

# ALL's Well that Ends Well

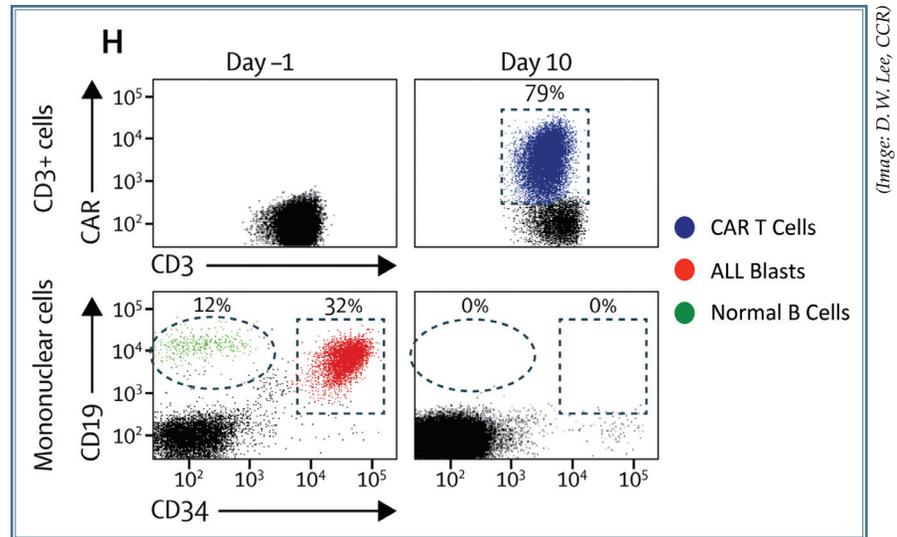
*A T-cell immunotherapy attacks most acute lymphoblastic leukemia.*

Recently, therapies that manipulate the immune system's response to cancer have become a new source of hope for many with otherwise intractable disease. One particularly promising strategy involves extracting and reprogramming a patient's own T cells with chimeric antigen receptors (CARs), and then reintroducing them to seek out and destroy cells bearing the specified antigen.

For the 15 percent of children with B-lineage acute lymphoblastic leukemia (B-ALL) which is refractory or relapsed after standard treatment, published case series have shown CAR T cells programmed to recognize CD19, a surface marker selectively expressed on almost all B cells, have some antitumor activity. "The anecdotal evidence is promising but does not have the rigor of a well-controlled clinical trial," said Crystal Mackall, M.D., Chief of the Pediatric Oncology Branch (POB).

So Mackall, Daniel W. Lee, M.D., Assistant Clinical Investigator in POB, and their colleagues set out to rigorously test this experimental therapy in a phase 1, dose-escalation clinical trial on consecutively enrolled patients. The results, published in the *Lancet*, showed a complete response rate of 70 percent among the 21 patients enrolled over a two-year period. By comparison, the most recent FDA-approved drug for the disease, blinatumomab, has a complete response rate of 41 percent.

After pretreatment with immune suppressants (fludarabine and cyclophosphamide), patients were infused with a single dose of CAR T cells over a 30-minute period. The maximum tolerated dose was defined at one million CD19-CAR T cells per kilogram, a dose that could be generated from the patients' cells in



CAR T cells expand dramatically (blue) in the peripheral blood of patients and coincide with elimination of CD19+ normal B cells (green) and leukemic blasts (red).

90 percent of cases. At this dose, side effects—the most serious of which being cytokine release syndrome—were reversible. Four weeks later, the response was assessed as a percentage of blast cells in the bone marrow and in circulation.

Complete response is defined as having less than five percent marrow blasts, no circulating blasts, and no other sites of disease. Almost all responding patients (12/14) lacked even Minimal Residual Disease (MRD), meaning that blasts were not found by the most sensitive test available. Moreover, two patients were cleared of leukemia that had spread into the central nervous system.

Because most patients who achieved remission went on to have hematopoietic stem cell transplants, the extent to which CD19-CAR T-cell therapy alone could be effective in maintaining remission is not clear. The T cells themselves only persisted in patients for approximately two months, for reasons that are not well understood. What is clear, however, is that they represent a highly effective bridge to transplant therapy.

"We have a study under way that incorporates a more intensive chemotherapy regimen in patients with extensive disease, in an attempt to increase the response rate, while potentially diminishing the risk for severe cytokine release syndrome," said Mackall.

In a *Lancet* commentary earlier this year, Persis Amrolia, M.D., and Martin Pule, M.D., from University College London, summed up the impact of this study: "This approach is without question the most significant therapeutic advance in acute lymphoblastic leukaemia for a generation, and might represent the beginning of a new era of engineered T cells for cancer therapy."

*To learn more about Dr. Mackall's research, please visit her CCR website at <https://ccr.cancer.gov/crystal-l-mackall>.*

*To learn more about Dr. Lee's research, please visit his CCR website at <https://ccr.cancer.gov/daniel-w-lee>.*