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Advances in Immunotherapy for Multiple Myeloma: From Monoclonal Antibodies to CAR-T Cells and Beyond

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ABSTRACT
Multiple myeloma (MM), an incurable hematologic malignancy, has seen transformative advances through immunotherapy, shifting treatment paradigms toward durable responses. This review synthesizes the mechanisms, clinical efficacy, and challenges of monoclonal antibodies (mAbs), bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapies, drawing from phase II/III trials and preclinical studies. Anti-CD38 mAbs like daratumumab achieve overall response rates (ORR) of 80–90% in relapsed/refractory MM when combined with immunomodulatory drugs, while anti-BCMA CAR-T therapies, such as idecabtagene vicleucel, yield ORR of 70–85% in heavily pretreated patients. Bispecific antibodies targeting BCMA (e.g., teclistamab) offer ORR of 60–70%, providing off-the-shelf options. Resistance, driven by antigen loss, T-cell exhaustion, and immunosuppressive microenvironments, limits long-term efficacy. Toxicities, including cytokine release syndrome (CRS) and neurotoxicity, pose management challenges. Emerging strategies, such as dual-target CAR-T cells, antibody-drug conjugates, and checkpoint inhibitors, aim to overcome these barriers. Ongoing trials explore combination regimens and biomarker-driven approaches to optimize patient selection. Artificial intelligence and genomic profiling enhance personalized therapy design. This review highlights immunotherapy's impact on MM, identifies gaps in durability and access, and proposes research priorities for sustained remissions. Collaborative efforts across academia and industry are vital to equitable delivery of these therapies.
Keywords: Multiple myeloma, immunotherapy, monoclonal antibodies, CAR-T therapy, precision medicine.

I. INTRODUCTION

Multiple myeloma (MM), characterized by clonal plasma cell proliferation in the bone marrow, affects ~35,000 patients annually in the United States, with a 5-year survival rate of ~55%.[1] Despite advances in proteasome inhibitors (e.g., bortezomib) and immunomodulatory drugs (e.g., lenalidomide), MM remains incurable, with most patients relapsing.[2] The advent of immunotherapy has revolutionized treatment, targeting specific antigens like CD38, BCMA, and SLAMF7 to achieve deeper responses. Monoclonal antibodies (mAbs), such as daratumumab, enhance immune-mediated cytotoxicity, while CAR-T therapies, like idecabtagene vicleucel, engineer T-cells to attack BCMA-expressing cells.[3,4] Bispecific antibodies, such as teclistamab, bridge T-cells and tumor cells, offering accessible alternatives.[5] However, challenges including resistance, toxicity, and high costs persist. This review synthesizes the mechanisms, clinical outcomes, and limitations of MM immunotherapies, drawing from recent trials and preclinical studies. It explores resistance mechanisms, emerging agents, and combination strategies, emphasizing precision medicine's role in improving outcomes. By highlighting ongoing trials and future directions, this article aims to guide clinicians and researchers in addressing MM's unmet needs, building on the momentum of precision oncology.

Molecular and Immunologic Landscape of MM

MM is driven by genetic aberrations, including translocations (e.g., t(11;14)), hyperdiploidy, and mutations in KRAS, NRAS, and TP53.[6] These alterations shape the tumor microenvironment, characterized by immunosuppressive cells (e.g., myeloid-derived suppressor cells) and cytokine dysregulation (e.g., IL-6).[7] Key antigens—CD38, BCMA, and SLAMF7—are highly expressed on MM cells, making them ideal immunotherapy targets.[8] Next-generation sequencing (NGS) identifies actionable alterations, guiding patient selection for targeted therapies. For example, BCMA expression levels predict CAR-T response.[4] Liquid biopsies enable real-time monitoring of minimal residual disease (MRD), refining treatment strategies.[9]

Current Immunotherapies

1. Monoclonal Antibodies

Mechanism: Daratumumab (anti-CD38) induces antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Elotuzumab (anti-SLAMF7) negligibly affects NK-cell activity.[3,10]

Clinical Data: Daratumumab with lenalidomide-dexamethasone achieves ORR of 91% and median progression-free survival (PFS) of 44.5 months in relapsed/refractory MM (POLLUX trial).[11] Elotuzumab combinations yield ORR of 79% (ELOQUENT-2).[10]

Limitations: CD38 downregulation and Fc-receptor polymorphisms reduce efficacy; infusion reactions occur in 40–50% of patients.[12]

2. CAR-T Cell Therapies

Mechanism: Idecabtagene vicleucel and ciltacabtagene autoleucel target BCMA, triggering T-cell-mediated tumor lysis.[4,13]

Clinical Data: Ide-cel achieves ORR of 73% and median PFS of 8.8 months in heavily pretreated patients (KarMMa trial).[4] Cilta-cel yields ORR of 97% (CARTITUDE-1).[13]

Limitations: CRS (80–90%), neurotoxicity (10–20%), and manufacturing delays; antigen escape via BCMA loss.[14]

3. Bispecific Antibodies

Mechanism: Teclistamab (BCMA-CD3) bridges T-cells to MM cells, inducing cytotoxicity.[5]

Clinical Data: Phase I/II trials report ORR of 63% and median PFS of 11.3 months in relapsed/refractory MM.[15]

Limitations: CRS (70%), infections, and hypogammaglobulinemia.[16]

4. Emerging Approaches

Dual-target CAR-T cells (e.g., BCMA/GPRC5D) reduce antigen escape, with phase I trials showing ORR of ~80%.[17] Antibody-drug conjugates (e.g., belantamab mafodotin, anti-BCMA) deliver cytotoxic payloads, with ORR of 31%.[18] Checkpoint inhibitors (e.g., anti-PD-1) show limited monotherapy efficacy but synergy in combinations.[19]

Resistance Mechanisms

Resistance to MM immunotherapies arises from tumor-intrinsic and extrinsic factors. Tumor-intrinsic resistance includes antigen loss (e.g., BCMA downregulation in CAR-T relapse) and genetic heterogeneity (e.g., RAS mutations).[20] Extrinsic resistance involves T-cell exhaustion, upregulation of inhibitory ligands (e.g., PD-L1), and immunosuppressive microenvironments driven by TGF-β and IL-10.[21] Epigenetic silencing of antigens further limits efficacy.[22] Strategies to overcome resistance include dual-antigen targeting, combination therapies (e.g., CAR-T with checkpoint inhibitors), and microenvironment modulators (e.g., anti-TGF-β).[23]

Clinical Challenges

Immunotherapies face hurdles:

- Toxicity: CRS (grade ≥3 in 5–15% of CAR-T patients) and neurotoxicity require tocilizumab and steroids.[14] Hypogammaglobulinemia increases infection risk.[16]
- Patient Selection: MRD status and antigen expression guide therapy but require costly NGS ($2,000–$5,000).[24]
- Access: CAR-T costs (~$400,000 per treatment) and limited manufacturing capacity restrict availability.[25]

Strategies include toxicity grading systems, expanded NGS access, and scalable bispecific antibodies.

Future Directions

The future of MM immunotherapy includes:

- Combination Therapies: Trials like NCT04108195 (teclistamab + daratumumab) explore synergy, with ORR of 70–80%.[26]
- Next-Generation CAR-T: Allogeneic CAR-T and dual-target constructs (BCMA/CD38) reduce costs and relapse.[27]
- Novel Targets: GPRC5D and FcRH5 antibodies show ORR of ~60%.[28]
- Technology: AI optimizes patient selection; liquid biopsies enhance MRD monitoring.[29]
- Trial Design: Platform trials accelerate multi-agent regimen evaluation.[30]

II. CONCLUSION

Immunotherapy has redefined MM treatment, with mAbs, CAR-T cells, and bispecific antibodies achieving unprecedented responses. However, resistance, toxicity, and access barriers limit durability and equity. Emerging strategies and technologies promise to address these challenges, paving the way for sustained remissions. This review calls for collaborative research and policy efforts to ensure all patients benefit from MM's evolving therapeutic landscape.

REFERENCES

[1]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025;75(1):7-33.

[2]. Kumar SK, Rajkumar SV. Multiple myeloma: evolving therapies. N Engl J Med. 2023;389(11):1009-1022.
[3]. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Daratumumab in relapsed MM. Lancet. 2016;387(10027):1551-1560.
[4]. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed MM. N Engl J Med. 2021;384(8):705-716.
[5]. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed MM. N Engl J Med. 2022;387(6):495-505.

Figure 1: Immunotherapy Mechanisms in MM
Description: Diagram illustrating mAb (daratumumab), CAR-T (ide-cel), and bispecific antibody (teclistamab) mechanisms targeting CD38, BCMA, and T-cell interactions.

Table 1: Key Clinical Trial Outcomes

Agent	Trial	Population	ORR	Median PFS
Daratumumab + Len/Dex	POLLUX (Dimopoulos, 2016)	R/R MM	91%	44.5 months
Ide-cel	KarMMa (Munshi, 2021)	R/R MM	73%	8.8 months
Cilta-cel	CARTITUDE-1 (Berdeja, 2021)	R/R MM	97%	Not reached
Teclistamab	MajesTEC-1 (Moreau, 2022)	R/R MM	63%	11.3 months