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HAEMATOLOGICAL CANCER

Ibrutinib supercharges CAR T cells

The Bruton tyrosine kinase inhibitor ibrutinib has been approved by the FDA as a treatment of mantle-cell lymphoma and chronic lymphocytic leukaemia (CLL). Now, experimental data reveal that prolonged treatment with ibrutinib, unlike other treatments of CLL, can reverse the T-cell defects associated with this form of leukaemia, and thus enhance the effectiveness of autologous chimeric antigen receptor (CAR) T-cell therapy.

Using a translational approach, researchers found that T cells from patients with CLL, compared with those derived from patients with multiple myeloma (MM) or acute lymphocytic leukaemia (ALL), have proliferative defects that significantly reduce the *ex vivo* expansion of these cells in response to synthetic antigens. However, T cells from patients with CLL who received 5–11 cycles of ibrutinib treatment seemed to lose these proliferative defects and had levels of *ex vivo* expansion similar to T cells from patients with MM. Furthermore, T cells from these ibrutinib-treated patients exhibited robust and uniform expansion *ex vivo* after anti-CD19 gene transfer, unlike many of those derived from patients who were ibrutinib-naive, or had received only one cycle of ibrutinib treatment; this improved T-cell viability was maintained *in vivo*, 90 days after infusion into patients with CLL.

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To test the effectiveness of ibrutinib administered with anti-CD19 (CTL019) CAR T cells, researchers used a mouse xenograft model of advanced-stage human CLL. Treatment with ibrutinib alone, or infusion of CTL019 cells alone, had no notable therapeutic effect; however, mice that received the combination of ibrutinib and CTL019 T cells had significantly improved CTL019-cell engraftment, and significantly increased overall survival.

These data reveal a promising interaction between ibrutinib and CAR T-cell viability and engraftment that has the potential to improve the outcomes of CAR T-cell therapy in patients with CLL, and possibly the outcomes of patients with other cancers.

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ORIGINAL ARTICLE Fraietta J. A. *et al.* Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. *Blood* http://dx.doi.org/10.1182/blood-2015-11-67913 (2016)