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 1

Therapy for Relapsed/Refractory Multiple Myeloma (RRMM)—Optimizing Use of Current Options

Learning objectives

- Relate mechanism of action of current and/or emerging therapies for RRMM to their expected and proven therapeutic effects and toxicities
- 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
- Plan strategies for selecting and sequencing therapy for patients with 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.

Evolving Therapeutic Landscape

- Newly diagnosed MM
  - Frontline triplet regimen: proteasome inhibitor (PI), immunomodulatory agent (IMiD), dexamethasone
  - Monoclonal antibodies (mAbs; anti-CD38 and anti-SLAMF7) being investigated in quad regimen or in other combinations
  - Majority of patients experience relapse
- RRMM
  - Revised International Staging System for MM (R-ISS)
  - International Myeloma Working Group (IMWG) response criteria

Defining Disease Progression

- IMWG response criteria used to define response and progression
- Biochemical relapse
  - Serum protein electrophoresis (SPEP) ~0.5 g/L increase from nadir
  - Urine protein electrophoresis (UPEP) >200 mg
  - Serum free light chain (SFLC) ratio >10:1
  - New lytic lesion or plasmacytoma
- Clinical relapse
  - Recurrence of CRAB criteria (calcium, anemia, renal dysfunction, detectable bone lesions)
- Use of minimal residual disease to measure response is still evolving

Frontline Standard of Care

- Triplet regimen (PI, IMiD, dexamethasone)
  - mAbs under investigation as part of quad regimen
- Autologous stem cell transplant (ASCT)
- Lenalidomide maintenance

Choosing Next-Line Therapy for RRMM

- Factors to consider
  - Most effective and tolerable options
  - Transplant status
  - Patient preference
  - Clinic accessibility
  - Affordability
  - Residual side effects from previous therapies
  - Current performance status

Choosing Next-Line Therapy for RRMM

- Consult up-to-date treatment guidelines
  - National Comprehensive Cancer Network (NCCN) Clinical Guidelines in Oncology
  - mSMART: Stratification for Myeloma & Risk-Adapted Therapy
  - International Myeloma Foundation
  - American Society of Clinical Oncology (ASCO) and Cancer Care Ontario Joint Clinical Practice Guideline

Case Study 1

- 75-year-old female patient with relapsed MM after frontline therapy, not eligible for transplant
- Very good partial response (VGPR) with initial triplet regimen
- Discontinued treatment after 9 months due to progressive neuropathy
- Follow-up shows incremental increases in SFLC

Treatment Considerations

- Determine biochemical or clinical relapse
- Patient's current life factors
  - Side effects from previous treatment (e.g., neuropathy associated with triplet regimen)
  - Updated performance status
  - Social/financial situation
- Triplet regimens are preferred over doublets
  - Meta-analysis of randomized phase 3 trials: triplets show significantly improved rates of PFS and OS versus doublets[1]

1. Sun Z, et al. *Crit Rev Oncol Hematol.* 2017;113:249-55.

Triplet Therapy Considerations

- Factor in cytogenetics and potential high-risk disease
- Consider PI carfilzomib in light of residual neuropathy
- Rechallenge with lenalidomide or switch to another IMiD
- Assess patient's ability to tolerate steroids
- Manage side effects: pulmonary, cardiovascular, gastrointestinal

Case Study 2

- 58-year-old male patient with R-ISS stage III, IgA lambda, t4;14
- VGPR after triplet regimen
- ASCT and lenalidomide maintenance
- Four months post-transplant, rising M protein and K/L ratio, and paraspinal plasmacytoma
- Developed diabetes and cardiomyopathy (45% ejection fraction)

Treatment Considerations

- Multiple high-risk factors
  - Cytogenetics: t(4;14)
  - Side effects: cardiomyopathy
  - Comorbidities: diabetes
- Radiation for paraspinal mass
- Employing multidisciplinary management
  - Cardiology, endocrinology, supportive care
- Second ASCT only for late relapse (> 2–3 years after first)[1]

1. Stadtmauer EA, et al. *J Clin Oncol.* 2019;37:589-97.

Summary of Key Points

- Risk-adapted treatment selection is key.
- Standards for evaluating response are evolving.
- Stay abreast of rapidly evolving science relative to RRMM.
- Consider mechanism of action when selecting and sequencing therapy for RRMM.
- Assess frailty and comorbidities to tailor treatment decision making and AE mitigation and management.
- Minimal residual disease to guide treatment remains investigational in this setting.