HAEMATOLOGICAL CANCER

T cell transfer after allo-HSCT in AML

Patients with acute myeloid leukaemia (AML) receiving allogeneic haematopoietic stem-cell transplantation (allo-HSCT) have a high risk of relapse. The results of a phase I study now published reveal that the infusion of T cells selected for the expression of T cell receptor (TCR) targeting a protein overexpressed in AML cells dramatically reduces the risk of relapse.

Aude Chapuis and collaborators screened $CD8^+$ T cell clones from haematopoietic stem-cell donors to identify cells expressing a high-affinity TCR specific for WT1, a transcription factor that is overexpressed in AML cells. These cells, referred to as $T_{TCR\text{-}C4}$, were expanded and their anti-tumour activity was assessed ex vivo. Subsequently, 12 patients with AML deemed at high risk of relapse but with no evaluable disease 28 days after allo-HSCT received at least one infusion of $T_{TCR\text{-}C4}$ cells; 7 patients received a second infusion 21–797 days after the first one.

At a median follow-up duration of 44 months after the first infusion, all patients remained alive, none of them with detectable disease in bone marrow. A comparator group included 88 patients who had concurrently undergone allo-HSCT at the same institution all of whom had no detectable disease 28 days after; relapse-free survival at the same time point in this group was 45%. The 3-year estimates of overall survival, relapse and non-relapse mortality were 100%, 0% and 0% versus 60%, 28% and 18%, respectively, in patients receiving $T_{TCR\text{-}C4}$ cells versus those in the comparator group ($P \leq 0.01$ for all comparisons).

Infusions were generally well tolerated. The number of patients with grade 1–2 graft-versus-host-disease (GVHD) before and after receiving $T_{TCR\text{-}C4}$ cells was 9 (in both cases); 1 patient had grade 3 acute GVHD 97 days after the infusion. The difference in the reported incidence of chronic GVHD between groups was not statistically significant (HR 0.78; $P = 0.57$). Taken together, the efficacy and safety results indicate that this T cell transfer approach should be tested in studies with larger cohorts of patients.

Diana Romero

ORIGINAL ARTICLE Chapuis, A. G. et al. T cell receptor gene therapy targeting WT1 prevents acute myeloid leukemia relapse post-transplant. *Nat. Med.* **25**, 1064–1072 (2019)

HEAD AND NECK CANCER

Induction chemotherapy improves efficacy

Chemoradiotherapy is the standard of care for patients with nasopharyngeal carcinoma. Despite this treatment, however, the disease will ultimately be fatal in approximately 70% of patients. Now, data from a large-cohort, open-label phase III randomized controlled trial demonstrate that the addition of induction chemotherapy to chemoradiotherapy leads to improved survival outcomes.

A total of 480 patients with locoregionally advanced nasopharyngeal carcinoma were randomized (1:1) to receive chemoradiotherapy with, or without, 3 prior cycles of gemcitabine plus cisplatin induction chemotherapy. Recurrence-free survival (RFS) was the primary end point.

Virtually all patients (94.6%) responded to induction chemotherapy. After a median follow-up duration of 42.7 months, patients in the induction chemotherapy group had significantly improved 3-year RFS (85.3% versus 76.5%, hazard ratio (HR) for disease recurrence or death 0.51, 95% CI 0.34–0.77; $P = 0.001$). Patients receiving induction chemotherapy also had improved 3-year overall survival (94.6% versus 90.3%, respectively, HR 0.43, 95% CI 0.24–0.77). Interestingly, however, no significant differences in 3-year locoregional RFS emerged from the analysis (91.8% versus 91.0%, HR for locoregional recurrence or death 0.77, 95% CI 0.42–1.41).

Patients receiving induction chemotherapy had an increased risk of adverse events: acute grade 3–4 adverse events occurred in 75.7% of patients versus 55.7% of those receiving chemoradiotherapy only, although the risk of late-onset serious adverse events was similar (9.2% versus 11.4%).

These data demonstrate that induction chemotherapy improves the efficacy of chemoradiotherapy, albeit with a substantial increase in the risk of adverse events. Longer follow-up monitoring will be required to determine the balance between tolerability and the risk of mortality associated with receiving chemoradiotherapy only.

Peter Sidaway

ORIGINAL ARTICLE Zhang, Y. et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1905287 (2019)

IMMUNOTHERAPY

TKI-based on/off switch for CAR T cells

Chimeric antigen receptor (CAR) T cells have promising anticancer activity but often cause serious, and potentially fatal, toxicities, most commonly cytokine-release syndrome (CRS). Now, preclinical evidence suggests that a pharmacological 'on/off switch' can be used to improve the safety of CAR T cell therapy.

In co-culture experiments, the tyrosine kinase inhibitor (TKI) dasatinib at a concentration that can routinely be achieved in patients (100 nM) rapidly and completely abrogated $CD8^+$ CAR T cell activation, proliferation and cytotoxicity. These effects lasted for >12 hours and were accompanied by complete inhibition of IFNγ, IL-2 and/or GM-CSF secretion by $CD8^+$ or $CD4^+$ CAR T cells. By contrast, dexamethasone, which is often used to treat severe CRS, suppressed the production of IL-2 but not IFNγ.

Mechanistically, dasatinib potently inhibited the autophosphorylation of LCK, a kinase that phosphorylates the T cell receptor (TCR) CD3 ζ-chain. Accordingly, activatory phosphorylation of the CAR CD3ζ domain and the CD3ζ-associated kinase ZAP70 was reduced by ~90%, which prevented downstream NFAT-driven gene expression.

Dasatinib was equally effective as an off switch regardless of the CAR target antigen (CD19, ROR1 or SLAMF7) or co-stimulatory domain (CD28 or 4-1BB). The drug was less effective, however, if added >1 hour after CAR T cell stimulation, but the results of sequential stimulation experiments suggested that most CAR T cells would eventually be inhibited upon subsequent encounters with target cells. Importantly, CAR T cells regained their full anticancer activity rapidly after dasatinib withdrawal, even after a week of exposure.

These findings were all closely recapitulated in a mouse lymphoma model. Moreover, in a mouse model of acute CRS after CAR T cell therapy of lymphoma, mortality at 48 hours after CAR T cell infusion was 75%, but was reduced to 30% when dasatinib was administered for 30 hours beginning 3 hours after cell transfer.

David Killock

ORIGINAL ARTICLE Mestermann, K. et al. The tyrosine kinase inhibitor dasatinib acts as a pharmacologic on/off switch for CAR T cells. *Sci. Transl Med.* **11**, eaau5907 (2019)