Letter to the Editor

Antagonist Antibodies to PD-1 and B7-H1 (PD-L1) in the Treatment of Advanced Human Cancer—Letter

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We read with great interest the comprehensive and timely review article by Sznol and Chen (1) in the March 1, 2013 issue of Clinical Cancer Research. This review summarized the PD-1 costimulatory (coinhibitory) signaling pathway in activated T cells mediated by PD-L1 or PD-L2 binding and its implications for antitumor therapy.

However, the authors did not comment on the strategy of combining PD-1 signaling blockade with adoptive T-cell therapy using antigen-specific T cells or tumor-infiltrating lymphocytes (TIL). Two recent murine studies have reported synergistic effects of anti-PD-1 or anti-PD-L1 blocking antibodies on CD8+ T-cell adoptive transfer in the B16 melanoma model and showed that the combination synergistically controlled B16 melanoma growth (2, 3). In each case, PD-1/PD-L1 blockade prevented downstream suppression of T-cell signaling and increased the trafficking and infiltration of CD8+ T cells into tumors and increased antitumor IFN-γ and CTL activity in the tumor (2, 3). A more recent study by Antony and colleagues using adoptive transfer of TRP-1-specific CD4+ T cells found that anti-PD-L1 together with Treg depletion (which also occurs during lymphodepletion regimens given to patients prior to receiving TIL) eradicated B16 melanoma recurrence (4). These papers, as well as other data from our group (5), strongly support the application of T-cell checkpoint blockade in clinical trials using adoptive cell therapy with autologous TIL for metastatic melanoma.

TIL therapy with IL-2 using the current nonmyeloablative preconditioning regimen has been quite effective, and durable responses have been observed in up to 50% of patients despite progression after first, second, and even third line treatments for stage IIIc–IV melanoma (5). Unpublished studies from our respective groups have found that subpopulations of human melanoma TIL express high levels of PD-1 indicative of a high state of activation, and that blocking PD-1 signaling significantly enhances tumor antigen-specific CD8+ TIL proliferation and IFN-γ production. Thus, PD-1 is a critical target in TIL adoptive cell therapy denoting an activated T-cell population in the tumor microenvironment that is highly tumor specific, which can also be further targeted using PD-1 blocking agents to increase their persistence and antitumor activity in vivo. Indeed, we have found that human CD8+ TIL infiltrating melanoma lesions following adoptive transfer are mostly PD-1+ (Radvanyi et al.; unpublished data). PD-1 blocking therapy given before TIL adoptive transfer can also increase T-cell infiltration into metastatic sites facilitating improved ex vivo TIL expansion for adoptive cell therapy. Studies from our clinical trial sites are currently testing this hypothesis. In addition, the effects of prior anti-CTLA-4 (ipilimumab) and BRAFV600E inhibitor therapies can also be analyzed in this context.

From a conceptual standpoint, combining TIL with PD-1 blockade therapy also offers tremendous opportunity to study predictive biomarkers in tumor biopsies and blood in a unique setting where an oligoclonal and enriched tumor-specific T-cell population is transferred whereas endogenous T cells are transiently absent due to prior lymphodepletion. Collectively, these points, together with the data from mouse models and with isolated human TIL in vitro, strongly argue for initiating clinical trials testing the combination of TIL and PD-1 blockade.

Disclosure of Potential Conflicts of Interest

J. Weber is a consultant/advisory board member of Bristol-Myers Squibb, Merck, GlaxoSmithKline, and Genentech. No potential conflicts of interest were disclosed by the other authors.

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