Multiple Expressed Endogenous Glioma Epitopes as Novel Vaccines for Gliomas

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A novel approach to immunization against glioma tumors is described. Immunization against 11 antigens expressed in malignant brain tumors elicits responses to one or more antigens in a large percentage of patients. This novel approach suggests that it could be extended to a phase III trial. Clin Cancer Res; 22(19); 4760–2. ©2016 AACR.

See related article by Rampling et al., p. 4776

In this issue of Clinical Cancer Research, Rampling and colleagues show the data from a first-in-man immunization of glioma patients with a vaccine containing 10 antigenic epitopes known to be expressed in glioma (1). Immunization to treat solid tumors has a long history. Nonspecific immunization led to some individual responses, and these early results were then adapted to novel contemporary understandings of immune system function. More recent successes in the treatment of melanoma, small cell lung carcinoma, and kidney cancer, as well as others being evaluated, with immunotherapy have reignited hope that similar approaches will work in patients with malignant brain tumors. Inhibitors of costimulating molecule pairs CTLA4–CD28 and PD1–PDL1 have shown strong antitumoral activities across disease stages, even after failure of standard of care and various stages of disease progression (2, 3). This comes after many years of various approaches to systemic immunization, providing partially effective results without any definite breakthroughs. Vaccination in cancer has employed potential tumor antigens deduced from tumor proteins, in vitro activation of tumor-infiltrating leucocytes, alone, or in combination with suppression of endogenous immune system, followed by bone marrow transplantation to potentiate leukocyte engraftment. Results were marginally effective, with only occasional complete responses and long-term patient survival. Checkpoint inhibitors have transformed the landscape of solid cancer immunotherapy, achieving, for the first time, complete and partial responses in untreatable diseases, such as advanced melanoma (4, 5).

Highly malignant gliomas (WHO grade 4; glioblastoma multiforme) remain universally fatal with a median survival of approximately 16-18 months. These are some of the most frequently targeted tumors, as long-term survival has improved marginally during the last 80 years. Surgery, radiation, and chemotherapy constitute the standard of care, yet long-term survival beyond 2 to 3 years is rare (6). Immunotherapy has been proposed and tested in patients with glioblastoma multiforme. Potential tumor antigens derived from potentially immunogenic proteins have been used to stimulate the immune response to recognize these antigens in the patients’ glioblastoma multiforme. Alternatively, studies have utilized patients’ own tumor lysates to stimulate the patients’ dendritic cells to be used as vaccines to elicit immunity against their endogenous tumor antigens. In spite of measurable T-cell responses, therapeutic results have been marginal, with occasional clinically significant responses (5).

Several of these approaches have entered phase III clinical trials. In spite of positive early-phase clinical trials results, the recent failure of a vaccine against EGRF/VIII to extend survival of patients in a phase III trial continues to challenge the approaches that target single antigenic epitopes (http://ir.cellcom/releasedetail.cfm?ReleaseID=959021; ref. 7). Analogously, trials utilizing some of the other vaccination approaches have shown increases in progression-free survival, but limited extension of overall survival (OS). Why has immunization not shown stronger clinical efficacy in extending the life of patients with glioblastoma multiforme?

Possible explanations are that immunizations and innate immune adjuvants are not strong enough, that exogenous antigens used are not the same ones as the endogenous ones presented by tumors on HLA, that not enough antigens are retrieved from tumors in approaches attempting to load dendritic cells with tumor antigens, or that tumor downregulation of HLA would sequester antigens from T-cell recognition. Studies of the tumor antigen repertoire are cumbersome, and thus, the recent description of the neoantigen repertoire in many different tumors is of great importance to tumor immunotherapy. Tumor neoantigen expression is highest in melanoma and lung cancer and lowest in AML, ALL, and in pilocytic astrocytoma. Interest in expression of tumor neoantigens reflects the theory that such antigens would not have been negatively selected during T-cell development. They therefore represent novel targets for the immune system. The correlation between the neoantigen expression repertoire and the clinical efficacy of the immune checkpoint inhibitors supports this hypothesis. It also predicts why vaccines utilizing a low number of antigens would be less likely to succeed.
Taking these practical and theoretical elements into consideration, Rampling and colleagues (1) present data on a novel vaccination clinical trial for patients with glioblastoma in which vaccines are loaded with endogenous epitopes known to be presented on HLA molecules in glioblastoma multiforme. Specifically, Dutoit and colleagues (7) characterized 46,000 HLA-bound peptides in glioblastoma multiforme, of which 3,000 were selectively bound to the most common HLA in humans, that is, HLA-A*02. They then concentrated on studying 10 glioblastoma multiforme–associated antigens based on levels of expression in glioblastoma multiforme and low expression in normal organs. Importantly, and as expected of neoantigens, actual patients did not display any T-cell tolerance for the selected peptides. Equally, patients’ CD8+ T-cells induced specific lysis of tumor cells in vitro, which expressed the novel antigens. Furthermore, the identification of T-cells specific for the novel antigens in the glioblastoma multiforme microenvironment supports the idea that such T-cells could be functionally lytic in vivo as well.

Rampling and colleagues, in this issue (1), report the translation of these exciting basic science findings into a first-in-human phase I trial of a novel multipeptide therapeutic vaccine in patients recently diagnosed with glioblastoma multiforme (Fig. 1). The study was performed in two cohorts of patients treated with standard-of-care and vaccine immunotherapy. All patients were positive for HLA-A*02 and were treated with 11 intradermal immunizations. GM-CSF was used as adjuvant and vaccines were administered over 6 months. Patients responded to either single antigens (90%) or to multiple antigens (50%). Importantly, pretreatment levels of Tregs, administration of chemoradiotherapy, or treatment with steroids did not affect the capacity of the vaccine to stimulate immune responses to glioblastoma multiforme antigens. These data, together with previous findings, of T-cells specific to glioblastoma multiforme antigens within the glioblastoma multiforme microenvironment, strongly support the use of future combinations of novel kinds of immunization combined with checkpoint inhibitors.

Figure 1.
The figure shows schematically the translational aspects of this work. Specifically, the top part of the figure describes the work of Dutoit and colleagues (7) who isolated glioma antigenic peptides presented specifically by HLA.A2 molecules (in red) on the membrane of glioma tumor cells. The middle part of the figure summarizes how Rampling and colleagues (1) utilized these antigenic peptides to immunize patients. The lower part of the figure illustrates the mechanism of action, whereby the antigenic peptides used as immunogens are taken up by dendritic cells (DC) and transported to the draining lymph nodes, where they are presented to naive T cells (TcN). The resulting T effector cells (TcE) then migrate to the tumor in the brain, where they recognize the antigenic epitopes presented by glioma cells on HLA.A2, and kill such target glioma cells. The progress made by this approach is the simultaneous immunization with 11 antigens to reduce the capacity of glioma cells to escape immune attack by reducing expression of such targeted antigens.
OS was not increased when patients responding to multiple antigens were compared with those only responding to one antigen; median survival was comparable with median survival of the general patient population. However, a striking difference in survival was detected when patients were evaluated in relation to the presence or absence of an injection-site response. Under this comparison, patients in whom an injection-site response was evident displayed twice the survival of those without an injection-site response. Although statistical analysis provides a significant P value, the authors are careful not to overinterpret these data given that this was a phase I rather than a double blind randomized phase III trial. The data from this trial thus provide strong support for the continued development of this vaccination approach. Although follow-up of larger trials of this approach would be predictable, rapid phase I trials combining this vaccination strategy and checkpoint inhibitors could provide stronger responses and increase the availability of a potentially useful treatment to desperately ill patients.

In context, there are currently a number of ongoing trials using varying approaches for glioblastoma multiforme; among others, oncolytic viruses are being tested in early-phase trials (8), as are small-molecule inhibitors of enzymes thought to be essential for the survival of glioma cells (9), gene and immunotherapy to reengineer the brain immune system (https://clinicaltrials.gov/ct2/show/NCT01811992; ref. 10), and novel radiation approaches. In view of the profound and urgent need of novel treatments for patients suffering from glioblastoma multiforme, we hope that all our efforts will significantly contribute to achieving clinical breakthrough results soon.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: P.R. Lowenstein, M.G. Castro
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.R. Lowenstein
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.R. Lowenstein
Writing, review, and/or revision of the manuscript: P.R. Lowenstein, M.G. Castro
Study supervision: P.R. Lowenstein

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