Nature Reviews Clinical Oncology | Published online 20 Feb 2018; doi:10.1038/nrclinonc.2018.32

IMMUNOTHERAPY

CAR T cell therapy efficacious against B-ALL across age groups

Anti-CD19 chimeric antigen receptor (CAR) T cells are the first FDA-approved cellular immunotherapy, and have the potential to revolutionize the treatment of both adults and children with certain haematological malignancies. The majority of patients initially respond to treatment, but much remains to be learnt about numerous aspects of this therapy, including the durability of responses and the ability to consistently deliver bespoke cellular therapies across different geographical locations. Now, two early-phase trials with results published in the *New England Journal of Medicine* provide further insight into the use of CAR T cells in patients with B cell acute lymphoblastic leukaemia (B-ALL).

Park *et al.* reported the long-term survival outcomes from a cohort of 53 adults with relapsed B-ALL who received a single infusion of 19-28z anti-CD19 CAR T cells, consisting of a CD19-binding domain, with intracellular signalling domains from the T cell receptor CD3ζ-chain and the co-stimulatory receptor CD28. Complete remission was observed in 83% of patients with a median event-free survival (EFS) of 6.1 months and median overall survival (OS) of 12.9 months. Grade ≥3 adverse events included neurotoxicities in 42% of patients, and cytokine-release syndrome (CRS) in 26%, including one death.

Investigators reported a correlation between a low pretreatment disease burden (defined as <5% bone marrow blasts) and longer disease remission: median EFS was 10.6 months, with a median OS of 20.1 months in these patients compared with 5.3 months and 12.4 months, respectively, in patients with a high pretreatment disease burden (≥5% bone marrow blasts and/or extramedullary disease). Investigators noted that the extent of *in vivo* peak CAR T cell expansion was the best predictor of both short-term responsiveness and acute toxicities.

> “The findings of these two trials revealed similarly high response rates with either approach across different age groups”

Elsewhere, a preplanned analysis revealed findings from the ongoing global, multicentre, phase I–II ELIANA trial, including data from 75 children or young adults (aged ≤25 years) with relapsed and/or refractory B-cell ALL. In this trial, patients received a single infusion of the anti-CD19 CAR T cell product tisagenlecleucel, which includes a 4-1BB, rather than CD28, co-stimulatory domain. At 3 months after infusion, 81% of patients were in remission, with EFS and OS of 50% and 76% reported after 12 months of follow-up monitoring; 88% of patients had at least one grade 3–4 adverse event, with 37% of patients receiving tocilizumab for severe CRS and 13% having grade ≥3 neurotoxicities.

Other notable aspects of this trial included the delivery of tisagenlecleucel to other centres in North America, Europe, Asia and Australia. Furthermore, investigators at several centres were able to deliver tisagenlecleucel infusions as an outpatient treatment, albeit after initial experience with use in an inpatient setting.

The findings of these two trials revealed similarly high response rates with either approach across different age groups, and both agents provided improvements in EFS compared with those typically obtained with blinatumomab. However, the findings of the ELIANA trial reveal both more sustained responses and a higher risk of adverse events. These differences in outcome might reflect differences in CAR design (tisagenlecleucel contains a 4-1BB domain, as opposed to a CD28 domain), and/or differences in the study population with adults, and in particular older adults, with B-ALL typically having inferior outcomes to those of children.

In conclusion, the findings of the trial conducted by Park *et al.* demonstrate that the majority of adults with B-ALL who receive treatment with anti-CD19 CAR T cells will ultimately relapse within 2 years of treatment. Long-term follow-up data on the risk of recurrence in children and young adults with B-ALL is eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLES Maude, S. L. *et al.* Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N. Engl. J. Med.* **378**, 439–448 (2018) | Park, J. H. *et al.* Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N. Engl. J. Med.* **378**, 449–459 (2018)