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Ezekiel Emanuel, M.D., Ph.D., professor of medical ethics and health policy at the University of Pennsylvania, said that oncologists need to focus immediately on eliminating unnecessary or unproven treatments, which account for up to a quarter of all health care costs, according to a recent Institute of Medicine report.

He cited examples such as bevacizumab (Avastin) for advanced metastatic breast cancer, proton beam therapy for prostate cancer, and advanced robotics in prostate cancer surgery. "We are up on a million surgeries and there still hasn't been a single randomized trial, and there is some evidence that it is not any better in terms of side effects," he said. "An innovation has to do one of four things or it's not an innovation: Improve survival, improve quality of life, reduce side effects, or reduce costs," he said. "Getting rid of low-value treatment is hard. We can easily start by getting rid of no-value treatments."

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Cancer Vaccines: Always a Bridesmaid, Never a Bride?

Anna Azvolinsky

The saying "Always a bridesmaid, never a bride" is apt for therapeutic cancer vaccines, which manage to garner excitement in early trials but despite many attempts do not achieve clinical efficacy. "This is an area that has been studied for a very long time, but there are, to my knowledge, no effective therapeutic vaccines for cancer," said Steven A. Rosenberg, M.D., Ph.D., chief of surgery and head of the tumor immunology section at the National Cancer Institute, who has been studying immunotherapy for more than 30 years.

Perhaps this time things will change. In the wake of many disappointments, new vaccine approaches have reached late-stage development, having conceivably learned from the pitfalls of predecessors.

In an August 2012 *Nature Medicine* study, researchers demonstrated early promise of IMA901, a 10-peptide therapeutic vaccine for renal cell cancer (RCC). Harpreet Singh-Jasuja, Ph.D., chief scientific officer of Immatics Biotechnologies, based in Germany, and colleagues developed the vaccine by isolating antigens directly from RCC patients' primary tumors.

Phase II results showed a 64% rate of immune response among 64 patients, 26% of whom responded to multiple antigens. Patients who responded to multiple antigens in the vaccine had extended survival. At 30 months, overall survival was approximately 25% for patients who responded to a single antigen, compared with more than 50% for those who responded to two or more antigens.

According to Carsten Reinhardt, M.D., Ph.D., and chief medical officer of Immatics, this result confirms that a broad immune system attack on multiple targets is a promising approach."

"The clinical utility of cancer therapeutic vaccines probably depends on many factors, including the potency of the vaccine, the inherent immunogenicity of the patient's tumor, and the ability to eradicate the tumor before it develops suppressive features that shut down the immune response," said Howard L. Kaufman, M.D., director of the Rush University Cancer Center in Chicago. Identifying the patients most likely to respond, whose cancer is inherently immunogenic, may be key.

Jeffrey Weber, M.D., Ph.D.

A phase III trial is now testing whether adding IMA901 to sunitinib treatment will improve the survival of treatment-naïve RCC patients. The trial uniquely evaluates whether either of two serum biomarkers can predict patients who are more likely to achieve a survival benefit.

More May Be Better

Reinhardt believes the failure of previous vaccines stemmed from not having enough quality antigens. Having more antigens may reduce the chance that a tumor can downregulate the antigens and escape immune system detection. "Only one antigen is not enough," said Hans-Georg Rammensee, Ph.D., head of the department of immunology at the University of Tuebingen, in Germany, who serves on the scientific advisory board of Immatics. "The tumor is proliferating and is mutating, so it is easy for the tumor to get rid of one antigen."

Rammensee is taking the multipeptide approach further. Using antigen data from prostate, colorectal, and ovarian cancer patients, he and colleagues are creating cocktails of 25–30 peptides for vaccines against those cancers. Personalized vaccines, based on selection of antigens mutated in a patient's tumor but not in healthy tissue, are also in the works.

Other vaccine developers are also taking the personalized approach. Argos Therapeutics, in Durham, N.C., is developing AGS-003, a vaccine made from a patient's own dendritic cells and modified with a CD40 ligand and the patient's own tumor mRNA. Researchers are testing AGS-003 on RCC patients in combination with sunitinib in a phase III clinical trial.

MAGE-A3 is another vaccine being tested as an adjuvant melanoma therapy in a phase III trial. A different version of the vaccine is being tested as adjuvant therapy for non–small-cell lung cancer patients. The MAGE-A3 protein is a tumor-specific antigen expressed on various tumors, including

melanoma and non–small-cell lung cancer, but not on normal cells. Like IMA901, the MAGE-A3 vaccine has different components.

Jeffrey Weber, M.D., Ph.D., tumor immunologist and director of the Comprehensive Melanoma Research Center at the H. Lee Moffitt Cancer Center in Tampa, Fla., believes the complexity of the MAGE-A3 vaccine makes it unique and potentially efficacious. "It is a multipronged adjuvant, not just a simple vaccine: a protein antigen fused with a bacterial protein that may itself act as an adjuvant, with its own complex adjuvant within it." He continued, "It is actually one of the few vaccines that is that complex, and it may be the complexity of having different parts of the immune system being stimulated that may cause it to work if it is successful."

Earlier-Stage Vaccine Therapy

Are cancer vaccines more likely to work in earlier-stage disease? "That was always the fantasy," said Weber. "If something doesn't work in metastatic disease, everyone's fallback position—including mine—was that it is because the patient has bulky tumors, and for immunotherapy to work, the patient must have earlier, resected disease."

Although rationale underlies this argument, according to Weber, it is not clear that it is true, with the recent evidence of immunologic antibodies against CTLA-4 and anti-PD1 showing robust longer-term responses in heavily pretreated metastatic patients.

But others still think earlier-stage disease is where vaccines will be effective. Michael Ciesielski, Ph.D., and Robert Fenstermaker, M.D., of the department of neurosurgery at Roswell Park Cancer Institute, in Buffalo, N.Y., have developed a subcutaneous peptide-mimic cancer vaccine, SurVaxM, that targets the protein survivin. (Most cancers, but not normal tissue, produce survivin.) "What we know about vaccines so far is that they tend to work best with minimal residual disease," said Ciesielski. Researchers will test the vaccine in an initial safety study in brain cancer patients. According to Fenstermaker and Ciesielski, SurVaxM is different from other vaccines because it was designed to elicit a concerted immune response, from both $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells.

"The biggest problems [with vaccines] are that there is an enormous tolerance to many of the antigens, the antigens are present on normal cells, and the tumors have a tremendous level of immune suppression."

A Strong Dose of Criticism, a Dash of Hope

Despite hundreds of trials, the field has not figured out how to use a vaccine to mediate antitumor effects, in either early or metastatic disease, said Rosenberg. Only one vaccine, sipuleucel-T, marketed as Provenge by the Seattle-based Dendreon, has been approved for cancer patients.

"Sipuleucel-T showed that survival can be prolonged by a few months, but everyone goes on to die of their prostate cancer. I don't see it as a significant step forward, even though survival is increased by a few months," said Rosenberg.

Weber is also a skeptic. "The biggest problems [with vaccines] are that there is an enormous tolerance to many of the antigens, the antigens are present on normal cells, and the tumors have a tremendous level of immune suppression." Although modern cancer vaccines have been available since the 1970s, only in the last 8 years has the field recognized that tumors have many ways to modulate immune responses, including antigenic downregulation and increased infiltration of myeloid-derived suppressor cells and regulatory cells. Researchers also do not understand what constitutes an appropriate antigen and how to identify patients likely to respond. "The odds are really stacked against a straightforward vaccine strategy," said Weber.

The field has not been able to get a vaccine to mediate a strong-enough immunologic response to affect the tumor, said Rosenberg. Vaccines can elicit an immune response, but these responses have not generally translated to meaningful clinical responses.

But that is not stopping researchers from trying. Vaccines are still an attractive therapy for cancer, associated with fewer toxic effects than chemotherapy, antibodies, and targeted agents, said Fenstermaker. As with other immunotherapies, potential exists for a long-term effect.

"I think, ultimately, it's going to take a multiprimed approach where you are [influencing] immune stimulation and immune suppression at multiple points," said Weber.

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