Annals of Surgical Oncology, **8**(5):386–388
Published by Lippincott Williams & Wilkins

Editorial

Treating Colon Cancer With a Melanoma Vaccine? Preposterous?

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Dr. Donald Morton and his group have never been afraid to think outside the box. While the rest of us were debating whether to do elective node dissections for melanoma, he developed a technique to identify nodal micrometastases in the "sentinel" node, revolutionizing the management of stage I and II melanoma in the process. But has he gone too far this time? After all, giving patients with colon cancer a melanoma vaccine![1] That's crazy—isn't it?

Maybe not. It certainly bucks the current trend toward ever more precisely defined single antigen vaccines, such as the rash of designer peptides that are not merely disease-specific but actually restricted to use in specific subsets of patients based on HLA expression. So giving patients a "gamish" of melanoma cells in hope of engendering an immune response to colon cancer antigens would seem to be proceeding in the opposite direction: firing blindly at the immune system and hoping a 'golden bullet' magically hits the target. Nonetheless, the limitations of defined-antigen vaccine strategies are becoming apparent,[2,3] and evidence that polyvalent, autologous, and allogeneic tumor vaccines can mediate an effective antitumor immune response is growing.[4,5] The question is no longer "If?" but "How?"

Limitations of Defined Antigen Vaccines

Human tumors develop in a series of evolutionary steps, during which time they evade the immune system's surveillance mechanisms. Thus, every clinically detectable tumor is already adept to some degree at disguising itself from the immune system. Antigenic heterogeneity is the rule in tumors: even within strongly antigen-rich tumors there are at least some cells that do not express the target antigen. Moreover, most tumors are eventually capable of down-modulating antigen expression in the face of sustained immune attack. Although it is clear that on occasion immunization with a single, defined antigen can result in regression of even extensive tumor, this is the exception and not the rule. So far, successes of immunotherapy with single antigen vaccinations have been virtually entirely restricted to malignant melanoma patients. The possibility exists that melanoma is a unique tumor arising in a regionally immunocompromised setting (ultraviolet radiation-exposed skin), not readily generalizable to other solid tumors.

Even if a tumor lacks antigen expression on a subset of its cells, a defined antigen vaccine can still induce regression of advanced disease by killing the majority population of antigen-expressors. Ultimately, unless a more generalized immune reaction occurs ("epitope spreading"), the antigen-negative population will grow out and cause clinical relapse. This limitation is particularly glaring in the adjuvant therapy setting, where cure and not transient reduction of tumor burden is the goal. It may be that this phenomenon explains the results of a recent phase III clinical trial in which a defined antigen vaccine (purified GM2 ganglioside conjugated to keyhole limpet hemocyanin) that achieved high levels of IgG and IgM antibody induction failed to match standard therapy with high-dose interferon-alfa 2b in high-risk melanoma patients.[2]

Limitations and Benefits of Autologous Vaccines

The use of autologous tumor vaccines, namely, tumor derived from the patient to be treated, has been evaluated by several different groups. Autologous tumor vaccines are attractive because of the high likelihood that any tumor-associated antigens potentially capable of eliciting an antitumor immune response will actually be present within the vaccine. These antigens, however, may be

Received March 27, 2001;accepted April 9, 2001.
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present in only limited amounts and must compete for the immune system's attention with multiple other irrelevant self- and tumor-associated antigens. More problematic than that, autologous tumor is a limited commodity that involves an invasive procedure to harvest in those situations where it is obtainable. In melanoma, this may not be an overwhelming obstacle, because cutaneous, subcutaneous and nodal deposits of tissue are accessible in many cases, and the surgery to remove such tumors is straightforward and rarely debilitating. In renal cell carcinoma, justification exists for removing a primary tumor from a patient with documented metastatic disease,[6] but nephrectomy is a procedure with significant associated risks of major complications and even death. For colon cancer, the target of the current investigation,[1] the prospects of an autologous vaccine are even poorer. The primary tumor sits in a bacteria-rich environment that is ill-suited to generate autologous vaccines, whereas most metastases are located in the liver or other visceral sites. Resection of metastatic deposits from colorectal primaries is occasionally undertaken, but extending the surgical indications for liver resection to include otherwise non-therapeutic tumor harvests would require far more evidence of efficacy than exists to date. Acknowledging the fact that some clinical trials with autologous tumor vaccines from colonic primaries have been carried out,[7] the prospects for widespread application of vaccination strategies requiring autologous colon cancer cells are limited to say the least.

Potential of Polyvalent, Allogeneic Vaccines

Allogeneic tumor vaccines provide many of the benefits of autologous tumor, albeit with a lesser degree of certainty that key regression antigens would be present, while offering far greater availability. They also offer a degree of consistency of formulation from patient to patient that is very attractive to the designers of large-scale clinical trials.

Which brings us back to our original quandary: does it make sense to use an allogeneic melanoma vaccine, chock full of totally irrelevant tumor antigens, to achieve an immune response against colon cancer—even if one or more shared antigens are present on the vaccine? The answer is a qualified yes. Dr. Morton and co-workers have shown that this approach successfully immunized colon cancer patients to the target shared antigen (TA90), as measured by induction of humoral and DTH responses. Although there was some correlation between TA90 immune response and survival duration, there were no objective antitumor responses. All of us in the vaccine field have come to recognize that correlations between immune response and survival may be epiphenomena rather than cause-and-effect, and hence cannot be accepted as clear evidence of vaccine benefit.

Thus we're left with the bland and somewhat unsatisfying clinical cliché that "further research is justified." Perhaps we can go a step further, though. Perhaps we can do more than just add additional patients to single-arm studies that will never fully define the clinical efficacy of this cross-tumor vaccination approach. Perhaps we can use this novel "outside the box" observation to create new clinical trials that will further dissect the human antitumor immune system. Consider the potential value of a randomized phase II trial that compares the allogeneic melanoma vaccine with a defined antigen vaccine composed of TA90 antigen alone, using appropriate immunologic endpoints, in a homogeneous population of patients with stage IV colorectal cancer. As pointed out by Habal et al., patients with resected and/or ablated stage IV disease may be an appropriate population to consider. Alternatively, the same clinical trial strategy could be applied to compare the allogeneic melanoma vaccine with a similarly prepared allogeneic colon cancer vaccine that expresses similar levels of TA90 antigen. In either case, the goal of such a trial would be to determine the relative levels of antitumor immunity elicited by the different strategic approaches. Besides examining the humoral responses induced by this vaccine, T-cell responses may also provide useful information about other mechanisms which might lead to tumor rejection. If the allogeneic melanoma vaccine were superior in eliciting an anti-TA90 immune response, it might yet fail to benefit patients because of the previously expressed reservations about single-antigen vaccination. Still, just that observation would constitute yet more proof that thinking outside the box was anything but preposterous!

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