***Abstract***

**CD19-Directed CAR-T Cell Therapy for Relapsed/Refractory Large B-cell Lymphoma in Older Adults**

**Introduction**

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has revolutionized the treatment landscape for lymphoma patients, especially those with relapsed/refractory large B cell lymphoma (R-R LBCL). Pivotal trials (ZUMA-1, JULIET, and TRANSCEND NHL-001) have led to approval of three CD19-targeted CAR T-cell therapies—axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel)—for use after two lines of systemic chemotherapy. However, in these trials older patients were underrepresented, raising concerns about extrapolating to this population. Given the common toxicities of CAR T-cell therapy, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), older patients may face increased risks, necessitating careful patient selection.

**Methods**

This systematic review and meta-analysis explored how older age impacts CD19-directed CAR T-cell therapy outcomes in patients with relapsed/refractory (R/R) LBCL. A total of 15 studies involving 4,272 patients were included. Incidence of CRS and ICANS, hospitalization rates, response and survival outcomes, were assessed in older (≥65-70 years) and younger patients.

**Results**

The overall incidence of any-grade CRS in older patients was 72.1%, comparable to 75.6% observed in younger patients. Additionally, the incidence of severe (grade ≥3) CRS was similar between the two groups. Meta-analysis confirmed no significant association between age and CRS rate (OR 1.12; 95% CI: 0.77-1.61). However, neurotoxicity was observed significantly more frequently in older patients, with 51.3% experiencing any grade neurotoxicity compared to 41.9% of younger patients (OR 1.55; 95% CI: 1.34-1.80, $p < 0.001$). Severe neurotoxicity (grade ≥3) was also more frequently observed in older patients (OR 1.40; 95% CI: 1.17-1.68, p=0.002).

Subgroup analysis revealed that axi-cel was associated with a significantly higher risk of any-grade neurotoxicity in older patients (OR 1.79; 95% CI: 1.45-2.22, $p < 0.001$), as well as severe neurotoxicity (OR 1.43; 95% CI: 1.16-1.75, $p < 0.001$). In contrast, liso-cel and tisa-cel did not show significant differences in neurotoxicity risk between age groups (OR 1.41; 95% CI: 0.74-2.68, p=0.30).

Despite increased neurotoxicity, older patients had comparable survival rates to younger patients. In some studies, older patients exhibited even higher complete response rates, possibly due to a selection bias favoring healthier individuals and differences in disease biology. However, no significant differences were observed in progression-free survival or overall survival between older and younger cohorts.

**Conclusion**

CAR T-cell therapy demonstrates significant potential as an effective treatment for R-R LBCL in older patients, with similar CRS rates but higher neurotoxicity compared to younger patients. This underscores the importance of careful patient selection and management strategies for this group. Enhancing our understanding of the efficacy and safety of CAR T cell therapy in older adults will improve therapeutic strategies and quality of life for this population.