VIEWPOINTS

CAR T-Cell Therapy: Paving the Path to a Brighter Future in LBCL

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Metabolic tumor volume as a prognostic marker of clinical outcomes with axi-cel in second-line LBCL

In the phase III ZUMA-7 trial, axicabtagene ciloleucel (axi-cel), a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, showed higher efficacy compared with standard of care (SoC) as second-line treatment for patients with large B-cell lymphoma (LBCL).[1] Based on these data, axi-cel was approved in patients who were refractory to or had relapsed within 12 months of first-line chemoimmunotherapy by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).[2,3] These regulatory approvals increased the visibility of the therapy but predictive biomarkers that can improve patient selection are not yet defined in this setting. While pretreatment lactate dehydrogenase (LDH) level and tumor burden (TB), measured as the sum of product diameters (SPD) of up to 6 reference lesions, were negatively associated with durable responses in the pivotal ZUMA-1 trial of axi-cel after ≥2 lines of systemic therapy,[4] neither were predictive of event-free survival (EFS) in patients treated with axi-cel in ZUMA-7.[5] Notably, patients with elevated LDH or high TB had shorter EFS in the SoC arm.

Results of an analysis of ZUMA-7 data that evaluated clinical outcomes by metabolic tumor volume (MTV) were presented at the ASH Annual Meeting and Exposition 2022.[6] Patients aged ≥65 years showed lower baseline MTV than those aged <65 years and LDH and TB significantly but moderately correlated with MTV (Spearman correlation, 0.4516 and 0.5232, respectively). While axi-cel remained superior to SoC in both patients with high (EFS HR: 0.417, PFS HR: 0.523) and low MTV (EFS HR: 0.423; PFS HR: 0.504), those with high MTV had inferior outcomes irrespective of treatment. In the axi-cel arm, high versus low MTV was associated with worse EFS (HR: 1.441) and PFS (HR: 1.644).

MTV positively correlated with axi-cel-related toxicity as patients who experienced grade ≥3 neurologic events or cytokine release syndrome (CRS) had higher median MTV compared with those who experienced grade 1–2 or no neurologic events or CRS, respectively.[6] Thus, MTV showed a better prognostic value than TB in second-line LBCL. This could be explained

by the differences in the tumor immune landscape that might influence the significance of TB in this setting. Indeed, pre-treatment tumor microenvironment (TME) features were associated with clinical efficacy following axi-cel treatment in the third- or later-line LBCL (ZUMA-1)[7] and emerging data suggested a more favorable immune contexture in earlier lines.[5] Further investigation on predictive biomarkers in ZUMA-7 is ongoing, including assessment of the TME and CAR T-cell phenotype.

The future of ASCT in second-line LBCL

The positive results from the ZUMA-7 trial of axi-cel and the TRANSFORM trial of lisocabtagene maraleucel (liso-cel) led to regulatory approvals of the two CD19-targeting CAR T-cell therapies in R/R LBCL within 12 months of frontline treatment.[2,8] A question emerges whether these will complement or challenge the role of autologous stem cell transplant (ASCT). Patients who relapse beyond 1 year of initial therapy should still receive ASCT if responsive to salvage chemotherapy. ASCT has proven efficacy in this setting and it remains to be established whether patients can derive similar clinical benefit with CAR T-cell therapy. Furthermore, liso-cel showed activity in patients who were ineligible for ASCT due to comorbidities or age in the PILOT study[9] and was thus approved in this population.[8]

Overall, these data indicate that CAR T-cell therapy for LBCL is definitely here to stay.

Conflict of interest

The author reports scientific advisory roles for A2, Allogene, Novartis, Celgene/Bristol-Myers Squibb, Kite/Gilead, GammaDelta Therapeutics, Calibr, Amgen, Wugen, and Allogene; has been a consultant with grant options for Cellular Biomedicine Group, Inc; has received research funding from Kite/Gilead; and is funded by the Leukemia and Lymphoma Society as a Clinical Scholar and the NCI/NIH.

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Author contributions

The author has created and approved the final manuscript.

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