IMMUNOTHERAPY

Cancer cells BiTE the dust

The concept of arming a patient's immune system against their own tumour is an intense area of research, and is now starting to bear its first fruit. The central challenge of this approach is to break immune tolerance, and enable cytotoxic T cells to detect and kill cancer cells. One strategy for achieving this is to physically tether cytotoxic T cells to tumour cells using bispecific antibodies, and to activate them 'on target'. Writing in *Science*, Bargou and colleagues now report on the first patients to be successfully treated in this way.

The antibody construct blinatumomab, designed as a bispecific T-cell engager (BiTE), was based on single-chain antibodies with dual specificity for CD19 (B cells) and CD3, the T-cell receptor complex. Previous *in vitro* studies had demonstrated that, in the presence of CD19-expressing target cells, it can induce the polyclonal activation of peripheral human T cells and target cell lysis. Importantly, the activation of T cells was strictly dependent on the presence of the target cells — a major safety concern, as polyclonal activation can lead to a potentially fatal cytokine-release syndrome (cytokine storm).

In a Phase I clinical trial, blinatumomab was tested in 38 patients with relapsed B-cell non-Hodgkin's lymphoma. The majority of the patients had already undergone multiple rounds of chemotherapy and treatment with rituximab, a B-cell-depleting antibody. Blinatumomab was administered by continuous intravenous infusion with a portable minipump system over a period of 4–8 weeks. Doses as low as 0.005 mg per m^2 were shown to lead to an elimination of target cells in the blood, and all seven patients in the treatment group with the highest dose of 0.06 mg per m^2 experienced tumour regression. Four patients achieved a complete response (disappearance of all known lesions and clearance of bone marrow from lymphoma cells). Moreover, no relapses have been observed so far in responding patients treated with doses of 0.03 mg per m^2 or higher.

Eight patients discontinued the trial owing to toxicity. Importantly, no cytokine release syndrome was evident in any of the patients, and the first confirmed responses to blinatumomab occurred at serum levels that were five-orders of magnitude lower than the serum levels required for rituximab to elicit a response. This enormous potency difference was attributed to the high lytic potential of the T cells and their proliferation at the site of activation.

The authors argue that the BiTE approach is particularly attractive as its independence from tumour-antigen presentation and T-cell specificity might allow it to overcome the immune-escape mechanisms that limit other immunotherapeutic strategies, such as therapeutic vaccination aimed at activating tumour-specific T cells. Efforts are also underway to expand the approach to other malignancies; a clinical trial of a BiTE antibody with dual specificity for T cells and an antigen expressed on adenocarcinoma and cancer stem cells has recently been initiated.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Bargou, R. *et al.* Tumor regression in cancer patients by very low doses of a T cell engaging antibody. *Science* **321**, 974–977 (2008)
FURTHER READING Brischwein, K. *et al.* Strictly target cell-dependent activation of T cells by bispecific single-chain antibody constructs of the BiTE class. *J. Immunother.* **30**, 798–807 (2007)