Neuro-Oncology
XX(XX), 1–4, 2024 | https://doi.org/10.1093/neuonc/noae225 | Advance Access date 19 November 2024

Letter to the Editor

Treatment of glioblastoma patients with personalized vaccines outside clinical trials: Lessons ignored?

The treatment of patients with glioblastoma remains a challenge. Several large clinical trials of the last decades have failed and had—in retrospect—been built on over interpreted uncontrolled or inadequately controlled phase II trials or retrospective case series. Despite this disappointing experience and critical reviews, the temptation to demonstrate the value of novel experimental treatments without randomized trials using external control data and then to report a positive outcome compared to those "historical" or "external" controls remains. Recently reported "real-world observation" of glioblastoma patients treated with a personalized peptide vaccine led by a German for-profit center[1] is yet another example of such an attempt. As we anticipate misunderstandings and erroneous conclusions from this publication, we reviewed the data and the conclusions presented from a clinical and translational science perspective.

A series of 173 patients with isocitrate dehydrogenase (*IDH*)-wildtype glioblastoma were treated with personalized peptide vaccines outside a clinical trial as individual named patient protocols (which the authors referred to as "individual healing attempts"). These "individual healing attempts" were designed by a German for-profit center.[1] Patients paid themselves for this expensive investigational treatment that was applied in Germany. Tumors were analyzed for somatic mutations using whole exome sequencing upon which a personalized peptide vaccine was designed. Their vaccine was applied with 4 injections with a 7-10 days interval in the priming phase, followed by a boosting phase with 3 vaccinations every 4-6 weeks. They report a median overall survival from diagnosis of 31.9 months and a significantly longer survival for patients with multiple vaccine-induced T-cell responses (53 months) compared to those with no/low induced responses (27 months). The authors call this series of named patient protocols without Institutional Review Board approval a "real-world observation." According to the report, the patients had to travel to the treating facility for each vaccine administration. Thirty patients were from Germany, 77 came from the United States of America, 42 came from other European countries, and 24 came from other countries. Seventy patients (70/173, 40%) were treated after initial treatment and 103/173 patients (60%) at progression. Ninety-two percent of patients had received standard of care, that is, radiotherapy (RT) plus temozolomide (TMZ). The authors conclude that "the overall survival rates of our cohort compare favorably to recently reported datasets." To arrive at this conclusion, they used propensity matching with external datasets.

This report represents a retrospective study of separate, experimental interventions based on self-payment by patients in a heterogeneous group of 173 glioblastoma patients that uses matched external controls from variable sources to provide an interpretation of the observations. The median time from diagnosis to the start of vaccination was 10.4 months, with an upper range of 54 months. The median observation time from diagnosis to last follow-up or death is 21.3 months, which implies that the average patient was followed for less than 12 months. On average, 4 months were needed to start the vaccination. Accordingly, the patients needed to remain in good condition for quite sometime before the start of treatment.

There is no mention of patients who had their tumor profiled but never made it to the vaccination phase. The authors mention in the section "Methods" that 4 treatment-related grade 3 adverse events occurred that resolved without the necessity of hospitalization and mention that one of these 4 patients chose to discontinue vaccine therapy. Further details on safety assessments only include the information that patients were observed for "at least 30 minutes after each vaccine dose." It remains unclear whether and if so how many patients prematurely discontinued treatment for any other reason.

A table summarizes the patient characteristics: 65% of patients had a KPS of 90 or 100 and a median age at diagnosis of 53 years. Comparison to a typical recurrent glioblastoma study illustrates the more favorable patient population in this program that is inherent to the nature of the treatment described, notably its logistics.[2] Here, the glioblastoma patients still had to be fit to travel long distances several times and many months after their diagnosis. This is unfortunately not the "real-world" of most patients with glioblastoma that require treatments.

For the 103 patients (60% of the total population) with progressive tumor, the median overall survival is described as 23.8 months from diagnosis, and 9.8 months from initiation of the vaccine therapy. These 9.8 months are in the range that is reported in prospective clinical studies on progressive glioblastoma, questioning whether any benefit from the vaccination was derived for these patients.[2] The median overall survival is reported as having not been reached for patients in the newly diagnosed setting (without progression) as less than 50% had died at data cutoff. However, as mentioned above, the follow-up time was limited (in the range of 12 months), more than 95% had received TMZ and/or RT and was still free from progression when starting the vaccination some 10 months after diagnosis. This report is on a highly selected population of glioblastoma patients.

The authors try to give credit to the efficacy of the vaccination by using external controls. They created a matched cohort from four publicly available datasets, with matching limited to age at diagnosis, sex, O^6-methyl guanine DNA methyltransferase (MGMT) gene promoter methylation status, concurrent TMZ during RT, and TMZ maintenance treatment. However, performance status, tumor status at the time of treatment, size of the tumor, or glucocorticoid dose that are important prognostic factors are neither controlled for. Similarly, any additional therapies beyond RT and TMZ are not controlled for.

Given the lead time between initial diagnosis to the start of the vaccination, the authors included only those external control patients that survived longer than the median time between diagnosis and first vaccination observed in their cohort (10 months). That still does not control for the performance status of patients, however. Of note, none of the studies where the authors derive their external controls from had been designed for this purpose and all introduce biases. The use of older studies and studies from a different geographic region (Eastern Europe) introduce time trend bias and performance bias.[3,4] A third dataset is from patients having undergone a reresection for tumor progression.[5] A fourth data set is from a US series on genomic profiling, which included 468 glioblastoma patients, with only essential survival and treatment data collected.[6] These limitations make comparisons futile. The importance of the performance status for outcome is actually a key observation made in one of these datasets.[4] This is even more relevant here considering the fact that the patients needed to be able to travel long distances repeatedly and for a period of time. Apart from lead time bias, there is a survivor bias, in that patients had to be able to wait for 3-4 months to start the vaccination and did on average not start until 10 months after the diagnosis while still being fit to travel. In fact, the external controls used here suffer from every bias recently described in a review on the use of external controls in Neuro-Oncology[7] and do simply not match the requirements needed for appropriate external control arms.[8,9]

Immune monitoring data were available for 97/173 patients. The authors identified 77 "responders" and 20 "nonresponders," and compared the overall survival within these subgroups, as stated in a display item. The definition of "responders" and "nonresponders" was not prespecified.[10] Overall survival is reported to be longer in 77 patients with an immune response compared with 20 "nonresponders." In the absence of prespecified immunological response criteria, clear data reporting on the number of vaccinations for each individual patient, and early discontinuations, while on treatment, it remains unclear to what extent this represents simply an association with survival, as opposed to a causation of long survival. The comparison of the overall survival of "immune responders" and "nonresponders" with external controls suffers from the same limitations as outlined above.

Access to this experimental therapy required self-payment while the authors recognized that a specific socio-economic status must have been required for participation and thus might be a limitation of their study and indeed results in an unknown selection bias. Moreover, publishing a "potential promising treatment" option without adequate controls available at a high cost only is enticing patients to spend resources and raise funds for this treatment because they fear to miss an important option. The long-term financial consequences for patients and their families are a source of concern.

Of note, 19 of 50 authors are affiliated with Zentrum für Humangenetik, CeGaT, CeCaVa, or with the MVZ Zentrum für ambulante Onkologie GmbH and thus disclose significant competing interests (eg ownership interests, employment status as outlined in the section "competing interests"). The author contributions section discloses that 7 authors have "directly accessed and verified the underlying data reported in the manuscript," and all these 7 authors are affiliated either with CeGaT or "Zentrum für Humangenetik."

Many terminologies in their report suggest a clinical trial setting (eg "Study Design and participants" in the section "Methods"), which is not the case here. What is furthermore confusing is the title "real-world observation." Real-world data usually reflect the scope of data generation of a commonly used (or at least commonly accessible) and registered therapeutic strategy that is broadly applied. This personalized vaccine treatment, however, was only available based on specific requests by patients or treating physicians, upon self-payment, and in only one specific German center. This does not meet the criteria for the label "real world."[10]

Individual-named patient protocols can be offered to patients in the absence of any available standard therapy. Most importantly, the intention of a physician to give treatments as a named patient protocol is the treatment benefit of the individual patient. Yet, the size of the program reported here and its commercial nature are clearly beyond that. We are not aware of any similar-sized series of named patient protocols. The authors concluded that their report can serve as "groundwork" for a clinical trial, and the company announces on the homepage that a registration trial will follow based on these data. We question whether the results of this retrospective, biased, and ill-standardized analysis of 173 "individual healing attempts" based on self-payment by patients is sufficient to warrant a registration-type trial.

In conclusion, this is another unfortunate example of a publication that neither contributes to the benefit of patients nor to the development of the field. The opposite is in fact true, as it will generate false hope in an expensive treatment without data supporting that treatment. The lack of an intent-to-treat report, of a trial protocol, and of a controlled design makes this publication nothing more than feasibility study. Feasibility has however been shown before. A clinical phase 1 trial demonstrated that a personalized vaccination approach for glioblastoma patients is feasible in a multicenter setting and results in immune responses.[11] In contrast to this phase 1 trial that was published in 2019, however, the retrospective series of named patient protocols presented by Latzer et al. did not attempt to benchmark their nondisclosed algorithm for selecting the treatment with existing computational tools nor did they validate the relevance of the therapeutic targets.

The German law allows individual-named patient protocols. In a limited noncommercial academic setting such treatment on a compassionate use basis can be informative

in preparation of a proper clinical trial.[12] We recommend, however, that regulatory authorities and policy makers (re) evaluate the regulatory scope and provide more guidance for what is acceptable from a legal and regulatory perspective in this sphere.

The treatment of glioblastoma remains a challenge. We remain convinced that immunotherapeutic strategies may have the potential to contribute to this currently unmet clinical need. A thoughtful continuation of the clinical development of immunotherapeutic strategies within the framework of clinical trials is required to provide relevant new insights that can eventually lead to a clear delineation of its value in clinical practice. Such clinical developments must entail thorough target selection, which is an important prerequisite for efficacy as shown in failed vaccine studies in glioblastoma previously.[13] The report by Latzer et al., unfortunately, does not contribute to this field nor to the understanding of this complex disease.[1]

Keywords

immunotherapy | glioblastoma | historical controls | personalized vaccines | real world

Conflict of interest statement

G.T. reports institutional funding to the University Hospital Tübingen that was provided for the following activities: Advisory boards, consultancy, lectures (Bayer, Boehringer Ingelheim, CureVac, Miltenyi Biomedicine, Novocure, Servier), steering committee member in noninterventional trials (Bayer, Novocure). M.Pl. holds patents on IDH1- and H3-directed peptide vaccines and is the founder of Tcelltech, has received research support from Bayer, Pfizer, Merck, and Roche, and honoraria for lectures or advisory board participation or consulting from Servier. M.Pr. has received honoraria for lectures, consultation, or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape, OncLive. M.W. has received research grants from Novartis, Quercis, and Versameb (institutional funding), and honoraria for lectures or advisory board participation or consulting from Anheart, Bayer, Curevac, Medac, Neurosense, Novartis, Novocure, Orbus, Pfizer, Philogen, Roche, and Servier (personal honoraria). W.W. has received honoraria for consultancy or participation to advisory boards from Bristol-Myers Squibb, Enterome, Roche, and Servier. M.vdB has received research support from Boehringer-Ingelheim, honoraria for consultancy or participation to advisory boards from Servier, Anheart Therapeutics, Boehringer Ingelheim, Fore Biotherapeutics, Geneta, Incyte, Chimerix, and Symbio Pharma, and support for travel from Servier.

Ghazaleh Tabatabai[†], Michael Platten[†], Matthias Preusser[†], Michael Weller[†], Wolfgang Wick[†], and Martin van den Bent[†]

Department of Neurology and Interdisciplinary Neuro-Oncology, Center for Neuro-Oncology, Comprehensive Cancer Center, University Hospital Tübingen, Hertie Institute for Clinical Brain Research, Eberhard Karls University Tübingen, Tübingen, Germany (G.T.); Department of Neurology, Medical Faculty Mannheim, Mannheim Center for Translational Neurosciences (MCTN), University of Heidelberg, Mannheim, Germany (M.Pl.); Clinical Cooperation Unit Neuroimmunology and Brain Tumor Immunology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany (M.Pl.); Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria (M.Pr.); Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland (M.W.); Department of Neurology, University Hospital and Heidelberg University, Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany (W.W.); The Brain Tumor Center, Erasmus Medical Center Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands (M.vdB.)

[†]All authors contributed equally to this work.

Corresponding Author: Martin van den Bent, MD, The Brain Tumor Center at Erasmus MC Cancer Institute, University Medical Center Rotterdam, Dr Molenwaterplein 40, 3015GD Rotterdam, The Netherlands (mjvandenbent@neuro-oncology.nl).

References

1. Latzer P, Zelba H, Battke F, et al. A real-world observation of patients with glioblastoma treated with a personalized peptide vaccine. *Nat Commun.* 2024;15(1):6870.
2. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med.* 2017;377(20):1954–1963.
3. Brennan CW, Verhaak RG, McKenna A, et al; TCGA Research Network. The somatic genomic landscape of glioblastoma. *Cell.* 2013;155(2):462–477.
4. Lakomy R, Kazda T, Selingerova I, et al. Real-world evidence in glioblastoma: Stupp's regimen after a decade. *Front Oncol.* 2020;10:840.
5. Barthel FP, Johnson KC, Varn FS, et al; GLASS Consortium. Longitudinal molecular trajectories of diffuse glioma in adults. *Nature.* 2019;576(7785):112–120.
6. Cloughesy TF, Yoshimoto K, Nghiemphu P, et al. Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. *PLoS Med.* 2008;5(1):e8.
7. Polley MC, Schwartz D, Karrison T, Dignam JJ. Leveraging external control data in the design and analysis of neuro-oncology trials: Pearls and perils. *Neuro Oncol.* 2024;26(5):796–810.

8. Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. *Ann Oncol.* 2022;33(4):376–383.
9. Rahman R, Ventz S, McDunn J, et al. Leveraging external data in the design and analysis of clinical trials in neuro-oncology. *Lancet Oncol.* 2021;22(10):e456–e465.
10. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963–1972.
11. Hilf N, Kuttruff-Coqui S, Frenzel K, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature.* 2019;565(7738):240–245.
12. Grassl N, Poschke I, Lindner K, et al. A H3K27M-targeted vaccine in adults with diffuse midline glioma. *Nat Med.* 2023;29(10):2586–2592.
13. Weller M, Butowski N, Tran DD, et al; ACT IV Trial Investigators. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol.* 2017;18(10):1373–1385.