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Abstract Title : Azer-cel, an allogeneic (allo) CD19 CAR T, in combination with low-dose interleukin-2 (IL-2) demonstrates clinical activity in patients with large B-cell lymphoma (LBCL) who relapsed after autologous (auto) CAR T

Category: 700s - Transplantation and Adoptive Cell Therapies

Review Category: 704. Cellular Immunotherapies: Early Phase Clinical Trials and Toxicities

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Abstract Body

Background: Relapse following auto CD19-directed CAR T-cell therapy remains a major challenge in LBCL as these patients (pts) have limited treatment options. Azer-cel is an allo, CD19-directed, CAR T-cell therapy derived from healthy donor T cells. Preclinical and early clinical studies suggest that low-dose subcutaneous (SC) IL-2 administration may enhance CAR T-cell persistence and function without exacerbating toxicity. Here, we report outcomes for pts enrolled in the Phase 1/1b study (NCT03666000) with r/r LBCL who had previously responded to autologous CAR T, subsequently relapsed, and were treated with azer-cel followed by low-dose SC IL-2.

Methods: Eligible pts with CD19+ r/r DLBCL, NOS, high-grade B-cell lymphoma (HGBCL), transformed indolent lymphoma or other LBCL subtypes. All pts must have received ≥ 2 prior lines of therapy, including auto CD19 CAR T, and relapsed following an initial response. Pts with active central nervous system disease, infection, graft-versus-host disease, or major comorbidities were excluded. Prior autologous stem cell transplant (ASCT) and bispecific T-cell engagers (TCEs) were allowed. Pts received lymphodepletion with fludarabine (30 mg/m²/day) and cyclophosphamide (750 mg/m²/day) for 3 days (Aug/Cy), followed by azer-cel infusion (500×10^6 cells) on Day 0 and SC low-dose IL-2 (1 million IU daily) on Days 1-14. Responses were evaluated by PET-CT using the Lugano criteria.

Results: Twelve pts received azer-cel with low-dose SC IL-2. Median age was 64 years (range: 47-82), 50% were female, 92% Not Hispanic/Latino, 8% Hispanic/Latino and 92% Caucasian. 75% of pts had DLBCL, NOS, and 1 pt each had HGBCL, RT or THRBCL and 58% had received ≥ 4 prior therapies. All had relapsed after auto CD19 CAR T, 25% had prior TCEs, and 17% prior ASCT. Primary refractory disease was present in 42%, 50% were refractory to their last line of therapy, and 58% had a duration of response to prior CAR T therapy of ≤ 6 months. Median tumor burden by SPD was 13.95 cm² (range: 3.12-50.37) and 42% had LHD > ULN at baseline. The overall response rate was 75% (9/12), with a complete response rate of 50% (6/12). This represents a marked improvement as compared to a similar cohort of auto CART-relapsed pts (N = 12) who were treated with Aug/Cy and the same dose of azer-cel without IL-2 where the ORR was 42% with a CR rate of 17%. Follow-up remains relatively short with a median of 5 mo (2.7-15.7). At the time of the data cut-off, the 2 pts with the longest follow-up on study have remained in CR at >15 and >11 months. Of the 12 treated pts, 9 remain alive. Two deaths were related to disease progression and one due to COVID-19. All deaths occurred after subjects withdrew from treatment. Pharmacokinetic (PK) data by flow cytometry were available for 11 of 12 pts. The mean CAR-T expansion was 311.05 cells/ul (SEM 159.41), mean AUC₀₋₂₈ of 1979.85 (SEM 725.89), mean time to peak expansion Day 8.7 (SEM 1.53).

In the prior cohort treated without SC IL-2, mean CART expansion was 26.74 cells/ul (SEM 18.62) and mean AUC₀₋₂₈ 341.2 (SEM 250.83) and mean time to peak expansion 7.8 days (SEM 2.4). This demonstrates that low doses of SC IL-2 can markedly improve azer-cel PK. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 2 pts (17%), including 1 Grade 2 and 1 Grade 3 event. Cytokine release syndrome (CRS) was observed in 8 pts (67%), consisting of 6 Grade 1 and 2 Grade 2 events. Four subjects experienced infections, all Grade 2, including 2 cases of COVID-19, 1 Upper Respiratory Tract Infection and 1 bacteremia. Four subjects experienced a serious adverse event and no Grade 5 events have occurred in the low dose IL-2 cohort. The safety profile was comparable to that observed in pts who did not receive IL-2 (CRS 42% - all Gr. 1-2 events, ICANS 17% - all Gr. 3 events, Infections 67% - 17% Gr. ≥3).

Conclusion: Azer-cel followed by low-dose SC IL-2 demonstrates encouraging clinical activity in pts with LBCL who relapsed after prior autologous CD19 CAR T therapy, which remains a significant unmet medical need. Promising response and CR rates, early evidence of durability, robust CAR T-cell expansion and a manageable safety profile support further investigation of this regimen as a potential treatment option for these patients.

Keywords: (CAR)-T Cell Therapies, Clinical Trials, Study Population, Clinical Research, Lymphoid Malignancies, Human, Diseases, Immunotherapy, Lymphomas, Treatment Considerations, Biological Therapies, Research, Non-Hodgkin Lymphoma, Drug Development

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