Low Blood Counts, Elevated Inflammation Signals Could be Predictors of CD19 CAR T-cell Therapy Efficacy on Acute Lymphoblastic Leukemia Patients

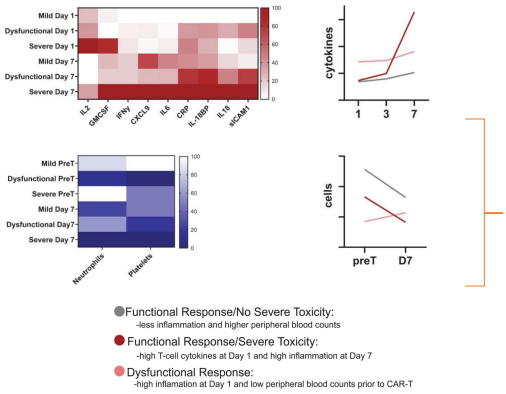
Katelyn Burleigh[1], Kelly G. Stratton[2], Jenny L. Smith[1], Michael C. Jensen[3], Cameron J. Turtle[4 5], Camille Keenan[1 6], Colleen Annesley[1 6], Corinne Summers[1 6], Bobbie-Jo Webb-Robertson[2], Alexandre V. Hirayama[7 8 9], Rebecca A. Gardner[1 6], Heather H. Gustafson[1 6]

1)Ben Towne Center for Childhood Cancer and Blood Disorders Research, Seattle Children's Research Institute, Seattle Children's Hospital, University of Washington, Seattle, WA, 2) Biological Sciences Division, Pacific Northwest National Laboratory, Richland, WA, 3) Seattle Children's Therapeutics, Seattle Children's Research Institute, Seattle, WA, 4) Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Camperdown, NSW, Australia, 5) Royal North Shore Hospital, St. Leonards, NSW, Australia, 6) Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA, 7) Integrated Immunotherapy Research Center, Fred Hutchinson Cancer Center, Seattle, WA, 8) Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, 9) Department of Medicine, University of Washington, Seattle, WA

THE PROBLEM

While CD19 chimeric antigen receptor T cell (CAR-T) therapy achieves a high rate of response in both pediatric and adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) – however

- Fails to achieve a complete remission (CR) in approximately 20% of treated patients at first disease evaluation post-CAR-T.
- Severe toxicities can occur, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.

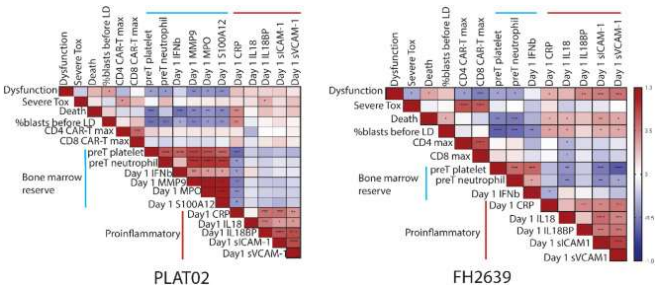


EXPERIMENTAL DESIGN

- Analyzed early time point serum samples from 86 patients (pediatric and adults) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL).
- Binned patients into three groups.
- Compared 15 cytokine concentrations for each group at each of the three time points using ANOVA to determine whether patients with either a dysfunctional or severe toxicity response can be differentiated from patients that responded with only mild toxicity (based on the cytokines measured).

RESULTS/DISCUSSION

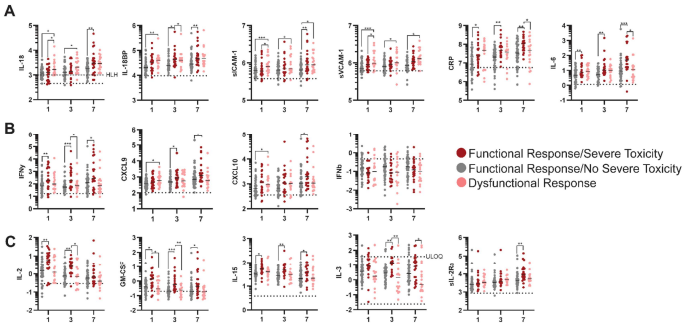
- Patients in both the dysfunctional response group and in the functional response with severe toxicity group have high levels of proinflammatory cytokines in the days following CAR-T infusion.
- Dysfunctional response patients were distinct in that they lacked sufficient levels of neutrophils and platelets prior to infusion and showed high levels of proinflammatory cytokines in the first-week post-CAR-T.
- Early inflammation after CAR T-cell infusion is connected both to poor treatment response and severe side effects, not just to how much cancer a patient has—suggesting that inflammation itself helps determine how well patients do.



The dysfunctional response group is characterized by low neutrophils/platelets/granulocytic cytokines (poor bone marrow reserve) and high proinflammatory cytokines. A Spearman's correlation of CBC and cytokines where the color indicates the rank correlation coefficient, and the stars indicate significance (*P*-value<0.05).

KEY FINDINGS

- Cell counts and inflammation signals in patients could help doctors predict which leukemia patients are less likely to benefit from CD19 CAR T-cell therapy.
- High cytokines at both the Day 1 and Day 7 time points were associated with poor survival.
- Low bone marrow reserve correlates with poor response and survival.
- Unexpected finding: the high day 1 IL-18 across all three groups with the large majority having pathologic levels seen during episodes of HLH.



The dysfunctional response group had low CBC counts pre-T while the functional response/severe toxicity group had elevated CAR maximum expansion. Tumor burden prior to lymphodepletion (A), platelets at pre-T (post-LD, pre-CAR-T), Day 7, and Day 28 (B), and neutrophils at pre-T, Day 7, and Day 28 (C) CD4 max (F), and CD8 max (G) were compared across groups. Linear regression was performed for pre-T neutrophils versus tumor burden (D) and for pre-T platelets versus tumor burden (E). No correlation between CAR max versus tumor burden (H).

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For additional information, contact:
Bobbie-Jo Webb-Robertson
+1 (509) 375-2292
Bobbie-Jo.Webb-Robertson@pnnl.gov