A PILOT STUDY OF AXICABTAGENE CILOLEUCEL FOR THE TREATMENT OF RELAPSED/REFRACTORY PRIMARY AND SECONDARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Abstract

Introduction:

Chimeric antigen receptor (CAR) T-cells are effective in chemorefractory large B-cell lymphoma (LBCL), where they enter the cerebrospinal fluid (CSF) and have been shown to have anti-lymphoma activity. We studied the safety and preliminary efficacy of axi-cel in patients with r/r primary and secondary CNSL, a set of diseases with a dismal prognosis.

Methods:

Adults with r/r CNSL were enrolled. No bridging other than continuing a stable corticosteroid dose was allowed. All patients had an Ommaya placed prior to axi-cel. Lymphodeletion and axi-cel dosing were according to product label. The primary endpoint was safety (treatment limiting toxicities [TLTs] and gr3+ adverse events [AEs]). Secondary endpoints were efficacy (objective response rate [ORR], complete response [CR] rate, duration of response [DOR], progression-free survival [PFS] and overall survival [OS]). Paired peripheral blood (PB) and CSF samples were drawn serially before and after axi-cel for flow cytometry, cytokine levels, axi-cel pharmacokinetics (PK), scRNAseq, and minimal residual disease (MRD) analysis to identify biomarkers of resistance and immune effector associated neurotoxicity syndrome (ICANS).

Results:

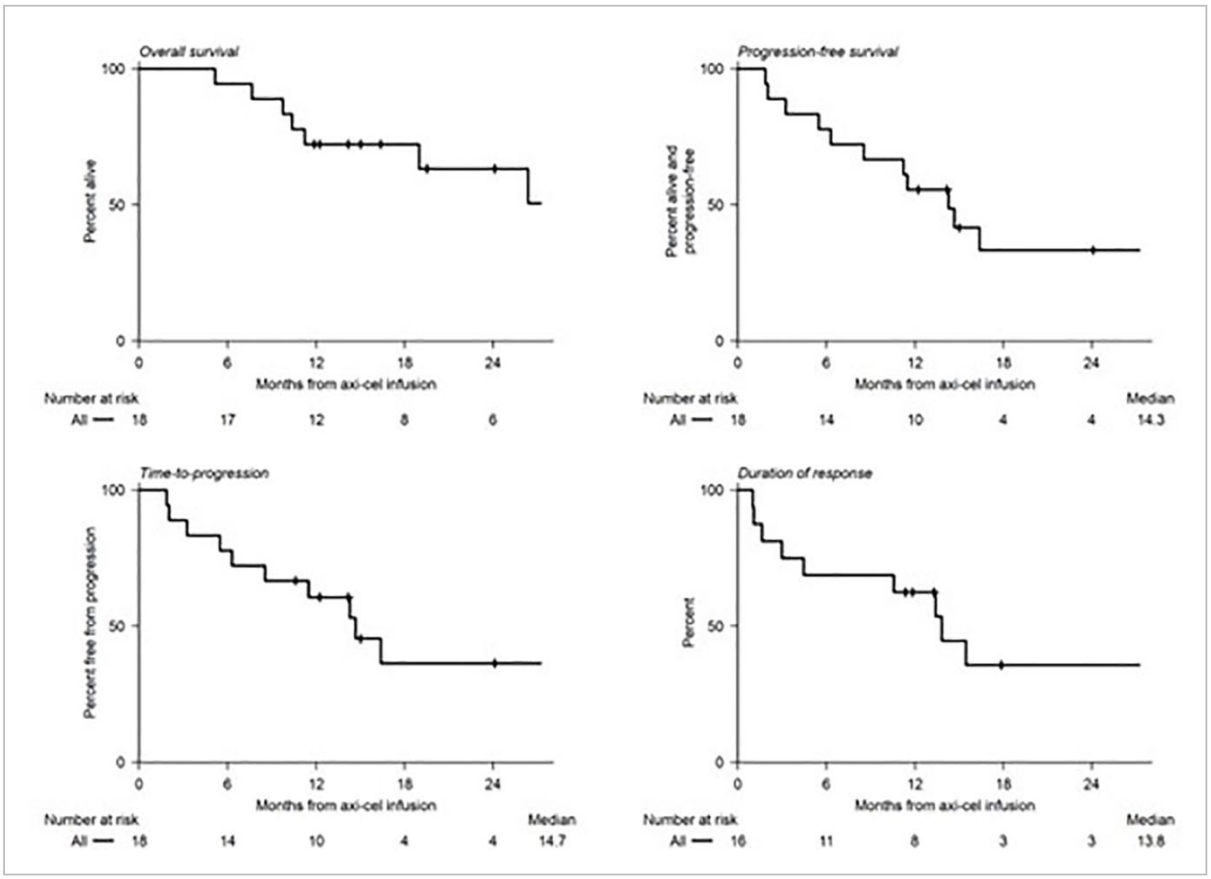
14 pts with PCNSL and 4 pts with SCNSL were enrolled; median age was 63 (33–80). Median number of prior therapies was 2 (1–6); 83% were refractory to last therapy. Median follow-up is 24.1 m (5.2–36.3 m). ORR is 89% with a CR rate of 67%. Rates of CR were similar in PCNSL (69%) and SCNSL (75%). Median DOR, PFS and OS were 13.8 m (1–30.4 m), 14.3 m (1.9–36.3 m), and NR (5.2–36.3 m), respectively. Only OS differed between PCNSL and SCNSL (median NR vs. 11.2 m, $p < 0.001$, respectively).

There were no TLTs. Cytokine release syndrome (CRS) occurred in 89% of pts; all gr1–2. ICANS occurred in 44% of pts and was gr3+ in 28%. One patient developed staphylococcus meningitis due to an Ommaya infection, requiring explant with full recovery. One patient developed myelodysplastic syndrome. There were 7 deaths, all due to PD.

CAR+ T-cells in the PB and CSF showed compartmental differences in gene expression, with CSF CAR T-cells enriched for type I IFN and T-cell dysfunction signatures. RNAseq analyses identified differentially regulated genes among CSF CAR+ T-cells at peak expansion between long-term responders and pts who progressed or relapsed, with increased expression of counter-inhibitory genes (TCF7 and CD226) in responders.

Conclusions:

Axi-cel has an acceptable safety profile in PCNSL and SCNSL with no apparent increased risk of ICANS or cerebral edema. Axi-cel is also effective for the treatment of CNSL (including in PCNSL) with a high CR rate that is more durable than available therapies. Extensive correlative studies offer unique insights into the CNS microenvironment and mechanisms of CAR T-cell therapy resistance and ICANS, identifying targets that will be explored to inform future CAR constructs/combinatorial strategies.



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