REVIEW ARTICLE

Immunotherapy and Treatments in Multiple Myeloma: Response, Durability, and Challenges

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Abstract

Multiple myeloma (MM) is a blood cancer wherein abnormal plasma cells accumulate in the bone marrow and overproduce monoclonal proteins, resulting in anemia, bone damage, kidney disorders, and increased infection risk. This narrative review compares newer immunotherapies, such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies, with established MM treatments in terms of effectiveness, durability of response, limitations, and their potential role in future treatment strategies. This narrative review of clinical studies and scientific literature focuses on treatment response, measurable residual disease (MRD) negativity, progression-free survival, treatment-related toxicities, resistance, and accessibility of treatment options. Based on the findings, immunotherapies can provide substantial responses and MRD negativity, especially in patients with relapsed or refractory MM. CAR T-cell therapy provides durable disease control after a single infusion, whereas bispecific antibodies can be used without individualized cell collection and manufacturing. However, these approaches have certain limitations, including infections, cytopenias, cytokine release syndrome, neurotoxicity, treatment resistance, high cost, and limited access. These findings suggest that immunotherapy should complement, rather than replace, established treatments. Future research should focus on personalized treatment selection, combination therapies, and sequencing strategies to improve response durability, reduce toxicity, overcome resistance, and expand equitable access to MM treatments.

Keywords

Biomedical and Health Sciences, Immunology, Multiple Myeloma, CAR T-Cell Therapy, Bispecific Antibodies.

Introduction

Multiple myeloma (MM) is a plasma-cell cancer of the bone marrow that impairs normal blood-cell production and causes an abnormal monoclonal protein (M protein) or excess monoclonal free light chains.[31] As illustrated in Figure 1, levels of monoclonal free light chains and the number of myeloma cells can differ substantially between patients, which also reflects the heterogeneous nature of the disease.[31] These abnormalities can lead to anemia, bone destruction, kidney dysfunction, and increased susceptibility to infection.[1] Despite major advances in therapy, MM varies among patients and can change over time, and the disease commonly relapses, which makes durable disease control a central clinical challenge.

MM occurs most often in older adults. In the United States, the incidence is higher among men and Black or African American individuals; family history and obesity are also associated with increased risk.[2] Monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic condition involving an abnormal monoclonal protein, is a recognized precursor state of MM. Although most people with MGUS do not progress to MM, a proportion eventually develop active disease.[3] These associations describe population-level risk and do not determine an individual's outcome.

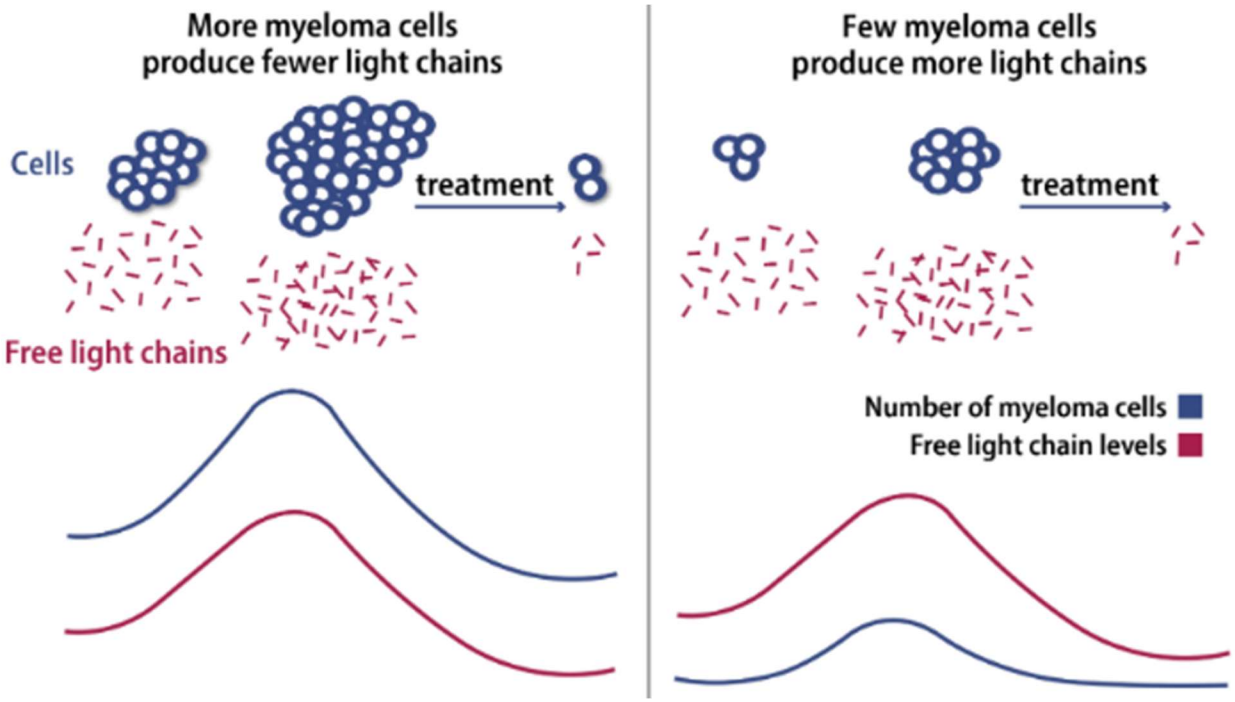


Figure 1. Example showing differences in monoclonal free light-chain levels and myeloma-cell burden between two patients with multiple myeloma.[31]

Established MM therapy, including multidrug induction, autologous stem-cell transplantation (ASCT) in eligible patients, and maintenance therapy, has improved response rates and overall survival. Nonetheless, recurrence is common because myeloma cells can withstand treatment, become resistant, and proliferate.[1,12] This challenge has increased interest in immunotherapy, which utilizes mechanisms of the immune system to target and kill cancer cells.

Immune-based approaches such as monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapy, and bispecific antibodies have shown positive results in patients with MM, with some even achieving MRD negativity.[4] MRD negativity implies the absence of detectable disease by a specific test at a certain sensitivity. Though MRD negativity is linked to favorable prognosis in most cases, it does not mean that all myeloma cells have been killed or that the patient has been cured. The use of MRD to determine treatment duration and sequence is still being studied. While anti-CD38 monoclonal antibodies have become part of most standard MM treatment regimens, T-cell redirecting processes, specifically CAR T-cell therapy and bispecific antibodies, are increasingly gaining a key role in modern research and clinical practice.[5]

This narrative review compares newer T-cell redirecting immunotherapies, CAR T-cell therapy and bispecific antibodies, with established MM treatments. It evaluates response depth, MRD negativity, duration of response, progression-free survival, overall survival (when reported), adverse effects, resistance, cost, and access to care. The review does not present immunotherapy as a universal replacement for established drug therapy or transplant-based treatment. Instead, it evaluates how newer therapies may be integrated and sequenced within increasingly personalized MM treatment strategies.

Discussion

Why Multiple Myeloma Relapses and Becomes Resistant

Treating multiple myeloma can be difficult because myeloma cells interact with the bone marrow environment and can develop clonally. These processes can allow treatment-resistant subclones to survive therapy and contribute to relapse.[6,11] Treatment resistance can develop through several mechanisms. Some myeloma cells may be less sensitive to treatment from the start, while others may acquire changes

after therapy. The bone marrow environment can also provide signals that support myeloma cell survival and weaken immune responses.[6,11]

These mechanisms matter especially when evaluating newer immunotherapies because targeted treatments depend on specific cancer cell characteristics. For example, therapies directed against BCMA or GPRC5D may become less effective if resistant myeloma cell populations reduce, alter, or lose the targeted antigen. Understanding resistance really helps explain why a strong initial response does not always result in long-term disease control.

Figure 2 illustrates why a deep initial response may not always produce durable disease control. Multiple myeloma comprises genetically diverse cell populations that can change over time due to mutation. Treatment may remove the most treatment-sensitive cells while leaving resistant subclones behind. In addition, the bone-marrow microenvironment can provide survival signals and suppress anti-tumor immunity, creating conditions in which residual myeloma cells persist and later cause relapse. Research on the marrow microenvironment therefore helps explain why resistance can involve both cancer cell changes and the surrounding immune and stromal environment.[6]

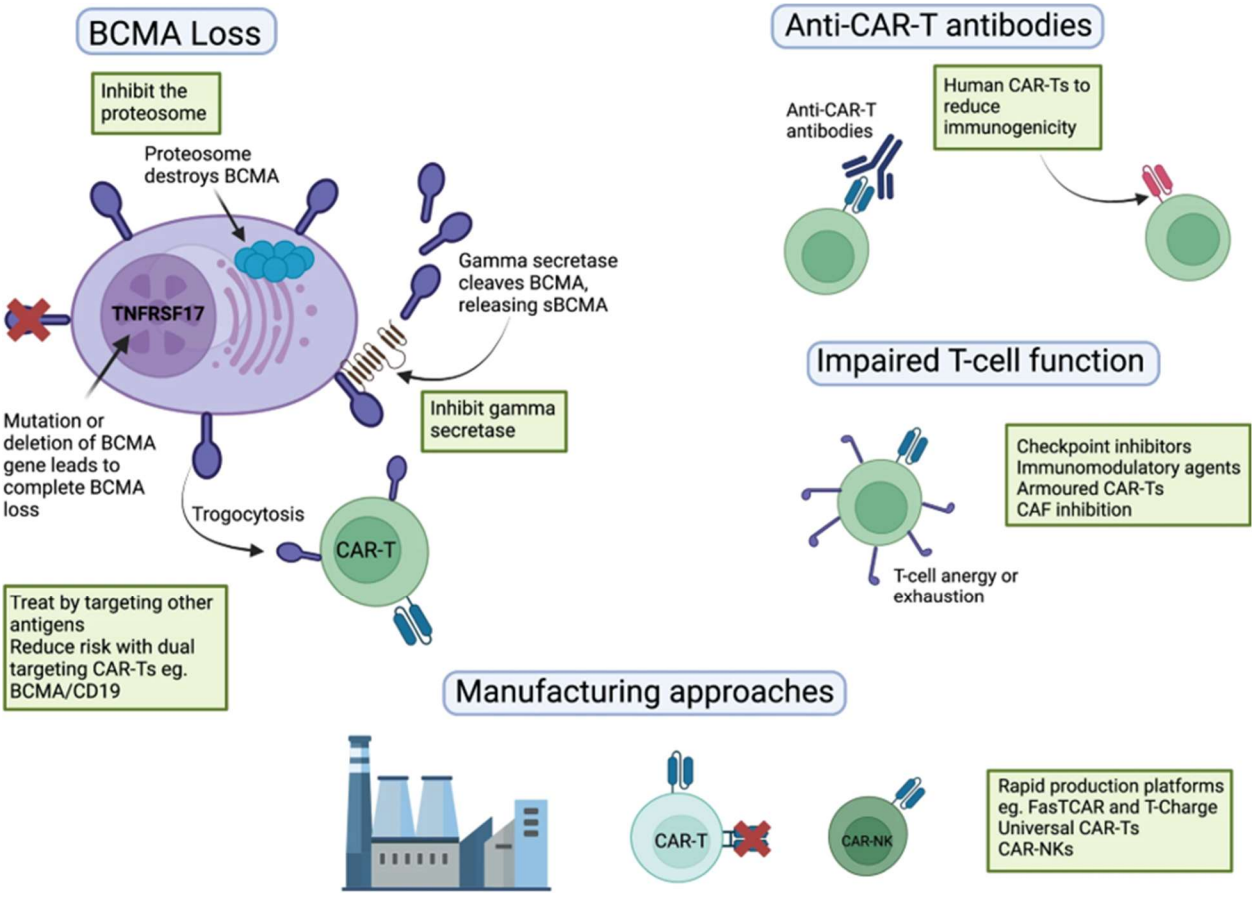


Figure 2. Bone-marrow microenvironment and treatment resistance in multiple myeloma. Myeloma cells interact with stromal cells, immune cells, cytokines, and bone-remodeling cells in the marrow. These interactions can promote myeloma-cell survival, impair anti-tumor immunity, and contribute to relapse after treatment.[11]

Established Treatment Approaches

Established treatment for multiple myeloma (MM) includes proteasome inhibitors, immunomodulatory drugs, corticosteroids, chemotherapy, and autologous stem-cell transplantation (ASCT). Anti-CD38 monoclonal antibodies are also widely incorporated into modern treatment regimens. Treatment is often

organized into several stages, including induction therapy, ASCT for eligible patients, maintenance therapy, and additional treatment if the disease relapses.[12]

Proteasome inhibitors include bortezomib, mainly used by injection and associated with peripheral neuropathy, and carfilzomib, an irreversible proteasome inhibitor given by infusion. Carfilzomib has a lower risk of peripheral neuropathy compared with bortezomib, but it has a higher risk of cardiovascular toxicity. These drugs inhibit proteasome function, which degrades damaged or unwanted proteins. Because myeloma cells produce large amounts of proteins, they are particularly dependent on proteasome activity.[13,14]

Immunomodulatory drugs (IMiDs), which include thalidomide, lenalidomide, and pomalidomide, are a key component of therapy for multiple myeloma. These drugs slow myeloma-cell growth, change the bone marrow environment that supports the cancer, and help strengthen certain immune responses against myeloma cells. Lenalidomide is frequently used in maintenance therapy after initial treatment and, for eligible patients, after autologous stem-cell transplantation (ASCT) to help keep the disease in remission longer.[12]

Corticosteroids, including dexamethasone and prednisone, also have direct anti-myeloma effects and are usually combined with other treatments to improve their effectiveness. Chemotherapy drugs such as cyclophosphamide and melphalan damage DNA, making it difficult for myeloma cells to reproduce. High-dose melphalan is commonly given before ASCT as conditioning treatment to destroy as many remaining myeloma cells as possible.[12]

Autologous stem-cell transplantation (ASCT) represents a critical therapy for individuals fit enough to undergo high-dose chemotherapy. Clinicians first extract the patient's stem cells. Clinicians collect the patient’s hematopoietic stem cells. High-dose chemotherapy is then given, often as melphalan, to eliminate as many myeloma cells as possible. After high-dose chemotherapy, the previously collected stem cells are reinfused to restore bone marrow function and blood-cell production. ASCT can improve outcomes and prolong remission. However, myeloma cells may remain after this procedure. Therefore, ASCT is not considered curative because residual myeloma cells may persist and later contribute to relapse.[12] As shown in Figure 3, ASCT includes intensified killing of the myeloma cells by high-dose melphalan, followed by the reinfusion of stored stem cells to help regenerate the bone marrow. The fact that residual myeloma cells can persist after the transplantation explains the connection between the procedure and relapse/treatment resistance.

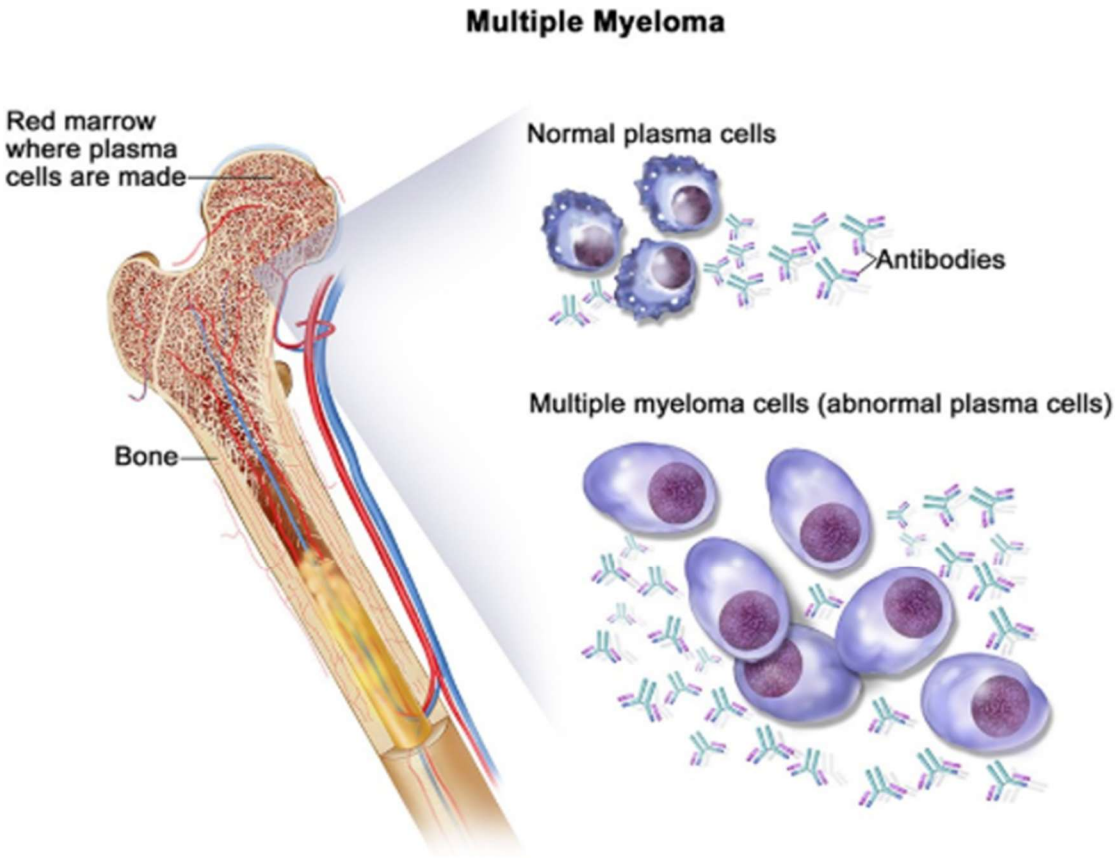


Figure 3. Autologous stem-cell transplant procedure for managing multiple myeloma. The patient's hematopoietic stem cells are collected and cryopreserved before high-dose melphalan chemotherapy. The cryopreserved stem cells are later infused to restore bone marrow function and blood cell production. However, even ASCT cannot eliminate all myeloma cells.[1,4]

Anti-CD38 monoclonal antibodies, specifically daratumumab and isatuximab, are part of many multiple myeloma treatment regimens. These medications bind to CD38, a protein highly expressed on myeloma cells, enabling the immune system to target and destroy cancer cells. Anti-CD38 antibodies support immune cell-mediated lysis and trigger complement to damage tumor cells. Additionally, anti-CD38 antibodies can stimulate macrophages to engulf myeloma cells. Moreover, anti-CD38 monoclonal antibodies may reduce immunosuppressive cells in the bone marrow microenvironment.[32] Isatuximab can also induce apoptosis, leading to myeloma cell death. Therefore, monoclonal antibodies should be considered an important component of the standard of care instead of experimental therapies competing with established treatments.

Standard treatments are still relevant at various MM treatment phases; however, they carry risks of treatment-related toxicity. Such side effects depend on the specific treatment regimen and include adverse events such as fatigue, cytopenias, infections, peripheral neuropathy, thromboembolic disorders, and organ-specific toxicities.

Rise of Immunotherapy

Immunotherapy has become an important part of MM treatment because it uses the immune system to recognize and attack myeloma cells. The major approaches include monoclonal antibodies, CAR T-cell therapy, and bispecific antibodies.[7] Monoclonal antibodies are already part of standard treatment. In contrast, CAR T-cell therapy and bispecific antibodies are newer immune-based treatments that have become especially important in relapsed or refractory MM.

These newer therapies can produce deep responses, including MRD negativity.[21-23] MRD negativity means that no measurable disease was detected using a particular test at a defined sensitivity level. It does not prove that every myeloma cell has been eliminated or that the patient has been cured.

How the Immune System Normally Fights Cancer

The immune system helps protect the body from abnormal cells, like cancer cells. Immune cells, including cytotoxic T cells, B cells, NK cells, and macrophages, help protect the body from these types of cells. Cytotoxic T cells can recognize specific antigens on abnormal cells and destroy them. B cells can become plasma cells and produce antibodies that recognize harmful substances. NK cells attack certain abnormal cells without recognizing their specific antigens, and macrophages help by engulfing damaged or abnormal cells. In contrast, dendritic cells gather antigens and activate T cells.

Some cancer cells acquire mutations that help them evade immune detection, while others escape immune attack through non-mutational changes in gene expression or by creating an immunosuppressive tumor microenvironment. These changes can weaken immune responses or prevent immune cells from functioning effectively. This process, known as immune evasion, allows cancer cells to avoid destruction by the immune system, survive, and continue to grow.[10]

In multiple myeloma, immune evasion is especially important because myeloma cells grow and survive in the bone marrow. The bone marrow contains cells and signaling molecules that can support myeloma cell growth and reduce immune activity.[6,11] This environment can make it difficult for immune cells and treatments to eliminate every myeloma cell.

Table 1: Immune Cells Involved in Cancer Immune Surveillance.[10,11]

Immune cell type	**Main function**	**Relevance to MM**
Cytotoxic T cells	Directly kill target cells.	They recognize specific antigens displayed on abnormal cells and destroy them.
B cells	Produce antibodies after differentiating into plasma cells.	Antibodies bind to specific foreign or abnormal targets, helping mark them for immune attack.
Plasma cells	Secrete antibodies.	Produce antibodies that recognize and bind particular antigens.
Natural killer (NK) cells	Rapidly kill stressed or abnormal cells.	They destroy certain abnormal cells without the antigen-specific recognition used by T cells.

Macrophages	Engulf cells, debris, and harmful material	Remove abnormal cells and cellular debris through phagocytosis
Dendritic cells	Capture and present antigens	Activate T cells by presenting antigens from abnormal cells, thereby helping to initiate an adaptive immune response.

Immunotherapy Treatment Approaches

Immunotherapy uses immune mechanisms to recognize and attack cancer cells. In multiple myeloma (MM), immunotherapy has become an important treatment approach because myeloma cells express surface proteins that immune-based therapies can target. The main modalities are monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapy, and bispecific antibodies. Although all aim to eliminate myeloma cells, they differ in mechanism, manufacturing and administration, treatment duration, and toxicity profiles. Monoclonal antibodies such as daratumumab and isatuximab bind antigens such as CD38 and activate immune mechanisms to help destroy myeloma cells. CAR T-cell therapy and bispecific antibodies redirect T cells against targets such as BCMA or GPRC5D. These approaches depend on treatment logistics and risks, including infusion reactions, cytokine release syndrome, neurotoxicity, cytopenias, and increased infection risk. [21–23]

Monoclonal Antibodies are targeted immune-based treatments that have become important components of standard MM therapy. Daratumumab and isatuximab target CD38, a protein expressed on many MM cells. Elotuzumab targets SLAMF7, a protein expressed on myeloma cells and certain immune cells.[15]

These antibodies bind to proteins on myeloma cells and help the immune system recognize and eliminate the targeted myeloma cells. They are often combined with proteasome inhibitors, IMiDs, and corticosteroids. Daratumumab can be incorporated into regimens for both newly diagnosed and relapsed MM.[25]

Because monoclonal antibodies do not require patient-specific T-cell collection or individualized cell manufacturing, they are generally easier to administer than CAR T-cell therapy. However, they usually require repeated treatments and can cause infusion- or injection-related reactions, infections, reduced blood-cell counts, and treatment resistance.[21] Reduced blood-cell counts can include low white blood cells, especially neutrophils, which can increase infection risk; low red blood cells, or anemia, which can cause fatigue, weakness, and shortness of breath; and low platelet counts, or thrombocytopenia, which can increase bruising and bleeding. These low blood-cell counts may result from the monoclonal antibody, the underlying myeloma, or other drugs used in the combination regimen, particularly proteasome inhibitors and IMiDs.

CAR T-Cell Therapy is a personalized form of immunotherapy that genetically modifies a patient's own T cells to recognize and attack myeloma cells. Doctors first collect T cells from the patient's blood. In the lab, scientists genetically modify these cells to produce a chimeric antigen receptor (CAR) that recognizes a specific protein on myeloma cells. After lymphodepleting chemotherapy, the modified cells are expanded and returned to the patient. The lymphodepleting treatment temporarily reduces competing immune cells and helps create an environment in which CAR T cells can expand.

Two major BCMA-directed CAR T-cell therapies used in MM are *idecabtagene vicleucel* (ide-cel) and *ciltacabtagene autoleucel* (cilta-cel). Both therapies target B-cell maturation antigen (BCMA), a protein

expressed on most myeloma cells. Clinical studies in heavily pretreated patients with relapsed or refractory MM have demonstrated high response rates for both therapies.[21,22]

CAR T-cell therapy can produce responses, including complete responses and MRD negativity, in selected patients. A potential advantage is that treatment is generally delivered as a single infusion rather than requiring continuous dosing. This can create periods in which patients do not need ongoing anti-myeloma treatment.[11]

CAR T-cell therapy has important limitations. Manufacturing requires collecting and genetically modifying the patient's T cells and can take several weeks. Patients may require bridging therapy while the CAR T-cell product is being manufactured. Treatment can also cause cytokine release syndrome (CRS), a systemic inflammatory reaction caused by immune-cell activation and cytokine release. Immune effector cell-associated neurotoxicity syndrome (ICANS) may also occur and can cause neurologic symptoms. Other complications include prolonged cytopenias, infections, and reduced levels of normal antibodies. [21,22]

Figure 4 shows that CAR T-cell therapy is not a single infusion but a multistep, patient-specific treatment process.[17] It requires referral to a specialized center, leukapheresis, manufacturing, lymphodepleting chemotherapy, infusion, and close monitoring for immune-related complications. Because manufacturing may take several weeks, patients with active or rapidly progressing myeloma may require bridging therapy to maintain disease control before infusion.

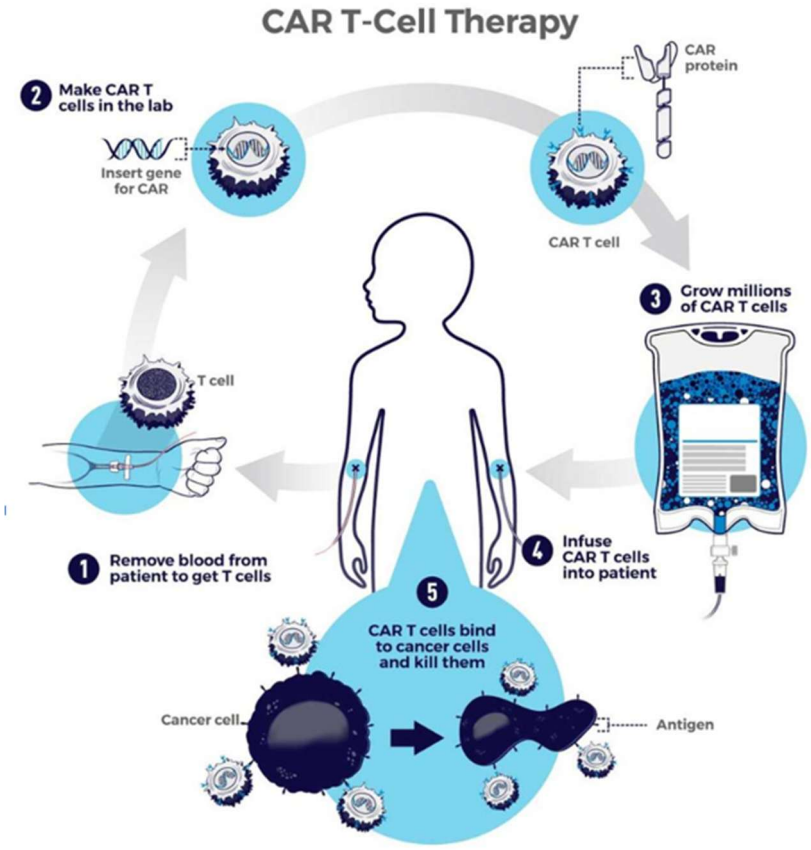


Figure 4. Typical CAR T-cell therapy pathway for multiple myeloma.[17] Leukapheresis collects a patient's T cells, which are genetically modified and expanded to create a personalized CAR T-cell product and then infused after lymphodepleting chemotherapy. Because manufacturing requires time, patients may require bridging therapy to control myeloma before infusion. After treatment, patients require close monitoring for cytokine release syndrome, neurologic toxicity, prolonged cytopenias, infections, and response durability.[4,16,17]

This pathway can limit access even for clinically eligible patients because it requires specialized facilities, manufacturing capacity, insurance authorization, travel, caregiver support, and frequent monitoring. Thus, CAR T-cell therapy must be evaluated not only by clinical response but also by manufacturing time, disease urgency, toxicity risk, and access feasibility.[26]

Bispecific Antibodies are another form of T-cell redirecting immunotherapy. Unlike CAR T-cell therapy, they do not require collecting and genetically modifying a patient's own T cells. Instead, these medicines are manufactured in advance and can be used as “off-the-shelf” treatments.

A bispecific antibody has two binding sites: one binds a target on the myeloma cell, such as BCMA or GPRC5D, and the other binds CD3 on a T cell. By bringing the T cell into proximity with the myeloma cell, the antibody promotes T-cell activation and cancer cell destruction.[18,19] As shown in Figure 5, both the therapeutic appeal and the biologic limitation of bispecific antibodies.[18] Their “off-the-shelf” availability can allow treatment to begin more quickly than autologous CAR T-cell therapy because it avoids patient-specific collection and manufacturing. However, treatment effectiveness depends on sufficient target antigen expression on the myeloma cell and on the ability of the patient’s T cells to function effectively. Low, altered, or lost expression of BCMA and/or GPRC5D in resistant cells, along with T-cell dysfunction, can compromise treatment effectiveness. These resistance mechanisms highlight the need for studies on dual-target therapies and other approaches to prevent antigen escape.

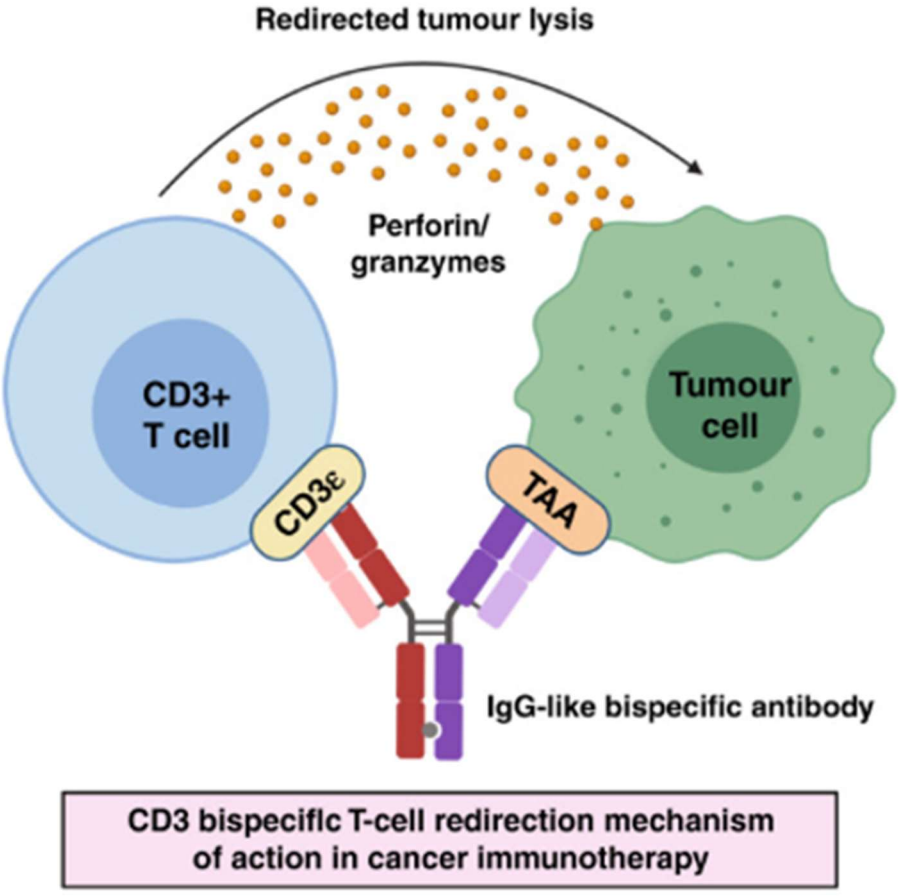


Figure 5. Bispecific antibody-mediated T-cell redirection in multiple myeloma. One part of the bispecific antibody binds to a myeloma-cell target. In contrast, the other binds to CD3 on a T cell, bringing the two cells together and promoting T-cell-mediated killing.[18-20]

Teclistamab and elranatamab target BCMA and CD3, while talquetamab targets GPRC5D and CD3.[19,23] The therapeutic landscape continues to evolve as additional T-cell redirecting therapies are investigated in

clinical trials. These therapies have demonstrated substantial responses in patients with heavily pretreated relapsed or refractory MM.[20,23]

Bispecific antibodies are generally available more quickly than autologous CAR T-therapy because they are manufactured in advance,[27] but they usually require repeated administration and ongoing monitoring. Important complications include cytokine release syndrome (CRS), infections, cytopenias, and reduced levels of normal antibodies. The toxicity profile can also differ by target: BCMA-directed therapies are particularly associated with infection risk, whereas GPRC5D-directed therapy such as talquetamab may cause taste changes, dry mouth, swallowing difficulties, and skin or nail abnormalities.[20] Thus, although bispecific antibodies offer greater treatment availability than personalized CAR T-cell manufacturing, ongoing treatment remains a key limitation.[26]

Comparing Established Treatment and Immunotherapy

Treatment methods differ across many clinical settings; therefore, comparison cannot be reduced to identifying the therapy with the highest overall response rate (ORR). Instead, treatment selection should balance response depth and durability with prior therapies, disease characteristics, patient age and overall health, treatment-related toxicities, treatment burden, monitoring requirements, availability, and patient preferences.[4,5,8]

Established therapies remain important because they can be used across multiple stages of MM and can often be combined or adjusted according to a patient's clinical condition. Newer immunotherapies may produce particularly deep responses in heavily pretreated patients, but they can introduce additional challenges involving toxicity, manufacturing, monitoring, and access.[5,8]

Table 2: Comparison of Major Multiple Myeloma Treatment Approaches

Feature	**Established therapies.**[4,12,13,15]	**Monoclonal antibodies.**[4,7,15]	**CAR T-cell therapy**[21,22]	**Bispecific antibodies**[20,23]
Examples	Proteasome inhibitors, IMiDs, corticosteroids, chemotherapy, ASCT.	Daratumumab, isatuximab, elotuzumab.	Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel).	Teclistamab, elranatamab, talquetamab.
How they work	Disrupt myeloma-cell survival pathways or reduce cancer-cell growth.	Bind targets on myeloma cells and promote immune destruction.	Genetically modify patient T cells to recognize myeloma cells	Connect T cells directly to myeloma cells.
Main targets	Multiple cellular pathways.	CD38 or SLAMF7.	Mainly BCMA	BCMA or GPRC5D on myeloma cells and CD3 on T cells.
Treatment format	Repeated drug combinations and/or ASCT.	Repeated infusions or injections.	Personalized cell infusion after manufacturing.	Repeated injections or infusions.
Potential advantage	Established and effective across many disease settings.	Targeted and combinable with other treatments.	Deep responses and possible treatment free periods.	No personalized cell manufacturing and generally faster availability.

Main challenges	Cumulative toxicity and eventual relapse.	Repeated treatment, infections, and low blood-cell counts.	Manufacturing time, cost, CRS, neurologic complications, and limited access.	Infections, repeated dosing, immune suppression, and CRS.

Note*:* IMiDs = immunomodulatory drugs; ASCT = autologous stem cell transplantation; BCMA = B cell maturation antigen; GPRC5D = G protein-coupled receptor class C group 5 member D; CRS = cytokine release syndrome.[4,5,8]

Clinical Evidence Comparing Treatment Responses

Although these treatment approaches differ in their mechanisms of action and administration, clinical studies provide additional evidence to compare their effectiveness. Response rates, complete response rates, measurable residual disease (MRD) negativity, and progression free survival (PFS) are commonly used to evaluate treatment outcomes. However, these measures need to be interpreted together because a high initial response rate does not necessarily mean the response will be deep or long lasting.

The trials summarized below were conducted independently in different patient populations. Differences in prior treatment exposure, disease characteristics, eligibility criteria, outcome definitions, follow-up duration, and study design limit direct comparisons among therapies.

Table 3: Selected Clinical Outcomes from Trials of Immunotherapies in Heavily Pretreated Relapsed or Refractory Multiple Myeloma.

Treatment & Clinical trial.	**ORR**	**Complete response or better**	**MRD-negative result**	**Median D OR**	**Median PFS**
Idecabtagene vicleucel (ide-cel), KarMMa.[21]	73%	33%	26% of treated patients were MRD-negative; 79% of patients achieving CR or better were MRD-negative.	10.7 months	8.8 months
Ciltacabtagene autoleucel (cilta-cel), CARTITUDE-1[22]	97.9%	82.5% had stringent CR	56 of 61 MRD-evaluable patients were MRD-negative at 10^5	33.9 months	34.9 months

Teclistamab, MajesTEC-1[20,23]	63.0%	39.4%	26.7% of treated patients were MRD-negative; 46% of patients achieving CR or better were MRD-negative.	18.4 months	11.3 months
Talquetamab, weekly dose, MonumenTAL-1.[20]	74.1%	32.9%	64.3% of MRD-evaluable patients were MRD-negative at 10^5	9.5 months	Not included because it varies by follow-up analysis
Talquetamab, every-2-week dose, MonumenTAL-1.[20]	69.5%	40.3%	65.2% of MRD-evaluable patients were MRD-negative at 10^5	17.5 months	Not included because it varies by follow-up analysis

Note: ORR = overall response rate; CR = complete response; MRD = measurable residual disease; DOR = duration of response; PFS = progression-free survival. These studies were separate clinical trials and were not direct head-to-head comparisons. Differences in patient populations, previous treatments, eligibility criteria, follow-up duration, and study design limit direct comparison of outcomes.[20–24]

Table 3 summarizes evidence demonstrating that CAR T-cell therapies and bispecific antibodies can produce substantial responses in heavily pretreated relapsed or refractory MM. In the individual trials summarized, ide-cel had a reported ORR of 73% in KarMMa; cilta-cel had a reported ORR of 97.9% in CARTITUDE-1; teclistamab had a reported ORR of 63.0% in MajesTEC-1; and talquetamab had reported ORRs of 74.1% with weekly dosing and 69.5% with every-two-week dosing in MonumenTAL-1. These values describe results within their respective studies and should not be interpreted as direct evidence that one therapy is superior to another.[20-23]

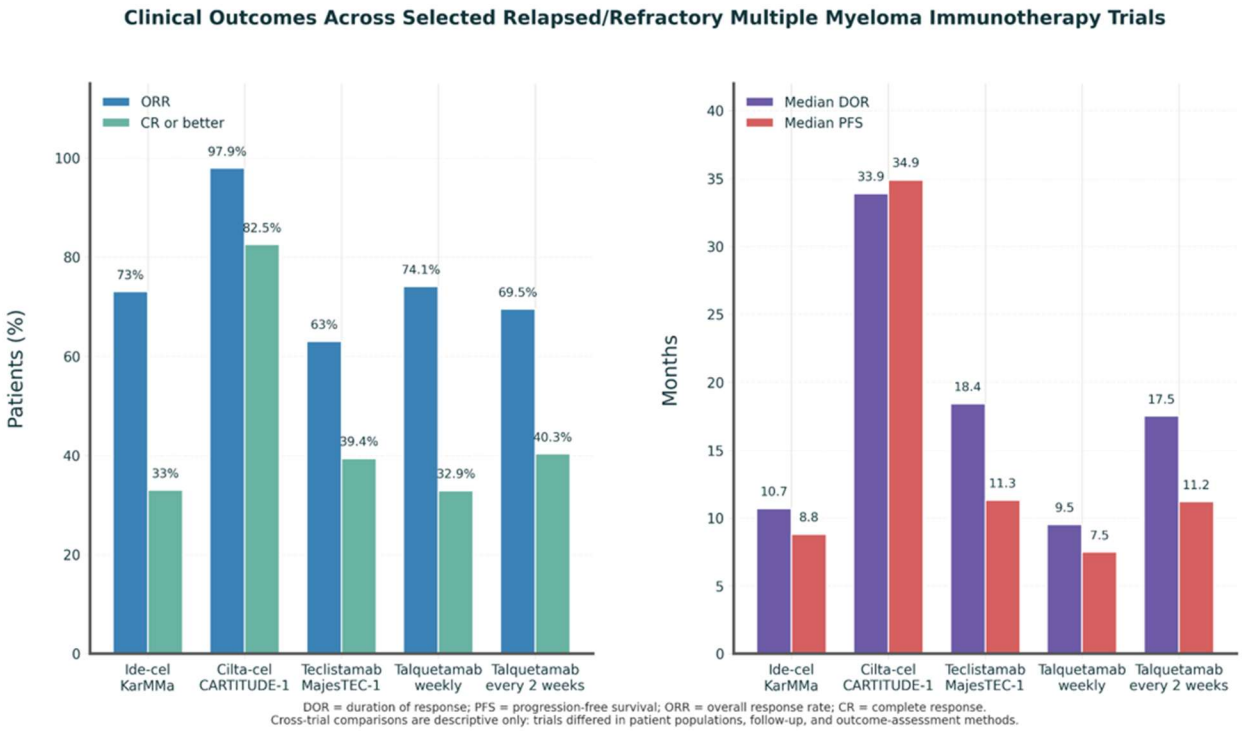


Figure 6. Comparison of ORR, complete response or better, median DOR, and median PFS across selected CAR T-cell and bispecific-antibody trials in relapsed/refractory multiple myeloma.

Additional measures of response provide additional information beyond ORR. DOR measures how long a response lasts among patients who respond, whereas PFS measures the time from treatment until disease progression or death. These measures therefore provide different information about treatment effectiveness.[24]

Taken together, the evidence suggests that CAR-T therapies and bispecific antibodies can produce deep responses in heavily pretreated MM. At the same time, their potential value must be considered alongside response durability, toxicity, treatment burden, and accessibility. Because these studies were not head-to-head trials, randomized comparisons are needed to determine whether observed differences reflect the treatments themselves or differences in study populations.[5,8]

Treatment Resistance, Toxicity, and Access

Even after a strong response, MM can become resistant to treatments. One such mechanism is antigen escape, in which myeloma cells change the proteins the treatment targets. Both CAR T-cell therapies and bispecific antibodies depend on targets such as BCMA and GPRC5D. When cancer cells do not express these targets at the required levels, treatment may become less effective. The emergence or selection of altered target-expressing myeloma-cell clones has been described following targeted immunotherapy.[25]

T-cell exhaustion is another potential resistance mechanism. T-cell exhaustion occurs when T cells are exposed to persistent cancer-related signals and gradually lose their ability to proliferate and destroy cancer cells. The bone marrow microenvironment can further weaken immune responses through inhibitory immune cells, signaling molecules, and metabolic conditions that support myeloma cell survival. In addition, clonal evolution may produce treatment-resistant subclones that survive therapy and expand once the more treatment-sensitive cells are destroyed.[6,11]

Toxicity is an important consideration when comparing treatment approaches. Established therapies and immunotherapies reduce red blood cell, white blood cell, and platelet counts, and can cause fatigue, infections, and other complications. CAR T-cell therapy and bispecific antibodies can cause CRS. CAR-T

therapy can also cause ICANS. These toxicities require close monitoring by medical teams experienced in immune-based cancer treatment.[22,27]

Bispecific antibodies also carry a significant risk of infection, particularly with BCMA-directed therapies. These treatments reduce normal antibody-producing plasma cells and lower immunoglobulin levels, resulting in hypogammaglobulinemia. Because bispecific antibodies are often administered repeatedly, immunosuppression and infection risk may continue throughout treatment. This makes infection prevention, blood-count monitoring, immunoglobulin monitoring, and supportive care important components of treatment.

Access is another important challenge. CAR T-cell therapy requires specialized treatment centers, trained medical staff, cell collection facilities, manufacturing capacity, insurance coverage, travel, and caregiver support. Following CAR T-cell infusion, patients may need to remain near the treatment center for frequent monitoring and rapid management of treatment-related complications.[27]

Bispecific antibodies do not require personalized cell manufacturing and can often be initiated more quickly than CAR T-cell therapy. However, bispecific antibodies can be costly and may require frequent clinic visits, dose escalation, CRS monitoring, and ongoing infection prevention. Therefore, the benefits of newer immunotherapies must be considered alongside treatment resistance, toxicity, monitoring requirements, cost, and access to care.[5,27]

Future Directions

Future MM research aims to make treatment safer, more effective, more durable, and more accessible. One active area of investigation is dual-target CAR T-cell therapy, in which engineered T cells are designed to recognize more than one myeloma associated antigen. Studies are exploring CAR T-cells that target both BCMA and GPRC5D or other combinations. The goal is to reduce the likelihood that myeloma cells can escape treatment by losing or reducing the expression of a single target. These approaches remain experimental and require further study.[29]

Another research direction is developing allogeneic or donor-derived CAR T-cell products. Unlike autologous CAR T-cell therapies, which are manufactured from the patient's own T cells, allogeneic products are produced from healthy donor T cells. Allogeneic products may improve availability, but immune rejection, graft versus host disease, long-term safety, and response durability must be addressed before they can be widely used. [16,26]

Researchers are also investigating whether to introduce immunotherapy earlier in MM, before extensive treatment resistance and T cell dysfunction develop. Earlier treatment could allow immunotherapy to target a smaller, less treatment resistant population of myeloma cells. However, the early use of such drugs poses some risks in terms of toxicity, treatment sequencing, and whether or not the benefits outweigh the risks when there is an alternative treatment available. [30]

Predictive biomarkers may help doctors determine which patients can benefit most from certain treatments. Researchers are studying tumor genetics, target antigen levels, tumor burden, immune system characteristics, and treatment-response patterns. Personalized treatment selection could reduce unnecessary toxicity while increasing the likelihood of deep and durable responses.[29,30]

Measurable residual disease (MRD) testing may also become increasingly important in treatment decision-making. MRD negativity is associated with longer progression free survival and, in many studies, improved overall survival rates.[24,30] Researchers are investigating whether MRD results can safely guide treatment intensity, such as identifying patients who might eventually reduce or stop treatment after sustained MRD negativity or patients who may benefit from additional therapy when the MRD remains detectable.

However, MRD guided treatment decisions are still being studied. They are not yet standard practice for every patient with MM.[4,30] MRD results must be interpreted with the disease-risk category, treatment type, timing of testing, and assay sensitivity.[30]

Taken together, these approaches may lead to more personalized MM care in the future. This is because the primary objective is not only to deepen the response but also to create treatment that is durable, safe, specific, and accessible. These developments may allow overcoming many of the limitations mentioned in this review.

Conclusion

Immunotherapy is among the new approaches that have been developed to treat multiple myeloma, particularly for those who are suffering from relapse and therapy resistance. Patients can reach MRD negativity with CAR T-cell therapy and bispecific antibodies. However, traditional methods should not be overlooked, as they remain in use across all disease settings.

This review shows that assessing treatment benefit should not rely solely on response rate. Response duration, MRD, side effects, treatment burden, accessibility, cost, and other factors affect the appropriateness of therapy for a specific patient. Because the trials analyzed differ substantially, variations in outcomes across trials cannot be taken as proof of comparative superiority.

Future success will depend on patient selection, optimal therapy combinations, infection prevention, toxicity management, methods to overcome antigen escape and T-cell dysfunction, and greater availability of immunotherapies. Future immunotherapies are not intended to replace current therapy but rather are expected to play an increasing role as part of personalized therapy for myeloma.

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