How to integrate immunotherapy into standard of care in glioblastoma

Michael Platten

Department of Neurology, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany, and German Cancer Consortium, Clinical Cooperation Unit, Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center, Heidelberg, Germany

Corresponding Author: Michael Platten, MD, Department of Neurology, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, Germany (michael.platten@umm.de).

See the article by Karachi et al in this issue, pp. 730–741.

Checkpoint inhibitors, such as the programmed cell death protein 1 (PD-1) antagonists nivolumab and pembrolizumab are currently being tested in more than 50 clinical trials worldwide in patients with glioblastoma. Of these, more than 20 clinical trials are being conducted in patients with newly diagnosed glioblastoma. While the field eagerly awaits the results of the CheckMate 548 randomized phase III clinical trial, testing the efficacy of nivolumab added to standard radiochemotherapy with temozolomide (TMZ) in patients with O⁶-methylguanine-DNA methyltransferase (MGMT) methylated newly diagnosed glioblastoma (based on the results of the CheckMate 143 trial), it is fair to assume that the majority of patients will not benefit and that relevant responses will be restricted to a subgroup of patients, possibly only those with a hypermutator phenotype.¹

While resistance to immune checkpoint inhibitors is probably driven by a lymphodepleted phenotype² and poor immune recognition as a result of low mutational load,³ the relevance of concomitant alkylating therapy as a confounder is less clear. The pragmatic approach is to simply integrate immune checkpoint inhibitors in clinical trials with newly diagnosed glioblastoma with MGMT methylation into adjuvant TMZ chemotherapy at the standard dosing (SD) regimen of 200 mg/m² given in 5/28 day cycles as is being done with any other non-immune intervention aiming at improving outcome in MGMT methylated glioblastoma patients. Interestingly, this pragmatic approach is also taken in many vaccine trials aiming at eliciting a tumor-specific T-cell response, even in highly sophisticated personalized approaches.⁴ The general view is that TMZ induces lymphopenia, which in turn allows for an expansion of tumor-reactive T cells in the peripheral circulation as it is practiced using low-dose cyclophosphamide for preconditioning before vaccines or adoptive T-cell transfer.⁵ The opposite view is that circulating tumor-reactive T cells are simply killed when repetitively exposed to high doses of TMZ. While both views may be biologically rationalized, there is surprisingly little data on the actual immunological effects of the standard

TMZ dosing schedule. When the epidermal growth factor receptor variant III vaccine was developed to be integrated into standard of care, intensified 21/28 dose intensity (DI) at 100 mg/m² resulted in more pronounced lymphopenia and vaccine responses compared with SDTMZ despite increased peripheral frequencies of regulatory (immunosuppressive) T cells (Tregs).⁶ This illustrates that dosing and timing of TMZ chemotherapy is critical for antitumor immune responses and that standard read-out parameters such as assessing frequencies of T-cell subsets is not sufficient to characterize the detailed immunological consequences of TMZ chemotherapy.

In this issue of *Neuro-Oncology*, Karachi et al dissect the effect of TMZ on antigen-specific T-cell responses in 2 experimental syngeneic glioma models using SD TMZ compared with metronomic dosing (MD) when given concomitantly to anti-PD-1 antibody.⁷ Importantly, as opposed to DI TMZ, the cumulative dose between both regimens was identical and MD was given for only 10 days. The most compelling finding in this preclinical study is that SDTMZ abrogates the antitumor effect of anti-PD-1 treatment, while anti-PD-1 efficacy is preserved in MD TMZ-treated animals. While in this study not mechanistically proven, it is likely that the abrogation of the anti-PD-1 treatment effect by SDTMZ is due to an upregulation of exhaustion markers on tumor-infiltrating lymphocytes which unfavorably shifts the rheostat to a less inflamed tumor microenvironment, which in turn is an important prognostic parameter for response to checkpoint inhibition across tumor entities.⁸ This is in line with previous work in the GL261 model demonstrating that TMZ 5 days prior to initiation of checkpoint blockade enhances antitumor efficacy of PD-1 blockade but compromises long-term immunological memory.⁹

What are the implications for patients and clinical trial design? When considering immunotherapy, patients should first be off dexamethasone, as there is sufficient data demonstrating that dexamethasone is certainly more detrimental for effective antitumor immunity than alkylating

chemotherapy.¹⁰ The elegant preclinical study by Karachi and coworkers illustrates the value of preclinical models to address important clinical questions, but due to the known limitations of most preclinical models, thoroughly designed clinical studies are required. As more and more sophisticated immunotherapies are tested, it is time for controlled clinical trials defining the impact of standard of care in glioblastoma including SD and MD or DI TMZ regimens on antitumor immunity induced by immune checkpoint inhibitors and vaccines not only in the peripheral circulation but also in posttreatment tumor tissue, as potential detrimental or possibly beneficial effects of TMZ can only be faithfully assessed in the tumor microenvironment, not in the peripheral circulation. In this respect, the field requires more clinical trials where a resection of tumor tissue after the initiation of an experimental immunotherapy is an integral part of the protocol as exemplified in the currently recruiting VXM01-AVE-04-INT (ClinicalTrials.gov identifier NCT03750071) or NOA-21 (ClinicalTrials.gov identifier NCT03893903)¹¹ trials. That being said, a prerequisite for further development in this area is a proof of concept from a controlled clinical trial that immunotherapy works in patients with glioblastoma.

References

1. Bouffet E, Larouche V, Campbell BB, et al. Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency. *J Clin Oncol*. 2016;34(19):2206–2211.
2. Thorsson V, Gibbs DL, Brown SD, et al. The immune landscape of cancer. *Immunity*. 2018;48(4):812–830 e814.
3. Hodges TR, Ott M, Xiu J, et al. Mutational burden, immune checkpoint expression, and mismatch repair in glioma: implications for immune checkpoint immunotherapy. *Neuro Oncol*. 2017;19(8):1047–1057.
4. Hilf N, Kuttruff-Coqui S, Frenzel K, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature*. 2019;565(7738):240–245.
5. Chandran SS, Somerville RPT, Yang JC, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(6):792–802.
6. Sampson JH, Aldape KD, Archer GE, et al. Greater chemotherapy-induced lymphopenia enhances tumor-specific immune responses that eliminate EGFRvIII-expressing tumor cells in patients with glioblastoma. *Neuro Oncol*. 2011;13(3):324–333.
7. Karachi A, Yang C, Dastmalchi F, et al. Modulation of temozolomide dose differentially affects T cell response to immune checkpoint inhibition. *Neuro Oncol*. 2019;21(6):730–741.
8. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359(6382):1350–1355.
9. Park J, Kim CG, Shim JK, et al. Effect of combined anti-PD-1 and temozolomide therapy in glioblastoma. *Oncoimmunology*. 2019;8(1):e1525243.
10. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature*. 2019;565(7738):234–239.
11. Friedrich M, Bunse L, Wick W, Platten M. Perspectives of immunotherapy in isocitrate dehydrogenase-mutant gliomas. *Curr Opin Oncol*. 2018;30(6):368–374.