Immunotherapies in Multiple Myeloma: A Practical Approach to Optimizing Care and Managing Treatment-Related Toxicities

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Abstract

Immunotherapies have heavily contributed to disease control in multiple myeloma and are often included in treatment regimens due to their strong efficacy and general tolerability. This broad class of drugs includes immunomodulatory drugs, monoclonal antibodies, cellular therapies with CAR T and NK cells, and bispecific antibodies. Strategies to mitigate toxicities lack standardization and vary across institutions. This article provides advanced practitioners with information regarding the most common immunotherapies and recommendations to manage common treatment toxicities based on consensus recommendations by myeloma experts and the International Myeloma Working Group.

Treatment advances in multiple myeloma (MM) have allowed for renewed hope, significantly improving the management and prognosis of the disease. Survival in MM has improved with immunomodulatory drugs (IMiDs) and proteasome inhibitors. Utilizing monoclonal antibodies (mAbs) in newly diagnosed and relapsed patients has improved the rate of complete responses (CR) in MM. Novel approaches using chimeric antigen receptor (CAR) T lymphocytes and bispecific antibodies (BsAbs) are options that have added to improved outcomes for many patients with MM (Lakshman & Kumar, 2022; Sperling & Anderson, 2021). However, both are associated with significant toxicities, and effective management strategies are rapidly evolving.

This article aims to provide advanced practitioners (APs) with information about common immunotherapies in myeloma to increase their knowledge about the management of symptoms based on the most recent myeloma expert recommendations, including consensus guidelines from the International Myeloma Working Group (IMWG). Recommendations are noted where the evidence is robust and the guidelines are strongly endorsed by expert consensus. More detailed information on clinical evaluation and intervention can be found in the IMWG and National Comprehensive Cancer Network (NCCN) guidelines.

IMMUNOMODULATORY DRUGS

The use of IMiDs remains relevant and highly prominent in the treatment of MM, with broad applicability in different disease settings. Immunomodulatory drugs exert an antimyeloma effect through a multitude of mechanisms, including immune regulation by enhancing T-cell and NK cell activity, while suppressing regulatory T-cell activity. Each generation of IMiDs (thalidomide [Thalomid], lenalidomide [Revlimid], and pomalidomide [Pomalyst]) has resulted in improvements in efficacy, but resistance remains a barrier. Cereblon E3 ligase modulators (CeLMods) are next-generation agents currently under investigation and can overcome lenalidomide and pomalidomide resistance. Drugs within this class, including iberdomide (Zenbexus) and mezigdomide, show promise and a place in the future of MM management (Zuo & Liu, 2022).

MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) can activate the immune system by binding with myeloma targets on the cell surface. Currently approved mAbs include daratumumab (Darzalex) and isatuximab (Sarclisa), which target CD38, and elotuzumab (Empliciti), which targets SLAMF7 (Romano et al., 2021). CD38-targeting mAbs kill MM cells through several different pathways: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), indirect and direct apoptosis, and can also exert an immunomodulatory effect by inhibiting regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells (van de Donk & Zweegman, 2024). Daratumumab is a fully human IgG1 kappa antibody, while isatuximab is a chimeric IgG1 kappa antibody. Both share the same target with similar mechanisms of action but differ in that daratumumab is more effective at using the CDC pathway, while isatuximab exhibits greater direct anti-MM activity through apoptosis of the myeloma cells.

Elotuzumab is a mAb targeting SLAMF7 and capable of ADCC and ADCP but exerts a major effect of enhancing NK cell activity (Romano et al., 2021). It lacks single-agent activity and must be given synergistically in combination with other therapies such as IMiDs or bortezomib. Currently, it is approved in the relapsed/refractory settings and thought to be more effective earlier in the myeloma disease course when NK cell function is better preserved.

CAR T-CELL THERAPY

The success of CAR T-cell therapy in various hematologic malignancies has been well recognized, and its use in MM has significantly affected patients' treatment options. CAR T-cell therapy involves the harvesting of the patient's T cells, which are exported to an engineering facility where they are manufactured to recognize and attack MM-specific targets (Ludwig et al., 2023; Rodriguez-Otero et al. 2024). This therapy is a multistep collaboration among many health-care disciplines. Figure 1 describes the process of CAR T-cell collection, manufacturing, and infusion of cells. When a patient is deemed eligible for treatment, they undergo an apheresis procedure for cell collection, and the cells are then dispatched for cell manufacturing. During the manufacturing period, patients continue with bridging therapy treatment until T-cell manufacturing is complete. Once the cells are ready for infusion, the patient receives lymphodepletion chemotherapy prior to cell infusion. Afterwards, the patient can be admitted to the hospital for infusion or can receive the CAR T cells in the ambulatory setting, depending on if the facility has the infrastructure established for outpatient administration (Leinemann & Krutter, 2024). In either case, the patient is closely monitored for several days to assess complications.

The benefits of CAR T-cell therapy are significant, demonstrating greater depth and duration of response. Idecabtagene vicleucel (ide-cel; Abecma) and ciltacabtagene autoleucel (ciltacel; Carvykti) target B-cell maturation antigen

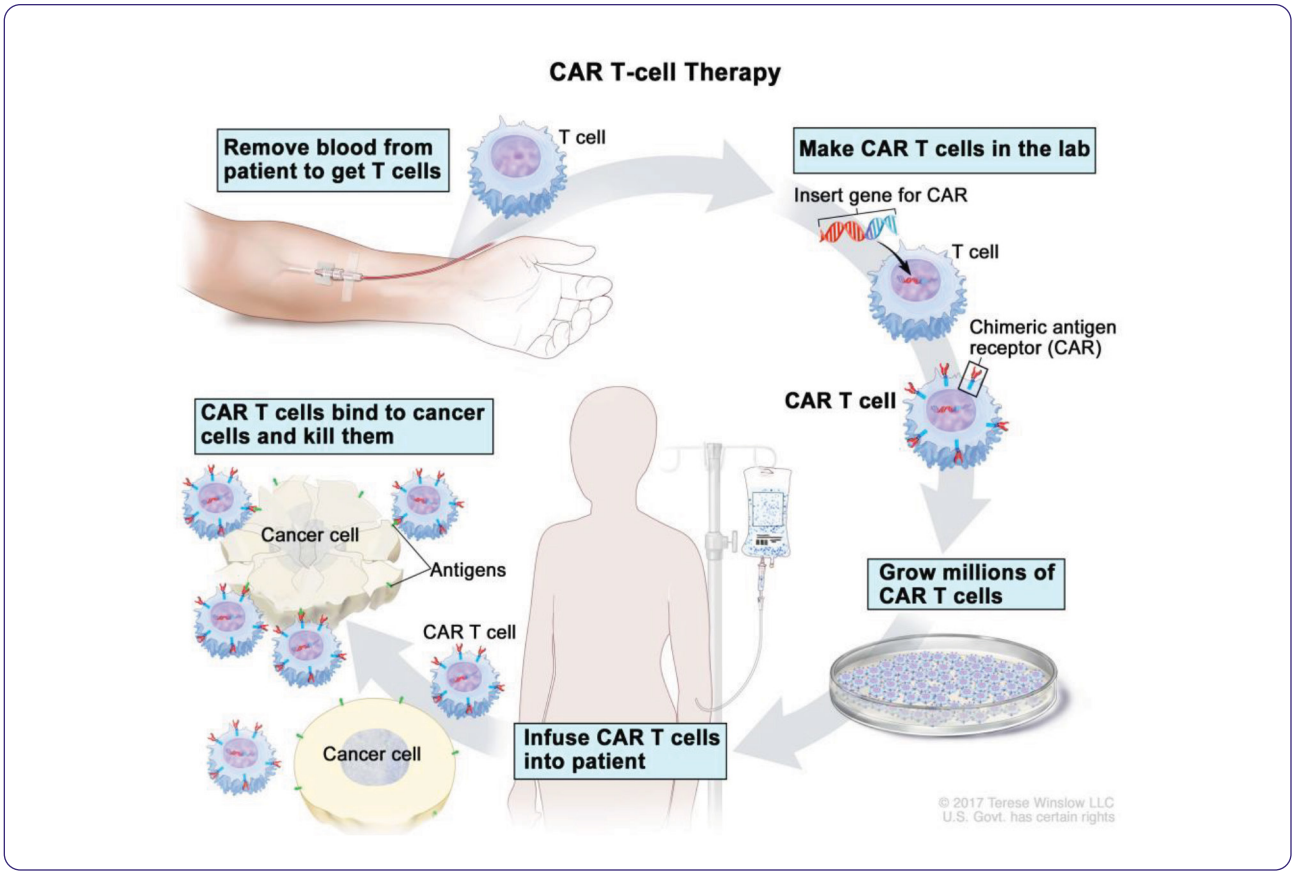


Figure 1. CAR T-cell process. © 2017 Therese Winslow LLC.

(BCMA) on the plasma cell and are the only two FDA-approved CAR T-cell therapies for MM. Table 1 summarizes the pivotal studies that led to accelerated approval and the landmark studies that led to earlier line approval, in addition to responses and toxicities. Cross-trial comparisons should be interpreted with caution, as toxicity rates in the table are drawn from different clinical trials with varying patient populations.

BISPECIFIC ANTIBODY THERAPIES

Bispecific antibodies, also known as bispecific T-cell engagers, draw T cells to the myeloma cell using a dual target approach. These engineered mAbs bind to CD3 found on T cells and the myeloma target so that when linked, the BsAb triggers the lysis of the tumor cell (Raje et al., 2023). Current targets include BCMA, GPRC5D, and FcRH5, although this is still under investigation. Bispecific antibodies are off-the-shelf products that can be administered without engineering the patient's T cells. There are currently four FDA-approved BsAbs, all with indications for four or more prior lines of therapy.

Bispecific antibodies targeting BCMA include teclistamab (Tecvayli), elranatamab (Elrexfio), and, most recently, linvoseltamab (Lynozyfic; FDA, 2025). Talquetamab (Talvey) was approved as a first-in-class BsAb targeting GPRC5D (Wang et al., 2024). Since current BsAbs require ramp-up dosing, hospital admission or daily visits to the ambulatory clinic during this period are required for several days for safety monitoring. Teclistamab, elranatamab, and talquetamab are all available subcutaneously, while linvoseltamab is only available for intravenous administration at this time. Table 2 reviews the BsAb medications, pivotal trials, indications, and toxicities.

TOXICITIES IN CONVENTIONAL IMMUNOTHERAPIES

A better understanding of toxicities and complications of immune therapies has enhanced

Table 1. Summary of Landmark CAR T-Cell Studies

Drug/study	Indication/ approval date	Response	CRS any	CRS ≥ 3	Neuro any	Neuro ≥ 3	Infection any	Infection ≥ 3
Ide-cel KarMMa-2	5th line 3/26/2021	ORR: 73% CR: 33% MRD: 26%	84%	5%	18%	3%	69%	22%
Ide-cel KarMMa-3	3rd line 4/04/2024	ORR 71% CR: 39% MRD: 20%	88%	4%	15%	3%	58%	24%
Cilta-cel CARTITUDE-1	5th line 2/28/2022	ORR: 97% CR: 67% MRD: 34%	95%	4%	21%	9%	58%	20%
Cilta-cel CARTITUDE-4	2nd line 4/05/2024	ORR: 97% CR: 73.1% MRD: 60.6%	76.1%	1.1%	20.5%	2.8%	62%	26.9%

Note. ORR = overall response rate; CR = complete response; MRD = minimal residual disease; CRS = cytokine release syndrome. Information from Munshi et al. (2021); Rodriguez-Otero et al. (2023); Berdeja et al. (2021); San-Miguel et al. (2023).

Table 2. Summary of Landmark Bispecific Antibody Studies

Drug/study	Approval	Response	CRS any	CRS ≥ 3	Neuro any	Neuro ≥ 3	Infection any	Infection ≥ 3
Teclistamab MajesTEC-1	10/25/2022	ORR: 62% CR: 28%	72.1%	0.6%	14.5%	3%	76.4%	44.8%
Elranatamab MagnetisMM-3	8/14/2023	ORR: 61% CR: 35%	57.7%	0%	3.4%	–	69.9%	39.8%
Linvoseltamab	7/2/2025	ORR: 71% CR: 50%	46%	0.9%	7.7%	2.6%	74.4%	35.9%

Note. Information from Moreau et al. (2022); Lesokhin et al. (2023); Bumma et al. (2024).

interventions and improved patient outcomes. Management of conventional immunotherapies such as IMiDs and mAbs is summarized in Table 3. Recommendations are adapted from consensus guidance and NCCN Guidelines. Both classes carry a risk for myelosuppression and infection, which are further discussed in later sections.

The primary toxicities of IMiDs include thrombosis, cytopenias, infection, rash, peripheral neuropathy, muscle cramps, and diarrhea. Thromboembolic complications can occur, especially when IMiDs are given in conjunction with steroids and other drugs (Ludwig et al., 2023). Prevention of thrombotic events includes prophylaxis with antithrombotic agents based on individual patient risk (NCCN, 2025a). Updated guidelines on the treatment of thrombotic events include therapeutic doses of low-molecular-weight heparin with transition to warfarin or the use of newer direct oral anticoagulant therapies like rivaroxaban or apixaban (Hong et al., 2021; Ludwig et al., 2023, Ortel et al., 2020). General management strategies for rash, peripheral neuropathy, muscle cramps and diarrhea are summarized in Table 3. Management is largely individualized, and there are no current standardized recommendations.

Additionally, thalidomide, a first-generation IMiD, remains relevant in international settings due to cost and availability. It is important to note that it carries a more substantial risk for peripheral neuropathy compared with its newer counterparts. This sensory neuropathy primarily manifests as paresthesia of the hands and feet (Ludwig et al., 2023). The management of neuropathy remains unsatisfactory, lacking clear recommendations to guide management. Treatment

Table 3. Summary of Recommendations for IMiDs and mAbs

Toxicities	Recommendations
Thrombotic events	• Prophylaxis is based on risk per NCCN guidelines • Duration is indefinite while on myeloma therapy and based on patient factors Low risk • Prophylaxis is based on risk per NCCN guidelines • Duration is indefinite while on myeloma therapy and based on patient factors High risk (any of the following): • Low molecular weight heparin (LMWH) • Rivaroxaban 10 mg daily • Apixaban 2.5 mg BID • Fondaparinux 2.5 mg daily • Warfarin (Target INR = 2.0–3.0)
Diarrhea	• Other causes should be ruled out before pharmacologic interventions are made • Dietary changes • Hydration • Locally active opioids (loperamide) • Bile acid sequestrants (BAS; colesevelam, cholestyramine, colestipol) should be taken separately from other drugs • Diphenoxylate with atropine • Rehydration
Infection	• Administer based on risk • Zoster prophylaxis (acyclovir or valacyclovir) • PJP prophylaxis (Bactrim): Consider any time a patient receives high-dose, ongoing steroids • Hypogammaglobulinemia: Administer IVIG < 400 or frequent infection per NCCN guidelines
Rash	Mild (minimal localized, mild extensive) • H1, H2 histamine blockers (cetirizine, ranitidine) • Supplements (L-lysine) • Topical steroids Moderate • Treatment interruption • Restart with complete resolution • Consider dose adjustments once rash improves to grade 1 or with resolution • Follow mild rash recommendations • Prednisone Severe • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Warrant permanent discontinuation

Note. BAS = bile acid sequestrants; IMiDs = immunomodulatory drugs; INR = international normalized ratio; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; LMWH = low-molecular-weight heparin; mAbs = monoclonal antibodies; NCCN = National Comprehensive Cancer Network; PJP = *Pneumocystis jirovecii* pneumonia; SNRI = serotonin-norepinephrine reuptake inhibitor. Information from NCCN (2025a); LeBlanc et al. (2022); Ludwig et al. (2023); Richards & Lee (2018).

is individualized and based on close monitoring of patient symptoms. Thalidomide's toxicity profile also uniquely includes neurotoxicity, which manifests as dizziness, tremors, sedation, and other cognitive changes (Liang & Sidana, 2023).

Monoclonal antibodies have a risk of infusion-related reactions (IRR), cytopenias, and immunosuppression. These often subside with time but are more pronounced after the first infusion of daratumumab (van de Donk & Zweegman, 2024). Subcutaneous administration of mAbs has rendered even lower incidences of IRRs. Infusion-related reactions occur from hypersensitivity or cytokine release and manifest as a range of symptoms, including fever, chills, rigors, shortness of breath, blood pressure changes, tachycardia, dizziness, nausea, and upper respiratory symptoms like nasal congestion and cough (Barroso et al., 2024; Ludwig et al., 2023). These side effects are usually effectively controlled with premedication regimens with antihistamines, antipyretics, and corticosteroids and post-treatment corticosteroids. In the event an IRR occurs, they are typically mitigated with corticosteroids and additional antihistamines.

Table 3. Summary of Recommendations for IMiDs and mAbs (cont.)

Toxicities	Recommendations
Peripheral neuropathy	• Close monitoring for dose adjustments or discontinuations • Rule out alternative causes (B12 deficiency, diabetes) • Topical: lidocaine and capsaicin • Anticonvulsant (gabapentin, pregabalin) • Antidepressants (SNRI) • Supportive care for pain • Supplements (acetyl-L-carnitine, alpha-lipoic acid) • Acupuncture • Grade 1 that is mild without loss of function: consider dose reduction • Grade 2: dose interruption until improvement • Discontinue treatment for grades 3 or 4, or lower grades that do not improve or resolve
Constipation	• Increase dietary fiber • Increase water hydration • Diet modification • Laxative (sennosides and polyethylene glycol) • Stool softeners (docusate sodium) • Laxatives can cause abdominal bloating and cramping • Avoid fleet enemas
Fatigue	• Rule out other causes (pain, other comorbidities, infection) • Endorse adequate sleep, nutrition, and gentle increases in activity • Dose adjust steroids if needed
Muscle cramps	• Fluid hydration • Electrolyte normalization (magnesium, potassium) • Muscle relaxants • Movement/stretching
Infusion-related reactions	Premedications for mAbs: • Steroids (dexamethasone, methylprednisolone or equivalent) • H1, H2 histamine blockers (diphenhydramine, ranitidine) • Antipyretics (acetaminophen) Considerations for obstructive disorders • Leukotriene receptor antagonist (montelukast) • Bronchodilators Post-medications for mAbs • Steroids (dexamethasone, methylprednisolone or equivalent) Treatment of IRR • Interrupt administration • Monitor vital signs every 30 minutes for 2 hours • Consider restarting at a lower infusion rate if administering IV • Administer steroids, histamine blockers, antipyretics • Once stable, resume infusion at half the rate • Discontinue in the event of a life-threatening emergency

Note. BAS = bile acid sequestrants; IMiDs = immunomodulatory drugs; INR = international normalized ratio; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; LMWH = low-molecular-weight heparin; mAbs = monoclonal antibodies; NCCN = National Comprehensive Cancer Network; PJP = *Pneumocystis jirovecii* pneumonia; SNRI = serotonin-norepinephrine reuptake inhibitor. Information from NCCN (2025a); LeBlanc et al. (2022); Ludwig et al. (2023); Richards & Lee (2018).

TOXICITIES IN IEC THERAPIES

The primary toxicities that result from immune effector cell therapies (CAR T-cell therapy and BsAbs) include cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), cytopenias, and infection. These toxicities are common and require prompt recognition and treatment. It is important to note that some side effects are target dependent. For instance, talquetamab produces a set of unique toxicities, which include oral, skin, and nail toxicities, as the GPRC5D target is expressed on the cells that produce hard keratin (Ravi & Costa, 2023).

Cytokine Release Syndrome

Cytokine release syndrome is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction (Frey & Porter,

Table 4. ASTCT Cytokine Release Syndrome Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
		With	With	With
Hypotension		Not requiring vasopressor	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or	And/or	And/or
Hypoxia		Requiring low-flow nasal cannula (≤ 6 L/minute) or blow-by (used in pediatrics)	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

Note. BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure. Information from Lee et al. (2019); Schuster et al. (2020).

2019). It is most prevalent in T-cell engaging cancer immunotherapies like CAR T-cell therapies and BsAbs (Lee et al., 2019). The first clinical signs of CRS are fevers, myalgias, and fatigue. Fevers may begin as low grade and escalate over several days. Cytokine release syndrome can progress to life-threatening vasodilatory shock, capillary leak, hypoxia, and end-organ dysfunction (Frey & Porter, 2019). Table 4 outlines the American Society of Transplantation and Cellular Therapy (ASTCT) grading of CRS (Lee et al., 2019). Cytokine release syndrome occurs within 1 to 14 days after infusion, depending on the product or condition and the type of patient being treated (Frey & Porter, 2019; Lakshman & Kumar, 2022). Patients with higher levels of disease burden are at a greater risk for CRS events. While the grading criteria are universal, the management differs depending on the product type (Table 5). Clinicians should follow the package inserts for recommendations, but tocilizumab (an IL-6 inhibitor) and steroids are the mainstays of treatment of CRS (Raje et al., 2023).

Patient assessment before and after administering CAR T-cell therapy and BsAb treatment is essential. Baseline and ongoing assessment and monitoring of CRS labs are key to the early detection of CRS. Specific labs needed to monitor and manage CRS include complete blood cell counts, chemistry, and pro-inflammatory laboratory markers that correlate with CRS such as C-reactive protein (CRP) and ferritin (Liang & Sidana, 2023). However, CRP levels are less meaningful after tocilizumab has been administered due to IL-6 inhibition, resulting in lower CRP concentrations (Rodriguez-Otero et al., 2024). Coagulation studies are important to monitor, especially as CRS can cause coagulation disorders and include prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT), fibrinogen, and D-dimer. Cytokine release syndrome can be accompanied by clinical signs and laboratory abnormalities that resemble infection; therefore, it is necessary to rule out bacterial or viral infections. Patient and caregiver education and frequent follow-ups are required when the patient is discharged from the hospital or clinic setting. Post-discharge, patients should be seen at least twice a week and more often as needed for the evaluation of toxicities.

Recent studies provide strong support for the administration of tocilizumab prior to BsAbs. Korst et al. (2024) report prophylactic tocilizumab was effective in reducing CRS rate in patients receiving teclistamab when given 4 hours prior to the first step-up dose. Kowalski et al. (2025) conducted a single-center study to evaluate prophylactic tocilizumab given prior to teclistamab and found not only a reduced incidence of CRS but also a reduced rate of reoccurrence, highlighting the belief that preventative administration may be more beneficial than reactive administration. Effective mitigation of CRS reduces the use of steroids (which can increase infection risk) to treat CRS and ICANS.

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity events, often referred to as ICANS, are another prevalent adverse event associated with CAR T-cell therapy. Immune effector cell–

Table 5. CRS Management Strategies

Grade 1

Supportive management: Fever, dehydration, nausea
- Acetaminophen
- IV fluids
- Antiemetics
- Telemetry

Fever workup to rule out infection/sepsis
- CBC with differential, CMP, chest X-ray, blood cultures, urine culture, respiratory viral panel
- Start broad-spectrum antibiotics if neutropenic

CRS monitoring:
- CRP, ferritin, PT/PTT, fibrinogen, D-dimer
- Monitor for organ toxicities
- Consider anti-cytokine therapy (IL-6 blocker: tocilizumab, siltuximab)

Grade 2

In addition to the above supportive management and CRS monitoring in grade 1:
- Treat hypotension
  - » IV fluids for hypotension
  - » Vasopressor for hypotension
- Low-flow nasal cannula ≤ 6 L/minute
- IL-6 blocker
- Steroids

Grade 3

In addition to the above supportive management and CRS monitoring in grade 1:
- Tocilizumab every 24 hours and consider changing to anakinra or ruxolitinib
- Vasopressor support for hypotension
- Steroids: Dexamethasone or methylprednisolone every 6 hours based on number of vasopressors
- Consider ICU admission

Grade 4

In addition to the above supportive management and CRS monitoring in grade 1:
- ICU support
- Ventilation as needed
- Anti-IL-6 support with another agent
- Steroids: High-dose methylprednisolone

Note. CBC = complete blood count; CMP = comprehensive metabolic panel; CRP = C-reactive protein; CRS = cytokine release syndrome; ICU = intensive care unit; PT = prothrombin time; PTT = partial thromboplastin time. Information from Chohan et al. (2023); Jain et al. (2023); Ludwig et al. (2023); Markouli et al. (2023).

associated neurotoxicity syndrome can occur concurrently with CRS or as an independent condition, requiring aggressive monitoring and immediate intervention at the onset of symptoms. While neurotoxicity events were frequently observed in patients undergoing CAR T-cell therapies, the occurrence is less common in BsAbs.

The pathophysiology of ICANS is better understood in CD19-targeting CAR T cells but remains less clear in anti-BCMA CAR T-cell therapies. It is believed to be linked to disruption in the blood-brain barrier resulting from excessive cytokine release and the central nervous system infiltration of CAR T cells (Markouli et al., 2023). Neurotoxicity events beyond ICANS have also been observed and may have more enduring and irreversible effects than CRS or ICANS. These events can encompass movement disorders like Parkinsonism, tremors, Guillain-Barré syndrome, bradykinesia, apraxia, micrographia, and gait changes impacting cognition and personality.

The ASTCT has established consensus guidelines for encephalopathy screening using the Immune Effector Cell–Associated Encephalopathy (ICE) scale. The neurotoxicity is graded by evaluating encephalopathy, seizures, dysphasia, tremor, headache, confusion, level of consciousness, and cerebral edema (Lee et al., 2019). Patients should receive a baseline MRI prior to initiating therapy. Neurologic assessments are crucial and should be conducted at least daily, with increased frequency as necessary (Gonzalez Castro & Dietrich, 2020).

For any neurotoxicity event, it is recommended to conduct neuroimaging in addition to consulting a neurologist. The prompt treatment and management of CRS symptoms using IL-6 inhibitors, such as tocilizumab, have demonstrated efficacy in reducing the occurrence of severe ICANS (Markouli et al., 2023). Neuroprotective measures should be implemented, including ensuring the patient is kept nothing by mouth (NPO) and initiating IV hydration as required. At the onset of ICANS, the patient should receive a brain MRI and intracranial pressure monitoring (Lin et al., 2024). Prophylaxis for seizures should be administered for the first month for patients receiving CAR T-cell therapy.

The primary approach to managing ICANS involves the use of glucocorticosteroids. The recommended regimen for grade 1 to 2 ICANS events is dexamethasone 10 mg administered every 12 to 24 hours. Steroids should be decreased quickly and as tolerated by patients whose symptoms are improving (Lin et al., 2024). For high-grade ICANs, anakinra may be used. Patients should be considered for transfer to the intensive care unit for high-grade ICANS above grade 2 (Rees, 2022). Seizure management should involve the administration of therapeutic levels of anticonvulsant therapy.

Immune Effector Cell–Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by unmitigated T cell and macrophage activation, resulting in hyperferritinemia, hepatic dysfunction, coagulopathy, and cytopenias (Hines et al., 2023). Hemophagocytic lymphohistiocytosis symptoms that occur in CAR T-cell patients are unique from primary HLH and are known as immune effector cell–associated HLH-like syndrome (IEC-HS). This is a rare and potentially fatal complication of CAR T-cell therapy and can occur after BsAb treatment (Rodriguez-Otero et al., 2024). It must be addressed quickly to prevent mortality.

The ASTCT developed a consensus grading scale that includes evaluation of ferritin levels, liver transaminases, fibrinogen levels, triglyceride levels, and cytopenia. It also includes manifestations commonly associated with CAR T-cell therapy, such as fever, coagulopathy, hyperbilirubinemia, neurotoxicity, and organ damage (Lee et al., 2025). The treatment strategy for IEC-HS is focused on providing therapies that target the cytokine storm and therapies that promote T-cell proliferation and expansion. Given the serious nature of this condition, urgent treatment and close monitoring are necessary.

Immune Effector Cell-Associated Enterocolitis

Immune effector cell–associated enterocolitis (IEC-EC) is a rare but potentially serious complication found in CAR T-cell therapy. It is a maladaptive immune activation in the gastrointestinal tract. While CRS and ICANS are well characterized by short-term systemic inflammation, IEC-EC involves localized immune-mediated damage of the colic mucosa that histologically and mechanistically resembles acute graft-vs.-host disease (GVHD). While the pathophysiology is not fully understood, intestinal inflammation is reminiscent of GVHD: intraepithelial lymphocytosis, villous blunting, crypt dropout, and apoptosis are seen (Galarza Fortuna et al., 2024). Immune effector cell–associated enterocolitis typically manifests with non-bloody diarrhea in the weeks to months after CAR T-cell infusion, with symptoms starting around 1 to 3 months later (Banerjee et al., 2025). Important key points and risk factors to consider that may increase the development of CAR T-cell colitis include: (1) High-dose chemotherapy before CAR T-cell therapy, (2) preexisting inflammatory bowel disease, and (3) older age.

Diagnosing IEC-EC involves a thorough workup ruling out other causes of diarrhea and using endoscopy, biopsy, and histological studies (Somay et al., 2025). Prompt recognition and intervention is critical, as IEC-EC can progress to life-threatening complications such as severe dehydration, bacteremia, or bowel perforation. Rapid improvement is seen with the use of corticosteroids, but biologic agents can be considered for steroid-refractory colitis. Immunosuppressive therapy with corticosteroids is used in the first line.

Talquetamab-Related Toxicities

As a GPRC5D target, talquetamab produces unique toxicities that differ from its BCMA-directed counterparts (Table 6). GPRC5D receptors are present not only on plasma cells but also

expressed on the cells of the skin, nails and tongue. Subsequently, they produce a unique subset of toxicities. Skin-related events include dry skin, pruritus, eczema, fissures, lesions, hyperpigmentation, and other events (Chari et al., 2022). Nail toxicities included dystrophy, onycholysis, ridging, onychomadesis, hyperdystrophy, and nail bed disorder. Patients also reported oral symptoms including dry mouth, dysgeusia, dysphagia, and weight loss. Currently, there are no established recommendations for the management of these conditions. Best practices are summarized in Table 7 based on MonumenTAL-1 data and anecdotal reports from clinicians. Of note, most toxicities reported on study were grade 1 or 2 with minimal grade 3 or 4 events and subsided with time and supportive care techniques (Chari et al., 2022). Early recognition and comprehensive education are important in effective management.

MYELOSUPPRESSION

Bone marrow dysfunction results in cytopenia, which is prevalent across all immunotherapies and can vary in severity. Treatment is similar and often managed supportively. Immunomodulatory drugs and mAbs often manifest as neutropenia or thrombocytopenia. Patients can experience profound cytopenia with CAR T-cell therapies that usually improve with time (Liang & Sidana, 2023). Lymphopenias can occur in mAbs, BsAb, and CAR T-cell therapies, increasing the patient's risk for opportunistic infections (Liu et al., 2025).

Delayed cytopenia is often present in CAR T-cell and BsAb BCMA-targeting regimens. For CAR T-cell therapy, acute cytopenia can occur within 30 days, and delayed cytopenia can occur after 30 days. Reasons for this are multifactorial, involving the patient's level of disease burden, prior lines of therapy, and persistently circulating CAR T cells. In real-world studies, less heavily treated patients did not require granulocyte colony-stimulating factors (GCSF) support at 1 month and experienced cell recovery at around 3 months (Liang & Sidana, 2023). For BsAbs, cytopenia is common and can persist with time because of prolonged BsAb exposure and T-cell activation, which ultimately contributes to T-cell exhaustion. Cytokine release syndrome, ICANS, and steroid exposure can also contribute to prolonged myelosuppression (Liu et al., 2025).

Patients should be managed supportively with G-CSF or transfusion support. While the use of thrombopoietin-receptor agonists may be considered for prolonged cytopenia, patients require evaluation and should be assessed for infection. In addition, alternative causes like secondary malignancies should be ruled out.

Infections

Immune system dysregulation from MM coupled with myelosuppression and immune suppression can increase the risk for infection (Raje et al., 2023). However, infection risk and severity vary based on the class of regimen used, as well as the preventative and intervention strategies. Infection prevention strategies are largely based on risk, with consideration to clinical history, performance status, myeloma treatment history, and presence of immunoparesis. Effective prophylaxis with timely treatment can improve outcomes. Vaccination is an important component of preventative management and is summarized in Table 8. Vaccinations should be considered as early

Table 6. Summary of Talquetamab (Bispecific Antibody)

Summary of toxicities

Dose, µg/kg	CRS any	CRS ≥ 3	Neuro any	Neuro ≥ 3	Infection any	Infection ≥ 3
405	77%	0%	10%	0%	47%	7%
800	80%	–	5%	–	34%	7%

Summary of skin toxicities

Dose, µg/kg	Skin	Rash	Nails	Dysgeusia	Dry mouth	Dysphagia	Weight loss
405	67%	47%	57%	63%	30%	37%	30%
800	70%	30%	27%	57%	57%	27%	32%

Note. Study: MonumenTAL-1. Response: ORR, 73%; CR, 26%. Information from Chari et al. (2022).

Table 7. Recommendations for Talquetamab-Related Toxicities

	Prevent	Treat	Avoid
Skin toxicities (pruritus, desquamation of skin, dry skin)	• Fragrance-free moisturizers daily • Heavy emollients • Barrier creams • Use sunscreen	• Ammonium lactate for dry, scaly skin • Antihistamine for pruritus (cetirizine) • Topical corticosteroids (hydrocortisone, triamcinolone) with escalation in potency as needed • Oral steroids for severe cases • Dose interruptions • Consider dermatology referral	• Soaps • Scented cleansers • Hot showers • Excessive washing
Nail dystrophy	• Nail strengtheners • Vitamin E cuticle oil • Emollients • Biotin supplements	• Nail strengtheners • Vitamin E cuticle oil • Emollients • Biotin supplements	• Nail hardeners • Acrylics • Gels
Xerostomia	• Sodium lauryl sulfate-free toothpastes • Monitor for oral candidiasis	• Saliva substitutes • Increased hydration • Gum or hard candies • Sugar-free chewing gum	• Caffeine • Alcohol • Smoking • Dry, spicy, or salty foods
Dysgeusia	• Experimenting with food with different textures • Use of spices	• Baking soda mouth rinses • Liquid corticosteroids • Oral corticosteroids • Nystatin solution • Zinc gluconate	• Caffeine • Alcohol • Smoking • Dry, spicy, or salty foods
Dysphagia		• Small, frequent meals with small bites • Soft foods • Sit upright to eat • Dental evaluation • GI referral for greater severity	• Caffeine • Alcohol • Smoking • Dry, spicy, or salty foods
Weight loss		• Nutritional supplementation • Appetite stimulants • Consider referral to a nutritionist	

Note. Information from Catamero et al. (2024); Chari et al. (2022); Miller et al. (2025).

as possible (Raje et al., 2023), even though they may be less responsive in patients who have received CAR T-cell therapy and BsAbs (Mohan et al., 2023). For patients who have received CAR T-cell therapy, the recommended time frame for vaccination is 2 to 6 months post-treatment to allow for immune reconstitution. In general, vaccinations should be avoided until disease control is achieved. Immunomodulatory drugs can improve the vaccine response.

Infection Management in Conventional Immunotherapies

Conventional immunotherapies like IMiDs and mAbs carry a risk of infection, especially when given in combination with one another, due to neutropenia (Raje et al., 2023). These infections are typically represented by respiratory tract infections such as pneumonia and fever of unknown origin (Akhmedov et al., 2024). Because mAbs, particularly daratumumab, can cause severe lymphopenia and a higher incidence of neutropenia, there is an increased risk for pneumonia, reactivation of varicella zoster and hepatitis, and opportunistic infections such as *Pneumocystis jirovecii*. This risk is especially higher in the heavily pretreated patient population (Liu et al., 2025; Raje et al., 2023).

Table 8. Vaccine Recommendations

Vaccine	Recommendation
Influenza (inactivated)	• Annually • High dose preferred in patients aged ≥ 65 years or immunocompromised
SARS-CoV-2	• Annual booster
RSV bivalent	• Single dose of bivalent vaccine for multiple myeloma aged ≥ 60 years
Pneumococcal	• PCV13 at diagnosis, then PPSV23 ≥ 8 weeks later • PPSV23 every 5 years in patients aged ≥ 65 years • Update prior to starting bispecific antibody
Shingles	• Two doses, 2 months apart

Note. Information from NCCN (2025a); LeBlanc et al. (2022); Ludwig et al. (2023); Raje et al. (2023).

In such events, patients should follow practical considerations like standard universal precautions and may need dose adjustments or treatment holds to allow for recovery. Granulocyte colony-stimulating factor can augment neutrophil counts but did not reduce infection risk (Raje et al., 2023). Given the risk for viral reactivation, patients on mAbs should be provided with zoster prophylaxis of either valacyclovir or acyclovir. Hepatitis B evaluation should be conducted at baseline and include hepatitis B surface antigen and core antibody serologies. Quantitative viral loads should be drawn in patients with active hepatitis B. Individuals with a history of hepatitis B, either positive for surface antigen or core antibody, should be given prophylactic entecavir or tenofovir to prevent reactivation (Liu et al., 2025).

Infection Management in Immune Effector Cell Therapies

There is an increased risk for infectious complications caused by humoral and cellular immunity deficiencies from longstanding treatment represented by prolonged cytopenia, T-cell exhaustion, and reduced bone marrow reserves from MM and previous therapies, limiting the ability to fight infections (Little et al., 2023; Markouli et al., 2023; Nooka et al., 2024). Factors that increase the risk of infections following CAR T-cell therapy include age, prior lines of therapy, steroid use, development of CRS or ICANS, infectious history, hypogammaglobulinemia, and performance status (Little et al., 2023; Czapka et al., 2023; Mikkilineni & Kochenderfer, 2021). The presence of cytopenia and lymphopenias in the setting of symptoms warrants prompt initiation of a sepsis protocol (including broad-spectrum antibiotics; Shimabukuro-Vornhagen et al., 2022).

Currently, there are limited data to provide empirical evidence for best practices, especially for BsAbs, given the nascency of their treatment approvals. Current recommendations made by expert panels for BsAbs are based on the data collected from MajesTEC-1 and MagnetisMM-3. Further prevention and intervention strategies may evolve as more evidence is produced from other targeted MM BsAbs such as GPRC5D (Rodriguez-Otero et al., 2024). Infection risk stratification with respect to disease and patient-related factors, including infection history and previous therapies, is an important consideration and evolving concept, widely agreed upon by MM experts (Rejeski et al., 2023). CAR T-cell therapy infection prophylaxis recommendations are summarized in Table 9 and adapted from NCCN Guidelines (2025b), Mohan et al. (2023), and IMWG consensus reports from Lin et al. (2024) and Rodriguez-Otero et al. (2024).

Hypogammaglobulinemia often occurs from BsAb and CAR T-cell therapies due to T-cell exhaustion; it is also associated with CD38 mAbs (Liu et al., 2025). There is a high incidence of hypogammaglobulinemia in the acute phase of CAR T-cell therapies due to B-cell aplasia. However, BCMA BsAbs have an increased incidence and persistence of hypogammaglobulinemia past the acute phase because the treatment course is longer, contributing to prolonged T-cell activation, plasma cell destruction, and immune suppression. This cumulative risk of infection over time has led to the appearance of unusual infections in BsAbs (Mohan et al., 2023). Since BCMA is ubiquitous on plasma cells, continuous depletion of normal and

Table 9. Recommendations for Infection Prophylaxis in Immune Effector Cell Therapies

Prophylaxis		CAR T-cell therapy	BsAb
Bacterial	**Start**	Prolonged/severe ANC < 500/mm^3	
	Stop	Until neutrophil recovery without GCSF support	
	Prophylaxis	Levofloxacin 500 mg po daily	
	Alternatives	Cefdinir 300 mg BID Cefpodoxime 200 mg po BID	
Fungal	**Start**	Prolonged/severe ANC < 500/mm^3 High risk: Given IL-6 blocker or prolonged high-dose steroids for CRS/ICANS	
	Stop	Until neutrophil recovery without GCSF support	
	Prophylaxis	• High risk: Include mold-active azole posaconazole 200–300 mg daily • Standard risk: Fluconazole 400 mg daily	• Fluconazole 400 mg daily
	Alternatives	• High risk: voriconazole • Standard risk: fluconazole 400 mg daily	–
Viral	**Start**	• At start of lymphodepletion	• At start of treatment
	Stop	• Indefinite: 1 year after treatment or until CD4 > 200/mm^3, whichever is longer	• Indefinite: Continue for 3 months off treatment or until CD4 > 200/mm^3, whichever is longer
	Prophylaxis	Valacyclovir 500–1000 mg po daily or Acyclovir 400–800 mg po daily	
PJP	**Start**	• At start of lymphodepletion	• At start of treatment
	Stop	• Continue 1 year post-treatment and until CD4 > 200/mm^3	• Continue for duration of therapy and until CD4 > 200/mm^3
	Prophylaxis	• Pentamidine 4 mg/kg every 21 days then can transition to orals at clinician's discretion	• TMP-SMX DS 1 tablet MWF OR • TMP-SMX SS 1 tablet daily
	Alternatives	• TMP-SMX DS 1 tablet MWF • TMP-SMX SS 1 tablet daily	• Atovaquone for sulfa allergies or cytopenia • Dapsone (check G6PD before)

Note. Ab = antibody; Ag = antigen; ANC = absolute neutrophil count; BsAb = bispecific antibody; CAR-T = chimeric antigen receptor T-cell therapy; CMV = cytomegalovirus; CRS = cytokine release syndrome; DS = double strength; GCSF = granulocyte colony-stimulating factor; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; MWF = Monday, Wednesday, Friday; PJP = *Pneumocystis jirovecii* pneumonia; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole. Information from Lin et al. (2024); NCCN (2025b); Mohan et al. (2023); Rodriguez-Otero et al. (2024).

malignant plasma cells contributes profoundly to hypogammaglobulinemia. In contrast, GPRC5D BsAbs have a comparatively lower rate of hypogammaglobulinemia, as the target is not universally expressed on all plasma cells.

Immunoglobulin replacement treatment is critical in the treatment of hypogammaglobulinemia and can be protective against higher-grade, more serious infections (Rodriguez-Otero et al., 2024). 3. Traditionally, IVIG is administered for patients with IgG levels under 400 mg/dL and with recurrent infections. However, other factors, such as high tumor burden, immunoparesis, and evaluation of IgG subclasses, can prompt administration. Lower IgG2 subclasses have been associated with a higher risk of bacterial infections, while IgG1 and IgG3 subclasses have been associated with a higher risk of viral infections (Mohan et al., 2023). Given the high risk for infection, the NCCN Guidelines have been updated with the recommendation to administer IVIG monthly. While there is a lower threshold to administer

Table 9. Recommendations for Infection Prophylaxis in Immune Effector Cell Therapies (cont.)

Prophylaxis		CAR T-cell therapy	BsAb
Hypogammaglobulinemia	**Start**	• 30 days after treatment initiation	• 2nd month of treatment
		Frequent or recurrent infection, bacterial infection, life-threatening infections IgG < 400 mg/dL Immunoparesis CRS/ICANS Given IL-6 blocker or prolonged high-dose steroids	
	Stop	• Continue until 1 year or serum IgG > 400 mg/dL, whichever is longer	• Continue for duration or serum IgG > 400 mg/dL, whichever is longer
	Prophylaxis	IVIG every 4 weeks	
Hepatitis B	**Start**	At treatment start for HBsAg and HBcAb positivity	
	Stop	For the duration of treatment	
	Prophylaxis	Entecavir 0.5 mg po daily Monitor HBV DNA monthly	
GCSF		To maintain ANC > 1,000/µL	
Monitoring	**Screening**	Hepatitis B: HBsAg, HBcAb Hepatitis C: HCV Ab HIV-1/-2 Ag and Ab screen CMV IgG and IgM Check viral loads for any positivity	
	Monitoring	For CMV positivity, monitor by viral loads and treat as indicated	

Note. Ab = antibody; Ag = antigen; ANC = absolute neutrophil count; BsAb = bispecific antibody; CAR-T = chimeric antigen receptor T-cell therapy; CMV = cytomegalovirus; CRS = cytokine release syndrome; DS = double strength; GCSF = granulocyte colony-stimulating factor; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; MWF = Monday, Wednesday, Friday; PJP = *Pneumocystis jirovecii* pneumonia; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole. Information from Lin et al. (2024); NCCN (2025b); Mohan et al. (2023); Rodriguez-Otero et al. (2024).

IVIG in patients receiving IEC therapy, providers must also consider cost in addition to patient presentation and context. Further studies are needed to better understand IVIG replacement in the prophylactic setting to establish risk stratification and establish the timeframe of treatment.

CONCLUSION

The enduring role of immunotherapies in myeloma treatment underscores the importance of effective toxicity management. Conventional immunotherapies like IMiDs and mAbs remain relevant within the MM treatment landscape. Increased experience and understanding of these drugs have helped to improve the overall treatment tolerability along with patient experience. CAR T-cell therapies and BsAbs represent next-generation immunotherapies and have transformed the treatment paradigm. Current investigations in treatment sequencing and trispecific antibodies show promise in better controlling MM. As current understanding of these treatments and their toxicities continues to improve, providers are increasingly able to manage them effectively, ultimately improving patients' quality of life.

Disclosure

Ms. Lu has served as a consultant for Pfizer, Janssen, and Kite. Dr. Verina has served on speaker bureaus for Karyopharm, Janssen, Pfizer, and Sanofi and has served on advisory boards for Sanofi, Janssen, and Cardinal Health. Ms. Catamero has served as a consultant for Johnson & Johnson, GSK, Legend Biotech, and Sanofi and has received honoraria from Johnson & Johnson. Mr. Hellberg-Naegle has served as a consultant for Janssen and BMS, and received payment from Janssen for a

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