Investigator Commentary: What I Tell My Patients with Relapsed Non-Hodgkin Lymphoma Who Are Being Considered for CAR T-Cell Therapy

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What I say to a patient with multiple treatment-relapsed FL who is going to receive CAR T-cell therapy:

Dr Abramson

CAR T cells harness the power of your own immune system to fight the lymphoma. The treatment works extremely well for follicular lymphoma, including patients whose disease has relapsed despite multiple treatments. The vast majority of patients will go into a complete response, and responses last about 5 years on average, but far longer responses are possible, and some patients will never relapse after this treatment.

Dr Kamdar

My preferred CAR T construct for multiply relapsed FL is lisocabtagene maraleucel (liso-cel). Although axicabtagene ciloleucel and tisagenlecleucel have longer follow-up data, liso-cel offers an attractive balance of efficacy and tolerability. Early complete response (CR) rates approach 90%, and even patients whose disease has progressed within 2 yrs of last chemo, ie, POD24 disease, have an ~85% likelihood of achieving CR. Duration of response closely correlates with achieving a CR, suggesting potential for long-term remission. From a toxicity standpoint, CRS and ICANS rates are notably lower than with CD28-based constructs, while cytopenias are comparable across products. The therapy can be delivered outpatient at many centers. With 18-month and emerging 2-year data showing durable remissions, liso-cel is my go-to, especially given the encouraging results in early relapsers. When I counsel patients, I tell them that remission can be long-lasting — and possibly curative — but we remain humble in not calling it a “cure” until long-term data mature.

What I say to a patient with multiple treatment-relapsed FL who is going to receive CAR T-cell therapy:

Dr Nastoupil

I would recommend liso-cel for relapsed/refractory (R/R) FL, primarily because it is associated with a manageable safety profile, specifically favorable rates of grade 3 or higher CRS or neurotoxicity, and durable response. Safety is as important as efficacy in indolent lymphoma.

Dr Phillips

Preference would be liso-cel. Explain to the patient that treatment, while not curative, would provide substantial disease control w/ one-time infusion of the modified T cells. Would anticipate based on age of patient that the disease is likely to recur, but the hope is that w/ maturing data we might identify a subset of patients w/ FL that could potentially achieve a cure or a “functional” cure.

Dr Westin

Axi-cel. We will choose this treatment for you because more than half of patients are alive and did not require additional lymphoma therapy with more than 5 years of follow up — hopefully some of those patients are cured.

What I say to a patient with multiple treatment-relapsed FL who is going to receive CAR T-cell therapy:

Dr Lunning

You have evidence of refractory follicular lymphoma after 2nd-line therapy. We have no currently appropriate clinical trials. Based upon the behavior with second-line therapy with R^2 and no evidence of transformation let's consider CAR T-cell over a bispecific antibody. There are currently three FDA-approved CAR T-cell constructs. In the case of follicular lymphoma, despite longer data and follow-up with axi-cel, I do feel that the toxicity profile matters as follicular lymphoma is a marathon, not a sprint, even despite your disease behavior recently. In that case, I would consider liso-cel, which has excellent activity in obtaining a complete response. In other aggressive lymphomas, a complete response has been shown to lead to significant durability. The trial data also suggests that this carries a safe toxicity profile that balances the potential for efficacy. There are no head-to-head clinical trials to show which one is more efficacious and/or toxic. Unfortunately, we are unlikely ever to have this data in any lymphoma with a CD19-direct CAR-T.

What I say to a patient with multiple treatment-relapsed DLBCL who is going to receive CAR T-cell therapy:

Dr Abramson

CAR T-cells harness the power of your own immune system to fight the lymphoma, and have been proven to be effective even in patients where multiple types of chemotherapy have failed. The majority of patients in this situation will respond, and about half of patients will go into complete remission. Close to 40% of patients will be cured with this therapy, including the majority of patients who go into complete remission. “Less is more” with respect to the amount of lymphoma at the time of CAR T-cell therapy and likelihood of a long term remission, so given how much lymphoma we see on your PET CT now, our goal will be to decrease that with treatment called bridging therapy prior to giving you back your CAR T cells.

Dr Kamdar

I generally prefer liso-cel for relapsed/refractory DLBCL. The 5-year follow-up data across all constructs suggest a roughly 40% chance of long-term remission or cure, but liso-cel’s more favorable safety profile, esp with respect to low risk of high grade CRS and ICANS, makes it appealing, particularly in patients older or with multiple comorbidities.

For younger patients with bulky, fast-growing disease where manufacturing time may be critical, I sometimes favor axi-cel — albeit with a higher CRS/ICANS risk. Overall, I explain to patients that we now have curative potential for nearly 40% of these heavily pretreated cases, independent of tumor bulk or subtype, which is remarkable progress.

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What I say to a patient with multiple treatment-relapsed DLBCL who is going to receive CAR T-cell therapy:

Dr Nastoupil

For DLBCL patients, there are a few patient- and disease-specific characteristics that help inform which CAR T-cell product to recommend. I generally favor liso-cel for older or frailer patients given the favorable toxicity profile. For young, fit patients in need of cellular therapy quickly, I prefer axi-cel, in which the favorable manufacturing time and high rate of successful manufacturing may outweigh the higher rates of grade 3 CRS or neurotoxicity.

Dr Phillips

Preference would be based on age/fitness. For younger/fit patients would be axi-cel and for older patients choice would be liso-cel.

This would be administered w/ the intent to cure. Would explain that in the 2nd line space chance for cure is between 40% and 50%. Would image after 30 days and then 90 days. Most patients in remission at day 90 have a great chance of long-term cure. Disease factors will influence outcome given higher risk for complications in those w/ increased tumor bulk.

Dr Westin

Axi-cel. For your relapsed DLBCL, we have one chance to provide a curative intent therapy, and thus reliability of manufacturing is key. Axi-cel is extremely reliable and cures about 40% of patients with this otherwise fatal disease.

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What I say to a patient with multiple treatment-relapsed DLBCL who is going to receive CAR T-cell therapy:

Dr Lunning

You have had many different targeted therapies for your diffuse large B-cell lymphoma. We do not have any appropriate clinical trials currently. Despite these various approaches to cure your DLBCL, we have been unsuccessful. In this situation, after three or more lines of therapy, we still have curative intent options. Given that your disease has previously relapsed multiple times, I do believe CAR T-cell therapy remains a strong option. I do feel, regardless of the construct chosen, we can manufacture your CAR T cells in time with the intent to cure. In this situation, there are 3 CAR T-cell therapies available, but given the lack of efficacy in high-risk second-line CAR-T, I would defer Tisa-cel. These CAR-T therapies have never been compared head-to-head in a prospective manner. We now have long-term follow-up with these therapies to denote that obtaining an early complete response may lead to durability. In your case, I would prefer Liso-cel given its balance of efficacy and safety in your multiply relapsed DLBCL. It appears you would have a 93% chance of having an in-specification product, a 6% chance of having an out-of-specification product that would require an expanded access protocol, and a 1% chance of needing to re-manufacture. This CAR T cell would give you the option to be delivered as an outpatient with close monitoring by our team. I do believe it carries the least likelihood of having high-grade neurotoxicity compared to the other products.

What I say to a patient with multiple treatment-relapsed mantle cell lymphoma (MCL) who is going to receive CAR T-cell therapy:

Dr Abramson

CAR T cells harness the power of your own immune system to fight the lymphoma, and have been proven to be effective in patients where MCL has relapsed despite prior treatment with both chemotherapy and BTK inhibitors. The vast majority of patients in this situation will respond, and most patients will go into complete remission. Remissions last 1-2 years, on average, but some patients will stay in remission for much longer and may never relapse at all. “Less is more” with respect to the amount of lymphoma at the time of CAR T-cell therapy and likelihood of a long-term remission, so given how much lymphoma we see on your PET CT now, our goal will be to decrease that with a pill called pirtobrutinib prior to giving you back your CAR T cells.

Dr Kamdar

In mantle cell lymphoma, my preference depends on fitness and risk profile. For younger, fit patients, brexucabtagene autoleucel (brexu-cel) remains my preferred choice, with the longer follow-up data and about 40% of patients maintaining durable remissions.

For older or frail patients, I favor liso-cel due to its lower toxicity and outpatient feasibility, though follow-up remains shorter and no plateau has yet emerged. Neurotoxicity and CRS are more frequent and severe with brexu-cel.

What I say to a patient with multiple treatment-relapsed mantle cell lymphoma (MCL) who is going to receive CAR T-cell therapy:

Dr Nastoupil
I would prefer liso-cel for multiply relapsed MCL. I would favor brexu-cel for a young, fit patient with high-risk disease in first relapse.

Dr Phillips
Preference would be brexu-cel. Discuss w/ patient that treatment carries a high risk of complications including ICANS. Treatment is not curative and the disease will relapse. Long-term outcomes are directly related to risk factors as those w/ blastoid variant disease and p53 mutations have shorter remission durations. For those unable to receive brexu-cel then would use liso-cel with the understanding that outcomes will be inferior, especially for those for whom a BTK inhibitor has failed, but this agent has a preferable toxicity profile.

Dr Westin
Liso-cel. For your relapsed MCL, we want to balance concerns for effective treatment and risk of side effects. The other options are impressive but have a higher risk of severe side effects which could be dangerous, thus we will pick the treatment that protects you more from the risk of neurologic toxicity.

What I say to a patient with multiple treatment-relapsed mantle cell lymphoma (MCL) who is going to receive CAR T-cell therapy:

Dr Lunning

You have had had multiple relapses of your mantle cell lymphoma. You have had more than several years from BR exposure and recently have experienced disease progession while on a covalent BTK inhibitor. Given the refractory nature and symptomatic progression on the cBTK inhibitor, I would consider bridging with a non-covalent BTK inhibitor. At the same time, as we proceed towards CAR T-cell therapy, in situations where there has been progression on cBTK with cessation, I have experienced rapid progression when coming off all treatment. Furthermore, in this situation, I would expect the durability of a non-covalent BTK inhibitor to be relatively short. Therefore, I feel it's reasonable to use it as pre- and post-apheresis bridging therapy to avoid rapid progression with hope to decrease disease burden, which may help the CAR-T efficacy and mitigage risk of high-grade toxicities.

We have two CAR T-cell therapies that are available. In this situation, considering the activity of both in mantle cell lymphoma post-BTK exposure, I would prefer Liso-cel over Brexu-cel due to its safety profile, noting the differences in these single-arm trials. Neither of these CAR T cells has ever been compared head-to-head.

How do you explain the approved CAR T-cell products and the similarities and differences between them?

Dr Abramson

We have two CAR T-cell products to choose from in this situation, both of which target the same protein on the surface of the lymphoma cells and have overall identical efficacy. One of them is significantly less toxic than the other, so that is the one we typically prefer. That said, the less toxic CAR T cell takes about a week longer to manufacture than the more toxic CAR T cell, so I do prefer that if I think that one week will make a difference due to very symptomatic, rapidly growing disease. We can treat and reverse the toxicities in nearly all patients, regardless of which product we choose.

Dr Kamdar

I frame the discussion around costimulatory domains:

- CD28-based products (axi-cel, brexu-cel) expand rapidly and yield brisk tumor killing, but they carry a higher risk of CRS and ICANS and often require inpatient monitoring.
- 4-1BB-based products (liso-cel, tis-cel) expand more gradually, resulting in fewer severe immune toxicities and, in many cases, outpatient feasibility.

Beyond that, cytopenias, secondary malignancy risk, and infection risk are similar across constructs.

Manufacturing time is different across different products, with axi-cel having a manufacturing time of 17 days, liso-cel about 23-27 days and tis-cel closer to axi-cel.

How do you explain the approved CAR T-cell products and the similarities and differences between them?

Dr Nastoupil

Liso-cel is generally associated with lower rates of grade 3 or higher CRS and neurotoxicity with favorable efficacy in DLBCL, FL, and MCL. The safety profile allows for consideration of CAR T among older or frailer patients and those that are interested in outpatient management and shorter stay at a treating center. Most patients have recovery of cytopenias by day 90. The one limitation is the median manufacturing time is about 24 days and some attempts at manufacturing are unsuccessful, which can lead to longer median times from leukapheresis to start of lymphocyte-depleting chemotherapy. Axi-cel is approved for R/R DLBCL and FL and has a favorable manufacturing time and very high rates of successful manufacturing. It has favorable response rates but higher rates of grade 3 or higher CRS and neurotoxicity as well as prolonged cytopenias. Brexu-cel is approved for relapsed MCL with high response rates, though higher rates of grade 3 or higher neurotoxicity as well.

How do you explain the approved CAR T-cell products and the similarities and differences between them?

Dr Phillips

All CAR products are derived from the patient's own T cells. They are modified to better recognize and kill cancer cells.

Axi-cel/brexu-cel have a Ferrari engine, which means the cells expand and replicate faster in the body when they are re-infused, but the downside to this is that they also can cause more severe adverse events (AEs) that will occur sooner compared to the other two products. We generally can get these cells back sooner than the 4-1BB agents.

Liso-cel and tis-cel have a Corvette engine. Take longer to expand, have a later onset of AEs but overall have a better safety profile. There is some concern for efficacy especially w/ tis-cel but overall for most lymphomas, liso-cel is an appropriate alternative to axi-cel.

Dr Westin

Bottom line, the approved CAR T-cell products are very similar — we take your own T cells and turn them into lymphoma-fighting weapons. They are more effective to get into and stay in remission than other treatments available. The main differences are in the logistics and the side effects.

How do you explain the approved CAR T-cell products and the similarities and differences between them?

Dr Lunning

I often start with the fact that no head-to-head clinical trials are comparing CAR-T for third line plus as well as high-risk second-line population. I do pay a lot of attention on discussing mitigating the risk of high-grade toxicity, which I feel leads to long-term disability and length of stay issues. As we see more patients with advanced age and consideration of CAR-T, I do keep this in consideration as I do feel that the risk of this goes up with age even though it doesn't appear to impact efficacy.

How do you explain your approach to selecting a particular CAR T-cell product when you have a choice between multiple agents?

Dr Abramson

Selecting the best product for a given patient means considering multiple factors, including efficacy, safety, manufacturing time, and ability to administer in the outpatient setting. We use these considerations to personalize care for each patient.

Dr Kamdar

When I choose a CAR T product, I consider

- Disease subtype and efficacy data for that construct in that histology
- Tumor burden, patient symptoms, time it will take to manufacture one construct versus the other
- Patient profile: age, comorbidities, performance status, caregiver support
- Logistics: inpatient vs outpatient feasibility, manufacturing time, and caregiver support

The goal is to tailor the product to both disease biology and patient resilience.

Dr Nastoupil

There are patient- and disease-specific features, such as type of lymphoma, line of therapy, response to prior treatment and what the prior therapy was, comorbid conditions, disease burden and tempo. It also depends on how much social support a patient has as the CAR T products have slightly different rates of high-grade toxicity and timing of that toxicity. In my experience, liso-cel has a more favorable toxicity profile but axi-cel has a more rapid manufacturing time.

How do you explain your approach to selecting a particular CAR T-cell product when you have a choice between multiple agents?

Dr Phillips

Liso-cel is an appropriate alternative to axi-cel for DLBCL given that the outcomes appear similar despite the different kinetics. For a patient w/ high burden or aggressive disease the choice might be axi-cel if the patient is deemed fit enough to tolerate AEs, given the faster delivery and slight efficacy difference vs the 4-1BB agents.

For FL, the preference is liso-cel due to the improved toxicity compared to axi-cel and the fact that currently CAR T is not curative.

For MCL the preference is begrudgingly brexu-cel due to the poor response data noted w/ liso-cel in BTK inhibitor-refractory patients despite the overwhelming better toxicity profile w/ liso-cel in this patient population. As such, given the limited options post-CAR in MCL, would proceed w/ the more effective but clearly more toxic product.

Dr Westin

I weigh the pros and cons of each product:

- If the disease is progressing quickly, I choose speed and reliability of manufacturing.
- If the patient is frail, I choose safety of the toxicity of profile.

How do you explain your approach to selecting a particular CAR T-cell product when you have a choice between multiple agents?

Dr Lunning

I look at it backwards: high-grade ICANS and then work my way backwards, next being high-grade CRS — we've gotten so much better at managing CRS that it is quite rare. I then focus on discussing if we see CRS we act quickly to avoid ICANS, and if it occurs then we do everything to mitigate high-grade ICANS. This limits high cumulative doses of steroids, which I believe limits early infection risk. In the end, I believe liso-cel checks the box of balance with efficacy vs safety.

How do you explain the spectrum of potential CRS symptoms, the likelihood a patient will experience any of them and your approach to prevention and management?

Dr Abramson

CRS occurs in about half of patients who receive liso-cel and is usually mild and virtually always reversible. The most common symptom is fever, but it can uncommonly get worse and cause low blood pressure, low oxygen levels, or organ injury. We typically intervene and give an antidote called tocilizumab with or without steroids, which rapidly improves the CRS and usually prevents it from becoming severe.

Dr Kamdar

I describe CRS as the “immune storm” that tells us the CARs are expanding — fever, chills, low blood pressure, shortness of breath — ranging from mild to severe. Severity often correlates with tumor burden, LDH, CRP and extranodal disease at baseline. This is a unique side effect of CAR function and seen in all three products; however, severity might be higher with CD28-based products.

Prevention strategies include early recognition, supportive care and programmatic guidelines. Majority of academic centers follow the ASTCT Guidelines to manage CRS. These usually consist of steroids and an anti-inflammatory agent called tocilizumab. Sometimes in patients with MCL with high tumor burden with peripheral blood involvement we may give, preemptive steroids to prevent high-grade CRS. I reassure patients that the vast majority of cases are manageable and reversible, and that close monitoring (especially during the first two weeks) is crucial.

How do you explain the spectrum of potential CRS symptoms, the likelihood a patient will experience any of them and your approach to prevention and management?

Dr Nastoupil

The spectrum of CRS is dependent on the product regarding the likelihood of experiencing it at all and how serious it might be. Nearly all patients will have fever. Some will have fever and hypoxia or hypotension that is manageable with supportive measures. Very few will have serious or life-threatening CRS that requires ICU care including pressors and possibly mechanical ventilation or hemodialysis. Patients are monitored closely for CRS within the first 2 weeks post cell infusion. Some centers will administer prophylactic medications such as tocilizumab and/or corticosteroids. Some will monitor closely and intervene with tocilizumab and/or corticosteroids with persisting grade 1 CRS or grade 2 or higher CRS. Patients are also monitored closely for signs of infection given they are also immune compromised, and often started on antibiotics while data is being collected, if appropriate. Generally, the course of CRS is relatively short.

Dr Phillips

Explain that CRS is the most common AE associated w/ CAR T. Discuss that in general it is manifested by fever but this is generally preceded by tachycardia. Discuss that at onset of fever we will start steroids. We will then add another medication (toci) if the fever persists. Explain that if the CRS continues to progress then risk for shortness of breath (SOB) and hypotension — these complications are less common. I would use supplemental oxygen for the SOB and intravenous fluids for hypotension. If any escalation of symptoms noted, then possible need for ICU care and higher rates of oxygen and medication to support blood pressure. If no resolution w/ steroids/toci, then would add anakinra. For prevention of CRS, especially for those getting axi-cel or brexu-cel, would consider use of prophylactic steroids for the first few days of infusion.

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How do you explain the spectrum of potential CRS symptoms, the likelihood a patient will experience any of them and your approach to prevention and management?

Dr Westin

I describe CRS as similar to having an infection like the flu — sometimes you can have fever and body aches and that's it, other times that can be the start that turns into low blood pressure and a trip to the ICU, or very rarely into a risk for death. Depending on the CAR T-cell used, the rate of fever can range from half to ninety percent, but more serious side effects are much less common. We will try to prevent side effects by either using prophylactic treatment or early intervention to stop mild problems from becoming more severe. If CRS occurs, management is usually successful quickly with either steroids or immune-directed therapies, but rarely may require a longer course of treatment.

Dr Lunning

Similar to above, I focus on high-grade ICANS and then work my way backwards. I discuss what ICANS looks like to the family/caregivers. The patient doesn't remember ICANS but the family certainly does. High-grade CRS I would argue is less common now than high-grade ICANS. I focus on discussing if we see CRS, especially if early post-infusion, we act quickly as I believe this is the biggest predictor of odds of having ICANS. If we used a CD28 costim product, we used prophylactic dex on D+ 0, 1, and 2.

How do you explain the spectrum of potential ICANS symptoms, the likelihood they will experience any of them and your approach to prevention and management?

Dr Abramson

Neurologic symptoms occur in only 10%-20% of patients who receive liso-cel, and are usually mild and reversible. The most common symptoms are confusion, sleepiness, or word-finding difficulties. Uncommonly the neurologic symptoms can become severe, even causing a comatose state or seizures, but that is rare. If the neurologic symptoms are anything more than very mild, we give steroids, which usually lead to gradual resolution of the side effects. Additional medications are available if the steroids alone are not doing what we need them to do.

Dr Kamdar

ICANS often follows or overlaps with CRS. I tell patients to expect possible word-finding difficulty, handwriting changes, confusion, or somnolence, most commonly within 8-14 days post infusion. ICANS also correlates with the same factors as CRS; however, the risk of high-grade ICANS where patient is obtunded or having seizures is low, albeit slightly higher with high tumor-burden disease who receive CD28-based constructs. Management mirrors the ASTCT Guidelines for ICANS management and involves steroids, with a low threshold for anti-inflammatory agents such as anakinra or ruxolitinib in refractory cases. Early recognition is key, and we maintain daily neurologic checks during the acute phase.

How do you explain the spectrum of potential ICANS symptoms, the likelihood they will experience any of them and your approach to prevention and management?

Dr Nastoupil

ICANS is more variable and unpredictable. The likelihood of experiencing ICANS depends on the CAR-T construct as well as patient and disease characteristics. It generally will occur after a patient has experienced CRS. It can be rapid in onset and resolution. Generally, we first observe alterations in fine motor skills that are apparent with constructing and writing a sentence. This can be followed by word finding and disorientation. Patients are asked to perform a series of tests, and the rate of successful completion can inform the grade of neurotoxicity. Some centers will administer prophylactic corticosteroids to reduce the rates of neurotoxicity, particularly with axi-cel. Corticosteroids are generally the first approach to management of neurotoxicity. With serious or life-threatening neurotoxicity, patients are often monitored in an ICU setting, initiated on prophylactic anti-seizure medications, and cared for by a multidisciplinary team. The duration of neurotoxicity can be unpredictable and can sometimes take an extended period of time to return to baseline.

Dr Phillips

ICANS is less likely compared to CRS. Explain that this manifests in alteration of mental status. Could be mild confusion to comatose state. Explain that the initial management is w/ steroids, for which dose and frequency are dependent on severity and duration of symptoms. Risk is related to CAR-T product being highest w/ brexu-cel, then axi-cel, then the 4-1BB products. Discuss that for most patients this is reversible but there are unfortunately severe cases that can be permanent damage and or be fatal, especially those that lead to increased intracranial pressure.

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How do you explain the spectrum of potential ICANS symptoms, the likelihood they will experience any of them and your approach to prevention and management?

Dr Westin

I describe ICANS as an unusual side effect of CAR T-cell therapy where brain dysfunction, which is nearly always reversible, can happen during the first few weeks after treatment. It is rare, with most patients not suffering from ICANS, but if it happens, it could be severe with occasional ICU stays required. There are no effective preventative strategies yet, but treatments are directed at preventing ICANS from worsening and usually include high-dose steroids and less commonly more aggressive immune directed treatments.

Dr Lunning

I again start with what high-grade ICANS looks like, especially with family/caregiver. I state that people have died due to complications of CAR-T and namely that is a consequence of managing ICANS and the organ dysfunction that comes when high-grade CRS meets high-grade ICANS. Many times the odds increase for ICANS based on advanced age, and we are frequently doing CAR-T in 80-year-olds. My practice is full of them now. If ICANS does occur I've already readied them for a longer inpatient stay and that they may need acute rehab. We do steroids prophylaxis with a CD28 costim and are very aggressive with CRS management if CRS onset in first 72 post-infusion post a 41BB construct.

How do you explain bridging therapy to CAR T-cell treatment and when it is used?

Dr Abramson

Bridging therapy is treatment used to control the disease and symptoms while the CAR T-cells are being manufactured. If there is only a small amount of disease without symptoms, then we don't need to use bridging therapy. If we do choose to use bridging therapy, we have both systemic options and radiation therapy, and we personalize the choice to a given patient's clinical situation.

Dr Kamdar

Bridging therapy is anything we do to stabilize disease while CAR T cells are being manufactured. The goal is not necessarily a CR but to keep the disease under control. Options include steroids, radiation, chemotherapy, ADCs (eg, polatuzumab), and occasionally bispecific antibodies.
I explain to patients that this "holding pattern" helps prevent disease flare and ensures they remain well enough to receive their cells.

Dr Nastoupil

Patients are likely to have better outcomes both regarding safety and efficacy if they proceed with CAR T with disease regressing as opposed to progressing. Manufacturing of CAR T cells can also be highly variable and with aggressive lymphomas, it is important to stabilize the disease and the patient while awaiting the successful manufacturing. Bridging therapy is treatment aimed at reducing the lymphoma while awaiting the cells to be manufactured.

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How do you explain bridging therapy to CAR T-cell treatment and when it is used?

Dr Phillips

Bridging therapy is needed to slow the progression of cancer long enough to allow for collection, manufacturing and return of the CAR product. This is not needed in all patients but especially helpful for those w/ rapidly progressive disease, w/ pain or end organ damage from the lymphoma. In cases where radiation therapy is used, it can potentially augment the response of the CAR product.

Dr Westin

Bridging therapy gets us from here to there, from the decision to give CAR T cell to the day of infusion of CAR T cell. It is not always required, especially if the amount of lymphoma is low and speed of disease growth is slow. When it is required, the goal is to stay on track to get to the destination, and thus CAR T cells should be delivered as quickly as possible by minimizing risk of side effects or lymphoma-related harm. Radiation therapy, chemotherapy, targeted therapy, and steroids are options, but I recommend avoiding bispecific antibodies as the ramp up time is not consistent with the goals of bridging therapy.

Dr Lunning

I break it down to the journey of CAR-T. I use apheresis as a split in bridging as I may do something different before apheresis (pre-aph) and after apheresis (post-aph). I spend time talking about in the pre-aph what not to use (benda) and focus on disease stabilization without making them too sick for CAR-T. In the post-aph period we use what we've learned in the pre-aph period and we may switch to XRT (BOOM-BOOM) or even higher dose if a pending problem site. I believe disease burden is the biggest barrier to mCR and durability post-CAR-T, so in 2025 I am rarely forgoing some form of pre- and post-aph bridging therapy.

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How do you explain the key time points in the CAR T-cell therapy process and what patients can expect to experience?

Dr Abramson

CAR T cells are a multi-step process, but the actual treatment is given as a single infusion, not multiple cycles like prior therapies you've received. We start with apheresis where we collect the cells from your blood and send them off to be manufactured into CAR T cells. While the cells are being manufactured we have the option of giving a treatment to control the lymphoma if needed, which we call bridging therapy. Once the cells are ready, we give 3 days of chemotherapy with the goal of suppressing your immune system just enough to prevent your immune system from rejecting the CAR T cells, because even though they are your own cells, they are slightly modified with that new little receptor on their surface. We call that lymphodepleting chemotherapy. After those 3 days, we will admit you to the hospital to infuse the CAR T cells and then monitor for and treat any of the side effects we talked about. Most patients are admitted for 1-2 weeks, but it can be longer depending on whether we see the side effects, and how quickly they recover. Once you leave the hospital we will keep a close eye on your blood counts as they recover, and we will be vigilant about the risk of infections. We will get a PET CT a month after the CAR T-cell infusion to get an early look on how well it is working.

How do you explain the key time points in the CAR T-cell therapy process and what patients can expect to experience?

Dr Kamdar

I map out the process clearly:

1. Initial consult and eligibility review
2. Apheresis (cell collection)
3. Bridging therapy (if needed)
4. Manufacturing period (usually 3-5 weeks)
5. Lymphodepleting chemotherapy
6. Cell infusion (Day 0)
7. Monitoring phase (Days 0-14) for CRS/ICANS
8. Response assessment at Day 30 or 90, depending on institutional programmatic approach
9. Follow-up phase: infection prophylaxis, labs, and clinic visits for at least 6 months

I reassure them that if the first two weeks go smoothly, they can often transition home or to local lodging, continuing close follow-up.

How do you explain the key time points in the CAR T-cell therapy process and what patients can expect to experience?

Dr Nastoupil

First, patients will need to be considered for CAR T, and there are specific indications across B-cell lymphomas. Second, they will need to be referred to a treating center or treating team to be considered for CAR T. Once they are determined to be a candidate, they will be arranged for leukapheresis. Once this is completed, generally, bridging will be arranged either at the originating center or at the CAR T center. Once the manufacturing has been confirmed to be successful, patients will be contacted to arrange for return to the treating center to undergo lymphodepletion (LD) chemo and CAR T infusion. They will then be monitored at the treating center until they are deemed safe to return home. Generally, they will be monitored closely for the first 90 days for low blood counts, risk of infection, and disease monitoring.

Dr Phillips

Explain that the first step is insurance approval. This can vary from patient to patient. Next step after approval is obtaining an apheresis slot, for which thereafter we will collect cells. If the patient requires bridging, we will need to work out timing to ensure enough time of therapy for collection. Explain to patients that collection is similar to dialysis save for the collection of a particular immune cell, thereafter there is a time delay for manufacturing then QC, after which the cells are returned. Once we have a date for return we will start LD, and during this time we explain that this is to help w/ the survival of the CAR product. Will possibly notice fever, nausea/vomiting, lethargy and bowel issues w/ the LD. The LD will be continued for approximately 5 days. Two days of rest then reinfusion of the CAR product. After receiving the patient will be monitored for AEs. If outpatient the patient will need a 24-hr caregiver, if inpatient then pending product will plan for hospitalization for up to 14 days before transition to hotel and outpatient clinic. Will thereafter be monitored close until day 30 scan.

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How do you explain the key time points in the CAR T-cell therapy process and what patients can expect to experience?

Dr Westin

The key time points are the decision, the approval, the collection, the manufacturing, the delivery, and the follow-up. Patients should expect to be engaged with their care team in the decision if CAR T cell is right for them, and may be involved in the financial approval if the business team needs additional information to share with the payor. For the collection, patients should expect to have an IV placed and to wish their T cells 'good luck' on their way to 'boot camp,' and to tell them to hurry home soon. For the delivery, patients should expect to receive light chemotherapy for 3 days, then infusion of the CAR T cells either as an outpatient or inpatient with close monitoring for 2 or more weeks. We are not rooting for the patient to have a fever, but if they occur it can be one of the signs that the CAR T cells are active. They can expect that their care team will take great care to manage side effects like CRS or ICANS, which if significant could include potential long hospital stays or rehabilitation. For the follow-up, patients can expect to have testing like PET CT scans and blood work, with their CAR T-cell team and with their local oncologist, and to work on recovering from any leftover side effects.

Dr Lunning

Brain to Vein encapsulates, desire to do it and actually getting to go to aphersis. The challenge here is insurance approval, tests necessary, and getting a chair for apheresis. Once aphed then we are in the Vein to Vein time, which has been pretty stable for the products and we very reliably now infuse products to near 100% either in speciation or OOS on a trial. Then the Vein to Gain time. We do a PET/CT at D+29 as we now have early post-CAR-T trials with BsAb. We do a PET/CT at D+100 and then based on image results we may do a 6-month PET/CT.

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What are some of the financial issues associated with CAR T-cell therapy, including insurance coverage, that you discuss with the patient?

Dr Abramson

Insurance covers the CAR T cells and all associated care. There may be costs associated with needing to stay within an hour of our center for 2-4 weeks after receiving the CAR T cells, but there are support and reimbursement programs available to help with that and our social worker will guide you through those resources.

Dr Kamdar

We discuss insurance coverage, which generally includes both product and hospitalization, though out-of-pocket costs can vary. I emphasize the importance of caregiver support, possible work or income disruption, and the option of FMLA for caregivers.

Our financial counselors and social workers assist in navigating approvals, transportation, and lodging support.

Dr Nastoupil

Most patients will need to be referred to a treating center. This will result in financial burden on the patient and the caregiver given the need to travel and secure housing. Insurance coverage may also impact what centers are available to them and this can result in large distances needed to travel. Patients will likely have several visits to the treating center, the first eval to determine whether they are a candidate, second visit for leukapheresis, third visit for LD chemo and cell infusion. Sometimes even more visits are needed, and each visit will likely be several days to weeks. The post cell infusion period can also be unpredictable as patients and caregivers will need to remain at the treating center until toxicity is resolved, or they are no longer perceived to be at risk. During this entire process, patients are generally not able to work, and this too can be a financial stressor.

What are some of the financial issues associated with CAR T-cell therapy, including insurance coverage, that you discuss with the patient?

Dr Phillips

Insurance coverage is one, but the other issue is work. Sometimes the patient is unwilling or unable to not work for the required time. Also, there is need for a caregiver. This would require another person to be off work for an extended period, which for some is not financially feasible. If the patient is w/o a caregiver, then they would need to be able to pay for one. This is sometimes covered by insurance, but when it is not then it renders CAR inaccessible for those patients.

Dr Westin

As anything complicated, CAR T cells can have surprising or unexpected issues arise. These can include financial challenges, like needing to be away from home for monitoring and needing to have a caregiver(s) to take off work. The unpredictable nature of what side effects may occur can create anxiety regarding what follow-up will be needed — not being able to return to work if neurologic side effects are slower to recover or if rehab is needed can be an issue for some patients.

Dr Lunning

I think the biggest issue is knowing when you can go fast — in my experience that is Medicare with a supplement. Medicare with managed plan of private insurance requires single-case agreement, which delays apheresis. I know what insurance they have before I walk into the consult room as that may impact my Brain to Vein decision. Rarely after that is it an issue.

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How do you explain the potential long-term issues associated with CAR T-cell therapy, including risk of infection, the need for preemptive anti-infection prophylaxis and vaccines?

Dr Abramson

After the acute CAR T-cell period we still monitor for late side effects, such as ongoing risk for infections from suppression of the immune system. We will keep you on prophylactic antibiotics until we see that your healthy lymphocytes have recovered enough to stop them. We will also monitor antibody levels, and if you have severe or frequent infections with very low antibody levels, we can put you on antibody replacement therapy called IVIG. We will also talk about certain vaccines we will recommend helping prevent infections, particularly respiratory viral infections.

Dr Kamdar

Concern is immunosuppression and infection risk due to prolonged B-cell aplasia and hypogammaglobulinemia. I keep patients on antiviral and PJP prophylaxis for at least 6 months and often longer if cytopenias persist.

Vaccination is deferred until at least 6-12 months post-CAR T, when immune recovery allows. Prophylactic IVIG replacement for an IGG level of under 400 is used. Rare late events include secondary malignancies and protracted cytopenias, so we monitor blood counts long term.

I frame it as: the therapy can be transformative, even curative — but it comes with a lifelong membership in the “post-CAR T immune-monitoring club.”

How do you explain the potential long-term issues associated with CAR T-cell therapy, including risk of infection, the need for preemptive anti-infection prophylaxis and vaccines?

Dr Nastoupil

We generally describe the late toxicity associated with CAR T as prolonged cytopenias that do not resolve within the first 90 days, B-cell depletion that can increase the risk of infection, particularly viral infections, and some will have prolonged time to recovery from neurologic toxicity that can lead to significant deconditioning. Many patients will be monitored closely for cytopenias and supported with growth factor support, transfusions, and/or prophylactic antimicrobials such as HSV/VZV antiviral and PJP antibacterial prophylaxis. Vaccine strategies are also discussed. Monitoring IgG levels and IVIG replacement is also a consideration to reduce the risk of infection.

Dr Phillips

Major long-term issues are failure of count recovery, typically prolonged neutropenia as well as infectious complications. Explain that this is due to the LD, direct killing (B-cell aplasia), prior treatments and inflammatory milieu induced by the CAR product. We would continue anti-infection prophylaxis until count recovery (antifungal until no longer neutropenic), generally will continue PJP prophy for 60-90 days and acyclovir pending recovery of immunoglobulins. Will consider IVIG for hypogammaglobulinemia as well, with goal based on prior infections or to maintain IgG >450 g/dL. We have not formalized an internal plan as yet for repeat vaccinations for our patients.

How do you explain the potential long-term issues associated with CAR T-cell therapy, including risk of infection, the need for preemptive anti-infection prophylaxis and vaccines?

Dr Westin

I describe to patients that not dying from lymphoma is the primary goal, but if CAR T cells help us achieve that it can come with new risks related to how CAR T cells work, including weakening the normal immune cells. CAR T cells kill B cells, both good and bad ones, and not having good B cells for months afterwards can open you up to unusual infections. To prevent that, we will give you preventative treatments like antibiotics and antivirals, and may recommend you repeat vaccines. You may need to receive replacement antibodies via an infusion until your body starts to make its own again.

Dr Lunning

I have started to do more BM in heavily treated patients with cytopenias to look for MDS, CHIP and CCUS. This can impact downstream risk for infection and need for transfusion, and if MDS then less likely to do CAR-T. I do use infection x 1 then IVIG, I don't do IVIG post-CAR-T without infection unless they are on it going into CAR-T. Secondary malignancies are real, but it is way more myeloid than T-cell concerns. We use prophylaxis until 1 year and a CD4 count >200 for HSV and PJP. GCSF for ANC >500 after D+14. Mold coverage if multiple doses of toci or prolonged steroids. Levetiracetam for 7 days after completion of steroids for those who experience ICANS.