Early CAR-T Intervention in DLBCL: Clinical Advances and Real-World Effectiveness of Axi-cel

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Autologous anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) is now a standard-of-care for relapsed and/or refractory (R/R) large B-cell lymphoma (LBCL), but optimal patient selection, sequencing with other novel agents and bridging strategies are areas for improvement. Tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) have been publicly funded in Australia since January 2020 and August 2021, respectively.

In this lecture, I will first review the outcomes from pivotal trials that lead to the approval of CAR T-cell therapy in second- and third-line R/R LBCL. I will then review evidence for management of CAR T-associated toxicities (cytokine release syndrome, CRS) and immune effector cell-associated neurotoxicity syndrome, ICANS) with axi-cel from the safety cohorts of ZUMA-1. Next, I will review real-world evidence for the use of commercial CAR T-cell therapies. I will particularly focus on the Australian experience, as presented at ASH2025. The Australian data is characterised by a high use of bridging therapy to control disease prior to infusion, which we believe has led to outcomes that are comparable or superior to the pivotal trials for both toxicity and durable disease control.

We evaluated the impact of baseline clinical and laboratory risk factors known at (1) apheresis and (2) pre-lymphodepletion (pre-LD), on efficacy and toxicity of CAR-T to inform clinical decision making. Adult patients with R/R LBCL eligible for CAR-T according to the Australian national criteria (ECOG <2, ≥2 prior lines or autologous stem cell transplant (autoSCT), adequate organ function) were included if they underwent apheresis with intent to receive CAR-T at 6 Australian centres between January 1, 2020 and December 31, 2024. For infused patients, progression-free survival (PFS) and overall survival (OS) were calculated from date of infusion. Univariable and multivariable Cox proportional hazards (CoxPH) models using routinely-available risk factors were applied at apheresis and pre-LD, and predictive scoring systems were established.

632 patients were included. The median age was 66 years (16 to 85), histologies were high-grade B-cell lymphoma (HGBL) 11%, diffuse large B-cell lymphoma (DLBCL) 63%, transformed lymphoma 16%, Richters transformation 4%, primary mediastinal large B-cell lymphoma (PMBCL) 2%, T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) 2%. Bridging therapy was used in 87% (46% systemic, 24% radiotherapy, 17% combined). 210 tisa-cel-intended patients underwent apheresis; 190 (90%) were infused. The best overall and complete response rates (ORR and CRR) were 73% and 59%, respectively. The 12-month PFS was 34% (intention-to-treat (ITT)), and 38% (infused). Grade (G) ≥3 CRS occurred in 9%, and G≥3 ICANS in 7%. 422 axi-cel-intended patients underwent apheresis; 395 (94%) proceeded to infusion. The best ORR and CRR were 85% and 72%, respectively. The 12-month PFS was 47% (ITT), and 50% (infused). G≥3 CRS occurred in 4%, and G≥3 ICANS occurred in 22%.

CoxPH factors included: age (>75 vs ≤75), sex, ECOG (0 vs ≥1), histology (HGBL vs DLBCL vs transformed lymphoma), number of prior lines of therapy (2 vs 3 vs ≥4), prior autoSCT, history of primary refractory disease, relapsed/refractory to most recent systemic therapy, LDH (high vs normal), bridging response (PD/SD vs PR/CR vs no bridging, at pre-LD only). At pre-LD, a three-factor model including ECOG, bridging response and LDH, was selected. For tisa-cel patients the 12-month PFS (infused) stratified by number of risk factors was, 0: 72% (58–89%), 1: 49% (38–63%), 2: 28% (17–46%), and 3: 3% (0–23%). For axi-cel 12-month PFS (infused) was, 0: 66% (54–80%), 1: 65% (55–76%), 2: 52% (43–63%), and 3: 23% (15–35%). Amongst tisa-cel patients with all 3 risk factors, the rate of G≥3 CRS was 22% and G≥3 ICANS was 12%, compared with 5% and 7%, respectively, with

≤2 risk factors. Amongst axi-cel patients with all 3 risk factors, the rate of G≥3 CRS was 9% and G≥3 ICANS was 31%, compared with 2% and 19%, respectively, with ≤2 risk factors.

In conclusion, real-world Australian outcomes of CAR-T for R/R LBCL in third-line and beyond are favourable. Response to bridging was associated with improved outcomes with either product. In the absence of identified risk factors outcomes were excellent with either product, with axi-cel more effective relative to tisa-cel as risk factors increased. These findings offer a simple and clinically useful framework for consideration of patient selection, product choice and bridging strategy in the era of alternative highly-effective therapies. CAR-T is a therapeutic modality that requires close collaboration between treating centres and referrers, and can be optimised in the real world.