

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Status of Colon Cancer Vaccines

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H&O What is the background of colon cancer vaccine development?

Previous Vaccines

MM The oldest immunotherapies were bacterial cell wall products that caused nonspecific inflammation, but tumor vaccines today are designed to activate immune responses specifically against tumor associated antigens. The earliest of these used autologous tumor or tumor cell lines that were irradiated or lysed and then injected intracutaneously, along with Bacille Calmette-Guerin (BCG) or bacterial cell wall products to activate an immune response against antigens within the tumor vaccine. There were several clinical trials that used autologous tumor plus BCG for patients with resected colorectal cancer. Initially it was suggested that colon cancer (versus rectal cancer) and earlier stage disease (stage II versus stage III) was where there was more of a benefit. However, those studies, for a variety of reasons, never really proceeded to the studies which could lead to FDA approval. So then people started thinking about ways to modify the tumors, for example by using viruses to infect the tumor to deliver genes for cytokines such as GM-CSF or IL-2, or developing viruses which could lyse the tumor cells and produce an immunogenic mixture of tumor cell lysates.

Subsequently, scientists identified antigens within the tumor against which T-cells and antibodies responded (such as carcinoembryonic antigen [CEA] and EpCAM); vaccines were developed to deliver these antigens in a way that the immune system would be activated. These vaccines included anti-idiotype vaccines and viral vectors encoding the tumor antigen. Viral vector-based vaccines remain of interest because additional molecules to enhance immune response may also be cloned into them.

Dendritic Cell Vaccines

MM Around that time, dendritic cell vaccines became popular. This is what our lab has done much work on. The theory is that all these other vaccine strategies—whether it is using peptide fragments of CEA, autologous tumor, or viral vectors—those antigens ultimately are taken up by dendritic cells and processed, and presented to T-cells resulting in activation of T-cells specific for the particular antigen. Also, T-cell help is provided for induction of antibody responses. Therefore, why not grow autologous dendritic cells in a lab, add the antigen to them, and use that as a vaccine? Then you are sure that as many as dendritic cells as possible are going to be able to present that antigen. Plus, dendritic cells can be grown in vitro, modified into various ways so that they are more efficient with antigen presenting, more likely to migrate to regional lymph nodes, or that they secrete IL-12. That is where we are at right now: trying to find the best way of utilizing dendritic cell-based vaccines.

I am currently doing a randomized study that is supported by the National Cancer Institute (NCI), where half the people are randomized to receiving dendritic cells that have been infected with a viral vector encoding CEA, and the other half are receiving the viral vector encoding CEA. We hope that the study will be able to tell us whether the dendritic cells really matter, or if it is a case where the viral vector is effective enough without having to go through the extra trouble of growing dendritic cells in vitro. We are planning to enroll 72 patients for this multicenter study; we currently have 55 now. The endpoint is disease free survival at 2 years. Participating patients have had colon cancer metastasis resected from the liver or the lungs and have no advances in the disease. One of the potential pitfalls of some vaccine studies is that people with very advanced cancer often have poor immune responses—but we have taken that out of the equation. This trial is enrolling patients

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who have no active disease but do have a high risk of recurrence, and we believe that this is a cleaner scenario to test the dendritic cell question.

H&O Are colon cancers more or less immunogenic than other cancers?

MM There is a lot of controversy about why some tumors appear to be more immunogenic than others. In melanoma, there is a consistent 10% response rate with almost whatever you try. Why do we not see that in colon cancer? There are some molecular reasons suggested: downregulation of major histocompatibility complex (MHC) molecules, immunosuppressive cytokines in the tumor milieu (such as IL-4, IL-10, and IL-6), and activation of regulatory T-cells which dampen the effector T-cell response. Nonetheless, we can activate antigen specific immune responses in colon cancer patients, and some researchers have suggested that patients who have an immune response to the vaccine will have a better clinical outcome. Even more importantly, there was a study published in *Science* where investigators looked at resected colon cancers and studied lymphocyte infiltration within the tumors, specifically those with CD8+ lymphocytes and granzyme expressing lymphocytes.¹ Patients who had a higher degree of lymphocyte infiltration had a better prognosis. Researchers also looked at a series of genes that are commonly associated with a T-helper type 1 (Th1)-adaptive immune response, which is the sort of helper response you want because it is the one that is able to give help to cytolytic T-cells. They found that people who had most of those Th1-related genes upregulated also had a better prognosis. This is even with people not having been immunized, which tells me that some colon cancers do attract an immune infiltrate, and that there are markers of immune response that indicate whether a person is going to get a better outcome.

Our goal as oncologists, therefore, is to a) identify patients whose immune response is likely to be most beneficial, or b) identify patients who seem to have a weak immune response and try to figure out how to get a better immune response within their tumors. That is my way of saying that colon cancers are immunogenic. It may be that we have not yet found the right cocktail—the right type of vaccine—that really increases the chance of getting lymphocyte infiltration into the tumor and gets the lymphocytes to express the right pattern of genes.

H&O In your opinion, what is the status of current vaccine trials?

MM I believe it is safe to say that the ongoing studies of vaccines in colon cancer are mainly in early phases. There

continue to be dendritic cell vaccines, viral vector strategies such as TroVax (Oxford BioMedica)—a pox vector-based strategy encoding a molecule called 5T4—new viral vector strategies such as AVX-701 (AlphaVax, Inc.) which is based on Venezuelan Equine Encephalitis virus, and novel strategies such as CDX-1307 (Avant Pharmaceuticals) which is a fusion molecule of an antibody against the mannose receptor found on dendritic cells and the tumor antigen HCG-beta. We are performing studies with AVX-701 and CDX-1307 now.

H&O What do you see in the future of cancer vaccines? What are some of the obstacles?

MM I really think that in terms of the platforms (eg, viral vectors, dendritic cells), we may make some incremental improvements. We may find platforms that are more immunogenic. We may identify more immunogenic antigens. However, the real next step is once you get that immune response, how do you maintain it? How do you get those T-cells to the site of the tumor? How do you get them to kill the tumor once they get there? How do you avoid selecting for tumors that have down-regulated the target antigen? How do you keep the tumor from suppressing the immune response? Answering these questions is going to require combining the vaccine with other drugs. We reported a study in *Blood* this year, testing dendritic cells infected with fowlpox encoding CEA and costimulatory molecules (rF-CEA(6D)-TRICOM).² To enhance the immune response, we used ONTAK (denileukin diftitox), which is a fusion molecule that basically poisons CD25+ regulatory T-cells so they cannot inhibit the development of a CEA-specific immune response. We observed enhanced CEA-specific T-cell activation.

Others and we are exploring combinations of anticancer targeted therapies with vaccines now. Using these combinations of vaccines with other drugs can be challenging because often the most promising agents are being developed by different companies. It is our hope that as interest in cancer vaccines continues to rise, more collaborations will become possible to advance the field more rapidly.

References

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