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Original Research Article

Daratumumab, Lenalidomide, and Dexamethasone for the Treatment of Newly Diagnosed Multiple Myeloma Patients Ineligible for Autologous Stem Cell Transplantation

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Abstract: Daratumumab, lenalidomide, and dexamethasone (D-Rd) has emerged as a transformative therapy for newly diagnosed multiple myeloma (NDMM) patients who are ineligible for autologous stem cell transplantation (ASCT). This review synthesizes the latest clinical trial data, mechanisms of action, outcomes, safety profiles, and patient-centered considerations for D-Rd use in this population.

Keywords: Daratumumab, Lenalidomide, Multiple myeloma, Autologous stem cell transplantation (ASCT), D-Rd regimen.

INTRODUCTION

Multiple Myeloma in the Elderly and Frail

Multiple myeloma is an incurable plasma cell malignancy, predominantly affecting older adults. Many NDMM patients are not candidates for ASCT because of age, frailty, or comorbidities. Therefore, optimizing frontline nonsurgical therapies is essential to improve outcomes and quality of life in this group[1].

Mechanisms of Action

- **Daratumumab** is a monoclonal antibody targeting CD38 on myeloma cells, inducing direct cytotoxicity and immune-mediated killing.
- **Lenalidomide** is an immunomodulatory drug that enhances anti-tumor immunity and induces apoptosis of myeloma cells.
- **Dexamethasone** is a corticosteroid with potent anti-inflammatory and anti-myeloma activity.

Together, these drugs create a synergistic regimen that impairs myeloma progression at multiple mechanistic levels.

CLINICAL TRIAL EVIDENCE: MAIA STUDY AND OTHERS

The Phase 3 MAIA Trial

The landmark MAIA trial randomized 737 transplant-ineligible NDMM patients to D-Rd or lenalidomide/dexamethasone (Rd) alone[1]. Key results after over five years (median follow-up 64.5 months):

- **Progression-free survival (PFS):**
  - D-Rd: 61.9 months
  - Rd: 34.4 months
  - Hazard Ratio (HR) for progression or death: 0.55 (P<0.0001)
- **Overall survival (OS):**
  - Median OS was not reached in D-Rd vs 65.5 months in Rd
  - 5-year estimated OS rates: 66.6% (D-Rd) vs 53.6% (Rd)
  - HR for death: 0.66 (P=0.0003)
- **Depth of response**:
  - Complete response or better (≥CR): 51.1% (D-Rd) vs 30.1% (Rd)
  - Minimal residual disease (MRD) negativity: 32.1% vs 11.1%[1][2]

Response and Efficacy in Subpopulations

- D-Rd provided substantial benefit irrespective of age or frailty, with consistent improvements in PFS and OS across all analyzed subgroups, including patients ≥75 and ≥80 years[1][2].
- Benefits are observed in patients with renal impairment and high-risk cytogenetics[3].

Other Clinical Data

- Real-world studies confirm high response rates and favorable outcomes for D-Rd in transplant-ineligible NDMM[4].
- Regulatory bodies, including the FDA, have approved this regimen based on MAIA and supporting data[5][6].

Safety and Tolerability

Hematological and Non-hematological Toxicities

D-Rd has an acceptable and manageable toxicity profile[7][8][9]:

- **Most frequent adverse events (≥20%)**:
  - Neutropenia (91% any grade, 39% grade 3, 17% grade 4)
  - Lymphopenia, anemia, thrombocytopenia
  - Diarrhea, fatigue, peripheral edema
  - Upper respiratory tract infection, pneumonia

Adverse Event	D-Rd Any Grade	D-Rd Grade 3	Rd Any Grade	Rd Grade 3
Neutropenia	91%	39%	77%	28%
Diarrhea	57%	7%	46%	4%
Pneumonia	26%	14%	14%	7%
Infusion reactions	41%	2%	0%	0%
Fatigue	40%	8%	28%	4%

- **Serious adverse reactions >2% more in D-Rd:** pneumonia, bronchitis, dehydration[9].

Long-Term Safety

Five-year follow-up analysis indicates no new safety signals and no cumulative toxicity with extended duration of D-Rd. Infusion-related reactions are most commonly seen during the first infusion and are typically mild-to-moderate[7].

Clinical Use and Regimen Details

Patient Selection

D-Rd is recommended for NDMM patients ineligible for ASCT due to:

- Age typically ≥65
- Frailty or comorbidities

- Patient preference or contraindication to other regimens[10]

Dosing Schema (MAIA Protocol)

- **Daratumumab**: Intravenously 16mg/kg weekly (Cycles 1-2), biweekly (Cycles 3-6), then monthly
- **Lenalidomide**: 25mg orally, days 1–21 of every 28-day cycle
- **Dexamethasone**: 40mg orally, weekly

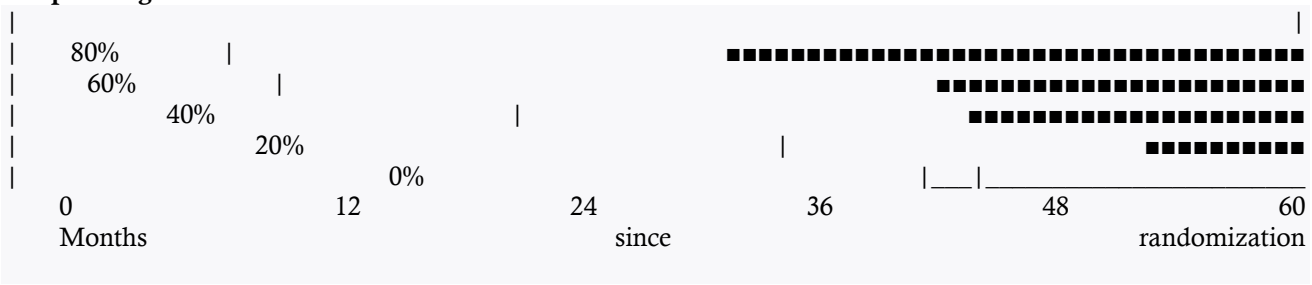
Modification (subcutaneous daratumumab or split-dose dexamethasone) is sometimes used for tolerability[8].

EFFICACY AND SURVIVAL OUTCOMES

Kaplan-Meier Survival Curves and Response Rates

D-Rd confers significant improvements in both PFS and OS compared to Rd. Estimated 60-month OS rate with D-Rd exceeds 65% in this high-risk patient group, a major step forward for non-transplant candidates[1].

Graph: Progression-Free Survival



- **D-Rd** (solid line): Higher PFS through entire follow-up.
- **Rd** (dashed line): PFS drops sharply by month 34.

Management Considerations

Monitoring

- CBC, renal, hepatic, and electrolyte panels before each cycle
- Infection vigilance, prophylaxis as indicated
- Pre-infusion medications for daratumumab to minimize reactions

Adverse Event Mitigation

- Growth factors for neutropenia
- Antivirals and antibiotics per institutional protocol
- Dose modifications for cytopenias and non-hematological toxicities[8]

DISCUSSION

Implications for Clinical Practice

D-Rd is now a frontline standard of care for frail or elderly NDMM patients, providing superior outcomes compared to non-daratumumab-containing regimens. Its survival and response benefits, coupled with manageable toxicity, have redefined expectations for this patient population[1][11][2].

Outstanding Challenges

- Managing cytopenias and infection risk, particularly in very elderly/frail patients
- Ensuring patient adherence and quality of life

Future Directions

- Exploration of D-Rd as a backbone for quadruplet regimens
- Biomarker-driven personalization of treatment
- Further studies in special subgroups (renal failure, significant frailty)

CONCLUSION

Daratumumab in combination with lenalidomide and dexamethasone represents a paradigm shift for transplant-ineligible newly diagnosed multiple myeloma patients. It delivers clinically meaningful survival and response benefits with a tolerable safety profile, offering new hope for those unable to undergo stem cell transplantation. Ongoing real-world pharmacovigilance and research will continue to refine and optimize its use.

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