Unmasking the invisible: CAR T-cell therapy for intravascular large B-cell lymphoma

Irit Avivi

Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel

Correspondence: I. Avivi
iritavi@tlvmc.gov.il

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Intravascular large B-cell lymphoma (IVLBCL) represents a rare and aggressive manifestation of diffuse large B-cell lymphoma (DLBCL), typically characterized by a non-germinal center B-cell subtype. Its hallmark biological behavior – the preferential growth of malignant lymphocytes within the lumen of small-sized blood vessels – defines its "angiotropism". This unique pattern creates a diagnostic "mask", often leading to delayed identification due to the infrequent involvement of lymphadenopathy or discrete tumor mass formation.[1-3]

The clinical presentation of IVLBCL is protean and exhibits distinct geographical variations. While Asian populations more commonly present with hemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia, Western cohorts frequently display central nervous system and skin involvement.[1-3] The disease typically affects elderly patients and is characterized by an aggressive course, elevated lactic dehydrogenase levels, and B symptoms.

Management strategies have historically been extrapolated from DLBCL paradigms, yet outcomes remain suboptimal. While rituximab-based immunochemotherapy (e.g., R-CHOP) improved initial responses, 3-year overall survival rates hover around 60%.[2,4-6] Although upfront intensification and autologous hematopoietic cell transplantation seem to be associated with improved outcomes, most patients experience relapse. For relapsed/refractory disease, the prognosis is dismal; the median survival is often only a few months, as these patients are frequently ineligible for autologous hematopoietic cell transplantation due to age, poor performance status, or rapid clinical deterioration.[1-3,6,7]

In the era of chimeric antigen receptor (CAR) T-cell therapy, IVLBCL patients have remained largely "invisible", systematically excluded from pivotal trials such as ZUMA-1 and TRANSCEND due to the rarity and fulminant nature of their disease.[8,9] Consequently, evidence has been limited to anecdotal case reports. In this issue of *Haematologica*, Patel and colleagues provide a critical beacon of clarity, reporting the first registry-based analysis of commercial CD19-directed CAR T-cell therapy in relapsed/refractory IVLBCL utilizing the Center for International Blood and Marrow Transplant Research database.

Their analysis of nine patients (median age 66 years; median 2 prior lines of therapy) offers interesting insights. Notably, the median time from diagnosis to infusion was 22 months, and the cohort exhibited relatively preserved performance status (Karnofsky score of 90% in 66% of patients) with minimal baseline central nervous system involvement. This suggests a selection bias toward "fitter" patients with more indolent or chemosensitive biology who survived long enough to access cellular therapy, rather than the fulminant cases typically seen in practice.

The complete response rate was 66.7%, confirming that CAR T cells can effectively traffic to the intravascular compartment. However, unlike in patients with classic DLBCL,[8,11] these responses were frequently transient, with the 8-month progression-free survival dropping to less than 30% without a clear plateau.[10]

This discordance raises fundamental questions regarding IVLBCL biology. It remains unclear whether the intravascular niche acts as a sanctuary promoting antigen escape and T-cell exhaustion, or whether the absence of a stromal tumor microenvironment within the blood vessels impairs the persistence of memory CAR T cells.

Interestingly, the safety profile was surprisingly encoraging, with 0% grade 3 cytokine release syndrome and 11% grade 3 immune effector cell-associated neurotoxicity syndrome, potentially reflecting a relatively low tumor burden at CAR T-cell administration in this selected cohort.

Future perspectives

The study by Patel *et al*. establishes the feasibility of CAR T-cell therapy in IVLBCL but highlights that maintaining disease control remains an elusive challenge. Future

strategies may require exploring consolidative approaches or combination therapies after the CAR T cells to sustain remissions, as well as investigating "off-the-shelf" bispecific antibodies, which may be more accessible for rapidly progressing patients.

Disclosures

No conflicts of interest to disclose.

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