Chimeric antigen receptor-modified T cells represent a new approach to immune therapy in the treatment of hematologic malignancies. The clinical activity of chimeric antigen receptors (CARs) has been published in acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The results have been remarkable, although only a very small number of patients have been treated. We are anticipating further clinical trials and further development of this technology for more widespread treatment opportunities for patients.

The CARs that have been the most successful clinically have a similar basic make-up. They are genetically modified T cells. The T cells are collected from the patients through leukapheresis, then they are genetically modified to express an extracellular recognition domain that is connected in the intracellular signaling domains of the T cells. Various extracellular recognition domains have been engineered, but the target of CD19 has proven most successful in patients with B cell malignancies, and CD19 is widely expressed on CLL and B-cell ALL. The cells are infused back into the patient, sometimes after undergoing chemotherapy to lymphodeplete the patient (which may improve the recovery and persistence of the cells after treatment). The infusion responses have been dramatic in some patients, with severe cytokine storm described in reports, usually several days after treatment. This is thought to reflect the very rapid identification of the target protein and response of the T cells to the target. Those patients with acute leukemia who have responded also appear to respond rapidly, with disappearance of blasts from the peripheral blood within a month. The cells have been detectable in some patients for months after treatment.

Some of the limitations to the use of CARs include the necessity to manufacture the cells, targeting the cells, as well as long-term survival of the cells after infusion. The manufacturing process will hopefully become more streamlined and readily available as the technology improves. The current T cells are directed toward a protein on the tumor cells; in the reports most successful, against CD19. However, all cells expressing CD19 were targeted and the patients remained depleted of B cells after therapy. This may limit the expansion to some other malignancies, unless tumor specific targets are able to be identified. It also appears one mechanism of relapse after this therapy was the loss of CD19 from the leukemia cell phenotype. Of note is that the CAR-modified T cells have no interaction with major histocompatibility complex, and there should be no risk of graft versus the host disease after infusion. The activity of CARs has been improved in patients recently by incorporating costimulatory domains on the CAR structure, increasing the T cells antitumor activity. The cells also appear to expand in vivo after administration to the patients and persist as memory T cells.

In summary, the clinical results reported with CAR-modified T cells are very encouraging. They represent countless hours of laboratory work and have become clinically relevant as our understanding of the power of immune therapy has increased. It is hoped the technology will be able to offer therapy to more patients with hematologic malignancy, and as more targets are identified, also patients with solid tumors.

References