMM (ORR: 67%)[2]
- Phase 3[3]
  - 2-fold higher risk of death in Vd-Ven arm (HR 2.03; 95% CI 1.04–3.94)
  - FDA placed study on hold
  - Most deaths attributable to sepsis, pneumonia, and cardiac arrest

1. Kumar S, et al. Blood 2017;130:2401-9.
2. Moreau P, et al. *Blood.* 2017;130:2392-400.
3. Pharmiweb.com. Press Release. https://www.pharmiweb.com/press-release/2019-03-19/abbvie-provides-update-on-venclexta-venclyxto-venetoclax-multiple-myeloma-program.

Summary of Key Points

- Treatment options for patients with > 3 relapses is an unmet need.
- Recent clinical trials offer hope with novel mechanisms of action, new combinations, new administration routes, and newer cellular therapies.
- Consider mechanism of action of novel agents and combinations when selecting and sequencing therapy for RRMM.
- Restage patients at each relapse to guide treatment selection and sequencing.
- Integrate clinical trial data and national guidelines to mitigate and manage treatment-emergent AEs associated with novel agents.
- Consider a clinical trial for any patient with RRMM.