

Chemotherapy Delivered Through Intra-Arterial Route for Brain Gliomas: An Overview of Current Strategies and Future Prospects

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Abstract High-grade glial tumors pose formidable challenges in oncology, characterized by infiltrative growth, proliferative activity, and a propensity for relapse. The standard Stupp protocol, combining radiotherapy with temozolomide, remains suboptimal, with recurrence rates underscoring the critical need for novel therapeutic strategies. Intra-arterial chemotherapy delivery emerges as a promising avenue, offering the potential to achieve elevated local drug concentrations at tumor sites while mitigating systemic side effects. This comprehensive review navigates the historical context of intra-arterial therapy, emphasizing its evolution since the pioneering experiments of Bierman and Klopp in the 1950s. Contemporary advancements, facilitated by radioimaging and endovascular instruments, showcase renewed interest, with approximately 3,000 global procedures annually. However, the blood-brain barrier persists as a formidable hurdle, necessitating exploration of barrier disruption techniques. Insights from phase I studies affirm the safety and tolerability of intra-arterial chemotherapy, prompting the imperative for phase 3 validations. Future research trajectories spotlight the optimization of therapeutic combinations, integration of advanced imaging for precise vascular target identification, and the development of quantitative monitoring methods for direct drug delivery assessment. This article significantly contributes to intra-arterial therapy knowledge, acting as a linchpin for innovative treatment strategies. The potential to enhance prognoses in high-grade glial tumors underscores the relevance of this review, offering a foundation for continued advancements in glioma treatment modalities.

Keywords Intra-arterial chemotherapy, Glial tumors, Glioblastoma, Anaplastic astrocytoma

1. Introduction

Intracerebral glial tumors arising from neuroglial cells pose a formidable challenge in contemporary oncology due to their infiltrative growth, high proliferative activity, and propensity for relapse. The incidence of primary central nervous system (CNS) tumors exhibits regional variability, ranging from 5 to 14 cases per 100 thousand population. In 2014, Russia reported an incidence of 5.55 cases per 100 thousand population, while developed countries recorded figures between 8.4 to 11.8 in men and 5.8 to 9.3 in women [4,7,13,18].

Since the introduction of the Stupp protocol in 2005, incorporating radiotherapy with oral temozolomide, this approach has become the standard for treating glial brain tumors [6,7,9]. Despite these efforts, a majority of patients experience tumor recurrence within six months after treatment, underscoring the need for novel therapeutic approaches. Existing methods, unfortunately, offer limited

progress, rendering glial tumors largely incurable.

Traditional chemotherapy faces challenges such as restricted penetration of the blood-brain barrier and elevated systemic toxicity, diminishing its efficacy [1,19,44]. Consequently, the scientific community explores alternative drug delivery methods, including intra-arterial delivery. Techniques like intrathecal, intracavitary, and convection-enhanced delivery are under investigation, offering potential in glial tumor treatment [2,3,7].

Intra-arterial chemotherapy, proposed in the 1950s, involves directly delivering drugs to the tumor through arterial vessels [15,16,18,22,38]. Initial limitations stemmed from the neurotoxicity of available drugs, hindering research and development.

Advancements in radioimaging and endovascular instruments have enhanced the accuracy and safety of intra-arterial drug delivery. Approximately 3,000 such procedures are now conducted globally, reflecting renewed interest. Improved technologies enable precise catheter guidance and cerebral blood flow modification, opening new avenues for glial tumor treatment [44,45].

However, the blood-brain barrier remains a significant

hurdle for direct drug delivery to brain tissue. Techniques like mannitol-induced barrier disruption require further evaluation for efficacy and safety.

Exploring various approaches, intra-arterial chemotherapy for glial tumors considers not only traditional drugs but also antibodies, engineered cells, viruses, and radiotherapies. These innovative strategies hold promise, but their clinical implementation demands thorough investigation.

A review of research in this field contextualizes the historical development of intra-arterial therapy for glial tumors, delineates past challenges faced by researchers, and outlines future prospects for this treatment modality. Emphasizing the need for ongoing research to enhance delivery methods, mitigate toxicity, and improve overall effectiveness in glial tumor treatment, this review underscores the evolving landscape of intra-arterial chemotherapy [11,14,16,18].

The inception of intra-arterial chemotherapy in the 1950s saw pioneering experiments by Bierman, Klopp, and colleagues, exploring the direct delivery of high doses of nitrogen mustard to liver tumors through arterial blood supply. Despite initial promise in rabbit experiments, the use of nitrogen mustard proved ineffective due to low therapeutic benefits and severe hematopoietic system effects. In the 1970s, Ekman demonstrated the potential of intra-arterial chemotherapy for achieving higher drug concentrations in targeted tumors, while Stanley Rapaport investigated blood-brain barrier permeability mechanisms, emphasizing the role of tight junctions [12,13,15,19].

A pivotal study by Levine and collaborators in 1978 revealed significantly enhanced drug delivery to target sites with intra-arterial administration compared to intravenous delivery, affirming the efficacy of this method for chemotherapy delivery to blood vessels.

2. Intra-arterial Drug Infusion: Overcoming Blood-Brain Barrier Challenges

The blood-brain barrier (BBB) stands as a formidable shield, safeguarding the brain from toxins and pathogens, yet concurrently creating formidable barriers for drug delivery, notably chemotherapy drugs, to brain tumors. This selective barrier effectively hinders the passage of molecules with a molecular weight exceeding 180 Da, restricting the access of many chemotherapeutic agents within the range of 200-1200 Da. The challenge of traversing the BBB is particularly pronounced in glioblastoma and other brain tumors, necessitating the direct delivery of drugs to the disease site at concentrations conducive to effective treatment [24,28,29].

In response to these challenges, diverse methods have emerged to enhance drug delivery across the BBB. One such method involves intra-arterial infusion of a hyperosmotic solution, such as mannitol, which transiently opens the tight junctions between endothelial cells, augmenting barrier

permeability. While this approach holds promise in improving the delivery of chemotherapeutic agents to brain tumors, its implementation demands meticulous monitoring to avert potential neurological complications.

Distinct characteristics of the BBB and the brain-blood-tumor barrier (BTB) underscore the imperative for innovative approaches in the treatment of malignant gliomas. Elevated expression of vascular endothelial growth factor (VEGF) and angiogenesis contribute to the formation of aberrant vessels in tumors, intensifying the complexities of drug delivery. While high-grade gliomas may exhibit partial permeability in the barrier, low-grade gliomas present a nearly fully functional BBB, heightening the challenge of chemotherapy delivery [25,27,30].

Continual research in drug delivery methodologies across the BBB and BCOM [brain-blood-tumor barrier] includes the exploration of microcatheters, nanotechnology, and other innovative strategies. These evolving techniques hold the promise of providing novel avenues for treating brain tumors by enhancing drug penetration through these barriers, ultimately amplifying therapeutic efficacy [31,32].

3. Intra-arterial Chemoinfusion for Brain Tumors: Unlocking Therapeutic Potential

Intra-arterial chemoinfusion (IAC) emerges as a highly promising avenue for treating brain tumors, notably glioblastoma multiforme, owing to its capability to directly deliver elevated drug concentrations to the tumor site while mitigating systemic side effects. This holds particular significance for glioblastoma multiforme, renowned for its aggressiveness and resistance to conventional treatments like surgery, radiotherapy, and systemic chemotherapy, often hindered by the formidable blood-brain barrier (BBB) [33,34].

Mannitol serves as an agent to disrupt the BBB, heightening its permeability and facilitating more effective delivery of chemotherapy drugs to tumor tissue. Clinical trials exploring IAC chemoinfusion with diverse chemotherapeutic agents, including platinum analogs, methotrexate, vincristine, and novel antibodies like bevacizumab and cetuximab, underscore the potential of this approach in glioblastoma multiforme treatment [32,35,36].

Monoclonal antibodies such as bevacizumab, blocking VEGF action, and cetuximab, inhibiting EGFR, demonstrate promising results in combination therapy for brain tumors. Particularly, when combined with other treatments, these agents show potential to enhance the prognosis for glioblastoma multiforme patients [32,35].

While intra-arterial chemoinfusion presents new avenues for enhancing survival and quality of life in brain tumor patients, further research is imperative to optimize treatment regimens, identify optimal drug combinations, and minimize the risk of side effects.

4. Mechanisms of Action for Bevacizumab and Cetuximab

Bevacizumab disrupts VEGF-A binding to endothelial cell receptors, suppressing angiogenesis pivotal for tumor growth and spread. Its ability to normalize tumor vasculature enhances oxygen delivery, reduces permeability, and amplifies the efficacy of complementary therapies like chemotherapy and radiotherapy. Studies validate its impact on improving progression-free survival in diverse cancers, including glioblastoma multiforme [34,36,38].

Cetuximab inhibits epidermal growth factor receptor (EGFR), often overexpressed in tumor cells, curtailing signaling pathways crucial for tumor growth, angiogenesis, and metastasis. Effective in certain cancers, especially KRAS wild-type colorectal cancer, cetuximab is under investigation for glioblastoma multiforme [39,41].

5. Synergistic Potential of Bevacizumab and Cetuximab

The combined use of bevacizumab and cetuximab may yield a synergistic effect, concurrently suppressing angiogenesis and tumor growth by targeting distinct molecular pathways. This approach holds promise for improving outcomes in tumors resistant to standard therapies [24,42].

6. Consideration of Side Effects

Despite potential benefits, careful consideration of side effects is crucial. Bevacizumab may contribute to hypertension, heightened bleeding risk, and thromboembolic events, while cetuximab is associated with skin reactions and infections. Inclusion of these drugs in treatment regimens necessitates a meticulous benefit-risk analysis tailored to each patient [43,45].

7. Conclusions

Intra-arterial chemotherapy delivery emerges as a promising methodology in the treatment arsenal for high-grade glial tumors, facilitating the attainment of concentrated drug levels at the tumor site while curbing systemic side effects. While phase I studies underscore the safety and favorable tolerability of this approach, the imperative confirmation of its efficacy demands robust phase 3 investigations.

The authors adeptly chart key trajectories for future research, with a focus on optimizing therapeutic amalgamations, leveraging advanced imaging techniques for precise identification of tumor vascular supply target areas, and formulating quantitative methods for monitoring drug delivery directly to tumor tissues.

This article stands as a significant contribution to the knowledge repository concerning intra-arterial therapy for glial tumors. It holds the potential to serve as a linchpin for

the development of innovative treatment strategies poised to elevate the prognosis for patients grappling with these formidable diseases.

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