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INNOVATIVE TREATMENT STRATEGIES FOR MULTIPLE MYELOMA: CAR T-CELL THERAPY, BISPECIFIC ANTIBODIES, AND BEYOND

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Abstract: Multiple myeloma (MM) remains largely incurable despite advances in proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody therapies. Recent years have seen the advent of revolutionary immunotherapies – notably CAR T-cells, bispecific T-cell engagers, monoclonal antibodies (MoAbs), and antibody–drug conjugates (ADCs) – that target myeloma cells in novel ways. These modalities have produced unprecedented response rates in heavily pretreated patients but also introduce unique toxicity and cost challenges. For example, BCMA-directed CAR T-cell products yield high overall response rates (e.g. ORR ~70–90%) with deep remissions, and the BCMA×CD3 bispecific teclistamab achieves ORRs ~63–67% in triple-class refractory MM. Daratumumab and isatuximab (anti-CD38 MoAbs) have been integrated into frontline regimens to deepen responses, while the anti-BCMA ADC belantamab mafodotin has shown ~32% ORR albeit with notable ocular toxicity. This review summarizes current standard treatments and focuses on innovative approaches – including their clinical trial results, safety profiles, and practical challenges – highlighting ongoing research directions for the hematology community.

Keywords: multiple myeloma, innovative treatment, CAR T-cell therapy, bispecific antibodies, monoclonal antibodies, antibody-drug conjugates, minimal residual disease, immunotherapy, hematology, clinical trials.

Introduction

Multiple myeloma is a plasma-cell malignancy whose prognosis has substantially improved with modern therapy, but it remains incurable in most patients. Advances in treatment have extended survival such that patients are now "living longer". However, nearly all patients eventually relapse or become refractory, necessitating sequential use of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 antibodies, and other classes. With each line of therapy, remission durations shorten and outcomes worsen. In parallel, basic research has yielded a wave of revolutionary agents: novel monoclonal antibodies, cellular therapies, and precision agents have entered trials and, increasingly, clinical practice. Immunotherapies such as CAR T-cells and bispecific T-cell engagers have shown especially "promising" efficacy in advanced MM. In this review, we briefly outline standard care for MM and then delve into innovative strategies (CAR T-cells, bispecifics, monoclonal antibodies, ADCs,

and MRD-driven approaches), emphasizing recent phase II/III trial results, safety, real-world challenges, and future directions for hematology practice.

Current Standard Therapies for Multiple Myeloma (Brief Overview)

Frontline therapy for newly diagnosed multiple myeloma (NDMM) typically includes multi-drug combinations leveraging proteasome inhibitors, IMiDs, and steroids. In transplant-eligible patients, induction regimens are usually triplets (often bortezomib-lenalidomide-dexamethasone [VRd] or carfilzomib-lenalidomide-dexamethasone [KRd]) followed by high-dose melphalan with autologous stem-cell transplantation (ASCT) and maintenance therapy. Anti-CD38 antibodies (daratumumab or isatuximab) have been integrated into these regimens, creating potent quadruplets (e.g. Dara-KRd or Dara-VRd) that achieve very deep responses. For transplant-ineligible patients, combinations such as daratumumab-lenalidomide-dexamethasone (Dara-Rd) or bortezomib-melphalan-prednisone (VMP) are common. Key points:

Triplet induction is standard: VRd is widely used for fit NDMM patients. Alternative triplets include KRd and bortezomib-cyclophosphamide-dexamethasone (CyBorD).

Quadruplet regimens: Addition of daratumumab (anti-CD38) to VRd or KRd is becoming common to deepen remissions. For example, the recent PERSEUS trial found much higher MRD-negativity with daratumumab-VRd vs VRd alone. (Notably, MRD as an endpoint is now gaining FDA interest.)

Autologous SCT: Remains standard consolidation for eligible patients, achieving deeper remission and prolonging progression-free survival.

Maintenance: Post-transplant lenalidomide maintenance improves PFS/OS; subcutaneous daratumumab is also being explored as maintenance.

At relapse, therapy is individualized based on prior exposures. Common relapse regimens include pomalidomide-based triplets (e.g. pomalidomide-bortezomib-dexamethasone [PVd]), carfilzomib-pomalidomide-dexamethasone, or combinations with monoclonal antibodies (e.g. daratumumab- or isatuximab-containing regimens). Immunomodulatory agents (lenalidomide or pomalidomide), next-generation PIs (carfilzomib, ixazomib), and anti-CD38 mAbs all have established roles in salvage therapy, often in doublet or triplet combinations. Despite these options, outcomes after multiple relapses remain poor in practice.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy, a novel immunotherapy, has emerged as a powerful option for relapsed/refractory multiple myeloma (RRMM). The two FDA-approved CAR T-products target B-cell maturation antigen (BCMA) on myeloma cells: idecabtagene vicleucel (ide-cel, bb2121) and ciltacabtagene autoleucel (cilta-cel, JNJ-4528). In clinical trials, these agents induced remarkably high response rates in heavily pretreated patients. For example, in a subanalysis of the KarMMa phase II trial of ide-cel, patients (median 6 prior lines) achieved an overall response rate of ~89%, with 56% attaining stringent complete response[1]; the median duration of response was not reached after ~13 months follow-up. Similarly, the pivotal CARTITUDE-1 trial of cilta-cel reported ORRs ≈98% and CR rates >80% (not cited here, but consistent with company reports). Importantly, depth of response translated to durable remissions: many patients remain progression-free at 2–3 years.

Adverse events with CAR T are distinctive. Nearly all patients experience cytokine release syndrome (CRS), typically within the first week. In KarMMa, CRS events were mostly mild-to-moderate (all treated patients had ≤ grade 2 CRS). Neurotoxicity (immune effector cell–associated neurotoxicity, ICANS) occurred less commonly (1/9 patients had grade 2). In practice, severe CRS/ICANS can occur and require intensive management. Other concerns include prolonged cytopenias and risk of infection.

Bispecific T-Cell Engagers

Bispecific T-cell engagers (BiTEs) are antibody constructs that simultaneously bind a T-cell (usually via CD3) and a tumor antigen (e.g. BCMA) on MM cells, redirecting T-cells to kill myeloma. Multiple bispecifics are in late-stage trials or approved. The first-in-class BCMA×CD3 bispecific, teclistamab, was approved in 2022 for heavily pretreated MM. In the phase II MajesTEC-1 trial, teclistamab (given weekly subcutaneously) achieved an ORR of ~63% with ~25% ≥CR in triple-class refractory patients. Its efficacy has held up in real-world use: an international IMWG study reported an ORR of 67% (55% ≥VGPR) in 188 patients, with 6-month PFS ~53%. These outcomes are comparable to the registration study, showing brisk, durable responses in a difficult-to-treat population.

Other bispecifics target alternative antigens. For example, talquetamab (GPRC5D×CD3) and elranatamab (BCMA×CD3) have yielded ORRs ~60–70% in phase II studies. For instance, talquetamab produced ORRs ≈67% in patients with multiple prior therapies. Numerous bispecific antibodies are in development, many advancing to phase III trials (e.g., MajesTEC-3 comparing teclistamab vs standard therapy; MagnetisMM for elranatamab).

Safety of bispecifics is dominated by immune-mediated events. Cytokine release syndrome occurs in a majority of patients but is usually Grade 1–2. In the real-world teclistamab series, CRS occurred in 54% of patients (mostly low-grade). The step-up dosing regimen mitigates severe CRS. Infections are a concern: 56% of patients developed infections (22% grade ≥3), reflecting immune suppression. Other toxicities can include cytopenias and, with BCMA-directed agents, hypogammaglobulinemia. BiTE therapy is typically given in an outpatient or short-stay setting after initial dosing, which aids accessibility compared to CAR T. Still, like CAR T, bispecifics are very expensive (annual drug costs likely in the six-figure range) and require specialized monitoring for CRS and neurotoxicity. Overall, bispecific antibodies represent a potent off-the-shelf approach that can be redosed or combined with other agents in future strategies.

Monoclonal Antibodies and Antibody–Drug Conjugates

Monoclonal antibodies (MoAbs) remain important in MM. Anti-CD38 antibodies (daratumumab, isatuximab) have been integrated into both first-line and relapsed settings. For example, adding daratumumab to VRd induction led to higher rates of complete response and MRD negativity compared to VRd alone. A pooled analysis of phase III trials showed that patients who achieve MRD-negativity and complete response with a daratumumab-based regimen had dramatically better PFS than those who do not. In relapsed MM, daratumumab or isatuximab combined with IMiDs or PIs has roughly doubled PFS relative to IMiD/PI alone. (E.g., the POLLUX trial of Dara-Rd vs Rd reported median PFS of 44 months vs 17 months). Elotuzumab, an anti-SLAMF7 antibody, is approved in combination with Rd or Pd in RRMM, though it shows more modest benefit (ORR ~30–40% with improvement in PFS by ~4–6 months). Novel antibody constructs include Fc-engineered anti-CD38 (CD38 with enhanced ADCC) and dual-target antibodies (e.g., targeting CD38+SLAMF7), but these are mostly investigational.

Antibody–drug conjugates (ADCs) combine a monoclonal antibody with a cytotoxic payload. The first ADC approved for MM was belantamab mafodotin, which targets BCMA linked to a microtubule inhibitor. In the DREAMM-2 trial of patients with ≥3 prior lines, single-agent belantamab (2.5 mg/kg IV q3w) induced an ORR of ~32% with a median PFS of ~2.8 months. Responses could be durable (median duration ~12.5 months), but severe ocular toxicity limited use. Keratopathy (corneal epithelium changes) occurred in ~27% of patients (Grade ≥3), necessitating frequent ophthalmologic monitoring and dose delays. Other ADCs are in development: for example, MEDI2228 (anti-BCMA ADC with pyrrolobenzodiazepine) and indatuximab ravtansine (anti-CD138 ADC) have shown encouraging signals in early trials. Overall, ADCs can deliver chemotherapy directly to myeloma cells, but the balance of efficacy and unique toxicities (ocular, hematologic) will determine their niche in therapy.

Minimal Residual Disease (MRD)-Guided Strategies

Minimal residual disease negativity has emerged as a crucial treatment endpoint in MM. Modern next-generation sequencing and flow methods detect 1 myeloma cell in 10^5–10^6 cells. Multiple analyses have established that achieving MRD-negativity (especially in the context of a complete response) is strongly prognostic of prolonged progression-free and overall survival. For example, a pooled analysis of 4 phase III trials found that patients with ≥CR and MRD-negativity had a 80% reduction in the risk of progression or death (HR ≈0.20) versus patients who did not achieve MRD-negativity. This benefit was consistent across both newly diagnosed (transplant-ineligible) and early relapse settings. Consequently, IMWG has recognized MRD-negativity as a new response category, and the FDA now considers MRD negativity as a valid surrogate endpoint for accelerated approvals.

Clinically, MRD is being used to tailor therapy intensity. Several trials (e.g., MASTER, GRIFFIN, IFM-2020) are testing MRD-driven approaches: escalating treatment until MRD is negative, or de-escalating once sustained MRD-negativity is achieved. Early results suggest that an MRD-guided strategy can safely limit exposure to intensive therapy for good responders, while identifying patients who might benefit from additional consolidation (e.g., adding anti-CD38 or maintaining therapy). In the PERSEUS trial (daratumumab + VRd), for instance, MRD-negativity rates were dramatically higher with dara-based therapy than VRd alone. Future use of MRD may include deciding on stopping maintenance or using MRD to select patients for emerging therapies. Overall, MRD-guided therapy represents a precision approach that aligns treatment with individual disease kinetics and may improve the therapeutic index.

Efficacy and Safety from Recent Trials (Phase II/III)

Major recent trials illustrate the impact of novel agents in RRMM:

CAR T-cells: In the phase II KarMMa trial (ide-cel), triple-class refractory MM patients (median 6 prior lines) had an ORR of ~73% with a ≥complete response rate of ~33% (median PFS ~8.8 mo)[1]. The phase III KarMMa-3 trial then showed ide-cel significantly improved PFS and ORR versus standard therapy in earlier relapse lines (unpublished NEJM 2023 data). CARTITUDE-1 (cilta-cel) reported ORR ~98% (82% ≥CR) and median PFS >2 years in heavily pretreated patients. These data confirm high efficacy of BCMA CAR T therapy in late-line MM.

Bispecifics: The MajesTEC-1 study of teclistamab yielded ORR ~63% (median PFS ~11 months) in triple-refractory MM. Real-world cohorts of teclistamab show similar ORRs (~67%) and 6-month PFS ~53%. Subgroup analyses indicate slightly lower efficacy in patients with prior BCMA therapy (e.g. ORR ~58% vs 74% in BCMA-naïve). New bispecifics in trials (talquetamab, elranatamab) have reported ORRs ~60–70% in Phase II studies.

Monoclonal antibodies: In the first-line setting, the phase III CASSIOPEIA trial showed that adding daratumumab to bortezomib-thalidomide-dexamethasone (VTd) improved stringent CR rates and 5-year PFS in transplant-eligible NDMM. In relapsed disease, the CASTOR and POLLUX trials demonstrated that daratumumab added to Vd or Rd nearly doubled PFS. Isatuximab combined with pomalidomide/dex (ICARIA trial) and with carfilzomib/dex (IKEMA trial) similarly improved outcomes over doublets.

ADCs: DREAMM-2 final analysis confirmed that single-agent belantamab mafodotin achieved an ORR of 32–35% in triple-refractory MM. Median PFS was <4 months, but duration of response could be ~6–12 months. Keratopathy (corneal toxicity) occurred in ~25% of patients at Grade ≥3, requiring dose modifications. DREAMM-3 (comparing belantamab vs pomalidomide/dex) and other DREAMM trials are ongoing to refine use of ADCs.

These trial results underscore those novel therapies can elicit deep remissions in patients who have exhausted conventional options. However, they also highlight toxicity: T-cell therapies invariably cause

immune toxicities (CRS/ICANS) whereas ADCs carry target-specific side effects (e.g., ocular with BCMA ADCs).

Conclusion

The therapeutic landscape of multiple myeloma has been revolutionized by immunotherapies and targeted agents. CAR T-cell therapy and bispecific T-cell engagers produce unprecedented remissions in refractory MM, while monoclonal antibodies and ADCs further expand options. These approaches complement rather than replace existing therapies, with early use of quadruplet regimens already raising the bar for depth of response. Importantly, achieving MRD negativity has emerged as a vital goal, as it portends improved long-term survival. However, novel therapies bring challenges of high cost, specialized administration, and unique toxicities, which must be managed carefully in practice. Moving forward, integrating these innovations in a rational, personalized way – guided by biomarkers such as MRD and supported by clinical trials – offers the prospect of markedly better outcomes for MM patients. Hematologists should remain informed about these strategies, participate in trials, and prepare to address practical barriers (e.g. by establishing CAR T/biTE programs and advocating for patient access). In sum, innovative treatments are rapidly reshaping MM management, bringing hope of longer remissions and potentially curative strategies when combined judiciously.

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