Sequencing Therapies in Non-Hodgkin Lymphomas

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Oncology advanced practitioners treating relapsed or refractory (R/R) B-cell non-Hodgkin lymphomas (NHLs) are practicing in a rapidly evolving landscape with options expanding to include BTK inhibitors, bispecific antibodies, and CAR T-cell therapies. At JADPRO Live 2025, speakers discussed sequencing and how mechanistic, safety, financial, logistical, and quality-of-life factors shape decision-making.

As the treatment landscape expands, oncology advanced practitioners are increasingly faced with the challenge of selecting and sequencing therapies for relapsed/refractory B-cell non-Hodgkin lymphomas. At JADPRO Live 2025, attendees were guided through considerations for integrating Bruton tyrosine kinase (BTK) inhibitors, bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapies into care by **F. Brianne Buchanan, PA-C,** a CAR T-cell therapy PA, and **Tatjana Grgic, PharmD, BCOP, CPP,** a Clinical Pharmacist Practitioner, both from the University of North Carolina at Chapel Hill.

BTK INHIBITORS

BTK inhibitors are a cornerstone of treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL; Table 1). BTK inhibitors inhibit BTK, an enzyme in the B-cell receptor (BCR) signaling pathway, thereby stopping abnormal B-cell growth, proliferation, and survival.

Ibrutinib (Imbruvica), acalabrutinib (Calquence), and zanubrutinib (Brukinsa) bind irreversibly to BTK by forming a covalent bond with the C481 residue in the ATP-binding pocket, whereas pirtobrutinib (Jaypirca) binds reversibly (noncovalently) and remains active against BTK with C481 mutations.

"These are oral medications given either daily or twice a day," said Ms. Buchanan. "They are given continuously until progressive disease."

These therapies also require proactive counseling and monitoring. "They should be held 3 to 7 days before and after procedures," advised Ms. Buchanan. "There is also cardiac toxicity, so you can have patients develop A-fib or a flutter, especially with earlier-generation BTK inhibitors."

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There are also drug-drug interactions to be on the lookout for, specifically with CYP3A inhibitors.

BISPECIFIC ANTIBODIES

Bispecific antibodies have two binding arms: one that binds to CD3 on the T cell and another that binds to CD20 on a B cell, which allows the T cell to engage and lead to cell death. There are three FDA-approved bispecific antibodies used in R/R NHL. Mosunetuzumab (Lunsumio) is indicated for follicular lymphoma after at least two lines of therapy, given as an IV infusion with a fixed duration (8 cycles if complete response; up to 17 if partial response or stable disease). Glofitamab (Columvi) is approved for DLBCL after two lines, given as an IV infusion for a fixed duration of up to 12 cycles. Epcoritamab (Epkinly) is approved for DLBCL after two or more lines and given subcutaneously with step-up dosing until progression or toxicity.

Bispecific antibodies are administered in clinic and often require careful monitoring.

"We use dexamethasone prophylaxis before each of the doses, which helps us to mitigate severe toxicity," noted Ms. Buchanan.

Infection risk is high in T-cell engaging therapies, so prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and varicella zoster virus (VZV) and monitoring for Epstein–Barr virus (EBV) and cytomegalovirus (CMV) reactivation are advised.

CRS and ICANS

The typical onset of cytokine release syndrome (CRS) is 2 to 7 days after CAR T-cell infusion but could be earlier with bispecific antibodies. The first symptom is typically fever. Hypotension and hypoxia are serious potential adverse events.

Immune effector cell-associated neurotoxicity syndrome (ICANS) often develops shortly after CRS. On the other hand, if patients don't experience CRS, there is a lower likelihood of ICANS.

ICANS is also less likely to develop with bispecifics than with CAR T-cell therapy. It typically manifests as encephalopathy and confusion in the patient. The Immune Effector Cell Encephalopathy (ICE) score evaluates orientation, attention, writing, and language to assess for changes in cognition. Severe events such as seizures and cerebral edema are rare but serious.

CAR T-CELL THERAPY

CAR T cells are genetically engineered autologous T cells with a CAR attachment that targets the CD19 antigen on lymphoma cells, engaging with cancer cells and causing cell death. The process entails collecting patients' T cells collected through leukapheresis, 3 to 4 weeks of manufacturing of the T cells, and bridging therapy to decrease disease burden. Treatment also requires lymphodepleting chemotherapy before the CAR T cells are infused, and then 2 weeks of monitoring for toxicities, particularly CRS and ICANS.

The approved agents are lisocabtagene maraleucel (liso-cel; Breyanzi), axicabtagene ciloleucel (axi-cel; Yescarta), brexucabtagene autoleucel (brexu-cel; Tecartus), and tisagenlecleucel (tisa-cel; Kymriah). There has been a shift into earlier-line therapy for diffuse large B-cell lymphoma (DLBCL): "Both liso-cel and axi-cel are approved in the second-line setting for primary refractory disease to first-line therapy or what is considered early relapse, which is defined as less than 12 months from first-line therapy to relapse in DLBCL," said Ms. Buchanan.

There are logistical requirements that patients and their care teams must discuss, such as the fact that driving is not allowed for 2 weeks after cell infusion and needing to remain near the center. Caregiver support is also mandatory. Longer-term monitoring includes cytopenias, infection prophylaxis, revaccination, and of course, disease monitoring.

CRS and ICANS

"Tocilizumab is the mainstay for CRS and dexamethasone for ICANS neurologic toxicity," stated Ms. Buchanan.

Levetiracetam is used for seizure prophylaxis.

Ms. Buchanan cautioned against using steroids: "Steroids may impair CAR T-cell function. Therefore, we're careful about using steroid therapy at certain points during treatment."

She contrasts this with bispecifics: "With bispecific antibodies...using steroids is much safer and it's used earlier and more aggressively."

"We can also use growth factor after the resolution of CRS. If we have prolonged cytopenias, we can do a stem cell boost," said Ms. Buchanan.

Ms. Buchanan also highlighted the importance of monitoring for hypogammaglobulinemia.

SEQUENCING THERAPIES

Sequencing choices depend on the aggressiveness of the disease, antigen expression, access, and patient constraints.

"The disease biology will impact things," said Ms. Buchanan. "If you have an aggressive disease, you may not be able to wait for manufacturing."

Feasibility for patients matters too: "The patient's age, performance status, and if they can remain in the local area: These are all factors," said Ms. Buchanan.

BTK inhibitors are the first option in the frontline and relapsed/refractory settings for both CLL and MCL. CAR T-cell therapy after bispecific antibodies, particularly in CLL, can still be effective. Bispecific antibodies prior to CAR T-cell therapy do not appear to impair the effectiveness of CAR T-cell therapy as long as the targets are different. However, early relapse after CAR T-cell therapy, which is defined as less than 3 months, is associated with poor outcomes with bispecific antibodies.

In addition, there is the tradeoff of bispecific antibodies being off the shelf, having easier logistics, but multiple infusions, while CAR T-cell therapy has a lengthy manufacturing time, requires only one infusion, but has considerable logistics.

Table 1. Therapies for Non-Hodgkin Lymphomas

BTK inhibitors	Bispecific antibodies	CAR T-cell therapies
MCL	DLBCL	DLBCL
CLL	FL	FL
	CLL	MCL
		CLL

Note. MCL = mantle cell lymphoma; DLBCL = diffuse large B-cell lymphoma; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma.

MECHANISTIC, SAFETY, LOGISTIC, AND QUALITY-OF-LIFE DRIVERS

Dr. Grgic discussed factors in treatment decision-making. "The first factor is mechanistic factors, and this is probably the most important one...that is to make sure that the target is still present on cells." Because antigen loss can occur over time, she stressed that "at the time of relapse, it's important to get a tissue biopsy and document that we still have the antigen expression to optimize the efficacy."

Safety considerations are shaped not only by therapy toxicities but also by comorbidities and access to specialists for monitoring. There is also a need for ongoing education to recognize delayed symptoms of CRS or ICANS after patients return home.

For example, cytopenias after CAR T-cell therapy tend to occur in two phases, with an early phase after lymphodepleting chemotherapy and a later "second dip" attributed to CAR T-cell therapy, often occurring "closer to 3 or 4 weeks." This requires access to growth factors and antibiotics, and clarifying transfusion thresholds. Some patients may require IVIG support during early months of immune recovery, followed by immunization planning once reconstitution occurs.

BTK inhibitors require baseline assessment and monitoring for cardiac toxicity, particularly with first-generation agents like ibrutinib. It is also important to have anticoagulation management strategies for patients at risk of thrombosis. There is also infection prophylaxis, such as vaccines to prevent therapy delays during respiratory virus season.

Logistics is another factor in decision-making, as delivery of cellular and T-cell–engaging therapies requires coordination across multiple systems: "It takes a village to bring those patients in and get them through therapy," commented Dr. Grgic.

Early referral is increasingly important to help prevent delays from insurance, testing, and bridging therapy, especially as CAR T-cell therapy moves into earlier treatment lines. Access disparities are pronounced for patients from rural areas, with therapy requiring travel and at least 2 weeks of extended stay with a caregiver who can commit to that time. There are also constraints at tertiary centers, including bed availability, staffing limitations, insurance network barriers, and limited manufacturing or apheresis capacity.

"The part that's likely the most important to our patients is their quality of life," Dr. Grgic stated. "People will define that differently depending on what they would like to focus on."

Some patients value stability over durability and opt for BTK inhibitors to keep the disease at bay with potentially less severe adverse events. Others prioritize their best chance at survival and

are willing to accept a higher risk of toxicities; thus, the "one-time shot" of CAR T-cell therapy is a more attractive option. Maintaining quality of life includes mitigating financial toxicities, with high monthly BTK inhibitor costs and the extremely high upfront cost of CAR T-cell therapy.

For all patients, early integration of palliative care has been shown to improve quality of life, as well as reduce physical and psychological symptom burden (Agarwal & Epstein, 2017).

"Palliative care helps with symptom management, providing patients with a better understanding of their prognosis, and establishing goals of care, especially as we move along every transition of treatment," concluded Dr. Grgic. ●

Disclosure

The presenters have no relevant financial relationships to disclose.

References

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