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Intensifying Tumor Immunity through Combination Therapy

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Combinations of cytotoxic chemotherapies are a mainstay of cancer treatment. Historically, the integration of multiple agents with distinct mechanisms of action and non-overlapping toxicities yielded curative regimens for some solid and hematologic malignancies¹. Currently, the clinical development of targeted drugs that block specific oncogenic pathways is proceeding along a similar course. For example, selective B-RAF inhibitors, which accomplish tumor regressions in a majority of malignant melanoma patients who harbor a V600E mutant B-RAF allele, are now being evaluated in conjunction with MEK inhibitors in an effort to suppress the emergence of drug resistant clones².

In this issue of *The Lancet Oncology*, clinical studies of van den Eertwegh and colleagues and Madan and coworkers provide initial evidence that combining immunotherapies constitutes another important investigative path. During the past two years, randomized Phase III trials have validated the idea that manipulating anti-tumor immunity can generate meaningful clinical benefits³. In castration resistant metastatic prostate carcinoma patients, the administration of a cancer vaccine (Provenge[®]) composed of autologous peripheral blood mononuclear cells exposed ex vivo to a fusion of prostatic acid phosphatase, a protein overexpressed in prostate carcinomas, and granulocyte-macrophage colony stimulating factor (GM-CSF), a cytokine that enhances dendritic cell function, prolongs median survival by approximately four months, with only minimal toxicity⁴. In advanced melanoma patients, the infusion of an antibody (Yervoy[®]) that blocks cytotoxic T lymphocyte associated antigen-4 (CTLA-4), a critical negative immune regulator that restrains anti-tumor T cell responses, similarly increases median survival by four months, with 15–20% of subjects achieving long-lasting benefits^{5, 6}. While the therapeutic effects of Yervoy[®] are associated with a risk of inflammatory pathology, most toxicities can be readily managed. Collectively, these clinical investigations have established tumor vaccines and blockade of negative immune regulation as efficacious cancer therapies.

Preclinical experiments in murine models provide a compelling rationale for combining these two immunologic strategies⁷. Cancer vaccines enhance the capacity of professional antigen presenting cells, particularly dendritic cells, to capture and process tumor antigens, empowering them with the ability to efficiently stimulate tumor-specific T cells, which mediate tumor cell killing. Vaccine-induced T cell responses are limited, however, by CTLA-4, which is expressed upon T cell activation and signals to attenuate proliferation and effector function. Correspondingly, the coupling of vaccines and CTLA-4 blockade intensifies tumor immunity, resulting in synergistic anti-tumor effects in many models. Although murine systems have proven somewhat limited for predicting the toxicities of CTLA-4 blockade in patients, the preclinical studies nonetheless indicate that this combinatorial strategy may be tolerable⁸.

To begin exploring the activity of combined therapy in patients, van den Eertwegh and colleagues employed a cellular vaccine composed of two allogeneic prostate cancer cell

lines engineered to secrete GM-CSF (GVAX[®]), whereas Madan and coworkers used recombinant pox viruses (PSA-TRICOM[®]) encoding prostate specific antigen and three T cell costimulatory molecules (CD80, ICAM-1, and LFA-3) along with recombinant GM-CSF protein as an adjuvant. Earlier work showed that either vaccine as a single agent could augment anti-tumor immunity in some patients. A Phase II randomized trial of PSA-TRICOM[®] raised the possibility that vaccination might improve overall survival, thereby motivating the initiation of a large Phase III study to address this issue rigorously⁹. GVAX showed promising results in Phase II trials as well, but in randomized Phase III studies failed to meet primary efficacy endpoints¹⁰. Both vaccination strategies manifest a very favorable safety profile, with toxicities limited to minor local skin reactions and constitutional symptoms.

In both of the trials reported in this issue, following an initial vaccination Yervoy[®] was administered concurrently with further immunizations over the course of several months. The combination therapies were generally well tolerated. Serious (grade 3 or 4) inflammatory pathologies were observed in each study, but these were manageable and did not appear more frequent than in prior investigations of CTLA-4 antibody blockade alone; the major toxicities were endocrinopathies (including hypophysitis), colitis, hepatitis, pneumonitis, and dermatitis. The combination therapies also stimulated host reactivity, with convincing evidence for enhanced dendritic cell activation and heightened anti-tumor T cell and antibody responses. Additionally, objective anti-tumor effects including decreases in PSA levels and tumor regressions were noted in a minority of subjects.

The important studies of van den Eertwegh et al. and Madan et al. should catalyze much more detailed investigation of combining cancer vaccines with CTLA-4 antibody blockade. Little is currently known regarding the kinetics of generating protective host responses or the requirements for maintaining these reactions. Thus, the determination of optimal dose, duration, and sequencing of the combined therapy will require comprehensive immune monitoring in many more patients, with a coupling of these results to clinical outcomes¹¹. As tumor immunity is more consistently intensified through combinatorial approaches, the opportunities for integration with targeted therapy will become increasingly compelling. Indeed, concurrently addressing both tumor cell intrinsic and host dependent pathways may provide the best possibility for durable disease control.

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