VACCINE-SPECIFIC IMMUNE RESPONSES CORRELATE WITH CLINICAL BENEFIT

The efficacy of cancer vaccines depends on the identification of tumor antigens that elicit a successful immune response. Walter and colleagues used an antigen discovery platform to generate the IMA901 vaccine, which is composed of multiple tumor-associated peptides (TUMAP) that were validated as naturally presented, overexpressed cancer antigens. This vaccine was then tested in clinical trials for the treatment of advanced renal cell cancer (RCC). In a phase I trial of 28 patients, the IMA901 vaccine was well tolerated and induced T-cell responses in 20 patients, as measured by in vitro detection of TUMAP antigen-specific T cells. Retrospective analysis showed that response to multiple TUMAPs led to an increase in disease control and that lower prevaccine numbers of regulatory T cells \( (T_{reg}) \) cells, which suppress T-cell-mediated immunotherapy, were correlated with this multipepptide immune response. The role of \( T_{reg} \) cells was further evaluated in a subsequent phase II study, in which 68 patients with metastatic RCC were given IMA901 or IMA901 in combination with a single-dose pretreatment of cyclophosphamide, which inhibits \( T_{reg} \) cells. As in the phase I trial, there was a high immune response rate, and the response to multiple TUMAPs extended patient survival time. Moreover, treatment with cyclophosphamide was associated with a prolonged median overall survival, particularly among immune responders, in which cyclophosphamide treatment led to a reduction in proliferating \( T_{reg} \) cells, suggesting that cyclophosphamide enhances the antitumor benefit of vaccine-induced immune responses. In addition, pretreatment analysis of cellular and serum biomarkers identified 2 subgroups of myeloid-derived suppressor cells and the proteins APOA1 and CCL17 as predictors of immune responses and increased overall survival in RCC. These results suggest that rational antigen discovery and validation, combined with monitoring of T-cell responses and biomarkers, may enable the development of effective cancer vaccines.

Proapoptotic Death Receptor Agonists Act as Vascular Disrupting Agents


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