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Achieving Efficacious Immunotherapy for Patients with Glioblastoma

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1. *Introduction: Success of Immunotherapy for the Treatment of Systemic Malignancies*

The discovery of immune checkpoint molecules heralded a revolution in cancer therapy that target the immune system to achieve a long-lasting anti-tumor effect [1]. There has been an explosion of success for immunotherapies against a variety of solid tumors, revolutionizing the care of metastatic disease for some malignancies, but glioblastoma has been noticeably absent from these success stories and patients diagnosed with malignant gliomas continue to face a poor prognosis with few long term survivors [2]. This review discusses different technologies and strategies for overcoming the challenges facing immunotherapy, specifically focusing on checkpoint inhibition, for patients with malignant gliomas.

2. *Challenges Facing Immunotherapy for Malignant Gliomas*

There are a variety of anatomical and physical hurdles, as well as local and systemic immunosuppressive mechanisms, that immunotherapy must overcome in order to be successful for patients with malignant gliomas [3,4]. One of the first barriers facing any immunotherapy is the physical blood-brain and blood tumor brain barriers, which prevent large compounds from entering the tumor from systemic circulation [5]. Certain delivery techniques, such as intratumoral injection or convection enhanced delivery, attempt to bypass this barrier, and technologies such as focused ultrasound can be applied to transiently alter the barrier and make it more permeable to systemic agents. It also does not help that the mainstay adjuvant therapies for patients with high grade glioma, temozolomide and radiation, are known to cause lymphopenia and limit the effectiveness of immune-based agents; and dexamethasone, which is given to reduce symptomatic cerebral edema, is also profoundly immunosuppressive [6–10].

Another major hurdle is the fact that glioblastoma is considered a “cold” tumor, with a profoundly immunosuppressive microenvironment that has proven to be unresponsive to immunotherapy so far [11]. Within GBM, populations of immunosuppressive regulatory T cells (Tregs), tumor associated macrophages, and myeloid derived suppressor cells (MDSCs) inhibit the function of cytotoxic T cells and the tumor cells themselves secrete soluble chemokines and cytokines that inhibit dendritic cell maturation and activation [12]. And, relative to the diffusely present immunosuppressive macrophages, which appear to be drawn into the tumor by the tumor-released chemokine osteopontin and other secreted factors, the population of cytotoxic CD3+ T cells in GBM is very small composition of the microenvironment [13]. The tumor cells themselves and immunosuppressive tumor associated macrophages express checkpoint inhibitors like PD-L1, which limit the activity of any potentially anti-tumor T-cells [14]. Additionally, outside of the tumor microenvironment there is also a degree of systemic immunosuppression, evidenced by a impaired cellular immunity and reduced proliferation capacity observed in circulating lymphocytes, as well as a sequestration of lymphocytes in the bone marrow found in GBM patients [15–19].

Moreover, the mutational load in GBM is relatively low compared to tumors that respond to well to immunotherapy, resulting in a low probability of numerous immunogenic neo-antigen presence [20,21]. Even in the small subset of glioblastomas with a high mutational burden, there

does not appear to be an increase in infiltrating CD8+ T cells, making this subset of tumors still unlikely to respond to checkpoint inhibition [22]. This "cold", immunosuppressive environment is likely a major reason for biggest failure of immunotherapy to date for patients with recurrent GBM - the Checkmate-143 clinical trial. [23,24]. Briefly, this randomized phase 3 clinical trial of 369 patients diagnosed with recurrent glioblastoma treated with PD-1 inhibition (nivolumab) failed to find a survival benefit compared with bevacizumab-treated control patients (9.8 months vs. 10.0 months) [25]. Moreover, the objective response rate in this study was actually higher in the bevacizumab treated group compared to the nivolumab group (23.1% vs. 7.8%), and nearly 20% of patients in the nivolumab group experienced a Grade 3 or 4 treatment related adverse event.

3. *Strategies for Overcoming the Hurdles to Immunotherapy for Glioblastoma*

Perhaps the simplest strategy for enhancing the efficacy of immunotherapy in glioblastoma is to combine multiple immunotherapeutic agents together in an attempt to overwhelm the immunosuppressive roadblocks and encourage an anti-tumor immune response. Combining multiple checkpoint inhibitors had been shown to result in more long term survivors in preclinical murine models, but there is an added risk of serious autoimmune related adverse events [26,27]. Combinations that employ multifaceted immunotherapies may have the advantage of synergistically overcoming the numerous ways glioblastomas impair immune function [28]. For example, combining check point inhibition with dendritic cell vaccines have produced better responses than dendritic vaccines alone [29]. Another strategy is to use oncolytic viruses, which replicate in and lysis tumor cells, to initiate an immune response. Not only are the viruses themselves immunogenic, but dying tumor cells release tumor associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) that are recognized by antigen presenting cells (APCs) [30], and this is the approach taken in an active Phase II clinical trial (NCT02798406).

Maybe, the failures of immunotherapy to date are not because of poor therapies, but inappropriate patient selection, and the lack of measurable biomarkers has made it difficult to appropriately select of which patients should be treated with immunotherapy. PD-L1 levels have proven effective at predicting response to anti-PD-1 and anti-PD-L1 treatments for other solid malignancies, however the ability of a single biomarker to predict response rates in GBM has been questioned [22,31,32]. Additionally, hypermutated tumors, either from TMZ exposure, mismatch repair deficiency, or *POLE* deficiency, may respond better to checkpoint inhibition, although emerging evidence suggests that post-treatment hypermutated tumors reflect a different hypermutation pathway than *de novo* hypermutated tumors and respond differently to PD-1 blockade [33]. Continuing to refine patient selection should result in more efficacious immunotherapy, albeit for a smaller percentage of patients.

Another tactic for improving the efficacy of immunotherapy is to convert glioblastoma from a "cold" tumor to a "hot" tumor. For instance, stimulator of interferon genes (STING) agonists have been tried to repolarize the immunosuppressive myeloid cells and induce a proinflammatory cytokine response [34]. Another approach is to deliver IL-12 into the tumor environment, which has improved the cytotoxic function of T cells and enhanced the efficacy of

checkpoint inhibitors in GBM [35]. Reverse translational studies are one approach for identifying targets that may be able to convert GBM to a more immunotherapy responsive tumor. One group recently used this strategy to identify a population of CD73 expressing macrophages in GBM and showed that mice lacking CD73 survived longer and responded better to combinatorial checkpoint inhibition compared to mice with CD73 [36]. It remains to be seen which immunomodulator target will have the biggest impact on the lives of GBM patients. If checkpoint inhibitors are analogous to cutting the brakes for the immune system, this technique can be thought of as putting a brick on the car's accelerator.

Finally, maybe the agents are being used, but the timing or mechanism of immunotherapy delivery, which are likely critical to the efficacy, are suboptimal. Rather than waiting until after surgery, neoadjuvant anti-PD1 therapy in conjunction with continued post-operative adjuvant therapy have been shown to enhance local and systemic antitumor immunity and improve survival compared to patients who only receive adjuvant immunotherapy [37–39]. Alternatively, combining checkpoint inhibition with MRI-guided laser ablation to disrupt the blood-brain barrier, is actively being explored in a clinical trial (NCT02311582).

4. Conclusions

The local and systemic immunosuppression found in patients with glioblastoma has limited the effectiveness of immunotherapy to date. Multiple strategies, like identification of biomarkers to optimize patient and therapeutic agent selection and immunostimulatory adjuncts, are being employed to overcome this hurdle. Additionally, novel technology may help improve the delivery of systemic immunotherapy to the tumor microenvironment, potentially turning previously ineffective options into viable tools in the treatment arsenal. While it remains to be seen which combination of immunotherapies will eventually breakthrough and improve outcomes for patients with malignant gliomas, the failure of checkpoint inhibitors in clinical trials for GBM patients has only mildly dampened the excitement surrounding this treatment approach.

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