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Abrogation of Immune Effector Cell Neurotoxicity Syndrome (ICANS) By Rimiducid (RIM) in Patients Treated with CD19-Specific Chimeric Antigen Receptor Modified T-Cells (CAR-T) Engineered with an Inducible Caspase 9 (iC9 CAR.19)

Clinical and Pharmacodynamic Correlates

UNC CANCER CARE

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Background

- CD19-targeted CAR T-cells are highly active in B-cell malignancies, but life-threatening toxicities include cytokine release syndrome (CRS) and ICANS.
- Early use of corticosteroids (CS) and tocilizumab can mitigate CRS.
- Tocilizumab may worsen ICANS, and CS are the backbone of ICANS management.
- Severe ICANS that is unresponsive to CS may be fatal due to cerebral edema or status epilepticus. Thus there is unmet need in the management of severe ICANS
- Rimiducid (RIM) is a dimerizing drug that induces apoptosis in cells engineered with an inducible caspase-9 (iC9) switch.
- A standard dose of RIM (0.4 mg/kg) resolved severe, prolonged, CS-refractory ICANS in a patient with B-lymphoblastic leukemia (B-ALL) by eliminating >90% of CAR T-cells[1].
- Ideally, ICANS could be mitigated before the development of life threatening complications, while preserving a higher percentage of therapeutic CAR T-cells.
- We sought to explore the effects of lower, pre-clinically less ablative[2] doses of RIM in patients with CS-nonresponsive ICANS.
- We report the clinical and pharmacodynamic courses of ICANS for four patients treated with RIM in an ongoing cell dose expansion cohort of a phase I/II study of iC9 CAR.19 cells in patients with B-ALL.

Results

- 14 patients were treated, 3 on DL1 and 11 on DL2.
  - Median age 32 years (range 21-69)
  - 13 had baseline platelets<100 and/or elevated lactate dehydrogenase, associated with short event-free survival in similar patients[4]
  - 6 with prior allogeneic transplant
  - 5 with prior CNS leukemia
- CRS developed in 11:
  - Maximum CRS grade was 2 in 5 and 1 in 6.
- ICANS developed in 5 patients:
  - Maximum grade 4 in 2, and grade 3 in 3.
  - One with CS-responsive ICANS did not receive RIM
  - Two with grade 3-4 for >72 hours received RIM 0.4 mg/kg
  - Two with grade 3 received RIM 0.1 mg/kg
- All RIM-treated patients had improvement of ICANS grade within 24 hours (Fig 1).
- ddPCR showed reduction in ΔNGFR transcripts by >80% at 4 hours after start of RIM infusion in each of the 4 patients (Fig 2).
- PK parameters were distinct between the two RIM doses (Fig 3) but kinetics of ΔNGFR decay were similar regardless of RIM dose (Fig 4)
- IL-6, TNF-α and IFNγ levels declined in the 48 hours after RIM (Fig 5)
- Peak cytokines (Figs 6 &7) and ΔNGFR transcripts (Fig 8) tended to occur earlier after iC9 CAR.19 infusion for RIM-treated patients compared to RIM-untreated patients.
- Rates of overall response (CR+CRi+MLFS at 4 weeks) were 2/4 RIM subjects versus 10/10 in others.
- Median (95% CI) Relapse-free survival was 5.0 months (2.8, not reached).
- Median (95% CI) Overall survival was 12.8 months (7.3, not reached)

Figure 1: Clinical ICANS Grade after RIM dosing

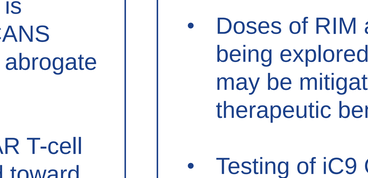

Figure 2: post-RIM ddPCR for ΔNGFR & FC

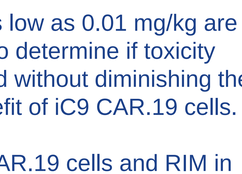

Figure 3: Rimiducid Pharmacokinetics

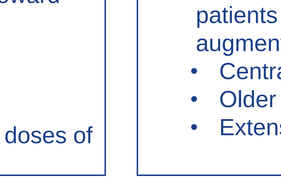

Figure 4: Copies ΔNGFR (ddPCR) according to RIM dose

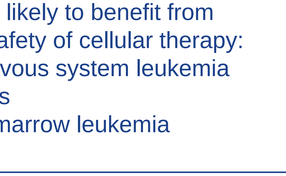

Figure 5: Cytokines within 48 hours after RIM

Figure 6: IL-6 concentration trends post CAR T-cell infusion according to RIM administration

Figure 7: IFNγ concentration trends post CAR T-cell infusion according to RIM administration

Figure 8: ΔNGFR ddPCR trends post CAR T-cell infusion according to RIM administration

Conclusions

- RIM administration to patients with CS-unresponsive grade 3-4 ICANS is associated with abrupt reduction of circulating iC9 CAR.19 cells and ICANS grade, suggesting that the iC9 switch holds promise as a potent tool to abrogate the most severe CAR T-cell toxicities
- No clear association between RIM pharmacokinetics and degree of CAR T-cell ablation has yet emerged. It is possible that a pharmacodynamic trend toward improved CAR T-cell persistence will emerge using lower doses of RIM
- Response rate was lower in RIM-treated patients, suggesting that tested doses of RIM abrogated both toxicity and efficacy of CAR T-cells

Future Directions

- Doses of RIM as low as 0.01 mg/kg are being explored to determine if toxicity may be mitigated without diminishing the therapeutic benefit of iC9 CAR.19 cells.
- Testing of iC9 CAR.19 cells and RIM in patients most likely to benefit from augmented safety of cellular therapy:
  - Central nervous system leukemia
  - Older adults
  - Extensive marrow leukemia

Methodology

- Subjects were adult patients with: B-ALL in 2nd or greater bone marrow (BM) relapse, relapse >100 days after allogeneic stem cell transplant, disease refractory to ≥2 induction therapies, or with measurable residual disease (MRD) persistence/recurrence.
- T-lymphocytes were collected from the subjects, and CAR-T cell products generated by gene modification with a γ-retroviral vector encoding for iC9, ΔNGFR (for selection and tracking) and CAR.CD19 (encoding 4-1BB) genes[2].
- Subjects underwent lymphodepletion with fludarabine and cyclophosphamide followed by infusion of iC9 CAR.19 cells at one of two dose levels (DL1: 5 x 10^5 CAR-T cells/kg; DL2: 1 x 10^6 CAR T-cells/kg).
- Toxicities graded by CTCAE v5 or ASBMT consensus grading for CRS and ICANS.
- CAR-T cell expansion in peripheral blood (PB) was measured by flow cytometry (FC) and droplet digital PCR (ddPCR).
- Cytokines were measured by commercially available multiplex (Luminex®) cytokine assays.
- Leukemia response was per NCCN criteria[3].
- Subjects who experienced grade 3-4 ICANS despite CS for >72 hours received RIM 0.4 mg/kg IV over 2 hours.
  - After protocol amendment, subjects with ≥ grade 2 ICANS for >24 hours despite CS received RIM 0.1 mg/kg IV over 2 hours.
  - FC, ddPCR, plasma RIM concentration (PK) and cytokine levels were measured prior to RIM, at 4 hours after the end of RIM infusion and daily until ICANS resolution.

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References

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