Understanding the Role and Clinical Management of Bridging Therapy During CAR T-Cell Therapy for Relapsed or Refractory Multiple Myeloma

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Abstract

Background: Chimeric antigen receptor (CAR) T-cell therapy has emerged as a highly effective treatment for relapsed or refractory multiple myeloma (MM). However, manufacturing CAR T cells can take 3 to 4 weeks, leaving patients vulnerable to disease progression during this waiting period. Bridging therapy aims to address this gap by controlling disease and improving CAR T-cell efficacy. **Objectives:** This review summarizes the role of bridging therapy in CAR T-cell therapy for MM, focusing on the rationale and goals of bridging therapy, timing of initiation, infection risk management, selection of bridging regimens, and clinical implications, including patient education and communication. **Methods:** Relevant literature on CAR T-cell therapy and bridging therapy in MM was reviewed, including clinical trials and real-world data. **Findings:** Bridging therapy may be crucial for some patients, particularly for those with rapidly progressive disease. The optimal timing for initiating bridging therapy remains under investigation, but it can begin as soon as leukapheresis is completed. Prophylactic antibiotics or antivirals and close monitoring are essential for preventing infections during this period. The choice of bridging regimen depends on individual patient characteristics and prior therapies. Effective patient education and communication between local oncology teams and CAR T-cell centers are critical. **Implications:** Bridging therapy plays a vital role in optimizing CAR T-cell therapy outcomes for MM patients. Further research is needed to define the optimal use of bridging therapy in this evolving treatment landscape.

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells accounting for approximately 10% of hematologic malignancies (Rajkumar, 2022). It is estimated that 36,110 new cases will be diagnosed and 12,030 deaths will occur from MM in the United States in 2025 (Siegel et al., 2025). The prognosis has improved significantly over the past decade due to the emergence of novel therapies (Rajkumar, 2022). A median survival of over 10 years has recently been reported (Joseph et al., 2020).

Among various evolving immunotherapies in the advanced treatment paradigm, chimeric antigen receptor (CAR) T-cell therapy has been demonstrated to be a highly effective treatment with manageable toxicity in heavily pretreated patient populations. Two CAR T-cell constructs targeting B-cell maturation antigen (BCMA), idecabtagene vicleucel (ide-cel; Abecma) and ciltacabtagene autoleucel (cilta-cel; Carvykti), have gained approval from the US Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory MM after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (Parikh & Lonial, 2023; Manjunath et al., 2021). In early April 2024, the FDA expanded the approvals of these two CAR T-cell therapies as options to treat MM at an earlier stage. The results from the phase III CARTITUDE-4 and KarMMa-3 trials demonstrated a significant risk reduction of disease progression and death with earlier use of cilta-cel (59%) and ide-cel (51%). Cilta-cel was approved to treat MM at earlier relapse with one to three prior lines of therapy. Ide-cel was FDA-approved to treat patients with relapsed disease who had two to four prior lines of therapy.

As CAR T cells involve manufacturing cells for each patient, the wait time for cell product infusion can vary per patient and has implications for patient management. Bridging chemotherapy is a treatment given to patients before CAR T-cell infusion to prevent the underlying disease from progressing uncontrollably. The goal is to keep the patient in good clinical condition for the CAR T-cell infusion. The decision to use bridging therapy is individualized for each patient and takes into account tumor burden, prior lines of therapy, and expected time from leukapheresis to CAR T-cell infusion (Bhaskar et al., 2021). Bridging therapy after leukapheresis may prevent rapid disease progression during the manufacturing period before CAR T-cell infusion. This article reviews the T-cell harvesting process, bridging therapy, and advanced practice implications during CAR T-cell treatment.

T-CELL HARVEST

The manufacture of CAR T cells begins with leukapheresis (Qayed et al., 2022; Pessach & Nagler, 2023), which is a procedure used to collect T cells from the patient's blood. The patient's whole blood is drawn through a catheter into an apheresis machine that separates the blood cells through a centrifuge (Cohen, 2022; Pessach & Nagler, 2023). Once T cells are collected, they are frozen and sent to CAR T-cell manufacturing for enrichment (Levine et al., 2016; Cohen, 2022). Residual blood cells such as red cells, monocytes, and platelets are returned to the patient (Levine et al., 2016). Leukapheresis of T cells is typically well tolerated with few side effects (Pessach & Nagler, 2023) and is similar to the apheresis used in collecting cells for stem cell transplantation (Cohen, 2022).

The T-cell dose target for collection differs depending on the manufacturer's requirements (Piñeyroa et al., 2022). CD3 count at leukapheresis can predict the clinical outcome of CAR T-cell therapy (Wada et al., 2022). Patients are usually on the apheresis machine for 1 to 2 days, for approximately 5 hours a day. Patients with lower white blood counts may require additional collection days (Pessach & Nagler, 2023). Washout periods from the patient's last chemotherapy can also be a factor (Pessach & Nagler, 2023).

Once a time slot is secured from the manufacturer, leukapheresis is conducted at a Risk Evaluation and Mitigation Strategy (REMS)-certified CAR T-cell center (Cohen et al., 2022). The therapy that the patient is currently receiving should be timed so that the patient has an adequate absolute lymphocyte count (ALC) for leukapheresis. Each CAR T-cell center and each CAR T-cell product has different requirements, but the norm among them is an ALC of 1.5×10^9 to 4×10^9, CD3 cells $\geq 150/\mu L$, adequate platelet and hemoglobin levels in accordance with the CAR

T-cell center's institutional guidelines, and vascular access (Qayed et al., 2022; Pessach & Nagler, 2023).

Other requirements for apheresis are that the patient be free of active infection and tolerate needles. Allergy to citrate anticoagulant is also a contraindication (Connelly-Smith et al., 2023).

BRIDGING THERAPY

Role of Bridging Therapy

Bridging therapy may reduce tumor burden and prevent rapid progression of MM during the manufacturing process following leukapheresis (Zhang et al., 2023). Since reengineering T cells in the laboratory can take several weeks, patients may require bridging therapy to maintain some level of disease control before CAR T-cell administration. Eighty-eight percent of patients in the phase II KarMMa trial and 75% in the CARTITUDE-1 trial received bridging therapy. The response rate of bridging therapy was 5% in KarMMa and 45% in CARTITUDE-1 (Munshi et al., 2021; Berdeja et al., 2021).

There are limited data on how bridging therapy for disease control ultimately affects clinical outcomes in patients receiving CAR T-cell therapy. A study of real-world data of 235 patients from 11 US academic centers reported no difference in complete or overall response rate from CAR T-cell therapy among patients who received and did not receive bridging therapy (41% vs. 52%, p = .2; 84% vs. 87.5%, p = .8, respectively). In the same study, patients without bridging therapy had better overall survival (OS) and progression-free survival (PFS) than patients receiving bridging therapy following ide-cel treatment. The median PFS in patients without bridging therapy was 11.5 months compared to 8.1 months in patients with bridging therapy (p = .03). The OS was not reached at the time of analysis in the group without bridging therapy vs. 13.8 months in the bridging therapy group (p = .002; Afrough et al., 2023).

Although some data suggest bridging therapy does not impact clinical outcomes, it likely allowed many patients with relapsed/refractory MM to receive CAR T-cell therapy by preventing the development of significant organ dysfunction from uncontrolled disease that would exclude patients from receiving CAR T-cell therapy. Bridging therapy is often recommended for patients with rapidly progressive disease. Patients with a relatively low cancer burden and slow-growing disease may not need to receive bridging therapy after leukapheresis. However, this strategy assumes that the disease remains stable during the manufacturing period and may expose patients to a risk of rapid progression by the time they return for CAR T-cell infusion (Manjunath et al., 2021). The decision to proceed with bridging therapy should be individualized for each patient, requiring a thorough evaluation of the disease's nature, risk for rapid progression, and expected wait time from apheresis to CAR T-cell administration.

Initiation Timeframe

CAR T-cell manufacturing protocols vary depending on the product and on cell processing, cell expansion, and quality control, which can lead to vein-to-vein times of upwards of 5 weeks (Geethakumari et al., 2021). A major concern is that patients with aggressive disease may not make it to CAR T-cell infusion due to rapid disease progression or clinical deterioration. In the CARTITUDE-4 clinical trial, 18% of apheresed patients never received CAR T cells due to rapid progression (San-Miguel et al., 2023). The recommendation is to start bridging immediately following leukapheresis due to the need to control disease. Before the initiation of bridging therapy, confirmation of receipt of the apheresed product, as well as confirmation that the cells are adequate for manufacturing, is important in case additional product is required (Bhaskar et al., 2021). With this, bridging therapy can commence immediately following leukapheresis. In clinical trials, washout periods of up to 2 weeks before lymphodepleting chemotherapy were required. In the real-world setting, one complete cycle is often given with a 1-week washout period before lymphodepletion (Ailawadhi et al., 2024).

Infection Risk

Infection is a common complication of CAR T-cell therapy leading to morbidity and mortality. The incidence of infection for BCMA-directed CAR T-cell therapies is reported at 58% to 69% (Meir et al., 2021). Most issues with infection arise after CAR T-cell infusion. However, infection can also occur during the steady state harvest and bridging

therapy while the T cells are manufactured. During manufacturing, patients typically have active, often refractory myeloma with significant immune compromise and an increased risk of infection. Myeloma therapies prior to cell infusion, including bridging therapy and lymphodepletion regimen, likely attribute to pre-infusion infections. Viral infections, including upper respiratory viruses, are commonly seen during this timeframe. The consensus guidelines of the International Myeloma Working Group (IMWG) recommend screening for HIV, hepatitis, cytomegalovirus, parvovirus B19, or other past infections (Lin et al., 2024). If an infection occurs during this time, a timely workup and treatment should be initiated, since the goal is to have patients receive their genetically modified T cells immediately once they are available and without delay due to active infection.

Preventing infection and monitoring for emerging infections is important. Antimicrobial prophylaxis and close monitoring for infection are strongly recommended. The IMWG guideline recommends antiviral prophylaxis from lymphodepletion for 1 year after CAR T-cell therapy, antibacterial and antifungal prophylaxis during periods of neutropenia, high steroid use, or multiple immunosuppressive medication use, and anti-*Pneumocystis* prophylaxis until the CD4+ count is > 200 cells/μL. Intravenous immunoglobulin replacement can be considered if IgG < 400 mg/dL or in the case of recurrent infections (Lin et al., 2024). As protocols and resources may vary among institutions, institutional guidelines need to be followed in patients with hypogammaglobulinemia or infections.

Selection of Bridging Therapy Regimen

The choice of bridging regimen is typically individualized to each patient's disease characteristics and previous therapies. The selection of the regimen is based on the treatments to which patients have previously been exposed and if they responded well, while minimizing the risk of adverse effects. The FDA initially approved CAR T cells to treat patients who had already been heavily treated with four or more prior lines of therapies. These patients were refractory to most of the available drugs, which was the main challenge for bridging therapy. The newly expanded FDA approvals for the two CAR T-cell products to be used at earlier disease stages provide more options for choosing an effective regimen as bridging therapy.

In general, any effective agent can be considered for bridging regimens, such as systemic steroids, conventional chemotherapies, immunomodulatory drugs, proteasome inhibitors, anti-CD38 antibodies, and other targeted therapies. The role of T-cell–engaging bispecific antibodies in bridging therapy is unclear, and the effectiveness of BCMA-targeted treatment is controversial (Richter, 2024). Some studies reported inferior clinical outcomes with anti-BCMA CAR T-cell therapy in patients who had exposure to BCMA-directed T-cell engaging bispecific antibody therapies. Therefore, it was hypothesized that bispecific antibodies may result in exhaustion of T-cell compartment or loss of target antigens, which could negatively impact the efficacy of anti-BCMA CAR T-cells (Gagelmann et al., 2024; Ferreri et al., 2023). Another study reported bridging with bispecific antibodies (teclistamab [Tecvayli] and talquetamab [Talvey]) resulted in a higher response rate with improved reduction in myeloma disease burden, indicating bridging with bispecific antibodies before CAR T-cell therapy is safe and effective. But this study also reported a significant reduction in BCMA expression at leukapheresis and day 100 after CAR T-cell therapy in patients who had bridging therapy with BCMA-directed teclistamab (Fandrei et al., 2025). In patients with triple-class refractory disease, some centers use the GPRC5D-targeting bispecific talquetamab as bridging to BCMA-targeting CAR T-cell therapy (Richter, 2024). More studies are warranted to further investigate whether switching targets is a more effective strategy for bridging to CAR T-cell therapy. The current practice recommendation is to consider avoiding BCMA-targeted bispecific antibodies or antibody-drug conjugates prior to BCMA-directed CAR T-cell therapy (Hungria et al., 2023).

Regimens containing a high intensity of alkylator-based drugs, for example, VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide), modified hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), and DCEP (dexamethasone, cyclophosphamide, etoposide,

and cisplatin), may cause prolonged myelosuppression and a significant risk of infection and are not recommended for bridging therapy (Bhaskar et al., 2021). Intensive chemotherapy is not necessarily more effective for disease control when used as bridging therapy (Bhaskar et al., 2021). A study showed that the use of high-intensity cyclophosphamide as bridging therapy did not result in superior disease control nor improved PFS. A high-dose cyclophosphamide-based bridging regimen was associated with prolonged cytopenia and poor overall survival after CAR T-cell therapy for MM (Zafar et al., 2023).

Involved field radiation therapy has been safely used as an effective bridging regimen for MM patients with bulky plasmacytoma. A study reported bridging radiotherapy as safe and feasible for CAR T-cell therapy (Manjunath et al., 2021). A recent study reported a 100% local control rate of plasmacytoma bridged by radiation treatment prior to BCMA-targeted CAR T-cell therapy (Ababneh et al., 2023). Radiotherapy can directly result in apoptosis of myeloma cells and also sensitize and activate CAR T cells through immunogenic cell death (Zhang et al., 2023). In eligible patients, radiation can be considered as the choice of bridging approach to limit the adverse effects of systemic bridging therapy.

CLINICAL IMPLICATIONS

Referral to CAR T-Cell Center

Referral to the CAR T-cell center should be made as soon as the provider and patient have discussed and agreed upon this treatment or when patients want to learn more information about the procedure as a future option (Bristol-Myers Squibb, 2021). This is best done early in the patient's long-term treatment plan because of the 6 to 8 weeks needed to manufacture CAR T cells. The recent approvals of cilta-cel and ide-cel as first- or second-line therapy in MM means that patients and their care teams will need to make decisions soon after the patient's diagnosis as to whether and when to refer the patient for CAR T-cell therapy. Continuing patient education of the CAR T-cell process by providers is important from the beginning and should be an ongoing process.

Once the patient is formally referred to the CAR T-cell program, the CAR T-cell center coordinator will send the physician and patient a timeline of events and procedures. Various procedures and laboratory tests will be required with the results sent to the CAR T-cell program coordinator. The center will then determine if the patient meets eligibility requirements for CAR T-cell therapy (Bristol-Myers Squibb, 2021).

In addition to the FDA requirements for CAR T-cell products, each institution may have their own guidelines for patient eligibility (Table 1). Patients must also have a competent care partner who can be present with them throughout their treatment. The patient and care partner must be able to stay close to the CAR T-cell center for 4 weeks; financial assistance may be applied for if available. Some institutional guidelines may require patients to live within a 2-hour drive of their referring medical center, as late critical complications can occur (Bristol-Myers Squibb, 2021; Hoffmann et al., 2023).

Table 1. Guidelines for Patient Eligibility for CAR T-Cell Therapy

- Ciltacabtagene autoleucel is indicated for adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.
- Idecabtagene vicleucel is indicated for adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
- CrCl ≥ 45 mL/min
- LVEF > 45%
- ALT < 2.5 × ULN
- ANC > 1,000/μL
- Platelets > 50,000/μL
- Adequate organ function and an ECOG PS of 0 or 1

Note. ALT = alanine aminotransferase; ANC = absolute neutrophil count; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group performance status; LVEF = left ventricular ejection fraction; ULN = upper limit of normal. Information from Janssen (2023); Bristol-Myers (2021, 2023).

The patient's local oncology care team must have an understanding of the possible side effects of CAR T-cell therapy and their treatment (Bristol-Myers Squibb, 2021). Side effect management of adverse events such as cytokine release syndrome (CRS) or immune effector cell–associated neurotoxicity syndrome (ICANS) can be new to providers (Hoffmann et al., 2023). Communication between the local care team and the CAR T-cell center is imperative.

There is no upper age limit for acceptance at most CAR T-cell centers, but adequate organ function is required (Hoffmann et al., 2023). Evaluation of the patient for mental and psychiatric competence is important for compliance with this complicated regimen that requires diligent and prolonged monitoring. The patient's allergy history should be checked (the T-cell product may contain dimethyl sulfoxide), and any prior or current neurological conditions should be noted. Patients should be advised to refrain from driving or operating machinery for 8 weeks following the CAR T-cell infusion (Bristol-Myers Squibb, 2021).

Patient Education

Prior to collecting T cells, patient education should incorporate the pre-apheresis evaluation, which includes a review of echocardiogram and pulmonary function tests, recent imaging, lab work (to assess renal and liver functions, and myeloma disease-specific labs), as well as a review of current medications. Holding angiotensin-converting enzyme inhibitors during the harvest day to avoid a potential hypotensive event is recommended. Patients may have previously undergone peripheral stem cell harvest prior to autologous stem cell transplant, so there may be a familiarity with this process. It is important to note that there are no mobilization medications, such as granulocyte colony-stimulating factors or stem cell mobilization agents, given during this type of harvest. Assessment for central vs. peripheral collection is done to determine if a temporary apheresis catheter is required for this one-time collection.

Although rare, if manufacturing fails, a repeat harvest may be considered or conducted. Adequate ALC greater than 0.5 may predict that an adequate amount of T cells will be successfully collected for the manufacturing process. However, successful manufacturing has occurred in patients with less than 0.5 ALC.

After T cells are collected, it is important to educate patients about bridging therapy to control their disease while the T cells are shipped to a specialized facility where they are manufactured into CAR T cells. The bridging therapy may simply be continuing current therapy or require a complete change in therapy. Not only is bridging therapy considered essential for maintaining patients' performance status, but it also aims to keep tumor burden as low as possible, thereby helping minimize CAR T-cell side effects. There is a clear association of increased incidence and severity of CRS and ICANS when there is bulky disease at the time of infusion. Patients may receive their bridging therapy locally or at a REMS-certified CAR T-cell facility. This requires close coordination and communication with community providers and CAR T-cell centers (Anderson et al., 2024).

A main challenge in managing myeloma patients undergoing CAR T-cell therapy is the risk for disease progression during the waiting period for CAR T-cell manufacturing. When faced with potential delayed manufacturing process due to manufacturing availability or availability at the REMS-certified center, patients require additional bridging therapies, which may increase treatment adverse effects and complexity. Health-care providers need to educate patients on the benefits and risks of all treatment options and identify those who would benefit most from CAR T-cell therapy. Fortunately, there has been a significant increase in the availability of manufacturing slots. This has been immensely helpful in starting the process quickly and avoiding complications from relapsed/refractory disease and the development of infection. However, as CAR T-cell therapy moves forward in earlier lines of therapy, we may see increased wait times for harvesting slots and manufacturing delays. If this occurs, close communication and active therapy decisions by both community and CAR T-cell providers will be required during these critical phases of steady state harvesting and bridging during manufacturing phases. Active patient assessment is essential for timely identification of an emerging issue. This may prompt holding therapy to allow for recovery

of blood counts and prevention of, or treatment for, infection, and additional treatment such as radiation therapy or a change in therapy.

CONCLUSION

With the approval of two CAR T-cell products in MM and several more products under investigation, treatment options for patients have expanded. The goals of bridging therapy are to control disease progression, improve the effectiveness of CAR T-cell therapy, and reduce the risk of complications from CAR T-cell therapy. It may be beneficial for high-risk patients with rapidly progressing cancers. Bridging therapy can take many forms, including chemotherapy, immunotherapy, and radiation therapy. The decision to use bridging therapy requires careful consideration and weighing the potential benefits against the risk of reduced survival and increased toxicity. More research is needed to determine the optimal use of bridging therapy for patients receiving CAR T-cell therapy, especially in the evolving landscape of CAR T-cell utilization. ●

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