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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Intravenous IL-1 Receptor Antagonist for Prevention of Severe Immune Effector Cell-Associated Neurotoxicity Syndrome

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Background and Significance:
The management of toxicities from autologous CD19-directed chimeric antigen receptor (CAR) T cell therapy have evolved and the rates of severe cytokine release syndrome (CRS) have declined from nearly 50% in early trials to 8% (CRS grade 3 or higher) from real-world retrospective data with axicabtagene ciloleucel (axi-cel) (Jacobson et al. TCT 2022). However, the rate of severe immune effector cell-associated neurotoxicity (ICANS) has only marginally improved since CAR-T cell therapy has become commercially available. With expanding indications for CAR-T cell therapy, the prevention and management of ICANS remain an unmet need. We previously conducted a pilot, investigator-sponsored phase II study using Anakinra, an IL-1 receptor antagonist, administered subcutaneously at the onset of grade 2 CRS or any grade ICANS (Oliai et al. ASCO 2021) which demonstrated that anakinra is safe and feasible. There are several prospective studies that are currently open to accrual that incorporate subcutaneous Anakinra for prevention and treatment of severe ICANS (NCT04359784, NCT04148430, NCT04150913, and NCT04432506).
Anakinra crosses the blood brain barrier and has been shown to be safe and efficacious in rheumatologic conditions. Relatively high doses of IV Anakinra have been shown to be safe in severe sepsis and in subarachnoid hemorrhage. We hypothesize that IV Anakinra is safe and effective in preventing severe ICANS in patients undergoing standard of care axi-cel therapy for large B cell lymphoma.
Study Design and Methods:
This investigator-sponsored trial (NCT4205838) is a phase Ib/II study of adults eligible for standard of care axi-cel for large B cell lymphoma. Anakinra will be administered intravenously using a standard 3+3 design with cohort 1 receiving 200mg IV loading dose, followed by 100mg IV q6h maintenance dose and cohort 2 receiving 400mg IV loading dose, followed by 200mg IV q6h. The trigger to initiate Anakinra is any grade ICANS or grade $\geq$2 CRS in the absence of ICANS, based on ASTCT 2019 criteria. In addition to Anakinra, participants will receive standard of care interventions for CRS and ICANS. Subjects with secondary CNS involvement are included. Key exclusion criteria are primary CNS lymphoma, Burkitt's lymphoma, transformed DLBCL from CLL, prior allogeneic stem cell transplantation, < 30 days of exposure to immune check point inhibitor therapy. The study is open to accrual at University of California, Los Angeles (UCLA) with 2 additional sites within the University of California Hematologic Malignancies Consortium (UCHMC).
Objectives:
The primary objective is to evaluate the safety and tolerability of Anakinra given intravenously in patients undergoing CAR-T cell therapy and to estimate the efficacy of Anakinra in prevention of severe ICANS (grade $\geq$3). Secondary objectives include the impact of Anakinra on the efficacy of CAR-T cell therapy for large B cell lymphoma, the duration of ICANS, and the pharmacokinetics of Anakinra. Exploratory objectives focus on changes in inflammatory cytokines during ICANS in the peripheral blood.
Statistics and Current Status:
Using historical control from the real-world experience using axi-cel for relapsed/refractory large B-cell lymphoma (38%, Jacobson et al. ASH 2018), a sample size of 36 patients achieves 80% power to detect a 50% reduction in the rate of severe ICANS when comparing to the historical control using a one-sample exact binomial test at the two-sided type I error rate of 0.10. This study has been open at UCLA since February 2023. Two of 4 enrolled participants met criteria to receive IV Anakinra.

Conclusions:
The safety and tolerability of IV Anakinra is being evaluated in patients with large B cell lymphoma undergoing treatment with axi-cel in order to prevent severe ICANS.

References:
Jacobson, C. A. *et al.* Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States. *Transplant. Cell. Ther.* **28**, 581.e1-581.e8 (2022).

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