

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Harnessing the Immune Response

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H&O What is immunotherapy?

TG The idea behind immunotherapy is to provoke or augment the body's immune response against cancer and have the immune system destroy the tumor, instead of using a chemotherapy drug that kills the tumor cells directly. As such, this strategy promotes the host to control the tumor rather than controlling the tumor directly. If a patient responds clinically to immunotherapy, he or she can frequently be cured, as the responses can be very durable in the metastatic setting. In contrast, the use of standard cancer therapeutics may result in tumor shrinkage, death of tumor cells, and subsequent growth of resistant cells. Thus, it is in fact very hard to get durable complete responses with conventional cancer therapeutics in the metastatic setting.

There is growing excitement around immunotherapy in part because of this possibility of durable responses. The host immune response also seems to participate in the control of the tumor even when standard therapies, such as chemotherapy, targeted inhibitors, or radiation, work well. This idea is analogous to a scenario in which a patient with a low white blood cell (WBC) count is being treated with antibiotics for a bacterial infection. Because the immune system is weak, it makes it very hard to fight the infection with antibiotics, and the patient will not have clearance of the infection until the host WBC count is restored to normal. Similarly, when cancer-targeted agents work well, they seem to involve the host immune response, and immunotherapy is given to directly provoke that host immune response and amplify this effect.

H&O There has been evidence of synergy between immunotherapy and chemotherapy. Can you discuss this?

TG We now know from animal studies that have been done in the last several years that a patient's natural immune response collaborates with standard therapies like chemotherapy, targeted inhibitors, monoclonal antibodies, or radiation to produce a therapeutic effect. This means that it may be possible to combine an immunotherapy with standard therapies and see synergy, and to convert this transient clinical response that is often seen with chemotherapy or radiation. In melanoma, more than 50% of patients have an activating mutation in the BRAF kinase. There are specific drugs, which inhibit this kinase activity that can produce dramatic clinical responses. These responses, however, are short lived, with a median duration of approximately 6 months. Thus, we are now thinking about how to combine immunotherapy with these BRAF inhibitors in order to produce a durable and complete response. The first clinical trials are just beginning in this area of research.

H&O What is the current status of immunotherapy in cancer treatment?

TG Immunotherapy has gone through fits and starts in terms of progress, and the reason for this is largely because the biology was not completely understood. Although we do not yet have complete understanding, we do in fact know a lot more about the dynamics between a growing tumor and the host immune response. It is known that a large subset of cancer patients generates a spontaneous immune response

against their cancer, even without treatment. This spontaneous immune response has prognostic value; patients who have it do better than those who do not. Thus, the main barrier in this subset of patients is tumor-induced inhibition of the immune response after it is induced. With this information in hand, a lot of the field has shifted to focusing on inhibitory pathways that have held the immune response against the tumor in check. The first of those targets to be explored is cytotoxic T-lymphocyte antigen 4 (CTLA4), which is the target of ipilimumab (Yervoy, Bristol-Myers Squibb), the recently approved immunotherapy for melanoma. This CTLA4 antibody blocks this inhibitory receptor and improves T-cell function. There are multiple other inhibitory pathways that are being targeted in the clinic that have already been validated in mice; several companies are now conducting phase I and II clinical trials inhibiting these pathways.

The most interesting target is a cousin of CTLA4, a molecule called PD1. This is also an inhibitory receptor that is expressed on the activated T cells that are trying to recognize and destroy the tumor. The ligand for this receptor gets expressed on the cancer cells.

Emerging therapies are focusing on how to boost offense and counter defense. Ideally, to get the best response, these strategies would be done together. Antibodies against PD1 and its ligand, PD ligand 1 (PDL1), have been investigated in early-phase clinical trials and have shown major clinical response. Approximately 30% of melanoma patients (advanced patients who have had 3–4 prior therapies) enrolled in these early-phase studies have had responses. Clinical activity was also seen in kidney cancer and non-small cell lung cancer (NSCLC) patients. We hope that this pathway will be more generally applicable in a broader range of tumors.

H&O What are the challenges in immunotherapy development, and how do we overcome them?

TG There are several limitations that are seen in immunotherapy development. Immunology is complicated, the inhibitory pathways are numerous, and the therapies have special considerations and side effects. Thus a large fraction of the oncology community is unfamiliar with these principles. It is possible that because of the historical fits and starts in the field, there is also some skepticism about immunotherapy. Therefore, one of the barriers is the lack of education of the general oncology community, as well as the next generation of trainees who are going to be entering the field of immunotherapy as it is blossoming. A second barrier is the availability of agents to push things forward more rapidly in the clinic. Numerous pathways and molecules

have been targeted in preclinical models with a lot of excitement, but moving those agents forward into the clinic has been sluggish.

There is an organization dedicated to immunotherapy called the Society for Immunotherapy of Cancer (SITC), which is working on liaisons with the American Society of Clinical Oncology, with disease-specific foundations, and with other cancer research organizations. The goal is to educate oncologists on the principles of immunotherapy and to provide discussions about approved agents and those coming through the pipeline.

To overcome the lag in getting new immunotherapy agents to the clinic, the National Cancer Institute (NCI) has funded a new immunotherapy trials network (Cancer Immunotherapy Trials Network). It was launched this year and has more than 20 participating institutions. The purpose of creating this network was to have a very concerted effort to prioritize novel agents as they become available for clinical trial testing and to get these agents tested quickly with the right scientific endpoints on a multicenter level.

Another general barrier is decreased funding for clinical translational research in patients. In the past, the NCI sponsored a funding mechanism called the Quick-Trials program. This program was a funding opportunity to support clinical protocols with novel scientific endpoints; however, the program was discontinued last year. Many clinicians in the field agree that better funding platforms to support translational clinical trial efforts are needed.

We recently published a position paper in the *Journal of Translational Medicine* that included about 15 international cancer immunotherapy societies. In this paper we identified 9 key hurdles in immunotherapy research and development, and we discussed proposals to overcome these hurdles.

H&O How has the approval of immunotherapies affected research?

TG The success of the recently approved agent ipilimumab has catalyzed the development of cancer immunotherapy programs in several large pharmaceutical companies. Bristol-Myers Squibb, the company that brought ipilimumab to market, has a large portfolio of agents that are being investigated; they are evaluating an anti-PD1 antibody, along with agents that are targeting other pathways. Additionally, there are several other companies with anti-PD1 antibodies that are being developed.

The success of the prostate cancer vaccine sipuleucel-T (Provenge, Dendreon) has also helped to motivate some other pharmaceutical companies to continue their work and has increased confidence in the field. As such, there are several other vaccines that are fairly far along in devel-

opment. GlaxoSmithKline is developing a vaccine against an antigen called MAGE3; it is being studied in phase III trials in NSCLC and melanoma. The melanoma trials have accrued, and we are awaiting results from these randomized clinical trials, which will emerge over the next several years.

H&O What are researchers excited about in the field of immunotherapy?

TG There is a lot of discussion in the field about the long durability of response with immunotherapies, as previously discussed. Many of the patients on the anti-PD1 antibody phase I study who responded to therapy (even if response was partial), had tumor control for 2 years or greater with few toxicities. We know that in patients who have a complete response with interleukin-2 and/or with ipilimumab, most will not recur. We now want to achieve that level of clinical benefit with a larger fraction of the population.

Another modality that is being tested is adoptive cellular therapy. The Rosenberg group at the NCI and Carl June's group at the University of Pennsylvania have generated some interesting results in this area. With adoptive cellular therapy, instead of vaccinating a patient or blocking negative regulators to release the

patient's endogenous immune response, the tumor-specific T cells are grown in large quantities outside of the patient in a laboratory to prepare them for transfusion back into the patient. With this modality, the clinical responses in melanoma have consistently been over 50% in the phase II trials of the Rosenberg group. Carl June's group recently published a paper in the *New England Journal of Medicine*, in which they discussed targeting genetically modified T cells to make them specific for the tumor in chronic lymphocytic leukemia. The results were very dramatic, with some patients showing complete clearance of their tumor. Although this treatment approach appears promising, it is much more cumbersome, labor intensive, and expensive to expand T cells outside of the patient. However, we might find that this is the best approach in certain circumstances.

Suggested Readings

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365:725-733.

Fox BA, Schendel DJ, Butterfield LH, et al. Defining the critical hurdles in cancer immunotherapy. *J Transl Med*. 2011;9:214.

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