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HAEMATOLOGICAL CANCER

Lenalidomide improves response

Lenalidomide consolidation can repair T-cell synapse signalling in patients with chronic lymphocytic leukaemia (CLL) and improve response in those treated with immunotherapy, according to a phase II consolidation trial published in *Blood*. "There was both a clinical and an immunological rationale for this study," says Tait Shanafelt from the Mayo Clinic, who is the co-primary investigator of the trial. He continues, "from the clinical perspective, we know that PCR (pentostatin, cyclophosphamide and rituximab) chemoimmunotherapy (CIT) is highly effective for patients with CLL, but causes extensive damage to T-cells. Because of that, there has been interest in consolidation strategies ... ideally with agents that don't cause damage to the immune system."

Molecular and functional studies had previously defined a novel mechanism whereby tumour cells are able to induce T-cell defects including deregulated cytoskeletal signalling, impaired immunological synapse formation and diminished effector mechanisms via direct-contact signalling. "An important translational finding from my preclinical research was that lenalidomide repairs T-cell synapse signalling and activation of endogenous T-cell function," says the other co-primary investigator, Alan Ramsay from Barts Cancer Institute London, "this science led to the use of the immune synapse bioassay in this latest *in vivo* human clinical study."

In total, 34 out of 44 patients completed six cycles of PCR induction and received lenalidomide consolidation. Nine patients tolerated lenalidomide and had their dose increased to 10 mg/day. Dose reduction to 5 mg every other day was required in 18 patients, and in three of these patients the dose was reduced to 5 mg twice a week due to haematological toxicity. Although toxicity affected patients, there were no cases of tumour lysis syndrome or tumour flare reaction.

Out of the 34 patients who received lenalidomide, eight patients had an improved quality of response and some patients with residual disease post-CIT induction converted to a minimal residual disease-negative remission. "In essence, from a clinical view, some 24% of patients treated with lenalidomide had an improved response," says Shanafelt. Comparison with a historical study further suggests that lenalidomide consolidation prolongs time to salvage therapy and results in more durable remissions.

An increase of T-cell synapse activity was observed after PCR induction in 23 of 28 patients, and notably those patients who had a stronger response to induction therapy had a better recovery of synapse activity than those patients who only achieved a partial remission, or no response—illustrating the utility of the T-cell immune synapse bioassay for measuring T-cell function following CIT regimens. "The T-cell immune synapse bioassay allows longitudinal analysis of T-cell function during the clinical trial," comments Ramsay, "we plan to utilize the immune synapse bioassay in combination with biomarkers of T-cell activation to measure anti-tumour T-cell function following novel targeted therapy and immunotherapy treatment approaches in cancer."

Importantly, T-cell function was improved and maintained in all patients following lenalidomide consolidation. Enhancing T-cell function might be one of the ways lenalidomide improves the depth of remission after CIT in patients with CLL. The authors suggest that clearance of immunosuppressive tumour cells might influence repair of function, thus highlighting the suitability of using PCR CIT in combination with immunotherapy. "There remains great interest in finding approaches to improve the depth of remission in CLL," says Shanafelt, "randomized trials of lenalidomide consolidation are ongoing. There are also a number of new treatments that target the B-cell pathway, such as ibrutinib, that are in development. The hope is that these strategies will have the same efficacy, but will be less toxic."

Bryony Jones

Original article Shanafelt, T. D. *et al*. Long-term repair of T-cell synapse activity in a phase 2 trial of chemoimmunotherapy followed by lenalidomide consolidation in previously untreated chronic lymphocytic leukemia (CLL). *Blood* doi:10.1182/blood-2012-12-470005