Testimony from the Bedside: From Coley's Toxins to Targeted Immunotherapy

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A new clinical study reported in the *New England Journal of Medicine* unveils the long-awaited outcome of anti-CTLA-4 therapy for melanoma. It provides grounds for continued enthusiasm for cancer immunotherapy, deepens our thoughts on underlying mechanisms, and suggests exciting next steps.

The immune system's ability to recognize and kill tumor cells has been appreciated since William Coley, who suspected a causal link between streptococcal infection and tumor regression in his patient, "therapeutically" infected those having unresectable cancer with live or mixed killed bacteria, and brought some actual success more than a century ago (Coley, 1893). The cancer remission was thought to occur because of the immunostimulatory effects of Coley's inoculum. The emerged concept of immunotherapy, however, did not immediately rise to a status in cancer treatment broadly comparable to surgery, radiotherapy, and chemotherapy. However, immunotherapy has been received with increasing enthusiasm with our better understanding of tumor immunology.

Metastatic melanoma is one of the most aggressive cancers and is also highly refractory to conventional cancer therapy. A recent report of a Phase 3 clinical study assessing the efficacy and adverse effects of ipilimumab (Hodi et al., 2010) ushers in a new stage of immune-based treatment of advanced melanoma, and perhaps of cancer immunotherapy in general. Ipilimumab is a fully human monoclonal antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) that has shown promising results in potentiating a tumor-specific immune response and limiting metastatic melanoma and other tumors (Fong and Small, 2008). This new study of more than 600 advanced melanoma patients demonstrates that administration of the antibody, either alone or in conjunction with a peptide vaccine targeting the melanoma-derived antigen gp100, significantly extended overall survival when compared to vaccine alone. Improvements were seen in median survival and survival 1 and 2 years posttreatment. These are remarkable outcomes for melanoma clinical trials performed at a similar scale and represent the culmination of successful clinical translation of anti-CTLA-4 therapy since its inception and preclinical investigation by Allison and colleagues (Leach et al., 1996).

How does CTLA-4 blockade lead to tumor regression? The T cell-mediated immune response, including to tumors, kicks in when antigens are displayed to T cells by antigen-presenting cells (APCs). In addition, APCs express CD80 and CD86 on their surface for binding to CD28 on T cells to activate costimulatory signal, which is crucial for the induction of T cell proliferation and the onset of T cell immunity. APC activation of T cells is, however, subject to tight regulation. CTLA-4, structurally akin to CD28, is newly expressed on activated T cells, and, with its higher affinity for CD80 and CD86, replaces CD28 in APC-T cell interactions (Teft et al., 2006). Unlike CD28, CTLA-4 transmits an inhibitory intracellular signal in T cells to dampen the antigen-induced biochemical events. CTLA-4 expression is therefore important for limiting T cell activation and preventing an exaggerated immune response, but limits the T cell-mediated immune response against tumors. Interference with CTLA-4 function thus provides a point of targeting the immunosuppressive environment of tumor-bearing hosts.

The new study finds that the gp100 vaccine did not provide benefit beyond the effects of ipilimumab alone (Hodi et al., 2010), which suggests that inherent tumor immunogenicity may be increased to a clinically significant degree just by unfettering host immunity from certain endogenous regulatory mechanisms. What was less certain is whether such a boon would be granted without paying too high a price. Patients treated with ipilimumab manifested diverse immune-related adverse events, ranging from skin rashes to colitis, that were predictable from the action mechanism of the therapy and were manageable in many cases with steroid or anti-tumor necrosis factor agents (Hodi et al., 2010). Regardless, immune-related side effects will probably continue to be a major complication in using CTLA-4 antibodies for cancer. Many questions arise regarding the efficacy and adverse events of potentiating immune responses in cancer patients: Do antitumor immunity and autoimmunity depend on the same effector mechanisms of T cell immunity? Could the immune side effects be alleviated while preserving tumor-specific immune responses? Would there be a therapeutic window that differentiates self-destructive and tumor-killing reactions? The Phase 3 ipilimumab study offered new promises and also emphasizes new questions and opportunities.

We see several pieces of new information from mouse model studies that await clinical investigation. There is little doubt that CTLA-4 functions in drawing in the reins of CD28 in antigen-stimulated T cells. CTLA-4 is also expressed in $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells, which are a specific group of T cells with potent and broad immunosuppressive activities and play a central role in immune tolerance. This understanding prompted curiosity about the

specific roles of CTLA-4 in conventional activated T cells and Treg cells. With a conditional gene ablation strategy, it was shown that mice lacking Treg cell-specific CTLA-4 expression were prone to spontaneous autoimmune disease, albeit less severely than CTLA-4 null mice (Wing et al., 2008). On the other hand, restoration of CTLA-4 induction to activated conventional T cells but not Treg cells prevented infiltration of tissue-damaging T cells in the gastrointestinal and other vital tissues of CTLA-4 null animals (Jain et al., 2010). These results indicated that loss of CTLA-4 expression in Treg cells alone was sufficient for generation and aberrant activation of self-reactive T cells, but a full-fledged autoimmune disease still relied on CTLA-4 acting in *cis* in activated conventional T cells. Importantly, with mice expressing human instead of mouse CTLA-4 in specific subsets of T cells (therefore selectively targeted by a human CTLA-4-directed antibody), it was demonstrated that CTLA-4 blockade in conventional T cells is more important for inducing immune-mediated tumor regression, but maximal antitumor responses occurred only when the antibody was allowed to target both conventional T cells and Treg cells (Peggs et al., 2009). Taken together, these findings illustrate the potential that CTLA-4-mediated immunosuppressive mechanisms can be dissected into distinct functional modules depending on the cell types and processes in which CTLA-4 is expressed and functioning.

How does this work impact advanced melanoma patients? The application of CTLA-4 blockade seems destined to become a new standard of care for these patients, who otherwise have few options. Although the current trial had required patients to express HLA-A2 because of its importance for gp100 responsiveness (control arm), prior evidence suggested that HLA-A2 should not be required for efficacy of CTLA-4 blockade. The tail of the survival curve suggests a subpopulation for whom survival is significantly durable. Which features (of tumor and/or host) might predict efficacy or longevity of response? What mechanism(s) account for acquisition of resistance? How might those mechanisms be therapeutically targeted?

Today the melanoma community is bursting with excitement, both because of this striking efficacy of ''targeted immunotherapy'' and because of additional evidence of major clinical responses with targeted kinase-inhibitor therapies in advanced melanoma patients with mutations in either c-Kit or BRAF. Although these targeted approaches are transforming the oncologist's armamentarium against advanced melanoma, sustainable remission (i.e., cure) remains painfully elusive. An obvious next step is to combine these agents. Indeed, recent preclinical data have shown enhanced melanoma immunogenicity upon BRAF(V600E) suppression (Boni et al., 2010). The mutant-selective action of several BRAF(V600E)-targeted agents offers the key advantage of sparing MAP kinase pathway activity within host immune cells upon systemic drug administration. The ability of mechanism-based, targeted molecular strategies to exhibit major clinical efficacy in one of the most aggressive human cancers is a massive achievement. The opportunity to combine such immune-targeted and oncoprotein-targeted approaches is groundbreaking, both for scientific advancement and hopefully for patients.

REFERENCES

Boni, A., Cogdill, A.P., Dang, P., Udayakumar, D., Njauw, C.N., Sloss, C.M., Ferrone, C.R., Flaherty, K.T., Lawrence, D.P., Fisher, D.E., et al. (2010). Cancer Res., in press. Published online June 15, 2010. 10.1158/0008-5472.CAN-10-0118.

Coley, W. (1893). Am. J. Med. Sci. *105*, 487–510.

Fong, L., and Small, E.J. (2008). J. Clin. Oncol. *26*, 5275–5283.

Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D., Hassel, J.C., et al. (2010). N. Engl. J. Med., in press. Published online June 14, 2010. 10.1056/NEJMoa1003466.

Jain, N., Nguyen, H., Chambers, C., and Kang, J. (2010). Proc. Natl. Acad. Sci. USA *107*, 1524–1528.

Leach, D.R., Krummel, M.F., and Allison, J.P. (1996). Science *271*, 1734–1736.

Peggs, K.S., Quezada, S.A., Chambers, C.A., Korman, A.J., and Allison, J.P. (2009). J. Exp. Med. *206*, 1717–1725.

Teft, W.A., Kirchhof, M.G., and Madrenas, J. (2006). Annu. Rev. Immunol. *24*, 65–97.

Wing, K., Onishi, Y., Prieto-Martin, P., Yamaguchi, T., Miyara, M., Fehervari, Z., Nomura, T., and Sakaguchi, S. (2008). Science *322*, 271–275.