Future of Immunotherapy Drug Combinations and Biomarkers

By Charlie Schmidt

Plagued by uneven progress over its roughly 100-year history, cancer immunotherapy now is prospering, with 40 new drugs in clinical development, nearly a dozen of them in phase III testing. The U.S. Food and Drug Administration approved the first therapeutic cancer vaccine—one that treats an existing malignancy by turning immunity against it—back in 2010, when it cleared sipuleucel-T (Provenge) for use in late-state prostate cancer. FDA followed up in 2011 with a second approval, this time for ipilimumab (Yervoy), which accelerates antitumor immunity in patients with metastatic melanoma. Now phase III results show that yet another immunotherapy, a therapeutic cancer vaccine called BiovaxID, lengthens disease-free survival in patients with follicular lymphoma by an average of nearly 14 months, with virtually no side effects. The drug’s developer, Biovest International in Tampa, Fla., is seeking FDA approval.

Scientists attribute the recent success to a better understanding of how tumors fight off the immune system, as well as to the availability of more sophisticated vaccines that target antigens expressed mainly by cancer cells and not healthy tissues. If progress continues, immunotherapy will increasingly be used to prevent tumor recurrence in patients who complete first-line treatments, according to Jill O’Donnell-Tormey, Ph.D., director of scientific affairs at the Cancer Research Institute in New York. “You give these regimens after you have low or non-detectable levels of cancer in the body,” O’Donnell-Tormey explained. “And ideally they’ll attack any new cancer cells that appear, while leaving normal cells alone.” Eventually, she said, immunotherapies might be used alone or in combinations as first-line treatments. “What we hope is that these drugs turn all cancers into chronic, safely manageable diseases,” O’Donnell-Tormey said.

Immunotherapy faces many challenges. Tumors and their antigens change as a patient’s cancer moves from one disease state to the next, which can disrupt T-cell responses. A tumor’s microenvironment can evolve different immunosuppressive strategies, so as one is disabled, another one compensates. And meanwhile, immunotherapies don’t target tumors directly—they turn the immune system against cancer, so they take longer to work than other treatments. A patient’s tumor might even get larger after treatment (perhaps from T-cell infiltration), which fuels skepticism because survival might increase even without changes in how a tumor looks.

Now the field’s momentum is gaining in several key areas. In one, scientists are exploring how to use the drugs in combinations that trigger antitumor immunity while also delaying or preventing immune suppression. In another, they’re looking for biomarkers that might predict who responds best to immunotherapy in the first place.

**Combination Therapy With Ipilimumab**

One high-profile combination under consideration now involves the two most recently approved drugs for metastatic melanoma: ipilimumab and vemurafenib (Zelboraf), the latter being a targeted therapy against BRAF-mutated cancer cells, which occur in roughly half of melanoma patients. In a phase III clinical trial, vemurafenib was associated with 84% overall survival, compared with 64% for dacarbazine. But scientists believe that vemurafenib and other cancer treatments also fuel an “endogenous vaccination” against cancer triggered by the appearance of killed tumor cell fragments in the bloodstream. (The dumping of tumor antigens into blood after cancer cell death is called antigen release.) “But in the long term, that preexisting immunity might not be enough to keep the tumor in check,” added Axel Hoos, M.D., Ph.D., the medical lead in immunology at Bristol-Myers Squibb (BMS), ipilimumab’s manufacturer.

Here ipilimumab becomes important. Unlike therapeutic cancer vaccines, which present tumor antigens to the immune system to provoke a response, ipilimumab interferes with a natural checkpoint that suppresses T-cell activity. The body evolved checkpoints to keep the immune system under control—without them, T cells might be too responsive and trigger autoimmune disease. But checkpoints also have a downside for cancer if they block antitumor immunity. Ipilimumab binds with a checkpoint protein on the T cell’s surface called CTLA4. This protein’s normal function is to inhibit T cells over time, so interfering with it allows the immune system to mount more sustained antitumor attacks. Patients who took ipilimumab alone during the phase III study lived an average of 10 months, whereas control patients, who didn’t get the drug, lived 6.5 months.

Scientists expect that combining ipilimumab and vemurafenib will produce better results than giving either drug alone. Vemurafenib also promotes antitumor immunity because the antigen release attracts T cells. Ideally,
ipilimumab will sustain that response. BMS and Roche (which manufactures vemurafenib) have now agreed to test this hypothesis collaboratively in a phase I clinical trial scheduled for this year, Hoos said. Meanwhile, BMS has an ongoing phase III trial that combines ipilimumab with radiation in patients with late-stage prostate cancer. The rationale behind this trial mirrors that of the upcoming study with vemurafenib, in that radiation also triggers antigen release when it kills cancer cells. Adding ipilimumab to the T-cell response that follows is like pouring gasoline on fire, according to James Gulley, M.D., Ph.D., deputy chief of the National Cancer Institute’s Laboratory of Tumor Immunology. Launched in 2009, the trial has yet to complete enrollment; results are expected in 2013.

Some experts worry that the only combined treatment data with ipilimumab so far—generated during the drug’s phase III trial—don’t point in a positive direction. One group of patients in that study received ipilimumab along with an experimental peptide vaccine called gp100; these patients also lived approximately 10 months. However, the study’s corresponding author, Jed Wolchok, M.D., Ph.D., associate director of the Ludwig Center for Cancer Immunotherapy at Memorial Sloan–Kettering Cancer Center, said those results don’t necessarily predict how ipilimumab will perform with other treatments. According to Wolchok, gp100 isn’t a good cancer vaccine—it’s derived from an antigen that not all melanoma cells express, and cancer cells can easily live without the protein, so its expression is easily lost through natural selection.

**Progress on Cancer Vaccines**

A better vaccine, Gulley said, is one developed at the NCI over 10 years for patients with prostate cancer. Known as PROSTVAC, the vaccine’s primary target is prostate-specific antigen released by cancer cells that remain in the body should initial treatments fail to kill off the malignancy. Licensed now to Bavarian Nordic, a Danish biotechnology firm, PROSTVAC was given with docetaxel chemotherapy in a phase II trial published in *Cancer Therapy* in 2006. Patients who got the vaccine first, followed by docetaxel, had a longer time to tumor progression than patients who took only docetaxel. Gulley’s view is that chemotherapy and radiation each renders cancer cells more susceptible to immune attack, suggesting that these agents can be given in what he calls immunologically relevant ways. In a later phase II study, PROSTVAC alone improved overall survival by 8.5 months, associated with a 44% reduction in rate of death among patients treated with vaccine versus placebo. According to Gulley, PROSTVAC is undergoing phase III testing in patients with metastatic, castration-resistant prostate cancer who show no or minimal symptoms.

One of the vaccine’s principal advantages, Gulley said, is that it’s an off-the-shelf product made from poxviruses. That’s unlike sipuleucel-T, a personalized vaccine made with dendritic cells harvested from each specific patient. To formulate sipuleucel-T, scientists have to incubate the patient’s cells with a fusion protein comprising two parts: prostatic acid phosphatase, present in most prostate cancer cells, and an immune signaling factor called GM-CSF (granulocyte–macrophage colony-stimulating factor), which promotes dendritic cell maturation. The harvesting and incubation process is repeated for each of three doses given over 1 month, such that sipuleucel-T treatment is both cumbersome and costly, with a per-patient price of $93,000.

The vaccine’s approval met with some skepticism. That’s chiefly because the phase III study didn’t control for potentially confounding effects from GM-CSF, which also stokes the immune system and which might have contributed to the 4.1-month improvement in overall survival seen in treated patients compared with control subjects, according to Paul Chapman, M.D., a medical oncologist at Memorial Sloan–Kettering. Moreover, overall survival benefits weren’t accompanied by observable changes in tumor progression, Chapman said. Therefore, although treated patients may have lived longer, their tumors didn’t differ much from those of patients who didn’t get the vaccine.

**Delayed-Response Curves**

That seemingly paradoxical phenomenon challenges conventional interpretations of what it means for a cancer drug to work. When patients get chemotherapy and radiation, their tumors shrink in a response-based endpoint that theoretically predicts improvements in survival. Scientists monitor these endpoints during clinical trials. And if they don’t meet therapeutic expectations, then a trial might be canceled. Indeed, Pfizer pulled its CTLA4 antibody for metastatic melanoma (tremelimumab) from phase III simply because response-based endpoints revealed no observable benefits. But in a follow-up 2 years later, patients treated with the drug were living longer than control patients.

In retrospect, that outcome is not unusual, Hoos pointed out, given that immunotherapies never target cancer cells directly but instead work by building up antitumor immunity over time. Therefore, immunotherapy trials should use different methods from those applied during clinical studies with chemotherapy, he said. BMS took note of tremelimumab’s delayed-response curve by shifting the primary endpoint in its phase III study with ipilimumab from progression-free survival to overall survival, without any interim analyses. The FDA, in its new guidance for cancer vaccine development released in October 2011, endorsed that same approach. The FDA guidance acknowledged that cancer vaccines produce delayed effects (and sometimes early progression) that should be taken into consideration during clinical trial design.

“If the vaccine is effective, evidence of that effect may occur later in the study,” the FDA stated.

The challenge now will be to identify optimal responders to immunotherapy early, in the same way that scientists try to identify those most likely to benefit from targeted therapies such as vemurafenib, according to Thomas Gajewski, M.D., Ph.D.
a professor at the University of Chicago Medical Center and an associate editor of the Journal of Immunology. “We know that about 60% of patients treated with immunotherapy have tumor microenvironments that simply don’t provide access to T cells,” he said. “So those patients can’t respond clinically to a vaccine.”

Gajewski points out that biomarkers might reveal a tumor’s ability to attract T cells, including gene expression signatures associated with T-cell recruitment and T-cell infiltration in the tumor itself. Along those lines, Jerome Galon, Ph.D., from the Cordeliers Research Center in Paris, France, has found that the extent of tumor T-cell infiltration is a better predictor for colorectal cancer than traditional clinical staging. Galon published his findings in *Seminars in Immunopathology* in July 2011. “That’s a mind-boggling finding,” said Gajewski, adding that the Society for the Immunotherapy of Cancer is now considering T-cell infiltration as a standard criterion for patient evaluation. Meanwhile, a different marker, the NY-ESO-1 serum antibody, statistically correlates with better results among melanoma patients treated with ipilimumab, according to a study published in *Proceedings of the National Academy of Sciences* on Oct. 4, 2011. In that study, researchers from Memorial Sloan–Kettering, including Wolchok, found that 55% of patients seropositive for NY-ESO-1 showed evidence of clinical benefit (one complete response, four partial responses, and seven cases of stable disease among 22 treated patients), compared with 31% of seronegative patients. “The goals of immunotherapy as we know it are to increase the frequency of T cells that kill tumors and then to overcome the barriers of the tumor microenvironment,” Gajewski said. “If we can put those together, we should be able to achieve more meaningful clinical outcomes.”

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