Future Approaches in Immunotherapy

Brian Rini

Advances in our understanding of the complex mechanisms of immune regulation and the interactions between tumor cells and the immune system have provided a solid foundation for advancing cancer immunotherapy and have inspired novel therapeutic strategies. Optimizing the effectiveness of immunotherapy will require targeting the antitumor immune response at multiple levels, and this may be achieved through synergistic combinations. Examples include combining two cancer vaccines to achieve a "prime and boost" effect, combining two immune checkpoint inhibitors, combining immunotherapy with targeted agents, or combining immunotherapy with low-dose chemotherapy or radiation. Immune checkpoint inhibitors, such as ipilimumab and nivolumab, will likely play an important role in the future of immunotherapy. The ability to block key pathways by which tumor cells seek to evade or suppress the immune response is critical to realizing the potential of cancer immunotherapy. Other exciting advances include recombinant oncolytic viruses and adoptive transfer of chimeric antigen receptor T cells. However, many challenges remain if durable tumor eradication with minimal toxicity is to be achieved in a broader population of cancer patients.
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Recent advances in our understanding of the underlying mechanisms of tumor-induced immune suppression and immune checkpoints are converging to advance the field of immuno-oncology. Optimizing the effectiveness of immunotherapy will require targeting the antitumor immune response at multiple levels. Immunotherapies can be broadly characterized into three classes: (1) those that increase the frequency of tumor-specific T cells (eg, tumor vaccines, interleukin [IL]-2, and cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] inhibitors); (2) those that overcome immune suppressive mechanisms within the tumor microenvironment (eg, inhibitors of programmed cell death 1 [PD-1], indoleamine-2,3-dioxygenase [IDO], lymphocyte activation gene 3 [LAG-3], and regulatory T cell [Treg] depletion); and (3) those that trigger innate immune activation and inflammation in the tumor microenvironment (eg, Toll-like receptor [TLR] agonists, type I interferons, and inhibitors of myeloid-derived suppressor cells [MDSCs]).[1] Many agents are now in development within each of these distinct classes (see article by Disis in this supplement), and a range of new strategies is being investigated, most notably combinations of these agents.

COMBINATION THERAPY AS FUTURE OF IMMUNOTHERAPY

One strategy to improve the effectiveness of immunotherapy is to look for synergistic combinations. This may involve combining immunotherapy with traditional cytotoxics such as chemotherapy or radiation, or combining two immunotherapeutic agents that have complementary mechanisms of action.[2] The former strategy has been employed for more than a decade in the form of immunoconjugates that induce both direct and immune-mediated cytotoxicity.[3] Examples include radiolabeled anti-CD20 monoclonal antibodies (mAbs) such as ibritumomab tiuxetan and tositumomab for the treatment of B-cell lymphoma, and conjugates of mAbs with cytotoxic agents such as gemtuzumab ozogamicin for acute myelogenous leukemia (AML) and trastuzumab emtansine for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Combining two or more immunotherapeutic agents

Cleveland Clinic, Cleveland, OH.
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Address correspondence to Brian Rini, MD, FACP, Solid Tumor Oncology, Cleveland Clinic Main Campus, Mail Code R35, 9500 Euclid Ave, Cleveland, OH 44195. E-mail: rinib2@ccf.org.
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also appears promising, but the potential for additive toxicity must be considered. To date, this approach has mainly been limited to co-administration of well-characterized immune adjuvants, such as IL-2 or granulocyte-macrophage colony-stimulating factor (GM-CSF), together with tumor-specific mAbs, tumor-infiltrating lymphocytes (TILs), or cancer vaccines, in an attempt to stimulate the recruitment and/or activation of immune effector cells.[4] More recently, multiple examples of successful immunotherapy combinations have been evaluated in preclinical models,[1] and clinical studies have begun to explore the safety and effectiveness of these new combinations. Examples include combining two vaccines to achieve a so-called "prime and boost" effect, combining two immune checkpoint inhibitors with distinct mechanisms of action, or combining an immune checkpoint inhibitor with a vaccine. Another area of active investigation is the combination of immune checkpoint inhibitors with chemotherapy and targeted therapies.

Combinations of Two or More Immunotherapies

The concept behind vaccine combinations is to first prime the immune response to tumor antigens, and then boost the response with a second vaccine. This approach was recently tested in patients with metastatic pancreatic cancer, using a combination of pancreatic GVAX (Cell Genesys, Inc, San Francisco, CA) and CRS-207.[5] Pancreatic GVAX is a polyvalent vaccine containing irradiated, GM-CSF–secreting, allogeneic pancreatic cancer cell lines, and is administered intradermally. CRS-207 contains live-attenuated *Listeria monocytogenes*, which expresses mesothelin and stimulates innate and adaptive immunity. In animal models, the combination of GVAX and CRS-207 was synergistic. In the randomized phase II study of this combination, low-dose cyclophosphamide was administered prior to GVAX to inhibit Tregs, and overall survival (OS) was significantly improved by the combination of GVAX followed by CRS-207 compared with GVAX alone. Among patients who received at least three doses of vaccine (including at least one dose of CRS-207 in the combination arm), median OS was 9.7 months with the combination versus 4.6 months with GVAX alone (hazard ratio [HR] = 0.44; $P = .007$).[5] Moreover, this improvement in OS was achieved with manageable toxicity (local reactions to GVAX and transient fevers, rigors and lymphopenia after CRS-207). Further follow-up and supplemental studies are needed. Additional strategies to improve the effectiveness of therapeutic vaccines, such as combinations with Treg depletion (using either denileukin diftitox or anti-CD25 mAbs), homeostatic cytokines (eg, IL-7), or immune checkpoint inhibitors, are being investigated.[1] For example, a phase I trial in patients with advanced pancreatic cancer is currently testing the combination of the CTLA-4 inhibitor, ipilimumab, with a pancreatic tumor cell vaccine (NCT00836407).

Another approach that may have great potential is the combination of two immune checkpoint inhibitors (Table 1).[6–17] The success of ipilimumab for the treatment of metastatic melanoma has spurred development of other immune checkpoint inhibitors, most notably anti-PD-1 and anti–programmed cell death ligand 1 (PD-L1) mAbs. CTLA-4 inhibitors enhance early T-cell activation in lymphatic tissues and increase the frequency of tumor-specific T cells, whereas inhibition of the PD-1/PD-L1 axis modulates the T-cell effector phase to overcome T-cell anergy in the tumor microenvironment.[2,18] Thus, there is a strong rationale for combining an anti-CTLA-4 mAb (eg, ipilimumab or tremelimumab) with an anti-PD-1 mAb (eg, nivolumab) or anti-PD-L1 mAb (eg, MEDI4736). One of the hallmarks of immune checkpoint inhibitors is the durability of the objective responses. CTLA-4 blockade yields durable responses in approximately 10% of patients with advanced melanoma, with some patients from the initial phase II trials of ipilimumab having remained free of progression for more than 5 years.[18,19] Monoclonal antibodies targeting PD-1 and PD-L1 are much earlier in their clinical development but seem to induce a durable response in up to one-third of melanoma patients.[20] The hope is that the combination could yield a durable response in a much larger proportion of patients. Studies using a B16 melanoma model have demonstrated synergy between these two classes of mAbs.[21] The initial phase I study of the combination of ipilimumab and nivolumab, administered either concurrently or sequentially, demonstrated a 40% objective response rate (ORR) with concurrent administration (53% at the highest dose level tested), and a high proportion of patients had ≥80% tumor reduction at 12 weeks; however, more than half of patients experienced grade 3 or grade 4 immune-related adverse events (irAEs).[17] These data are very encouraging, but raise some concerns about the potential for additive toxicity. A number of clinical trials are currently ongoing to test combinations of these two agents in patients with advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), colon cancer, glioblastoma, and relapsed/refractory hematologic malignancies (Table 1). Of particular interest is a three-arm, randomized, phase III trial (NCT01844505) that is comparing ipilimumab and nivolumab monotherapy with the combination of both agents as first-line therapy for advanced melanoma. The outcome is eagerly anticipated.