Personalized, Multivalent, and More Affordable: The Globalization of Vaccines

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Active immunotherapy of cancer, and especially of brain tumors, has enjoyed little success thus far, although a number of approaches have been examined. These approaches rarely involved the determination of the immunologic status of a patient receiving the vaccination. More often than not, the target was a single antigen expressed in a fraction of patients and the patients were not preselected according to the antigen positivity. The procedures used to generate vaccines were laborious and expensive and failed in a vast majority of patients when the protocol required the isolation and maintenance of patients’ own cancer cells. Patients with malignant gliomas, in addition to treatment that is inherently immunosuppressive, receive immunosuppressive anti–brain edema drugs; these are very unfavorable conditions for active immunotherapy. A conviction that it is possible to vaccinate against brain cancer, however, brings continuously new ideas of how to tackle an ineffective immune surveillance of solid tumors.

The brain was considered only partially correctly as an immune-privileged site as primary brain tumors do generate immune responses. In standard treatment, malignant gliomas are surgically resected and/or debulked; this inadvertently leaves a residual tumor disease because surgery cannot remove all of the cancer cells residing in the brain. Radiation and/or chemotherapy are subsequently implemented. The blood-brain barrier is disrupted after surgery, which might be important for the transfer of CTLs or antibodies into the vicinity of residual cancer cells. Thus, a vaccine for brain tumors should serve as a preventive measure against disease recurrence. Yajima et al. (1), in this issue, describe the evaluation of a personalized peptide-based vaccination in a phase I clinical trial in patients with advanced malignant glioma, one of the most devastating human malignancies.

In the design of a vaccine against malignant gliomas, Yajima et al. conceptualized that a vaccine might have a better chance to be efficacious if the target antigens included in the vaccine are selected for each patient depending upon the reactivity against a panel of antigens. The authors opted for administration of “off-shell” premanufactured peptides corresponding to antigenic epitopes of tumor-associated proteins. As an eligibility criterion, the preexistent cellular and humoral responses to peptides corresponding to cancer-associated antigens were determined. Thus, the CTL activity was detected in peripheral blood mononuclear cells in a HLA-A24+ or HLA-A2+ restricted fashion as was the presence of peptide-specific IgGs. However, the lack of detectable T-cell responses at a given time point may also mean an insufficient number of precursor cells in patients rather than a difficulty to prime a response. The positively identified peptides, up to four per patient, were subsequently chosen for vaccination and their composition was different among the 25 patients evaluated. The vaccine was delivered in the form of repeated s.c. injections. Nine patients had the presence of three tumor-associated antigens verified by immunohistochemistry, and the gene expression of 11 other antigens was examined in cultured cells. Patients were treated according to a biweekly or weekly vaccination protocol. Increased cellular responses to at least one of the peptides were detected in more cases when the vaccine was given weekly rather than biweekly, and the same was found with increased humoral responses. Partial clinical responses to the vaccine were seen in ~25% of patients, including some major tumor regressions, whereas the survival in the whole treated cohort is encouraging. The treatment did not evoke any major toxicity. A follow-up on immunologic responses was conducted in patients with the best clinical responses compared with stable and progressive disease, and the degree of cellular and humoral response seems to be in agreement with the patients’ clinical outcome. The presence of immune response effectors was also examined in the cerebral spinal fluid and tumor cavity fluid. Again, the degree of the response to peptides seems to correlate with clinical responses in vaccinated patients.

In the past decade, a group of proteins that are overexpressed in malignant gliomas in a vast majority of patients, but not in normal brain, was revealed. The first is IL-13Ra2 (2), a glioma-associated plasma membrane receptor for interleukin-13 that is present in ~70% of patients with GBM, a cancer/testis-like tumor antigen. These antigens are naturally attractive targets for vaccination (3). Interestingly, Yajima et al. found major immune responses against intracellular proteins. The question remains, however, whether the cellular localization of antigens has any bearing on clinical responses to peptide-based vaccines.

One of the most attractive aspects of Yajima et al.’s work is the multivalent nature of the vaccine that promises applicability against a plethora of malignancies. More evidence accumulates in favor of a phenomenon that solid tumors share molecular denominators/antigenic proteins in their advanced stages. One example is Fra-1, a transcription factor that is overexpressed in cancers of the breast, thyroid, colon, and also of the brain (ref. 4 and references therein). Fra-1 has already been used as a target for vaccination in a breast cancer model (5). Another widespread factor is EphA2, which is also overexpressed in metastases, including the ones to the brain (6, 7). Thus, the peptide vaccination may offer the possibility of generating a vaccine against cancer, be it residual disease after surgical
resection and/or metastases. There is precedence to show that a peptide vaccination against a peripheral tumor has an effect on its brain metastases as well (8). It is conceivable that up to a six-peptide vaccination might cover most cancers, including cancers of the brain. Glinsky et al. (9) recently reported further evidence for the commonalities between advanced/metastatic cancers, including nonmetastatic gliomas, as 11 genes were demonstrated as a group that may represent a death-from-cancer signature. This supports the idea that immune gene groups may similarly characterize advanced cancers, including gliomas, and our hypothesis that malignant gliomas do not metastasize because they are already metastases-like. Perhaps, such a vaccine would be personal enough without the need for prescreening patients.

Yajima et al. propose to continue clinical trials using the described protocol. For the immediate future of developing antiglioma, and perhaps a general anticancer vaccine, and to remain true to their hypotheses, it is believed that performing more of both preclinical and clinical research focusing on immune response in cancer patients would provide closer to optimal peptide vaccination regimen. One task would be to catalogue a group of antigenic targets in malignant gliomas shared with other solid malignancies, the ones that produce both cellular and humoral responses effectively. All these targets should be relatively homogenously expressed in a majority of patients, which was not the case in the work described by Yajima et al. Furthermore, the identification of targets present in various tumor compartments might be of great benefit. For example, antigens specifically associated with tumor neovasculature in addition to tumor cells should be identified, if possible. It would be advantageous to determine how many peptides can or should be used to significantly augment the immune response. There should be more thought given to when and with whom to initiate vaccination versus standard therapy, in view of the fact that one third of patients with malignant gliomas become immunodeficient in the course of treatment.1 Nevertheless, peptide-based vaccines against cancer may enter a more global scene of an adjuvant cancer therapy because of a relatively convenient way of clinical testing of this particular approach to active immunotherapy.

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References

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