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Balancing tumor immunity and inflammatory pathology

Glenn Dranoff

Department of Medical Oncology and Cancer Vaccine Center, Dana-Farber Cancer Institute, and Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Glenn Dranoff: glenn_dranoff@dfci.harvard.edu

Gertrude Elion and George Hitchings, pioneers of cancer chemotherapy, taught that the search for selectivity in drug discovery often involved ‘enlightened empiricism’ together with a healthy dose of serendipity¹. Two recently published clinical trials that report the remarkable antitumor effects of combination therapy using antibodies targeting programmed death-1 (PD-1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4)^{2,3}, two negative immune regulatory molecules expressed on T cells, illustrate how these principles of drug development apply to cancer immunotherapy.

The passive transfer of tumor-reactive T cells via bone marrow transplantation and the use of tumor-selective antibodies are well-established cancer therapies, but the crafting of effective strategies to stimulate endogenous antitumor immunity has long proved elusive⁴. As many attempts at amplifying positive immune signaling networks failed to elicit clinically significant tumor destruction, an alternative approach aims to do the opposite—interfering with immune checkpoints that attenuate the function of activated T cells in the tumor microenvironment⁵. Inspired by promising findings in experimental tumor models, two large randomized studies showing that a fully human antibody to CTLA-4 (ipilimumab) prolonged survival in patients with advanced melanoma, with about 20% of treated subjects achieving durable clinical benefits (which in some cases exceeded ten years), finally took place. However, the treatment also caused a diversity of inflammatory pathologies, most commonly affecting the intestinal tract, skin and endocrine tissues, consistent with the phenotype of mice lacking CTLA-4. Serious toxicity was observed in about 20% of treated subjects, but this could be dissociated from the antitumor effects, indicating that tumor immunity and inflammatory pathology are closely related but, nonetheless, separable.

Motivated in large measure by the success of ipilimumab in patients, clinical exploration of blocking antibodies to PD-1 also began. Although many studies had delineated a key role for PD-1 in limiting T cell responses in diverse settings, including experimental tumors⁶, they did not anticipate the robust antitumor activities of anti-PD-1 antibodies in patients with cancer. The recent work with lambrolizumab² and an earlier trial using nivolumab⁷ have convincingly established the ability of anti-PD-1 antibodies to trigger clinically significant

tumor destruction in a high proportion of patients with advanced melanoma. The impressive durable regressions revealed in these two investigations exceed expectations gleaned from preclinical systems, highlighting some of the challenges in using murine models as a guide to designing new therapeutics for humans⁸ and illustrating the continuing role of serendipity in drug development.

About 38% of 135 individuals with metastatic melanoma treated at any dose-level of lambrolizumab and 52% at an apparently optimal level displayed a tumor response; remarkably, 77% of all patients showed some reduction in tumor burden². Even though small-molecule inhibitors of BRAF and MEK, key oncogenic drivers in melanoma, may also accomplish tumor regressions in genetically defined subsets, these typically are of short duration because of the rapid emergence of drug-resistant tumor cells⁹. In contrast, most responses to PD-1 blockade were sustained, although longer follow-up is required to clarify the durability of tumor control more precisely.

Anti-PD-1 antibodies may have a more favorable safety profile compared to ipilimumab, although severe pneumonitis developed in a small number of patients⁷. The reduction in toxicity is in accordance with the milder inflammatory pathology in PD-1– compared to CTLA-4-deficient mice, which probably reflects the more restricted role of PD-1 in constraining ongoing immune responses in contrast to the requirement for CTLA-4 in immune homeostasis⁶. Encouraging anti-tumor effects and safety profiles have also been described with blocking antibodies to PD ligand-1 (PD-L1)¹⁰, underscoring the therapeutic potential of interfering with this pathway in different ways. Moreover, anti-PD-1 and anti-PD-L1 antibodies seem to be broadly active against cancer, provoking tumor regressions in patients with advanced non-small-cell lung carcinoma, renal cell carcinoma and other tumor types¹¹.

Given the clinical efficacy of infusing anti-CTLA-4 or anti-PD-1 antibodies as monotherapy and the related but distinct functions of the molecules in the immune system⁶, combinations of the two agents might prove to be more potent than either alone. Anti-PD-1 antibodies elicited similar response rates in patients who were previously treated with ipilimumab (and presumably derived minimal or no clinical benefit) and in those who were not². This suggests PD-1-mediated immune inhibition may act, at least in some cases, to restrict the impact of CTLA-4 inhibition, which can increase amounts of PD-L1 in the tumor microenvironment (owing to an unleashed interferon- γ production by T cells) that can then engage PD-1 on activated T cells to dampen proliferation and cytotoxicity.

To explore this idea further, Wolchok *et al.*³ administered nivolumab and ipilimumab concurrently to 53 patients with metastatic melanoma. Antitumor effects were evident in 65% of subjects, including objective responses in 40%. In contrast to sequential treatment, the concurrent infusion of anti-CTLA-4 and anti-PD-1 antibodies led to a high rate of serious inflammatory toxicity (53% of patients), which often required immunosuppressive therapy for management. These results imply that CTLA-4 and PD-1 have nonredundant roles in the maintenance of immune tolerance in humans, an insight that should inform our understanding of the pathogenesis of some autoimmune disorders¹². Randomized clinical trials to delineate more thoroughly the potential advantages and risks of concurrent or

sequential combination therapy versus individual blockade of CTLA-4 or PD-1 are underway (Fig. 1).

The elevated incidence of toxicity with simultaneous CTLA-4 and PD-1 inhibition emphasizes the need to craft complementary strategies that afford a more favorable therapeutic index for antibody treatment. This might be accomplished through preferential targeting of antitumor T cells rather than homeostatic immune networks that preserve tissue integrity. Because CTLA-4 and PD-1 are both expressed upon T cell activation, combinatorial schemes should be directed toward enhancing the numbers of stimulated tumor-reactive T cells, which may allow less intense levels of immune checkpoint blockade to amplify tumor-specific immunity more selectively. Cancer vaccines that deliver tumor antigens in an optimal spatial and temporal fashion while promoting maturation of dendritic cells, which amplify antitumor T cell activation, constitute one promising approach to expand the effector T cell pool. Treatment strategies that may evoke immunogenic tumor cell death *in situ*, such as oncolytic viruses, focal radiation, tumor-directed antibodies (and drug conjugates) and some small-molecule inhibitors or cytotoxic agents, are also attractive options⁹. Antibodies targeting other immunoregulatory molecules expressed on T cells or natural killer cells, an innate cell population with potent antitumor cytotoxicity potential¹³, are additional compelling possibilities.

An alternative scheme to improve therapeutic index might aim to restore homeostatic networks that are compromised with immune checkpoint blockade. A recent clinical trial in patients with advanced melanoma suggests that systemic administration of the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) may reduce the incidence of severe colitis and pneumonitis caused by anti-CTLA-4 antibodies yet increase overall survival¹⁴. Although the precise basis for these intriguing findings remains to be clarified, the roles of GM-CSF in both supporting regulatory T cells that attenuate inflammation in the intestinal and pulmonary mucosa and augmenting antitumor immunity might be involved¹⁵.

The clinical success of CTLA-4 and PD-1 blockade alone and together may come as a surprise to the greater cancer research and cancer medicine communities. Earlier uncertainty regarding a role for immunity in tumor pathogenesis reinforced the investigation of tumor cell-autonomous alterations and encouraged the evaluation of therapeutics using human tumor cell xenografts propagated in immune-deficient mice. Nonetheless, the demonstration that two molecules expressed on T cells may be the difference between survival and death in a significant proportion of patients with advanced cancer should prompt a reexamination of these research strategies and focus attention toward illuminating the ways in which specific steps of transformation are directly coupled to immune escape¹⁶. A deeper understanding of the links between oncogenesis and host evasion should accelerate the crafting of new combinatorial treatments that intensify tumor immunity but temper inflammatory pathology.

References

1. Elion GB. Cancer Res. 1985; 45:2943–2950. [PubMed: 3891079]
2. Hamid O, et al. N. Engl. J. Med. 2013; 369:134–144. [PubMed: 23724846]
3. Wolchok JD, et al. N. Engl. J. Med. 2013; 369:122–133. [PubMed: 23724867]
4. Mellman I, Coukos G, Dranoff G. Nature. 2011; 480:480–489. [PubMed: 22193102]

5. Sharma P, Wagner K, Wolchok JD, Allison JP. *Nat. Rev. Cancer.* 2011; 11:805–812. [PubMed: 22020206]
6. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. *Annu. Rev. Immunol.* 2008; 26:677–704. [PubMed: 18173375]
7. Topalian SL, et al. *N. Engl. J. Med.* 2012; 366:2443–2454. [PubMed: 22658127]
8. Dranoff G. *Nat. Rev. Immunol.* 2011; 12:61–66. [PubMed: 22134155]
9. Vanneman M, Dranoff G. *Nat. Rev. Cancer.* 2012; 12:237–251. [PubMed: 22437869]
10. Brahmer JR, et al. *N. Engl. J. Med.* 2012; 366:2455–2465. [PubMed: 22658128]
11. Brahmer JR, Pardoll DM. *Cancer Immunol. Res.* 2013; 1:85–91. [PubMed: 24777499]
12. Ploegh HL. *Cancer Immunol. Res.* 2013; 1:5–10. [PubMed: 24777244]
13. Nowarski R, Gagliani N, Huber S, Flavell RA. *Cancer Immunol. Res.* 2013; 1:77–84. [PubMed: 24777498]
14. Hodi FS, et al. *J. Clin. Oncol.* 2013; 31 abstr. CRA9007.
15. Jinushi M, et al. *J. Clin. Invest.* 2007; 117:1902–1913. [PubMed: 17557120]
16. Schreiber RD, Old LJ, Smyth MJ. *Science.* 2011; 331:1565–1570. [PubMed: 21436444]

Figure 1.

The need to balance the antitumor activity and toxicity of single and combinatorial immunotherapies. Blocking the immune inhibitory molecules CTLA-4 and PD-1, alone or in combination, results in variable levels of antitumor activity and toxicity. Further understanding the human antitumor immunity and immunopathology will pave the way to improved treatments to achieve immune-mediated tumor destruction with minimal pathology.