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Original Article

Optimizing glioblastoma treatment: A systematic review and meta-analysis of local injection and systemic drug delivery system in murine models

Nicholas Calvin, Renindra Ananda Aman

Department of Neurosurgery, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

E-mail: Nicholas Calvin - nicholaspaulus.calvin@gmail.com; Renindra Ananda Aman - reninananda.aman@ui.ac.id

***Corresponding author:**
Nicholas Calvin,
Department of Neurosurgery,
Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

nicholaspaulus.calvin@gmail.com

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ABSTRACT

Background: Glioblastoma (GBM) is an aggressive primary brain tumor with a poor prognosis. The current gold standard for GBM treatment, known as the Stupp protocol, includes maximal safe surgical resection followed by radiotherapy and temozolomide chemotherapy. Despite extending survival modestly, this regimen is associated with significant side effects and limited efficacy, resulting in a median survival (MS) of 15 months and a 5-year survival rate of only 7%. A major challenge in GBM treatment is the blood–brain barrier (BBB), which restricts the penetration of therapeutic agents into the brain, thereby limiting the effectiveness of systemic therapies. To address these limitations, this systematic review and meta-analysis investigated the effectiveness of injectable local drug delivery systems (DDS) compared to systemic DDS in murine GBM models. This study aimed to provide robust evidence supporting the potential benefits of injectable local DDS for GBM treatment.

Methods: A comprehensive literature search was conducted using PubMed, Embase, and ScienceDirect databases. The studies included were original research on local DDS of anticancer agents compared to systemic DDS in orthotopic GBM tumor models. The data extraction process included information on survival rates, tumor growth, and other relevant outcomes. Statistical analysis was performed using Review Manager 5.4, employing a random-effects model to calculate the pooled mean difference (MD) in survival time between local and systemic DDS.

Results: Out of 1341 records, six studies met the inclusion criteria, totaling 129 murine models. The meta-analysis revealed that local injection of DDS significantly improved the MS compared to systemic administration (MD = 2.76; 95% confidence interval, 0.43–5.09; P = 0.03; I^2 = 93%). The local injection of the DDS bypassed the BBB, achieving higher local drug concentrations and sustained release at the tumor site, leading to enhanced therapeutic efficacy and reduced systemic toxicity.

Conclusion: This systematic review and meta-analysis provide compelling evidence that local injection of DDS significantly improves survival in GBM models compared with systemic therapies. These findings highlight the potential of local DDS to overcome the challenges posed by the BBB and deliver higher concentrations of therapeutic agents directly to the tumor site. However, further research is needed to validate these findings in human clinical trials and refine DDS formulations. Future research should focus on developing DDS formulations capable of delivering multiple therapeutic agents simultaneously, addressing the experimental variability in preclinical models, and conducting rigorous clinical trials to evaluate the safety and efficacy of local DDS in human patients. Standardizing the testing methods across studies will facilitate more accurate comparisons and data integration, ultimately advancing the clinical translation of this promising therapeutic approach.

Keywords: Blood–brain barrier, Drug delivery system, Glioblastoma, Survival, Mice

INTRODUCTION

Glioblastoma (GBM) is an aggressive and malignant primary brain tumor with a poor prognosis.[23] The current gold standard for GBM treatment involves maximal safe surgical resection followed by the Stupp protocol, named after Dr. Roger Stupp. This regimen combines radiotherapy with concomitant and adjuvant chemotherapy using temozolomide (TMZ). Patients typically receive radiotherapy 5 days a week for 6 weeks, with concurrent daily oral TMZ. After a 1-month break, patients underwent additional TMZ cycles for 6–12 months at dosages of 150–200 mg/m² for 5 days during each cycle.[18] While this protocol extended survival modestly, it was still associated with significant side effects and limited efficacy in achieving long-term survival. The median survival (MS) time for GBM patients remains around 15 months, with a 5-year survival rate of only 7%.[6,19]

One of the major challenges in treating GBM is the blood–brain barrier (BBB), a protective shield that restricts the penetration of therapeutic agents into the brain.[7] Systemic therapies, including chemotherapy, often fail to reach therapeutic concentrations within the tumor microenvironment due to the BBB's impermeability.[7] Furthermore, the intrinsic resistance of GBM cells to chemotherapy and radiotherapy complicates treatment strategies.

To address these limitations, local drug-delivery systems (DDSs) have emerged as promising alternatives. Local DDS aims to deliver therapeutic agents directly to the tumor site, bypassing the BBB and achieving higher local drug concentrations.[4,13] Figure 1 illustrates various emerging local DDS strategies, including convection-enhanced delivery, laser interstitial thermal therapy (LITT), stereotactic injections, implanted reservoirs, and intra-arterial delivery systems.[20] These approaches has the potential to enhance treatment efficacy while minimizing systemic toxicity. At present, the only Food and Drug Administration-approved local DDS for GBM is Gliadel® wafer, which releases carmustine chemotherapy. However, the Gliadel® wafer has drawbacks, including its rigid nature, which can lead to mechanical mismatches with the soft brain tissue, and the need for a suitable cavity to accommodate the recommended dose of eight wafers.[4,13]

The development of injectable local DDS offers a potential solution to these limitations. Injectable DDS allows for precise and targeted delivery of therapeutic agents directly into the tumor, reducing off-target effects and maximizing drug concentration at the tumor site. This systematic review and meta-analysis aimed to assess the efficacy of injectable local DDS compared to systemic DDS in murine models of GBM. By comparing survival rates and other relevant outcomes, this study sought to provide robust evidence supporting the potential benefits of injectable local DDS in GBM treatment.[17]

In summary, while the Stupp protocol remains the standard of care for GBM, its limitations highlight the need for innovative treatment strategies.[18] Injectable local DDS presents a compelling alternative that could revolutionize GBM therapy by overcoming the challenges posed by the BBB and delivering higher concentrations of therapeutic agents directly to the tumor site. This study aimed to shed light on the effectiveness of these promising systems and their potential to improve outcomes in patients with GBM.

MATERIALS AND METHODS

Literature search

The systematic review conducted in this study employed a rigorous methodology to synthesize and analyze the existing literature on local DDS. The process began with a comprehensive search of relevant medical databases, including PubMed, Embase, and ScienceDirect, without any time limitations. We used specific search terms and MeSH descriptors such as "GBM," "local drug delivery system," "systemic drug delivery system," "survival," and "pre-clinical" to ensure a targeted and exhaustive retrieval of relevant studies. To enhance the thoroughness of our search, we meticulously examined the reference lists of the included studies to identify additional relevant research. Two authors independently screened abstracts and assessed full-text articles for eligibility, ensuring an unbiased selection and evaluation process. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, guaranteeing a transparent and standardized approach.[11]

Eligibility

Following a systematic screening process, we evaluated the eligibility of articles in the initial pool. To be included, studies need to meet specific criteria, such as being written in English, containing original research on local DDS of anticancer agents compared to systemic anticancer DDS in orthotopic GBM tumor models, and involving interventions with injectable local DDS. To ensure a high level of evidence, articles focusing solely on *in vitro* and clinical studies without *in vivo* components were excluded from the study. Furthermore, review articles, case reports, case series, conference abstracts, and studies without available full text were excluded from the study.

Study selection

Two independent reviewers thoroughly assessed the titles and abstracts of each article according to predefined inclusion and exclusion criteria. After this initial evaluation,

full texts of potentially eligible studies were obtained and reassessed to confirm that they met the inclusion criteria. Discussions were conducted to reach a consensus in cases of disagreement between the reviewers, thereby ensuring the integrity and impartiality of the selection process.

Data extraction

The selected studies underwent data extraction, which involved the collection of information on the author, year, country, cancer cell line, mouse model, number of implanted cells, anticancer drugs used, drug, delivery vehicle, mean survival of the local DDS, mean survival of the systemic DDS, and percentage of mean survival change. The data were systematically organized into a comprehensive database for further analysis. Subsequently, qualitative synthesis was performed, highlighting the key findings and trends across the selected studies. The clinical heterogeneity of parasagittal meningiomas, as well as variations in treatment approaches and outcomes, were thoroughly examined. This systematic review also aimed to identify gaps in the existing literature and pinpoint areas where further research is needed to improve the understanding and management of these tumors.

Data analysis

Statistical analysis was conducted using Review Manager 5.4 (Cochrane Collaboration). A random-effects model was applied to calculate the pooled mean difference (MD) in survival time between local DDS and systemic therapies. Heterogeneity among the studies was assessed using the I^2 statistic to ensure the robustness of our findings. The meta-analysis results are presented in a forest plot.

Assessment of risk of bias (ROB)

The articles included in the systematic review were assessed for ROB using the ROB-2 tool for randomized studies and the

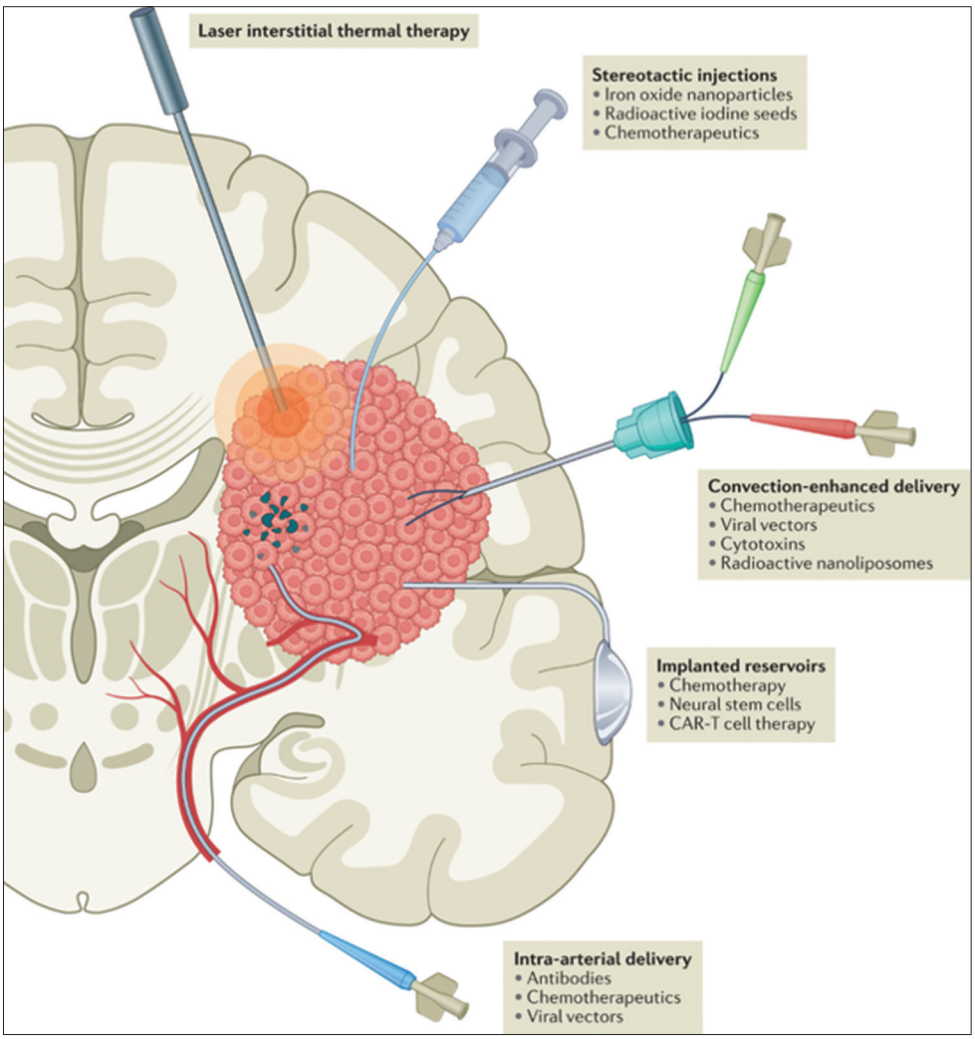

Figure 1: Current advances in local drug delivery for glioblastoma. CAR-T: Chimeric antigen receptor - T Cell

ROB in non-randomized studies of interventions (ROBINS-I) tool for non-randomized studies.[16,17] This assessment was conducted independently by two reviewers to ensure accuracy and objectivity.

RESULTS

Results of search strategy

Figure 2 outlines the article selection process. The search identified 1341 records, of which 650 were screened after duplicates were removed. Of the titles and abstracts of the screened articles, 489 were excluded from the study. Of the 161 studies that were assessed after full-text screening, 155 were excluded from the study. Six studies met the pre-defined criteria and were included in the review, totaling 129 murine models.[1,5,8,9,15,22]

Characteristics of eligible studies

This systematic review consists of six eligible studies, including three RCTs and three prospective cohort studies [Table 1]. The studies varied in their experimental setups across different countries, cancer cell lines, mouse models, and the number of implanted cancer cells. Moreover, each study used specific drug formulations and delivery vehicles tailored to their respective models. Based on the RoB-2 and ROBINS-I tools, two studies were deemed low in ROB, three studies were deemed moderate in ROB, and one study was deemed to have a high ROB [Figures 3 and 4]. The changes in MS differences percentages observed in these included studies range from a significant increase of 22–104% in five studies and a decrease of 59% in one study.[1,5,8,9,15,22]

Summary of results

Seven of the included studies compared systemic versus intra-tumoral administration of the same drug using a DDS. As outlined in Table 1, the systemic treatment group improved MS by < 50% compared to untreated controls, while animals treated with local DDS showed a prolonged MS of over 100% in four of seven studies.[1,5,9,15,22] Except for one study, local DDS demonstrated superior antitumor effects compared to systemic administration of the same drug.[8]

Chen *et al*. evaluated the antitumor efficacy of irinotecan liposomes delivered through different routes.[5] Two GBM xenograft models using cells derived from primary human

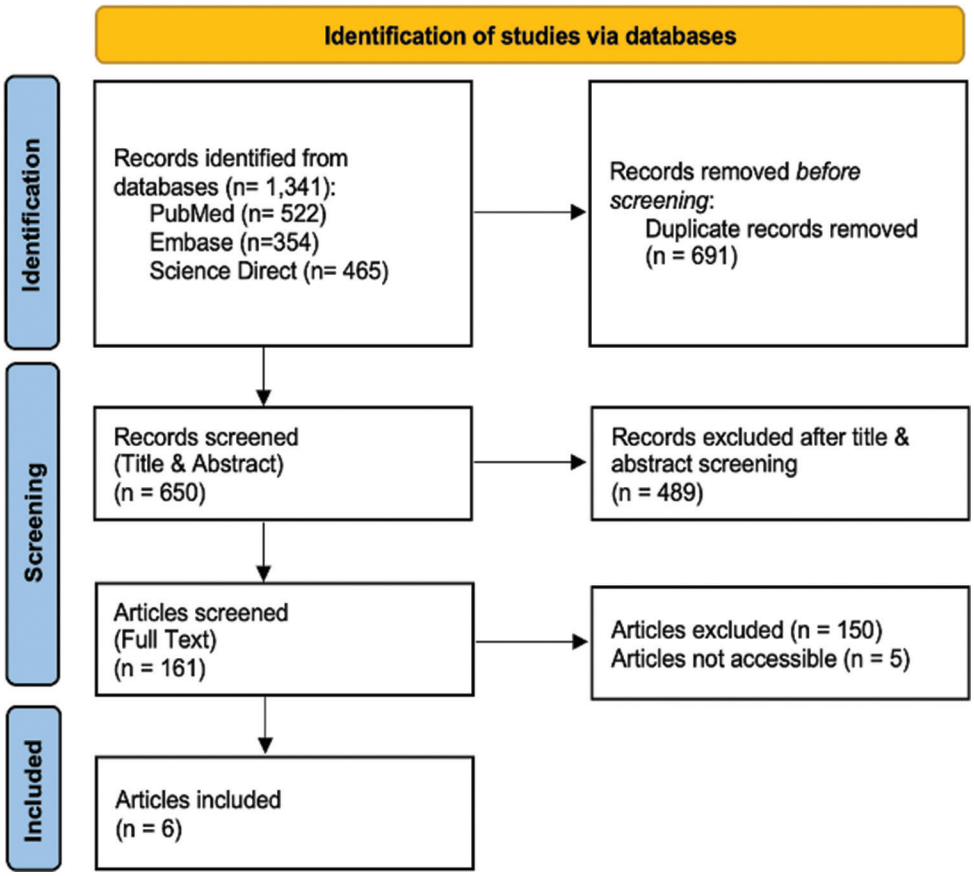

Figure 2: PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1: Summary table of results.

No	Author	Study design	Year	Country	Cancer cell line	Mice model	Number of implanted cells	Drug	Delivery vehicle	MS local delivery (days)	MS systemic (days)	% Change
1	Bastiancich *et al.*[2]	RCT	2017	Belgium	U87MG	Female NMRI nude	3 x 104	GemC12	Hydrogel	49	24	104%
2	Chen *et al.*[5]	Prospective cohort	2013	United States	GBM43	Female athymic	3 x 105	Irinotecan	Liposomes	55	27	104%
3					SF7796	Female athymic	3 x 105	Irinotecan	Liposomes	58.5	48	22%
4	Laine *et al.*[8]	Prospective cohort	2012	France	9L	Female Fischer F344	1 x 105	Fc-diOH	Lipid nanocapsules	11	26.5	-59%
5	Lin *et al.*[9]	Prospective cohort	2018	Taiwan	U76MG	Male Nu/Nu	1 x 105	TMZ	Liposomes	50	28.5	75%
6	Ren *et al.*[15]	RCT	2012	China	C6	Male BALB/c	2 x 105	Doxorubicin	Carbon nanotubes	43	30	43%
7	Zhang *et al.*[22]	RCT	2011	China	C6	Male Sprague-Dawley	2 x 106	TMZ	Microspheres	46.5	27	72%

RCT: Randomized controlled trials, Fc-diOH: Ferrochiphenol, NMRI: The Naval Medical Research Institute, TMZ: Temozolomide

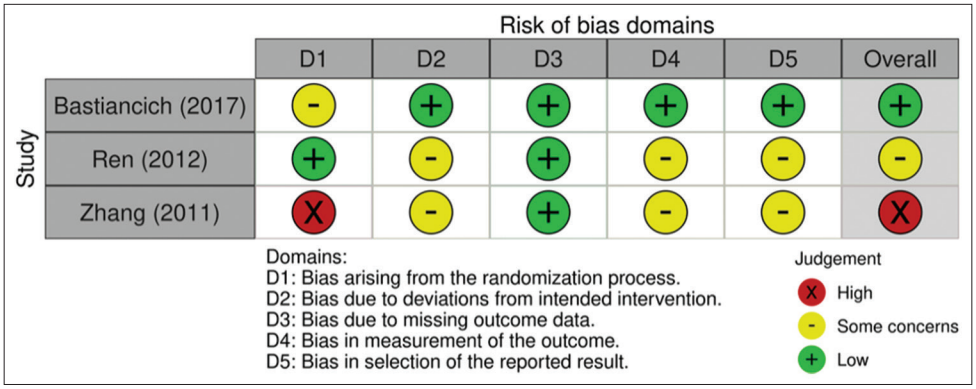

Figure 3: Risk of bias of randomized controlled trial studies.

GBM tissues (GBM43 and SF7796) were used to assess the *in vivo* efficacy of this DDS. GBM43 cells were radioresistant, and SF7796 cells were derived from a recurrent tumor. The results indicated that local delivery of irinotecan liposomes through convection-enhanced delivery (CED) significantly enhanced antitumor efficacy in both models compared to systemic administration through tail vein injection ($P < 0.001$ in the GBM43 model and $P = 0.048$ in the SF7796 model).[5]

Laine *et al.* devised an active targeting approach to deliver ferrociphenol using a cell-penetrating peptide (NFL-TBS.40-63) attached to lipid nanocapsules.[8] Their *in vivo* experiments using the 9L model showed that delivering ferrociphenol directly into tumors through CED notably decreased MS, whereas administering it through the intracarotid route increased MS.[8] This research underscored the advantages of active targeting in intracarotid therapy while also highlighting significant adverse effects associated with CED administration of ferrociphenol lipid nanocapsules.[8]

The current standard of care for GBM involves surgical resection followed by the Stupp protocol, in which TMZ, an alkylating agent capable of crossing the BBB, is orally administered. To evaluate the potential of local delivery, Lin *et al.* administered TMZ-loaded liposomes directly into the tumor using CED.[9] U87 MG-bearing mice treated twice with local TMZ liposomes showed significantly longer MS compared to the control group, while mice treated 3 times with oral TMZ did not show significant survival improvement.[9] Zhang *et al.* applied TMZ-loaded PLGA microparticles onto the tumor surface in the C6 glioma model. Rats treated locally with TMZ microparticles exhibited significantly longer MS than those treated with oral TMZ ($P = 0.002$).[22] These studies underscore the advantages of local delivery in enhancing antitumor effects and minimizing systemic toxicities by reducing the concentration of TMZ in the circulating blood.

Meta-analysis

The seven eligible studies included a systemic treatment group that used the same drug as the local administration group. A meta-analysis was performed to compare the antitumor efficacy of systemic and local treatment. As depicted in Figure 5, animals treated locally with DDS showed a significantly prolonged MS compared to those treated systemically with either the free drug or DDS (MD = 2.76; 95% confidence interval, 0.43–5.09; $P = 0.03$; $I^2 = 93\%$).

Ideally, a high I^2 would warrant subgroup analyses; however, due to the limited number of studies, the authors were unable to perform these analyses, as subgroup analysis typically requires more than 10 studies. In addition, the variation in all of the variables, which are drug types, delivery vehicles, GBM cell lines, and mouse models, further complicates the feasibility of subgroup analysis.

DISCUSSION

The results of this systematic review and meta-analysis provide compelling evidence that local injection of DDS significantly improves survival in GBM models compared with systemic therapies. This finding aligns with the growing body of literature that highlights the potential of local drug delivery strategies to address the challenges of treating GBM.

The superior efficacy of local injections can be attributed to several key factors. First, by directly injecting into the tumor, the BBB can be circumvented, which is a highly selective membrane that typically prevents most drugs from entering the brain.[2] This barrier poses a significant obstacle to systemic drug delivery, limiting the concentration of therapeutic agents that can reach the tumor site.[2] Local injection circumvents this limitation, allowing for higher concentrations of therapeutic molecules to target the tumor cells directly.

Second, a review study by Rahnfeld and Luciani stated that local injection with a delivery system allows for sustained drug release, maintaining therapeutic concentrations at

the tumor site over a longer period.[14] This is in contrast to systemic therapies, in which drug levels often decline rapidly due to metabolism and excretion.[14] Sustained drug release is particularly important for GBM, as tumor cells are known to be resistant to conventional chemotherapy.

Furthermore, local injection can be tailored to the specific needs of each patient, allowing for personalized treatment strategies.[21] This is not possible with systemic therapies, which deliver drugs uniformly throughout the body.[21]

Our analysis included multiple studies that demonstrated significant improvements in MS with local injections. For instance, Chen *et al*. reported that local administration of Irinotecan liposomes with CED markedly improved MS compared to systemic tail vein administration, with significant results observed in the GBM43 model ($P < 0.001$) and the SF 7796 model ($P = 0.048$).[5] Similarly, Lin *et al*. found that direct injection of TMZ-loaded liposomes into the tumor resulted in a 75% increase in MS compared to oral administration of TMZ.[9] Zhang *et al*. also observed that mice treated with local TMZ microparticles demonstrated significantly longer MS compared to those receiving oral TMZ ($P = 0.002$).[22]

Other notable findings include Bastiancich *et al*. study,[1] where local delivery of GemC12 significantly increased survival compared to intravenous injection of GemC12, and Ren *et al*.[15] research showing that intratumoral injection of doxorubicin with oxidized multi-walled carbon nanotubes and angiopep-2 increased glioma-bearing mice MS time.[1] However, not all studies were uniformly positive; Laine *et al*. reported that CED of ferrociphenol lipid nanocapsules significantly reduced MS compared to intracarotid administration of Fc-diOH, possibly due to large diffusion of ferrociphenol lipid nanocapsules affecting healthy cells and leading to severe side effects and morbidity.[8]

Despite these promising results, it is important to acknowledge the limitations of the present study. The included studies were conducted using murine models, which may not fully reflect the complexity of human GBM. Further research is required to validate these findings in human clinical trials. In addition, the heterogeneity of the study designs and treatment regimens used in the included studies may have influenced the results.

Ongoing clinical trials

Ongoing clinical trials investigating local DDS for GBM are actively working to translate the encouraging results from preclinical models to clinical practice. At least three ongoing

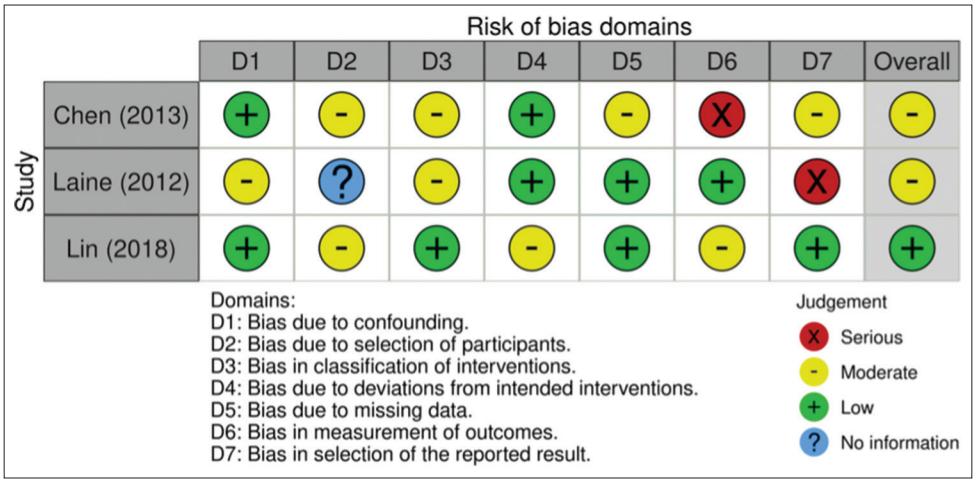

Figure 4: Risk of bias of prospective cohort studies.

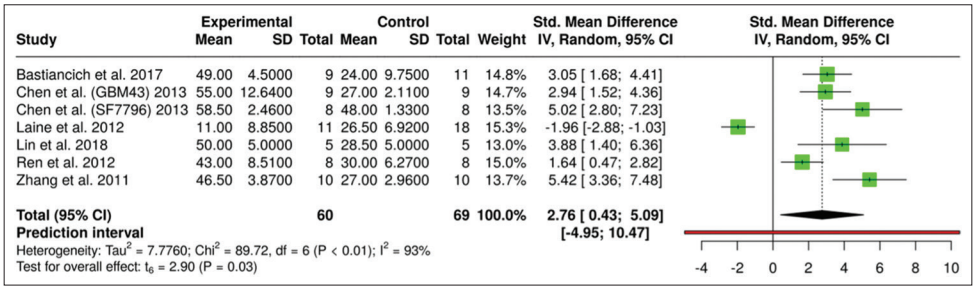

Figure 5: Forest-plot of included studies. CI: Confidence interval, SD: Standard deviation

clinical trials are investigating injectable local DDS for GBM.

Adipose-derived mesenchymal stem cells (AMSCs) for Recurrent GBM

This Phase 1 trial, conducted at the Mayo Clinic in Jacksonville, Florida, investigates the safety and preliminary efficacy of locally delivered AMSCs in recurrent GBM. The trial focuses on evaluating the incidence of adverse events and assessing clinical, survival, and radiographic outcomes compared to historical controls. The local delivery of AMSCs represents a promising avenue due to its potential to bypass the BBB and provide a direct therapeutic effect at the tumor site. The use of AMSCs in GBM treatment could herald a new era of cell-based therapies tailored to recurrent disease.[10]

AGuIX nanoparticles with radiotherapy plus concomitant TMZ in newly diagnosed GBM (NANO-GBM)

This Phase I/II trial, conducted by the Centre Jean Perrin in France, evaluates the combination of polysiloxane Gd-chelates based nanoparticles (AGuIX) with standard radiotherapy and TMZ for NANO-GBM. AGuIX nanoparticles are designed to enhance the efficacy of radiotherapy by increasing tumor-specific radiation sensitivity while limiting damage to surrounding healthy tissue. The trial is investigating three dose levels (50 mg/kg, 75 mg/kg, and 100 mg/kg) and aims to establish the recommended dose for future studies. In addition, progression-free survival (PFS) at 6 months will be evaluated as a key endpoint, offering insight into the potential benefits of combining AGuIX with radiochemotherapy.[3]

NU-0129 in treating patients with recurrent GBM or gliosarcoma undergoing surgery

This Phase 0 trial is conducted at Northwestern University in Chicago, Illinois. It investigates the safety and feasibility of NU-0129, a Spherical Nucleic Acid platform that targets the Bcl2L12 gene associated with tumor growth in GBM multiforme and gliosarcoma. NU-0129 is capable of crossing the BBB and targeting tumor cells to induce apoptosis. Preliminary outcomes, including PFS and overall survival, are being assessed alongside drug concentration in serum and tumor tissue expression levels of Bcl2L12. This trial represents a significant step forward in the use of nucleic acid-based therapies for recurrent GBM.[12]

These ongoing trials, taking place at leading institutions across the U.S. and Europe, highlight the potential of innovative DDS and novel therapeutic strategies that aim to improve treatment efficacy and extend survival in GBM patients. Continued investigation of these therapies may bring new hope for overcoming the challenges posed by this aggressive tumor.

Comparisons between preclinical findings and these ongoing human trials indicate that local DDS consistently show advantages in improving survival outcomes and enhancing drug bioavailability. However, translating these benefits into routine clinical practice requires further validation of safety, efficacy, and long-term outcomes in human subjects. The successful translation of these therapies will significantly advance the treatment landscape for GBM, offering more personalized and effective treatment options for patients.

Future directions

Future research should focus on several key areas to fully realize the potential of injectable DDS for GBM treatment. First, the development of DDS formulations capable of simultaneously delivering multiple therapeutic agents holds significant promise. Such multi DDS can target various pathways involved in GBM progression, potentially enhancing treatment efficacy.

Second, addressing the experimental variability and limitations associated with xenograft models is crucial. Although valuable, these models do not fully mimic the complexity of human GBM. Therefore, developing more representative preclinical models and standardized testing methods is essential to bridge the gap between preclinical findings and clinical applications.

Finally, conducting rigorous clinical trials to evaluate the safety, efficacy, and optimal protocols for local DDS in human patients is imperative. Standardizing testing methods across studies will facilitate more accurate comparisons and data integration, ultimately advancing the clinical translation of this promising therapeutic approach.

In summary, while local injection of DDS offers a transformative approach to GBM treatment, ongoing research, and clinical validation are necessary to overcome the existing challenges and fully leverage its potential to improve patient outcomes.

CONCLUSION

This systematic review and meta-analysis found that local injection of DDS significantly improved survival compared with systemic injections in GBM models. Injectable local drug delivery directly into GBM tumors bypasses the BBB, allowing higher concentrations of therapeutic molecules to target the tumor site effectively. This targeted approach shows great promise for overcoming the significant challenges posed by GBM treatment, including the resistance of tumor cells to conventional chemotherapy and the limitations imposed by systemic drug delivery.

Compelling evidence from various studies indicates that local DDS can enhance therapeutic efficacy and survival rates in GBM models. The ability to achieve sustained drug release

at the tumor site and tailor treatments to the specific needs of each patient further underscores the potential of this approach. However, translating these promising preclinical results into clinical practice requires careful consideration of the differences between murine models and human GBM, as well as addressing the heterogeneity of study designs and treatment regimens observed in the reviewed studies.

Ongoing clinical trials are critical in evaluating the real-world effectiveness of injectable DDS in GBM patients. These trials aim to assess not only the safety and efficacy of local DDS formulations but also to identify optimal dosing regimens and combination therapies. The results from these studies will provide valuable insights into the clinical applicability of local drug delivery strategies and may pave the way for new standard treatment protocols in GBM care.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Bastiancich C, Bianco J, Vanvarenberg K, Ucakar B, Joudiou N, Gallez B, *et al*. Injectable nanomedicine hydrogel for local chemotherapy of glioblastoma after surgical resection. J Control Release 2017;264:45-54.
2. Bastiancich C, Bozzato E, Henley I, Newland B. Does local drug delivery still hold therapeutic promise for brain cancer? A systematic review. J Control Release 2021;337:296-305.
3. Centre Jean Perrin. AGuIX nanoparticles with radiotherapy plus concomitant temozolomide in the treatment of newly diagnosed glioblastoma (NANO-GBM). Bethesda, MD: Centre Jean Perrin; 2024. Available from: https://clinicaltrials.gov/study/NCT04881032?cond=glioblastoma&intr=nanoparticle&rank=1 [Last accessed on 2024 Sep 06].
4. Cha GD, Jung S, Choi SH, Kim DH. Local drug delivery strategies for glioblastoma treatment. Brain Tumor Res Treat 2022;10:151-7.
5. Chen PY, Ozawa T, Drummond DC, Kalra A, Fitzgerald JB, Kirpotin DB, *et al*. Comparing routes of delivery for nanoliposomal irinotecan shows superior anti-tumor activity of local administration in treating intracranial glioblastoma xenografts. Neuro Oncol 2013;15:189-97.
6. Dobes M, Shadbolt B, Khurana VG, Jain S, Smith SF, Smee RI, *et al*. A Multicentre study of primary brain tumor incidence in Australia (2000-2008). Neuro Oncol 2011;13:783-90.
7. Hersh AM, Alomari S, Tyler BM. Crossing the blood-brain barrier: Advances in nanoparticle technology for drug delivery in neuro-oncology. Int J Mol Sci 2022;23:4153.
8. Laine AL, Huynh NT, Clavreul A, Balzeau J, Béjaud J, Vessieres A, *et al*. Brain tumor targeting strategies via coated ferrociphenol lipid nanocapsules. Eur J Pharm Biopharm 2012;81:690-3.
9. Lin CY, Li RJ, Huang CY, Wei KC, Chen PY. Controlled release of liposome-encapsulated temozolimide for brain tumor treatment by convenction-enhanced delivery. J Drug Target 2018;26:325-32.
10. Mayo Clinic. Clinical trials: Adipose-derived mesenchymal stem cells (AMSCs) for recurrent glioblastoma. Jacksonville, FL: Mayo Clinic; 2024. Available from: https://www.mayo.edu/research/clinical-trials/cls-20545768 [Last accessed on 2024 Sep 06].
11. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
12. Northwestern University. NU-0129 in treating patients with recurrent glioblastoma or gliosarcoma undergoing surgery. Bethesda, MD: Northwestern University; 2022. A vailable from: https://clinicaltrials.gov/study/NCT03020017?cond=glioblastoma&intr=nanoparticle&rank=3 [Last accessed on 2024 Sep 06].
13. Perry J, Chambers A, Spithoff K, Laperriere N. Gliadel wafers in the treatment of malignant glioma: A systematic review. Curr Oncol 2007;14:189-94.
14. Rahnfeld L, Luciani P. Injectable lipid-based depot formulations: Where do we stand? Pharmaceutics 2020;12:567.
15. Ren JF, Shen S, Wang D, Xi Z, Guo L, Pang Z, *et al*. The targeted delivery of anticancer drugs to brain by PEGylated oxidized multi-walled carbon nanotubes modified with angiopep-2. Biomaterials 2012;33:3324-33.
16. Sterne JA, Hernán M, Reeves B, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
17. Sterne JA, Savocić J, Page MJ, Elbers PG, Blencowe NS, Boutron I, *et al*. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ 2019;366:i4898.
18. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al*. Radiotherapy plus concomitant and

adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
19. Urhie O, Turner R, Lucke-Wold B, Radwan W, Ahn J, Gyure K, *et al*. Glioblastoma survival outcomes at a tertiary hospital in Appalachia: Factors impacting the survival of patients following implementation of the Stupp Protocol. World Neurosurg 2018;115:59-66.
20. Van Solinge TS, Nieland L, Chiocca EA, Broekman ML. Advances in local therapy for glioblastoma -taking the fight to the tumor. Nat Rev Neurol 2022;18:221-36.
21. Yu F, Asghar S, Zhang M, Zhang J, Ping Q, Xiao Y. Local strategies and delivery systems for the treatment of malignant gliomas. J Drug Target 2018;27:367-78.
22. Zhang YH, Zhang H, Liu JM, Yue ZJ. Temozolimide/PLGA microparticles: A new protocol for treatments of glioma in rats. Med Oncol 2011;28:901-6.
23. Zhao J, Chen AX, Gartrell RD, Silverman AM, Aparicio L, Chu T, *et al*. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. Nat Med 2019;25:462-9

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