The Oncologist, 2023, **XX**, 1–3
https://doi.org/10.1093/oncolo/oyad104
Advance access publication 2 May 2023
Commentary

Moving the Pendulum for Glioblastoma Treatment: One Injection at a Time

Xizi Wu[1], Christopher Alvarez-Breckenridge[*,1]

[1]Department of Neurosurgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

*Corresponding author: Christopher Alvarez-Breckenridge MD, PhD, Department of Neurosurgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd., Unit 442, Houston, TX 77030, USA. Tel: +1 713-563-8729; Email: CAlvarez11@mdanderson.org

Introduction

Gliomas are the most common primary central nervous system malignancy, with approximately 200 000 new cases each year in the US, and are associated with a poor clinical outcome.[1] Recent developments have incorporated molecular diagnostic features in the classification and grading of these tumors. This has been reflected in the 2021 WHO Classification of CNS Tumors in which gliomas are categorized into Astrocytoma, IDH mutant (grades 2-4), and Glioblastoma (GBM), IDH wild type (grade 4).[2] Despite intensive efforts defining the molecular underpinnings of GBM and their associated cellular heterogeneity,[3] current treatment options include surgical resection, chemoradiation, and tumor-treating field. Despite these incremental advances, GBM is characterized by exceptionally high rates of recurrence and resistance to therapy. As a result, there is an urgent need to develop novel, effective therapeutic strategies that leverage vulnerabilities of the tumor and associated microenvironment.

Oncolytic Virotherapy for Malignant Glioma and G47Δ Clinical Trial

Over 20 years of research in oncolytic viruses (OV) have resulted in the development of a wide-array of viral strategies for the treatment of solid tumors. With the need to develop novel approaches for patients with GBM, preclinical and clinical research has focused on various viral vectors including oncolytic herpes simplex virus (oHSV), adenovirus, and polivirus,[4-6] making these agents emerging treatment options for patients with GBM. Different from standard treatments, oncolytic virotherapy leverages the ability to preferentially replicate and kill cancer cells without affecting normal cells. This occurs through bioengineered mutations which ultimately result in immunogenic cell death. The oncolytic herpes virus G47Δ (Delytact or teserpaturev) has recently undergone a phase II trial with encouraging interim results ultimately prompting early termination of the trial. These findings led to the conditional approval for marketing authorization in Japan. In this issue of *The Oncologist*, Maruyama et al. published the Pharmaceuticals and Medical Devices Agency (PMDA) review of G47Δ injection for malignant glioma, in which the efficacy and safety results of G47Δ have been evaluated, along with the clarified approval conditions.[7]

G47Δ is a genetically modified, replication-competent HSV type 1, in which the *γ34.5* and *α47* genes have been deleted to attenuate neurotoxicity. In addition to, the *infected cell protein* 6 (*ICP6*) gene has been inactivated by *lacZ* gene insertion to ensure selective replication in tumor cells and enhanced immunogenicity. The agents were determined to be safe in a first-in-human trial in which patients underwent two intratumoral injections within 2 weeks.[8] In addition, preclinical studies have demonstrated that the virus works through two distinct mechanisms (1) direct tumor cell lysis secondary to oncolytic viral replication and (2) generation of T cell-mediated antitumor immunity.[9] Building upon this work, the Japanese phase II trial GD01 was a single-center study for patients with residual or recurrent GBM who had undergone previous radiation therapy and temozolomide.[10] Patients underwent up to 6 stereotactic intratumoral injections of G47Δ at 1×10^9 plaque forming units. Interim analysis in 13 patients demonstrated a 1-year survival rate after G47Δ injection of 92.3% which exceeded the prespecified primary endpoint of 15% and triggered early termination of the trial. Regarding secondary endpoints, the median overall survival was 20.2 months after G47Δ initiation and 28.8 (20.1-37.5) months from the initial surgery. Disease progression was observed in 14 of 19 patients and was associated with a progression free survival [95% CI] of 4.7 months.

PMDA Review of Phase II Trial GD01

While the results of the GD01 trial, which investigated multiple intratumoral injections of G47Δ into residual or recurrent glioma, provided encouraging signals regarding its clinical efficacy and broader clinical implementation, the PMDA identified several caveats to consider when interpreting the data.

1. This study was conducted at a single site with the capability of administering multiple intracranial injections and managing these patients postoperatively. In addition, the clinical consequences of fewer than 6 injections were not independently evaluated.

Received: 22 March 2023; Accepted: 23 March 2023.

2. The historical survival data which were used to determine the study's primary endpoint was not reflective of most recent clinical practices or survival data in Japan.
3. Patients were not stratified by current molecular classification and prognostic factors (eg, *IDH1* and MGMT promoter methylation).
4. The study utilized immune-related Response Criteria rather than Response Assessment in Neuro-Oncology criteria (PDMA ref 10), highlighting the lack of consensus regarding imaging studies for oncolytic viral therapies.

Based on these limitations, it was difficult to draw the conclusion that G47Δ was effective solely based on the 1-year survival rate exceeding the pre-determined threshold for efficacy. Therefore, PMDA further evaluated MRI results from patients enrolled in the GD01 trial. Among 18 patients assessed as stable disease (SD), 4 patients remained with SD for an extended period during G47Δ treatment. Considering the rapid progression of GBM, these MRI results suggest that multiple intracranial injections of G47Δ in recurrent or residual GBM has some degree of clinical efficacy.

In addition to the clinical utility of G47Δ, PMDA also reviewed the safety assessment of G47Δ. A total of 19 patients who received at least one dose of G47Δ were included in the downstream safety analysis. Among 3 patient who developed pyrexia, one patient was found to have a causal relationship with G47Δ. One patient with postprocedural infection led to treatment discontinuation, even though its causal relationship with G47Δ was ruled out. A decrease in lymphocyte count was observed in 5 patients, and a causal relationship with G47Δ could not be excluded. Seizures occurred in 9 patients and was causally linked to G47Δ in 6 patients. Brain edema occurred in 12 patients with a causal relationship in 9 patients; however, this did not result in treatment discontinuation. Based on these data, the PMDA concluded that G47Δ may be an effective and safe treatment for recurrent or residual malignant glioma.

Despite this approval, the PMDA outlined the need to perform ongoing evaluation of efficacy and safety during post-marketing studies. This work will continue for the next 7 years among GBM patients who have received prior radiation or temozolomide (TMZ) and are treated with G47Δ. Indications, dosages, and method of administration were outlined based on study GD01. Due to the clinical and technical nuances of stereotactic intratumoral viral administration, the PMDA review highlights the importance of physician experience in clinical decision-making regarding patient enrollment and viral administration. In addition, to better assess post-marketing efficacy and safety, a use-results comparison survey is necessary in which the safety and efficacy of G47Δ is compared between patients undergoing viral treatment and a matched control cohort of patients who would be eligible for G47Δ but do not pursue treatment. Regarding efficacy endpoints, the PMDA concluded that overall survival remains the appropriate primary endpoint for treatment efficacy while also taking into account confounding factors such as tissue type (grade), O6-methylguanine-DNA methyltransferase (MGMT) methylation status, and the presence of *IDH1/2* mutation.

Perspective

With a median overall survival (OS) of 20.2 months in a cohort of patients with recurrent or residual gliomablastoma, the results of the trial by Todo et al are a significant improvement compared to multiple prior trials and meta-analyses[11-14]for GBM. Notably, with the recent approval of tumor-treating fields in combination with TMZ for newly diagnosed GBM, the median OS was 20.9 months[15]; however, among patients with recurrent GBM, the median OS was 6.6 months.[16] In contrast, in the phase II trial of G47Δ by Todo et al, the median OS was 28.8 months from the initial surgery. While prior studies have explored oncolytic viral approaches in the context of recurrent GBM, Todo et al utilized a novel dosing scheduled that included 6 stereotactic intratumoral injections. This approach appears to significantly improve its therapeutic efficacy by achieving both direct tumor oncolysis and modulation of the tumor microenvironment toward a proinflammatory, anti-tumor state.

Additional multicenter studies are needed to achieve greater understanding of the biological underpinnings of the therapeutic response in the clinical context. Histologic studies from GD01 demonstrated CD4+ and CD8+ immune cell infiltration following G47Δ injection, and this was associated with low levels of FoxP3+ T cells. While immune infiltration persisted for months after injection, prior studies have demonstrated that injected virus is cleared within 4 weeks after inoculation.[8,9] These findings highlight the importance of both viral-mediated tumor clearance and immunomodulation with oncolytic viral therapy. Longitudinal studies utilizing a window of opportunity approach[17] are needed to perform immunoprofiling, single cell cellular spatial analyses, and T-cell clonotyping against tumor- and viral-specific antigens. Using these approaches, it will be possible to interrogate the dynamic interplay between pre- and postinfection tumor cells with the surrounding tumor microenvironment that includes both immune and neuronal interactions. In addition, further studies will be needed to explore the limitations of pre-existing anti-viral antibodies and the ability to achieve tolerance against these shared oncolytic viral antigens.

G47Δ has become the first OV to be granted a conditional 7-year marketing approval in Japan for GBM. This represents an immunotherapeutic milestone within the field of oncolytic viral therapy for the treatment of GBM. After its marketing launching, continuous assessment will provide novel insight into the ongoing safety and efficacy of G47Δ. With renewed energy and excitement surrounding the approval of G47Δ in Japan, this will provide additional motivation to build upon previously studied oncolytic viral approaches for GBM as novel dosing schedules and combinatorial strategies are explored.

Funding

Christopher Alvarez-Breckenridge: Cancer Prevention & Research Institute of Texas Early Clinical Investigator Award; MD Anderson Cancer Center Physician Scientist Program.

Conflict of Interest

There are no conflicts of interest amongst the authors.

References

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: primary brain and other central nervous system tumors Diagnosed in the United States in 2014-2018.

Neuro Oncol. 2021;23(12 Suppl 2):iii1-iii105. https://doi.org/10.1093/neuonc/noab200
2. Louis DN, Perry A, Wesseling P, et al. 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251. https://doi.org/10.1093/neuonc/noab106
3. Neftel C, Laffy J, Filbin MG, et al. An integrative model of cellular states, plasticity, and genetics for glioblastoma. *Cell*. 2019;178(4):835-849.e21. https://doi.org/10.1016/j.cell.2019.06.024
4. Desjardins A, Gromeier M, Herndon JE, et al. Recurrent glioblastoma treated with recombinant poliovirus. *N Engl J Med*. 2018;379(2):150-161. https://doi.org/10.1056/NEJMoa1716435
5. Lang FF, Conrad C, Gomez-Manzano C, et al. Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma. *J Clin Oncol*. 2018;36(14):1419-1427. https://doi.org/10.1200/JCO.2017.75.8219
6. Markert JM, Liechty PG, Wang W, et al. Phase Ib trial of mutant herpes simplex virus G207 inoculated pre-and post-tumor resection for recurrent GBM. *Mol Ther*. 2009;17(1):199-207. https://doi.org/10.1038/mt.2008.228
7. Maruyama Y, Sakurai A, Noda S, et al. Regulatory issues: PMDA - review of Sakigake designation products: oncolytic virus therapy with delytact injection (teserpaturev) for malignant glioma. *Oncologist*. 2023;X(X):1-7. https://doi.org/10.1093/oncolo/oyad041
8. Todo T, Ino Y, Ohtsu H, Shibahara J, Tanaka M. A phase I/II study of triple-mutated oncolytic herpes virus G47Δ in patients with progressive glioblastoma. *Nat Commun*. 2022;13(1):4119. https://doi.org/10.1038/s41467-022-31262-y
9. Todo T, Martuza RL, Rabkin SD, Johnson PA. Oncolytic herpes simplex virus vector with enhanced MHC class I presentation and tumor cell killing. *Proc Natl Acad Sci U S A*. 2001;98(11):6396-6401. https://doi.org/10.1073/pnas.101136398
10. Todo T, Ito H, Ino Y, et al. Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial. *Nat Med*. 2022;28(8):1630-1639. https://doi.org/10.1038/s41591-022-01897-x
11. Ballman KV, Buckner JC, Brown PD, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol*. 2007;9(1):29-38. https://doi.org/10.1215/15228517-2006-025
12. Wick A, Pascher C, Wick W, et al. Rechallenge with temozolomide in patients with recurrent gliomas. *J Neurol*. 2009;256(5):734-741. https://doi.org/10.1007/s00415-009-5006-9
13. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27(28):4733-4740. https://doi.org/10.1200/JCO.2008.19.8721
14. Brahm CG, van Linde ME, Enting RH, et al. The current status of immune checkpoint inhibitors in neuro-oncology: a systematic review. *Cancers (Basel)*. 2020;12(3):1-16. https://doi.org/10.3390/cancers12030586
15. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306-2316. https://doi.org/10.1001/jama.2017.18718
16. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48(14):2192-2202. https://doi.org/10.1016/j.ejca.2012.04.011
17. Srinivasan VM, Ene C, Kerrigan BP, Lang FF. Window of opportunity clinical trials to evaluate novel therapies for brain tumors. *Neurosurg Clin N Am*. 2021;32(1):93-104. https://doi.org/10.1016/j.nec.2020.09.002