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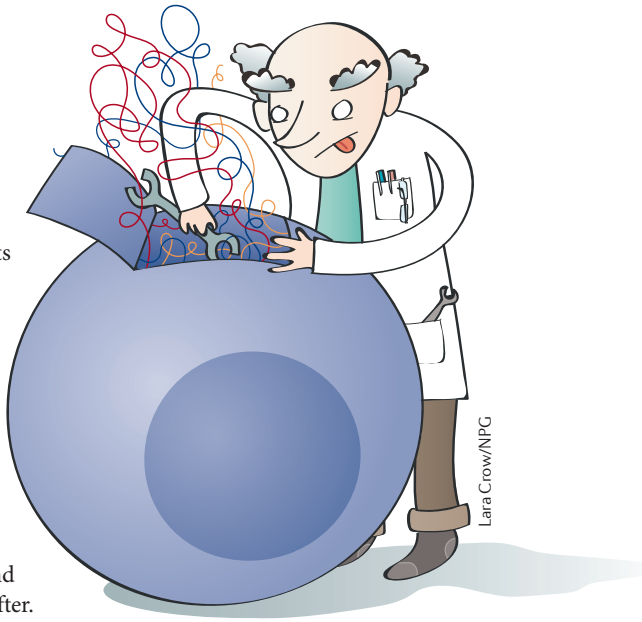
IMMUNOTHERAPY

Engineering a sTrategy for multiple myeloma



Lara Crow/NPG

Autologous T cell transfer of gene-modified T cells in patients with multiple myeloma has proven to be difficult. Early reports have shown that the expression of the inserted genes in the transplanted T cells only persists for a short period (<1 month), limiting the clinical efficacy. A plausible reason for this lack of expression is silencing of the transgene, a phenomenon described with other forms of gene transfer using γ-retrovirus technology. Accordingly, using gene transfer with lentiviruses that are less susceptible to silencing, and incorporation of T cell receptors (TCRs) with high affinities for tumour-specific antigens, is central to making T cell transfer a viable therapeutic option. With this in mind, Rapoport and colleagues recently reported on the clinical use of T cells with engineered TCRs that recognize NY-ESO-1, a cancer–testis antigen that is expressed by approximately 60% of advanced myelomas.

Specifically, the TCR-engineered T cells recognise the complex of HLA-A*0201 (human leukocyte antigen) with a peptide derived from NY-ESO-1 and LAGE1 (namely, SLLMWITQC). Accordingly, the 20 patients enrolled in this Phase I–II trial were HLA-A*0201-positive, and NY-ESO-1 and/or LAGE1 were expressed by the multiple myeloma cells. All patients had active disease, and one-third were categorized as high risk. After patients were conditioned with melphalan, autologous stem cell transplantation (ASCT) was undertaken, followed by infusion of engineered T cells. Responses were assessed at day 42, 100 and 180 after ASCT and every 3 months thereafter. T cell expansion, trafficking to the diseased tissues and persistence were all determined using PCR-based assays on samples from peripheral blood and bone marrow.

At 100 days, 14 patients had a near-complete response (no detectable multiple myeloma), 2 patients had a partial response, 1 had stable disease and 1 had progressive disease. At a median follow-up duration of 21.1 months, 10 of the patients were alive and progression-free, and 5 patients had died after progression.

Throughout the study, NY-ESO-1 expression in the bone marrow was inversely correlated with the presence of engineered T cells; indeed, levels of NY-ESO-1 decreased after transplant and remained low except in those patients who had a loss of the T cells. Partial responses were attributable to the presence of NY-ESO-1-negative multiple myeloma cells; those who eventually relapsed demonstrated antigen-negative disease. These findings suggest that targeting other antigens in addition to NY-ESO-1 could prevent antigen escape and provide durable responses in more patients.

Crucially, from a clinical perspective, the adverse events with this therapy were all manageable, and no patient died as a result of treatment; clinically evident cytokine-release syndrome reported in previous studies of T cell transfer was not observed. At 30.1 months of follow up, the estimated median overall survival was 32.1 months, which is particularly promising given the advanced stage of disease of the enrolled patients.

> “no patient died as a result of treatment”

Mina Razzak
Chief Editor, Nature Reviews Disease Primers

ORIGINAL RESEARCH PAPER Rapoport, A. P. *et al.* NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. *Nat. Med.* **21**, 914–921 (2015)