Journal of Posthumanism
2024
Volume: 4, No: 3, pp. 1222–1228
ISSN: 2634-3576 (Print) | ISSN 2634-3584 (Online)
posthumanism.co.uk

DOI: https://doi.org/10.63332/joph.v4i3.3211

Selective Intracranial Endovascular Chemotherapy: Alternative Treatment for Adults Diagnosed with Glioma

Thiago Andrés Navarro Álvarez[1], Andrés Fonnegra Caballero[2], María Sofía González Casagua[3], Ricardo Andrés Novoa Álvarez[4]

Abstract

Introduction: Minimally invasive intra-arterial (IA) drug administration is an innovative treatment strategy for patients with brain neoplasms that are difficult to manage and access. Methods: An exhaustive literature search was conducted in two databases (PubMed, Scopus) using MeSH terms "selective intra-arterial cerebral infusion," "endovascular chemotherapy," "glioma," and "glioblastoma." Thirty-five articles on selective endovascular infusion of chemotherapeutic agents for glioma treatment were identified.Results: The use of intra-arterial (IA) drugs has been described since 1950 with remarkable results for modern medicine, which requires disrupting the blood-brain barrier through various strategies to facilitate the distribution of biological or chemotherapeutic agents to brain tissue, including Bevacizumab in monotherapy or combined therapy.Conclusions: Minimally invasive therapeutic strategies offer significant benefits for patients with high-grade tumor lesions, particularly in cases of glioblastoma multiforme (GBM), minimizing complications and limited survival rates.

Keywords: *Glioma; Chemotherapy; Infusion, Intra-Arterial.*

Introduction

Gliomas are primary intracerebral neuroepithelial tumors that represent 70 to 80% of malignant brain tumors in adults (1). They are classified into four histological grades according to the World Health Organization (WHO) criteria, with grades III and IV corresponding to high-grade tumors, including anaplastic astrocytoma, oligodendroglioma, and glioblastoma multiforme (GBM), the most aggressive and common with an annual incidence of 2-3 cases per 100,000 people (2,3).

The prognosis for gliomas is unfavorable, with an average survival of approximately twelve to fifteen months after diagnosis due to the infiltrative nature of glial cells, disease progression, and aggressiveness (4). Traditional treatment options, including radical cytoreductive surgery combined with adjuvant chemotherapy and radiotherapy, aim to prolong survival and improve the quality of life of patients (5). However, the effectiveness of aggressive tumor management is questionable, mainly due to factors related to the composition of the blood-brain barrier and the insensitivity of gliomas to chemotherapeutic agents, posing a significant challenge for modern medicine (6).

[1] Corporación Universitaria Uninavarra, Colombia, ORCID: https://orcid.org/0000-0002-3272-4711.
[2] Corporación Universitaria Uninavarra, Colombia, ORCID: https://orcid.org/0000-0003-0453-5646.
[3] Corporación Universitaria Uninavarra, Colombia, ORCID: https://orcid.org/0000-0002-4023-3517
[4] Corporación Universitaria Uninavarra, Colombia, ORCID: https://orcid.org/0000-0001-9892-3468

As a result, alternative therapeutic approaches have been developed using microcatheters for the intra-arterial administration of biological and/or chemotherapeutic drugs for the selective treatment of brain tumor lesions, primarily retinoblastoma and hepatocellular carcinoma (7). The minimally invasive administration of drugs through the blood-brain barrier in selective brain areas via peritumoral vasculature limits the volume of tumor distribution, reduces neurotoxicity, and systemic toxicity (7,8).

This review summarizes the historical background, drugs used, and associated side effects of the administration of selective endovascular chemotherapeutic agents as treatment for adult patients diagnosed with gliomas.

Methods

A comprehensive literature search was conducted in three databases (PubMed, Scopus, EMBASE) on the selective endovascular infusion of chemotherapeutic agents for glioma treatment, using MeSH terms "selective intra-arterial cerebral infusion," "endovascular chemotherapy," "glioma," and "glioblastoma," along with the operators 'AND' and 'OR.' The search included all available articles in English and Spanish with adult populations from 1981 to December 2022. Articles were selected based on title and abstract reviews by two reviewers and subsequently reviewed by the other authors. Previous reviews on the topic were included, and reference searches were also performed. Manuscripts and studies focused on intravascular infusions (IV) were excluded.

Results

The assessment of publications was performed by reviewing the obtained abstracts, resulting in 35 articles that were read in full after removing duplicates.

Historical Background

The use of intra-arterial (IA) drugs for head and neck tumor treatment was first reported in the 1950s, with the accidental administration of nitrogen mustard to a patient with Hodgkin's lymphoma in the brachial artery, which led to the hypothetical consideration of potential therapeutic benefits in tumor lesions after local drug administration due to tissue dilution capacity and reduced toxic effects.

The implementation of intra-arterial (IA) drug delivery as a treatment for head and neck tumors was first reported in the 1950s with Calvin Klopp's publication on the accidental administration of nitrogen mustard in a patient diagnosed with Hodgkin's lymphoma in the brachial artery. This event led to the hypothetical consideration of potential therapeutic benefits in tumor lesions following local drug administration due to its tissue dilution capacity and lower frequency of toxic effects, as observed in subsequent animal studies (9); Additionally, authors like French et al. in 1952 suggested the use of regional IA therapies for the management of intracranial malignant neoplasms in humans (10).

In the 1960s, studies related to the blood-brain barrier (BBB) structure and the use of IA chemotherapeutic agents for the treatment of malignant brain tumors, particularly gliomas, were documented (11,12). In the 1970s, Stanley Rapaport highlighted key aspects of osmotic disruption of the BBB as a reversible method for transmembrane drug passage for therapeutic purposes (13–15). Unfortunately, despite the technological advances in modern endovascular medicine, interest in IA chemotherapy decreased progressively from the 1990s due to neurological complications related to neurotoxicity (16–18).

Physiology of the Blood-Brain Barrier (BBB)

The BBB is a dynamic structure responsible for limiting the entry and exit of biological substances through the blood to maintain a homeostatic microenvironment through physical and biochemical barriers (19). It is composed of tight junction proteins, adherent junctions, pericytes, podocytes, and microvascular endothelial cells expressing flow transporters such as P-glycoprotein, organic anion transporter polypeptide, breast cancer-resistant proteins, and multi-drug resistance receptors to regulate substrate movement and modulate the distribution of ionized molecules larger than 180 Da, among which chemotherapeutic agents stand out (20–22). Therefore, therapeutic options and alternative administration routes emerge to improve the effectiveness of pharmacological therapies for central nervous system (CNS) tumor treatment (23).

Superselective Endovascular Intra-Arterial Infusion

Currently, technological advancements have created minimally invasive treatment alternatives using superselective microcatheters for endovascular drug infusion through perilesional intracranial arterial pedicles for neurological conditions, such as tumor lesions (24). Additionally, agents are needed that reversibly disrupt vascular permeability, enhancing pharmacological penetration, increasing the concentration gradient, membrane diffusion coefficient, and transfer coefficient, thus facilitating chemotherapeutic distribution across the BBB (25). The key characteristics of IA pharmacological administration encompass the molecular size of drugs and the infusion rate; therefore, greater advantages have been reported with pulsatile and slow infusion of therapeutic agents related to laminar arterial flow toward the tumor lesion, maximizing tissue distribution and minimizing toxicity (24).

Osmotic agents: Rapport et al. (1972) documented for the first time the administration of hypertonic solutions as a disruptor method of the BBB through their administration into cerebral arteries, highlighting the use of mannitol primarily due to its favorable clinical outcomes (26,27). Between 1979 and 1981, clinical trials were conducted that demonstrated the physiological effects of its administration. Mannitol independently elevates the osmotic gradient, inducing endothelial dehydration and cell size reduction, facilitating openings between intercellular tight junction spaces, and transiently disrupting BBB permeability (28). Safe and effective therapeutic effects have been demonstrated in human studies with limited neurotoxic results (29–31). Therefore, the use of mannitol in patients with CNS-origin neoplasms successfully increases the permeability of chemotherapeutic agents up to 90 times (24,32).

Focused Ultrasound: Focused ultrasound guided by magnetic resonance imaging (MRI) is a non-invasive technique used in brain tumors and neurodegenerative disorders to enhance the administration of biological therapies and intra-arterial chemotherapeutic agents (33). It employs intravenous injection of perfluorocarbon microbubbles, low-frequency sound waves, and electrical energy transduction that generates changes in the acoustic cavitation of microbubbles, causing a mechanical disruption of the BBB through vascular stretching, physical alteration of tight junctions, tension, and endothelial porosities that temporarily and reversibly facilitate molecular passage into the neural parenchyma without secondary damage. This technique is used in conjunction with MRI-type imaging studies to confirm therapy effects and the dimensions of BBB disruption (24,34,35).

Thermal interstitial therapy with laser: This emerging minimally invasive technique involves the thermal ablation of tumor tissue and is used in clinical trials as a treatment for patients with

recurrent gliomas and lesions that are not amenable to standard open surgery. It employs YAG laser to induce tumor tissue necrosis through real-time thermotherapy and thermometry using MRI, leading to the destruction of the endothelial cell membrane and secondary disruption of the blood-brain barrier (BBB) for the administration of intra-arterial (IA) chemotherapeutic agents (23,36).

IA Treatment for Gliomas: Recent studies have documented the use of drugs for the treatment of brain tumors with reduced efficacy in malignant gliomas due to their diminished sensitivity to chemotherapy (23). Table 1 summarizes the main chemotherapeutic agents administered via IA for the treatment of gliomas, highlighting their key characteristics and dosages.

Medication	Description
Bevacizumab	Monoclonal antibody inhibitor of vascular endothelial growth factor, approved by the Food and Drug Administration (FDA) for intravenous (IV) treatment in patients with primary and recurrent glioblastoma multiforme (GBM), demonstrated safety and efficacy either alone or in combination with chemotherapeutic agents. Systemic toxic effects are described, including gastrointestinal perforation, infections, venous thrombosis, and skin lesions. The average dose is 2-15 mg/kg (23).
Carboplatine	Platinum analog agent that binds to the N-7 position of guanine in DNA. It crosses the blood-brain barrier, exerting its action on recurrent malignant gliomas with moderate efficacy in monotherapy. The main documented side effect/toxicity is myelosuppression. Dosage varies across clinical studies and the target area, ranging between 100 - 1400 mg/hemisphere (37).
Cetuximab	Recombinant human chimeric antibody that competitively inhibits the epidermal growth factor, FDA-approved for IA treatment of GBM. The main identified side effects are seizures and cerebral edema. The average dosage ranges from 100, 200, to 250 mg/m² (23).
Nimustine	Water-soluble nitrosourea compound used in high-grade malignant gliomas with limited effectiveness due to toxic effects on the hematopoietic system, leading to high rates of myelosuppression and neuropathies (38).
Temozolomide	DNA alkylating agent with potential to induce apoptosis in tumor cells, used in standard or adjuvant treatment for patients with malignant gliomas, showing benefits in survival rates for anaplastic tumors without 1p/19q codeletion, at doses of 75-250 mg/m² (39,40).
Vincristine	Alkaloid chemotherapeutic adjuvant agent for patients with low-grade gliomas. It induces cell death by binding to the mitotic spindle on the beta tubulin chain, leading to metaphase blockage. Dosages of 1.4 mg for 8 days followed by 2 mg until day 28 are described (37,41).

Table 1. Chemotherapeutic Agents

Early learning of these treatment alternatives could be facilitated through simulated training environments for postgraduate students in the field of neuroscience and minimally invasive procedures. This approach would enable safe practice in controlled settings, improving patient

safety standards and, in the medium and long term, enhancing the quality of life for individuals with these diagnoses (42).

Conclusions

The administration of intra-arterial chemotherapeutic agents constitutes a novel treatment modality for patients diagnosed with brain tumor lesions, among which glioblastoma multiforme stands out. The progress of modern medicine allows for minimally invasive management of this group of aggressively characterized tumor lesions, aiming to improve efficiency and reduce complication rates in recurrent or hard-to-reach cases, thus positively impacting survival and the quality of life of affected individuals.

References

Gusyatiner O, Hegi ME. Glioma epigenetics: From subclassification to novel treatment options. Semin Cancer Biol. 2018 Aug 1;51:50–8.

Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol [Internet]. 2017 Nov 6 [cited 2022 Nov 27];19(suppl_5):v1–88. Available from: https://academic.oup.com/neuro-oncology/article/19/suppl_5/v1/4596648

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol [Internet]. 2007 Aug 6 [cited 2022 Nov 27];114(2):97–109. Available from: https://link.springer.com/article/10.1007/s00401-007-0243-4

Vargas López AJ, Fernández Carballal C, Valera Melé M, Rodríguez-Boto G. Análisis de supervivencia en gliomas de alto grado: papel de la cirugía de rescate. Neurología [Internet]. 2020 [cited 2022 Nov 27]; Available from: https://www.elsevier.es/es-revista-neurologia-295-avance-resumen-analisis-supervivencia-gliomas-alto-grado-S0213485320301250

SAI K, YANG QY, SHEN D, CHEN ZP. Chemotherapy for gliomas in mainland China: An overview. Oncol Lett. 2013 May;5(5):1448–52.

Méndez-Aguilar P, Vera-Ponce VJ, Méndez-Aguilar P, Vera-Ponce VJ. Factores pronóstico de supervivencia en adultos por gliomas de alto grado en un Hospital de Lima, Perú. Revista de la Facultad de Medicina Humana [Internet]. 2020 Jul 9 [cited 2022 Nov 27];20(3):452–63. Available from: http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S2308-05312020000300452&lng=es&nrm=iso&tlng=es

D'Amico RS, Khatri D, Reichman N, Patel N v., Wong T, Fralin SR, et al. Super selective intra-arterial cerebral infusion of modern chemotherapeutics after blood–brain barrier disruption: where are we now, and where we are going. J Neurooncol. 2020 Apr 19;147(2):261–78.

Srinivasan VM, Lang FF, Chen SR, Chen MM, Gumin J, Johnson J, et al. Advances in endovascular neuro-oncology: endovascular selective intra-arterial (ESIA) infusion of targeted biologic therapy for brain tumors. J Neurointerv Surg. 2020 Feb;12(2):197–203.

Klopp CT, Alford TC, Bateman J, Berry GN, Winship T. FRACTIONATED INTRA-ARTERIAL CANCER. CHEMOTHERAPY WITH METHYL BIS AMINE HYDROCHLORIDE; A PRELIMINARY REPORT. Ann Surg. 1950 Oct;132(4):811–32.

French JD, West PM, von Amerongen FK, Magoun HW. Effects of Intracarotid Administration of Nitrogen Mustard on Normal Brain and Brain Tumors. J Neurosurg. 1952 Jul;9(4):378–89.

Wilson CB. Chemotherapy of brain tumors by continuous arterial infusion. Surgery [Internet]. 1964 May 1 [cited 2023 Jan 18];55(5):640–53. Available from: http://www.surgjournal.com/article/0039606064902144/fulltext

Owens G, Javid R, Tallon M, Stepanian G, Belmusto L. Arterial Infusion Chemotherapy of Primary Gliomas: A Report of Thirty Cases. JAMA: The Journal of the American Medical Association. 1963 Nov 23;186(8):802–3.

Rapoport SI. Opening of the blood-brain barrier by acute hypertension. Exp Neurol. 1976 Sep;52(3):467–79.

Rapoport S, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. American Journal of Physiology-Legacy Content. 1972 Aug 1;223(2):323–31.

Rapoport SI, Hori M, Klatzo I. Reversible Osmotic Opening of the Blood-Brain Barrier. Science (1979). 1971 Sep 10;173(4001):1026–8.

Dedrick RL. Arterial Drug Infusion: Pharmacokinetic Problems and Pitfalls. JNCI Journal of the National Cancer Institute. 1988 Mar 16;80(2):84–9.

Bullard DE, Bigner DD. Blood-brain barrier disruption in immature Fischer 344 rats. J Neurosurg. 1984 Apr;60(4):743–50.

Greenberg HS, Ensminger WD, Chandler WF, Layton PB, Junck L, Knake J, et al. Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. J Neurosurg. 1984 Sep;61(3):423–9.

Zhao Y, Gan L, Ren L, Lin Y, Ma C, Lin X. Factors influencing the blood-brain barrier permeability. Brain Res. 2022 Aug;1788:147937.

Kadry H, Noorani B, Cucullo L. A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS. 2020 Dec 18;17(1):69.

Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic B v. Blood-Brain Barrier: From Physiology to Disease and Back. Physiol Rev [Internet]. 2019 Jan 1 [cited 2023 Jan 18];99(1):21. Available from: /pmc/articles/PMC6335099/

Haumann R, Videira JC, Kaspers GJL, van Vuurden DG, Hulleman E. Overview of Current Drug Delivery Methods Across the Blood–Brain Barrier for the Treatment of Primary Brain Tumors. CNS Drugs. 2020 Nov 23;34(11):1121–31.

D'Amico RS, Khatri D, Reichman N, Patel N v., Wong T, Fralin SR, et al. Super selective intra-arterial cerebral infusion of modern chemotherapeutics after blood–brain barrier disruption: where are we now, and where we are going. J Neurooncol. 2020 Apr 19;147(2):261–78.

Srinivasan VM, Lang FF, Chen SR, Chen MM, Gumin J, Johnson J, et al. Advances in endovascular neuro-oncology: endovascular selective intra-arterial (ESIA) infusion of targeted biologic therapy for brain tumors. J Neurointerv Surg. 2020 Feb;12(2):197–203.

Shin BJ, Burkhardt JK, Riina HA, Boockvar JA. Superselective Intra-Arterial Cerebral Infusion of Novel Agents After Blood–Brain Disruption for the Treatment of Recurrent Glioblastoma Multiforme: A Technical Case Series. Neurosurg Clin N Am. 2012 Apr;23(2):323–9.

Rapoport S, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. American Journal of Physiology-Legacy Content. 1972 Aug 1;223(2):323–31.

Hendricks BK, Cohen-Gadol AA, Miller JC. Novel delivery methods bypassing the blood-brain and blood-tumor barriers. Neurosurg Focus. 2015 Mar;38(3):E10.

Neuwelt EA, Frenkel EP, Diehl JT, Maravilla KR, Vu LH, Clark WK, et al. Osmotic blood-brain barrier disruption: a new means of increasing chemotherapeutic agent delivery. Trans Am Neurol Assoc. 1979;104:256–60.

Fortin D, Desjardins A, Benko A, Niyonsega T, Boudrias M. Enhanced chemotherapy delivery by intraarterial infusion and blood-brain barrier disruption in malignant brain tumors. Cancer. 2005 Jun 15;103(12):2606–15.

Nakagawa H, Groothuis D, Blasberg RG. The effect of graded hypertonic intracarotid infusions on drug

delivery to experimental RG-2 gliomas. Neurology. 1984 Dec 1;34(12):1571–1571.
Burkhardt JK, Riina H, Shin BJ, Christos P, Kesavabhotla K, Hofstetter CP, et al. Intra-Arterial Delivery of Bevacizumab after Blood-Brain Barrier Disruption for the Treatment of Recurrent Glioblastoma: Progression-Free Survival and Overall Survival. World Neurosurg. 2012 Jan;77(1):130–4.
Williams PC, Henner WD, Simon RG, Dahlborg SA, Brummett RE, Tableman M, et al. Toxicity and Efficacy of Carboplatin and Etoposide in Conjunction with Disruption of the Blood-Brain Tumor Barrier in the Treatment of Intracranial Neoplasms. Neurosurgery. 1995 Jul 1;37(1):17–28.
Gasca-Salas C, Fernández-Rodríguez B, Pineda-Pardo JA, Rodríguez-Rojas R, Obeso I, Hernández-Fernández F, et al. Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. Nat Commun. 2021 Feb 3;12(1):779.
Bex A, Bex V, Carpentier A, Mathon B. Therapeutic ultrasound: The future of epilepsy surgery? Rev Neurol (Paris). 2022 Dec;178(10):1055–65.
Mainprize T, Lipsman N, Huang Y, Meng Y, Bethune A, Ironside S, et al. Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. Sci Rep. 2019 Jan 23;9(1):321.
Rodriguez A, Tatter S, Debinski W. Neurosurgical Techniques for Disruption of the Blood–Brain Barrier for Glioblastoma Treatment. Pharmaceutics. 2015 Aug 3;7(3):175–87.
Sangrador-Deitos M v, Villanueva-Castro E, Marian-Magaña R, Rodríguez-Hernández LA, Guinto-Nishimura GY, Gómez-Amador JL, et al. Carboplatin Plus Vincristine as an Alternative Chemotherapeutic Scheme in Patients With Glioblastoma. Cureus. 2022 Apr 25;
Saito R, Kanamori M, Sonoda Y, Yamashita Y, Nagamatsu K, Murata T, et al. Phase I trial of convection-enhanced delivery of nimustine hydrochloride (ACNU) for brainstem recurrent glioma. Neurooncol Adv. 2020 Jan 1;2(1).
Yang K, Wu Z, Zhang H, Zhang N, Wu W, Wang Z, et al. Glioma targeted therapy: insight into future of molecular approaches. Mol Cancer. 2022 Feb 8;21(1):39.
van den Bent MJ, Tesileanu CMS, Wick W, Sanson M, Brandes AA, Clement PM, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021 Jun;22(6):813–23.
Keogh RJ, Aslam R, Hennessy MA, Coyne Z, Hennessy BT, Breathnach OS, et al. One year of procarbazine lomustine and vincristine is poorly tolerated in low grade glioma: a real world experience in a national neuro-oncology centre. BMC Cancer. 2021 Dec 8;21(1):140.
Navarro-Parra SL, Chiappe A. Simulated learning environments as an interdisciplinary option for vocational training: A systematic review. Simul Gaming [Internet]. 2024;55(2):135–58. Disponible en: http://dx.doi.org/10.1177/10468781231221904.