Print ISSN: 2958-3675 | Online ISSN: 2958-3683
International Journal of Medical and Pharmaceutical Research
Available Online at https://ijmpr.in/
ORCiD ID: 0000-0002-3849-6959
Volume 4, Issue 1; (2023); Page No. 50-63
Original Article
Open Access

Endovascular Chemotherapy: Selective Targeting for Brain Cancer

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ABSTRACT
Establishing an effective and robust management option for brain cancers has proven to bean elusive challenge for the fields of neurosurgery and neuro-oncology. Despite decades of research efforts to improve treatment outcomes and increase patient survivability, brain cancer remains among the most fatal of all cancer classes. A significant barrier to this endeavor is the blood-brain barrier, a major protective border for brain tissue that primarily precludes the optimal delivery of chemotherapeutic drugs to the patient's brain circulation through tight junction formations and selective transporter proteins. This issue is often compounded by tumor location, particularly in inoperable regions near functional brain parenchyma. These obstacles necessitate the development of selectively targeted delivery of chemotherapeutic agents, such as endovascular super-selective intra-arterial injections. Recent experimental studies demonstrate the effectiveness of focused ultrasound to unseal the blood-brain barrier selectively and reversibly. Together, these new technologies can be leveraged to circumvent the limited permeability of the blood-brain barrier, thus improving drug delivery to tumoral locations and potentially enabling a more effective treatment alternative to surgical resection. This review attempts to place into context the necessity of these newer selective chemotherapeutic modalities by briefly highlighting commonly encountered brain cancers and explaining the prominent challenges that face chemotherapy delivery, as well as describing the current preclinical and clinical progress in the development of facilitatory focused ultrasound with selective endovascular chemotherapy.

Keywords: *Endovascular Chemotherapy: Selective Targeting for Brain Cancer .*

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1. INTRODUCTION

Cancer is described as a group of diseases that encompass abnormal, and often uncontrollable, growth and proliferation of tissue and organ cells. In 2021, an estimated 1.9 million people in the United States were newly diagnosed with cancer, amounting to roughly 600,000 cancer deaths in that year alone[1]. These numbers are expected to continue growing in alignment with the observed trend of the increasing median age of the U.S. population, with models projecting up to approximately 2.3 million new diagnoses by 2050. Such projections demonstrate a critical need for a multi-faceted approach to both reduce the current risks of developing cancers, as well as to develop better clinical management strategies to treat cancers[2]. Currently, common standard strategies to treat cancer in patients include chemotherapies, radiation therapy, and surgical resections—often through a combination of these methods. Newer advancements have also recently opened further avenues of treatment, such as stem cell therapy, ablation therapy, nanomedicine, and targeted therapy, to name a few[3].

Although a relatively rare subcategory of cancer diagnoses (~1% of total cancer cases)[4], brain cancers are markedly among the most lethal and account for the second most out-of-pocket expenditures for initial and end-of-life care out of all cancer subtypes[5]. In fact, estimates predict that about 93,000 new diagnoses of brain cancers, both malignant and non-malignant, will be made in 2022while maintaining a rate of mortality at 4.41/100,000 population per annum, according to data from the2015-2019 Central Brain Tumor Registry of the United States (CBTRUS)[6]. Despite the progress achieved in increasing the five-year relative survival rate of malignant brain cancers from 23% in 1975-1977 to 36% in 2009-2015, rates of improvement with older age groups remain stubbornly stagnant[4]. Additionally, the five-year relative survival rate of brain cancers remains substantially lower than the approximately 67% overall survival rate attributed to all cancer subtypes combined[1].

There are many factors contributing to the relatively disproportionate increase in brain cancer-related deaths, as compared to other cancer subtypes. At a gross anatomical level, many of these tumors can form in pocketed regions in the brain, located deep below and surrounded by functional brain parenchyma that is too delicate to surgically navigate and operate around, thus severely limiting surgical options as a first-line treatment[7]. These tumors are also often situated behind the blood-brain barrier (BBB), which occludes many commonly used chemotherapeutic agents from achieving their intended pharmacodynamic effects upon the tumoral tissue[7–9]. These tumors are difficult to target through cellular or genetic approaches since brain cancers typically exhibit unique genetic profiles and tumor microenvironments[7,10]. These challenges are further exacerbated by the relative rarity of brain cancers, therefore restricting crucial research funding – and arguably, overall research interest[7,11]. Herein this review, we discuss in detail the challenges primarily posed by the BBB when using chemotherapy approaches and focus on how recent research developments using assisted functional ultrasound (FUS) technology can improve the selective endovascular delivery of chemotherapeutic agents for the treatment of brain cancers.

2. Commonly Encountered Brain Cancers

Brain cancers entail complex pathologies and multisystem symptoms, requiring physicians and providers to have a sufficient understanding of their diagnosis and management. More recently, the incidence of brain tumors has risen, especially in certain populations, likely attributed to advancements in diagnostic capabilities[12]. The most common types of brain cancers include intracranial metastases, meningiomas, glioblastomas, and astrocytomas[13].

2.1 Intracranial Metastases

Primary brain tumors or intracranial tumors originate from the tissues and surrounding tissues of the brain. However, malignancies such as lung cancer, breast cancer, and melanomas can give rise to metastasis within the cranial region[12,13]. The incidence of brain metastases is roughly 10 times more than primary brain tumors, at 9-17%, but further research is needed in this field[12,14]. Subtypes include leptomeningeal metastases and dural metastases. These refer to invasion into the cerebrospinal fluid (CSF) and leptomeninges versus invasion outside of the BBB, respectively[15,16]. The former tends to present with signs of elevated intracranial pressure leading to focal neurologic deficiencies along with gait disorders and more severe cranial neuropathies[13]. Diagnosis is still a difficult task, particularly in leptomeningeal metastasis, and CSF cytology tends to be the gold standard for this neuropathy[13]. However, for general brain metastases, the National Comprehensive Cancer Network has developed an algorithm for diagnosis[17]. Magnetic resonance imaging (MRI)is the gold standard for neuro imaging purposes, but computed tomography (CT) is also sufficient[13]. Currently, the standard treatment method is through surgery - particularly in patients with rapidly growing tumors - and radiation therapy[13,18]. However, recent advances aim to develop therapies with better CNS penetration and have focused on the use of stereotactic radiosurgery rather than whole-brain radiotherapy[14,18].

2.2 Meningiomas

Meningiomas were the most prevalent non-malignant primary brain tumors, which accounted for ~37% of all CNS tumors[19]. Recently, the increase in the overall incidence of meningiomas has been primarily observed with increased age and in African Americans; however, it remains unclear the nature of this association[20,21]. Presentationis seen both on intracranial and spinal dural surfaces, but clinical symptoms can vary drastically from incidental to fatal[21]. The World Health Organization (WHO) has adopted a classification system for meningiomas with grades I to III. Grade I includes benign meningiomas while grades II and III include more aggressive tumors with higher mortality[21,22]. Although the majority are benign and can be dealt with via gross total resection, rare malignant meningiomas are aggressive and tend to be fatal, regardless of extensive resection or other treatment modalities[23]. Symptoms are classic of brain cancers such as headaches, other focal neurological symptoms, and seizures[13]. Diagnosis is typically done via radiographic imaging such as MRI and CT, but in cases of uncertainty or specific concern of higher-grade meningiomas, resection will better deliver a diagnosis[21]. Post-diagnosis management varies depending on symptoms and grade of the meningioma. Asymptomatic tumors with slow growth can be simply observed long-term[24]. In contrast, surgery is needed in symptomatic patients or those with aggressive tumors[25]. Further, radiotherapy is primarily used only in cases of grades II and III meningiomas associated with high mortality[21,25].

2.3 Glioblastomas

Gliomas are tumors derived from glial cells that provide anatomical and physiological support to neurons in the brain, including oligodendrocytes, astrocytes, and ependymal cells. They include the first and second most prevalent malignant intracranial tumors: glioblastomas (GBS) and diffuse astrocytomas. GBS, categorized as grade IV astrocytomas, are the most commonly encountered aggressive form of brain cancers in adults, making up roughly 15% of all primary brain tumors[22,26]. The designated WHO grade IV categorization is due to its associated necrosis and other malignant features[22]. Further, severe tumors such as anaplastic astrocytomas can also develop into GBS. An alternative characterization of tumors as “secondary glioblastomas” refers to those that are WHO grade II or III gliomas[22]. According to 2008-2012 data from the CBTRUS, the highest incidence rate for malignant tumors occurred in GBS,

followed by astrocytomas[19]. Presenting symptoms include headaches and other common tumoral features[21]. Due to the aggressiveness of GBS, MRI is the standard for neuroimaging-guided diagnosis[21]. Further confirmation is needed via surgical resection or biopsy. Management is done via a combination of surgery, radiotherapy, and chemotherapy[22]. Recent research has also focused on temozolomide(TMZ) therapy and other combination therapeutics such as chemoradiation[21].Currently, there is no standard treatment for recurring GBS, and further research is required.

3. Current Approaches to Cranial Chemotherapy

3.1 Chemotherapy Administration

There are several unique methods of administering chemotherapeutic agents for primary brain tumors: including oral, intravenous (IV), nanoparticles, focused ultrasound (FUS), and intra-arterial (IA)[27]. However, the prognosis remains dismal due to various obstacles, such as the blood-brain barrier and distinct heterogeneous vasculature of primary brain tumors. Recently, advancements in endovascular delivery methods of anti-neoplastic agents have gained traction due to their selective nature in targeting tumors. During endovascular treatment, catheters and/or micro catheters are percutaneously inserted to enter blood vessels, most commonly the femoral, radial, and brachial arteries, in order to reach the desired target location where the drugs are to be locally administered[28]. As a result of the increased demand for selective targeting techniques, there has been an increase in the development of flow-directed and magnetically-guided micro catheters that further increase the accuracy of placement[29].

Modern endovascular chemotherapy approaches can be classified into two categories: (1) intra-arterial (IA) delivery and (2) blood-brain barrier disruption (BBBD) to facilitate IA delivery[30]. IA chemotherapy enhances the intra-tumoral concentration of anti-neoplastic agents compared to IV administration through its local delivery, and it is distinctively used for drugs with higher clearance rates, such as carmustine and other nitrosoureas[31]. However, there currently lacks an empirical consensus concerning IA chemotherapy effectiveness, as it was shown by Chen et al. that IA chemotherapy failed to demonstrates periority to IV chemotherapy for treating malignant gliomas, with respect to efficacy and overall survivability[32]. Due to the stringent access of systemic blood flow to the brain resultant of the BBB, it has been suggested that simultaneous disruption of the BBB – in combination with IA delivery – will improve the delivery of chemotherapy to its desired location. Two methods that are commonly used alongside IA chemotherapy are (1) osmotic disruption and (2) the supply of mediators of the inflammatory response[30]. Reversible BBB disruption is frequently obtained by infusing hypertonic solutions, such as mannitol, into the cerebral arteries. This generates a gradient that extravasates water out of the endothelial cells, thus inducingcell shrinkage, which interferes with the tight junctions and increases the permeability of the BBB[30,33,34]. Alternatively, BBBD can be induced by introducing inflammatory response mediators, such as bradykinin or leukotrienes, that can temporarily induce vascular permeability[33,34]. Nevertheless, conflicting studies have shown osmotic disruption to be significantly more effective in enhancing the delivery of anti-tumor agents compared to bradykinin alone[35].

Historically, IA delivery of chemotherapy drugs was limited to the internal carotid and vertebral arteries, both of which could potentially cause significant harm to the surrounding parenchyma once administered[32]. As such, the therapeutic action of anti-neoplastic drugs was overshadowed by their toxic side effects (i.e. irreversible encephalopathy, seizures, ipsilateral visual loss)[36], and there was a need for more specific routes of administration. Recent advancements in the ability of modern catheters to reach distal vessels have shown great promise for targeting an area of interest. Endovascular super-selective intra-arterial (ESSIA) infusion is the selective administration of chemotherapeutic drugs into local tumor vasculature using microcatheters. This is achieved using live imaging techniques within the angiography suite to visualize the area of delivery. One such technique is cone beam computed tomography (CBCT), which is used to create a 3D perfusion map during angiography with microcatheters to increase the precision of delivery. CBCT has been favored over CT angiography (CTA) and CT perfusion (CTP) due to its higher spatial resolution and limited radiation exposure[37].

3.2 Common Cranial Chemotherapeutic Drugs

There are several different chemotherapeutic approaches that researchers use to target cancers of the brain (**Table 1**), including (1) alkylating agents (cell cycle inhibitors), (2) angiogenesis inhibitors, and (3) enzyme inhibitors. The first method encompasses interfering with the cell cycle of tumortissue and therefore limiting its replicative ability. TMZ is analkylating drug that modifies DNA by methylating guanine at the N^7 position (N^7G) or methylating adenine at the N^3position (N^3A). During DNA replication, TMZ induces base substitutions of thymine for cytosine, leading tomismatched base pairs that eventually induce apoptosis[38,39]. As an oral drug, TMZ is unique in its capability to diffuse across the BBB due to its small size and lipophilicity[40]. However, even with these factors at play, its concentration within the brain is limited to only 20% of its plasma concentrations[41]. While the standard method of administration of TMZ is oral, other administration methods – including IA infusion - have been investigated and have been shown to increase local delivery concentrations; however, they have also led to unwanted neurotoxicity[42]. Therefore, further research is required to strike an appropriate balance between optimally achieving an increase in local drug concentration while minimizing drug toxicity to the patient.

Another class of chemotherapy agents is angiogenesis inhibitors. These drugs prevent the progression of novel blood vessels that provide tumors with vital nutrients, allowing them to propagate and develop. One crucial element for the progression of angiogenesis is vascular endothelial growth factor (VEGF), a signaling protein that is necessary for the growth and development of newly formed blood vessels. While the majority of normal adult tissue is void of VEGF, the relatively active state of tumors promotes and recruits VEGF. Bevacizumab, a recombinant humanized monoclonal antibody and angiogenesis inhibitor, binds to VEGF and prevents binding to its receptor[43]. Willett et al. demonstrated, albeit with difficulty as it remains challenging to obtain tumor biopsies in clinical trials, a significant decrease in tumor microvasculature with regards to density, blood perfusion, and volume when administered bevacizumab[44]. The traditional method of delivering bevacizumab is intravenously alongside radiotherapy treatment[45]. However, recentlyseveral new forms of bevacizumab have been tested and proven to be effective in their delivery, including intratumorally via Alz et micro-osmotic pumps[46] and ESSIA infusions with simultaneous mannitol administration[10].

The final class of chemotherapy agents to be discussed in this review are enzyme inhibitors, more specifically topoisomerase inhibitors (Topo I). Topoisomerases relieve DNA torsional strain by creating and then repairing single-stranded nicks on supercoiled DNA. This step relaxes and untangles DNA, allowing DNA replicationto proceed without minimal hindrance. Topo I drugs inhibit this process and arrest the cell cycle in the G2 phase, which eventually inducesapoptosis in tumoral cells[48–50]. A phase II studyhas shown topotecan as a potential chemotherapy drug when combined with TMZ for the treatment of medulloblastoma[51].

3.3 Effectiveness of Current Chemotherapy Approaches

Unfortunately, despite several existing chemotherapeutic approaches, current approaches largely fail to yield ideal therapeutic outcomes across various types of brain cancers[7,52]. This is largely attributed to the high selectivity and low permeability of the BBB, which poses challenges for balancing systemic administration and localization of chemotherapeutic agents to target tissues[7,52,53]. In an examination of the outcomes associated with current chemotherapeutic approaches to managing patients with brain metastases, survival rates have remained relatively unchanged[54]. Although current chemotherapeutic approaches may be initially effective in the therapeutic management of GBS, tumor recurrence remains an inevitable outcome associated with high fatality, for which no therapeutic treatments are currently available[52]. In the context of meningiomas – due to the lack of supporting evidence– chemotherapy is not used clinically to treat these cancers, aside from various experimental studies[55]. Over the previous two decades, the use of ESSIA and various anti-neoplastic agents, such as bevacizumab and/or TMZ, have routinely been studied to examine their effects on median survival time of GBS, and have shown favorable results[36,37,56,57]. However, these studies have mostly been completed with small sample sizes and need to be performed in larger phase II and III trials to demonstrate safety and effectiveness. Further research is additionally warranted to establish tailored chemotherapeutic approaches that effectively target the various types of brain cancers, as variability in response to current chemotherapeutic approaches demonstrates the unique complexities associated with different types of brain cancers.

Table 1: List of common chemotherapy drugs, their target cancer types, and dosing schedules.

Drug	Target Cancer Type	Dosing
Temozolomide (TMZ) (oral/IV)	Newly Diagnosed Glioblastoma (GBS)	75 mg/m^2 for 42 days concurrent with focal radiotherapy Follow with maintenance dose of 150 to 200 mg/m^2 once daily for five consecutive days per 28-day cycle (six cycles total)[58]
	Refractory Anaplastic Astrocytoma	(*Phase II Study*) 200 mg/m^2 once daily for five consecutive days per 28-day cycle (median: five cycles total)[59]
Bevacizumab	GBS	5 to 10 mg/kg IV every two weeks[60]
TMZ and Topotecan	Medulloblastoma	*(Phase II Study)* Oral TMZ daily at 150 mg/m^2 Follow with daily IV topotecan at 0.75 mg/m^2 for five consecutive days per 28-day cycle (median: two cycles total)[51]

4. Challenges Facing Chemotherapeutic Delivery

4.1 Blood-Brain Barrier

Historically, the selective treatment of brain cancer via chemotherapy has been extremely limited - largely due to delivery impediments associated with the relative impermeability of the BBB[61]. The BBB is an exceptional gate to the central nervous system (CNS), comprised primarily of brain endothelial cells that are linked together by tight junctions (**Figure 1**)[62]. Together with pericytes and the foot-like astrocyte processes directly surrounding said endothelial cells, the BBB is restricted to the passage of small, hydrophobic molecules[63]. As a result, most substances that need to enter the brain require assistance via transcellular passage, which isbottlenecked by the lack of fenestrae and pinocytic vesicles normally characteristic of the continuous capillaries and basal lamina that make up the cerebral capillary endothelium[64]. Thus, these anatomic barriers are further complicated when considering the role of transporter proteins that are responsible for the delivery of essential nutrients and the disposal of waste in the brain internal milieu, i.e. glucose transporter 1 (GLUT1) for facilitating glucose transportation and monocarboxylate transporter 1 (MCT1) to enable the removal of low molecular weight monocarboxylic acids and lactic acid[65,66]. Nonetheless, small lipophilic compounds such as chemotherapeutics typically have no endogenous transporters and can enter via passive diffusion. However, the permeability of these compounds is strictly stratified according to lipid solubility, degree of ionization, molecular weight, and binding affinities for plasma, tissue, and intracerebral carriers[63,67]. Interestingly, a very significant number of small, uncharged, and unbound lipid-soluble molecules have a lower BBB permeability than would be predicted. According to Begley and colleagues, this phenomenon is known as “multidrug resistance” (MDR) and is facilitated by several different ATP-binding cassette (ABC) transporters such as multidrug resistance proteins (MRP), P-glycoprotein (Pgp), and breast cancer resistance protein (BCRP)[68]. This MDR occurs because small, lipophilic molecules, such as chemotherapeutics, are bindable substrates for ABC transporters and are thus effectively removed from the CNS—ultimately limiting intertumoral concentrations of anticancer drugs to the brain[61,68]. Taken altogether, the aforementioned characteristics of the BBB aid in explaining why nearly98% of drugs with small molecular weights and 100% of neurotherapeutics with larger molecular weights are excluded from crossing to the brain parenchyma[69]. Consequently, since endovascular chemotherapy relies on access to the brain, this mode of treatment is significantly fallibledue to the BBB’s unique properties.

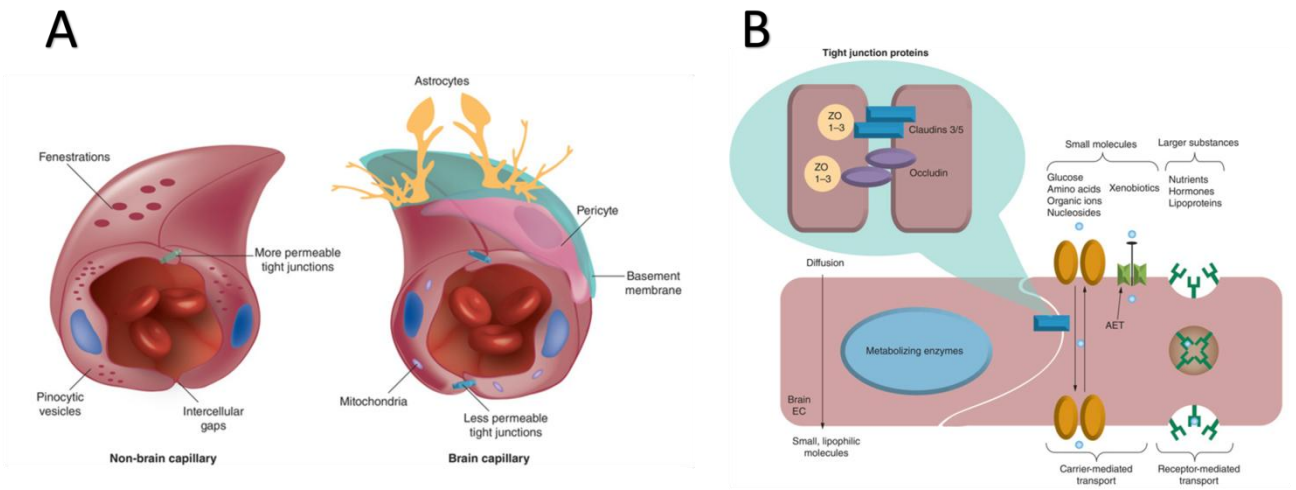

Figure 1: Anatomy and physiology schematic of the blood-brain barrier. ***A:*** Represents the physiological differences of brain capillaries as compared to extra cerebral capillaries. The brain capillaries contain less permeable tight junctions and a continuous basal lamina—void of fenestrae—that imparts it with its exceptionally impermeable characteristics. Endocytic capacity is lower due to fewer pinocytic vesicles, effectively limiting the nonspecific transport of vesicles from blood to the brain. Barrier function is further reinforced by pericytes and astrocytes that surround the endothelial cells of the brain capillaries. ***B:*** Represents the structure and transport mechanisms across the brain endothelium. Tight junction complexes restrict paracellular diffusion, while transcellular passage is facilitated by either carrier-mediated transporters or receptor-mediated transporters of small and large molecules, respectively. Active efflux transporters (AET) such as the various ATP-binding cassette (ABC) transporters block the passage of xenobiotics. Some movement of small lipophilic molecules is achieved through passive diffusion[62].

4.2 Endovascular Chemotherapy and Blood-Brain Barrier Disruption

Posing as the most formidable challenge for the delivery of chemotherapeutics to the brain, novel approaches have been developed in the hopes of circumventing the impermeability of the BBB. Among those is the concomitant employment of BBB disruption with endovascular chemotherapy. Presently, endovascular chemotherapy for brain tumors can be primarily categorized into two distinct classes: (1) neoadjuvant embolization and devascularization and (2) direct intra-arterial (IA) drug delivery[30]. In the context of improved permeabilization, the disruption of the BBB is paired with the latter of these two therapies. Specifically, a few well-known strategies to achieve said disruption include IA chemotherapy combined with osmotic disruption or vaso active compound administration[30]. In a 2012 study, Burkhardt et al. demonstrated that the combined use of IA bevacizumab after the infusion of hypertonic mannitol in cases of recurrent GBS—which were nonresponsive to standard of care treatment involving concomitant TMZ and radiation—experienced a median patient progression-free survival of 10 months[70]. Encouragingly, another clinical study demonstrated that combined IA of lobradimil, a bradykinin analog, and carboplatin in patients with recurrent GBS improved the localized administration of the therapeutic agent by approximately two-fold[29,71]. Nevertheless, some concerns do exist around these established chemotherapeutic treatments. Particularly, in the case of IA with osmotic disruption of the BBB, the literature points to potentially unintended neurotoxicity due to nonspecific permeabilization of where normal brain tissue resides[72]. Additionally, although the administration of bradykinin in combination with IA chemotherapeutic molecules has been proven clinically safe, tumor response has been consistently variable—perhaps due to the non-specificity of the BBB response to bradykinin analogs[30]. Nonetheless, as of the early 2000s, there are several other promising strategies currently undergoing clinical trials with the aim of enhancing BBB permeability (**Table 2**)[73].

Table 2: Summary of novel strategies to enhance blood-brain barrier permeability for treatment of brain cancer[73].

Strategy	Principal advantages	Potential problems	Clinical trial
Nanotechnology	Sustained release of payload Uptake by the tumor parenchyma	Rapid removal	Phase II
Hyperthermia	Easy to execute Compatible with drugs	Necrosis and higher intracranial pressure Possible tissue damage	Phase II
RMT	Site-specific	Potential toxicity Rapid degradation of the cargo Low dissociation rate	Phase III
CPPs	Great penetrating ability Low cellular toxicity	Rapid removal Lack of specificity Initiate immune response	Phase II
Cell-mediated delivery	Targeted transport Controlled drug release Low cytotoxicity	Cell damage Larger quantity of cells needed	Phase I

Abbreviations: CPPs, cell-penetrating peptides; RMT, receptor-mediated transport.

4.3 Additional Barriers to Endovascular Chemotherapy

As discussed above, the treatment of brain tumors with chemotherapy is largely limited due to the BBB, with which recent innovations in therapeutics have attempted to circumvent, i.e., barrier disruption with endovascular chemotherapy—with variable success. To complicate treatment even further, chemotherapy usually follows a time-consuming protocol. Thus, the transient disruption of the BBB is likely insufficient to deliver effective concentrations of anti neoplastic drugs at the tumor site[61]. In addition to the physiologic barriers and duration of exposure when considering endovascular chemotherapy, is the anatomical hurdle of accessing certain brain tumors. Historically, IA delivery of chemotherapeutics to cancers such as GBS was via non-selective routes such as the proximal carotid or vertebral arteries[36]. Resultingly, numerous studies noted toxicity and unintentional effects on surrounding, non-tumoral tissues such as healthy brain parenchyma and the eye, as well as sub therapeutic concentrations at the tumor site[28,32,74]. However, with recent technological advancements such as endovascular super-selective intra-arterial infusion (ESSIA), practitioners can now administer chemotherapeutic drugs through the distally located and otherwise inaccessible intracranial tributaries that supply a given tumor[36]. According to Blacklock et al., when combining selective IA infusion, such as ESSIA, with drug delivery viapulsatile injection and a lesser rate of infusion—approximately matching arterial laminar flow—delivery of the chemotherapeutic drug is optimally focused to distal tissues and off-target neurotoxicity is decreased[75–77]. Although the aforementioned next-generation of selective therapies is promising for the treatment of complex neuropathology such as malignant gliomas, not enough studies have critically evaluated the selectivity and effectiveness of ESSIA as compared to other less selective infusions.

Ultimately, the true merit of recent endovascular chemotherapy such as ESSIA, when combined with BBB disruption, is in its capability to effectively deliver chemotherapeutic drugs which otherwise have impeded efficacy via traditional routes of administration, i.e., orally or intravenously (IV). To date, ESSIA therapy for brain tumors has been solely focused on the delivery of established chemotherapies such as IV bevacizumab and oral TMZ, as the value of nonselective IA as an alternative delivery technique remains debatable compared to the known effectiveness of these agents and the like[36].Thus, future investigators must develop new chemotherapeutics to pair with the combined employment of ESSIA and barrier disruption to increase therapeutic selectivity and effectiveness in treating brain cancer.

5. Concurrent Use of Chemotherapies with Focused Ultrasound

5.1 Focused Ultrasound and Blood-Brain Barrier

As previously mentioned, the impermeability of the BBB poses a challenging obstacle to overcome when administering chemotherapeutic agents to treat neurological tumors. Recent developments such as ESSIA have attempted to circumvent this anatomical feature. ESSIA has shown the potential to increase the efficacy of chemotherapeutic drugs while specifically targeting pathological regions, thus limiting the neurotoxicity that can potentially spread otherwise. In addition to ESSIA, which is still a relatively new advancement in the neurological space, one intervention that shows particular promise in navigating past the BBB and treating neurological tumors is FUS. Ultrasonography is a popular tool with great familiarity in the medical community due to its ability to produce non-invasive diagnostic images in a relatively safe and inexpensive manner[78]. Furthermore, by increasing the intensity and frequency of the associated sound waves, this technology can also induce localized mechanical and/or thermal effects that can manipulate tissue structures[36,78]. This is done through the application of transducers that focus multiple beams of sound waves into a single focal point to produce the targeted effects[36]. These effects can range from irreversible tissue destruction via coagulative necrosis from high-intensity FUS exposure to neuro modulation via voltage-dependent ion channel

disruption through low-intensity FUS exposure[79]. Most importantly, the two main applications that FUS has in targeting brain tumors include thermal ablation of the tumor itself and opening of the BBB for drugs to pass through to the desired location[80]. To achieve these outcomes, FUS is typically coupled with magnetic resonance imaging (MRI) to aid in procedure guidance, together termed MRgFUS[81]. Currently, studies have shown that MRgFUS has been a safe and effective strategy to help treat various neurological conditions, including but not limited to Alzheimer's Disease[81], Parkinson's Disease[82], and essential tremors[80,83].

Due to its studied capabilities in altering tissue structures and documented application in treating other neurological ailments, FUS has since become an emerging candidate for concurrent use with chemotherapeutic drugs to treat brain tumors[84]. Studies have found that FUS enables transient, reversible, and safe opening of the BBB to enhance the delivery of chemotherapeutic agents. This has been particularly researched with intravenously administered gas-filled cavities termed "microbubbles". These microbubbles facilitate a process known as cavitation when paired with FUS. Cavitation is described as cycles of expansion and contraction in response to acoustic waves, which can alter the cellular structure of the BBB (**Figure 2**)[85,86]. The volumetric oscillations induced by cavitations in localized brain microenvironments cause physical stress and stretching of the endothelial vessels, causing pore formation in plasma membranes and perturbation of tight junctions to thereby open the BBB[87–90]. Furthermore, some studies demonstrate the ability of FUS to decrease MDR-mediated drug efflux, another critical limitation of endovascular chemotherapy[91]. Cho and colleagues found that MRgFUS and microbubble cavitations suppressed levels of Pgp, the main MDR protein expressed in the BBB, on a range of 63.2 +/- 18.4% compared to control levels when opening the tight junctions comprising the barrier[91]. This provides even greater opportunities for MRgFUS in cancer treatment, as it can not only open the BBB for chemotherapeutic entry but perhaps even mediate its effects even longer and more consistently without the extra vasation caused by MDR proteins.

With circulating microbubbles, the intensity of ultrasound needed to produce BBB changes was three orders of magnitude less than the intensity needed without microbubbles, suggesting this technique can be used for BBB opening without the histological necrosis observed in high-intensity FUS use[90,92–95]. Additionally, pulsated FUS (pFUS) has been particularly effective at generating the mechanical effects of BBB opening without thermogenic-induced tissue ablation by allowing time for cooling to occur between pulses[96,97]. Studies have demonstrated the closure and normal functioning of BBB hours after FUS use[98–100].

As with other medical interventions, there are limitations associated with MRgFUS. Recent investigations have shown MRgFUS can unintentionally induce large amounts of erythrocyte extravasation due to the excessive increase in vascular permeability[101,102]. In addition, short-term increases in neuro inflammatory markers have also been noted, but it has not yet been proven whether this has any detrimental effects[103]. The degree to which BBB permeability is affected, as well as the associated side effects, can however be reliably monitored by altering different features in the FUS application including pulse frequency, pulse size, microbubble size, microbubble material, and duration of therapy[104,105]. Optimizing parameters for use of MRgFUS is an area of open investigation. Taken together, MRgFUS shows significant promise for localized BBB opening given its mechanism, relative safety, and reversibility.

5.2 Focused Ultrasound in Cranial Tumor Treatment

The favorable profile of MRgFUS has made it a promising therapeutic approach for the treatment of brain cancers, though research is primarily investigational. BBB opening can be monitored in real-time and the movement of chemotherapeutic agents across the BBB and into the tumor microenvironment may be visualized by conjugation of the drugs with MRI contrast agents[106]. Several preclinical studies have shown the enhanced delivery of chemotherapeutics using FUS. In mice with glioblastoma multiforme(GBM) treated with TMZ with and without MRgFUS, Wei and colleagues showed that the subgroup that received MRgFUS treatment had enhanced CSF/plasma ratios of TMZ (38.7% vs. 22.7%), prolonged median survival (23 vs. 20 days), and reduction in one-week tumor progression ratio (24.03 to 5.06)[107]. Lui et al. concluded that FUS was able to significantly enhance anti-VEGF bevacizumab in the brain tissue in U87 GBM mice models, with effects ranging from 5.7 to 56.7-fold[108]. The increase in median survival in the FUS bevacizumab was 135% compared to 48% for bevacizumab alone, compared to no treatment control. Doxorubicin, known to have low bioavailability in the brain using traditional chemotherapy methods and significant systemic toxicity, was shown to have a 2.35-fold increase in tumor-to-normal brain doxorubicin ratio in GBM mice treated with FUS compared to GBM control mice not receiving FUS[109]. Notably, the mean peak concentration of doxorubicin was 10 times greater in the sonicated group. Thus, across the principal drug classes used for several brain cancers, FUS has shown significant promise in glioma models.

Thus far, most data from FUS and its ability to treat brain tumors has been limited to preclinical studies involving animal models[80]. However, there have been some documented clinical trials that have achieved therapeutic outcomes with the technology, as well as many more clinical trials that are currently evaluating its role in cancer treatment. One clinical trial in Toronto has recently completed its study evaluating potential adverse events associated with BBB

disruption by transcranial MRgFUS (tcMRgFUS) when attempting to increase the accumulation of doxorubicin in brain tumors, yet the results have not been published[110]. Given promising preclinical results, treatment of GBS using low-intensity pulsated FUS was pioneered in France using an implantable device in 21 GBS patients[111]. This study reported that FUS via SonoCloud-1, the device surgically implanted into the skull of patients, with IV carboplatin was well-tolerated. Moreover, they showed that progression-free survival was increased from 2.73 months to 4.11 months while overall survival was improved from 8.64 months to 12.94 months in patients who had evidence of BBB disruption, compared to those who did not[112].

In addition to studying how MRgFUS can increase BBB permeability for more targeted chemotherapy, clinical trials have been conducted to assess the efficacy and safety of FUS thermal ablation in removing brain tumors as well. In a Phase I study of three men with GBS, Mc Dannold and colleagues first found in 2010 that the Ex Ablate 3000 tcMRgFUS system could be safely applied noninvasively through the cranium[113]. ExAblate is currently the standard technology for MRgFUS. Coluccia and colleagues expanded upon this finding in a Phase I study in 2014 when, after excluding surgery due to the location of recurrence within intricate brain structures, they were able to ablate nearly ninety percent of tumor tissue in an elderly patient through tc MRgFUS[114]. Furthermore, two clinical trials evaluating the safety and efficacy of the ExAblate tcMRgFUS system in treating brain tumors in a larger sample of patients, ten adults in each study, are expected to be completed soon[115,116]. This data will be an early advancement in the path to clinical approval for MRgFUS in treating brain tumors without damaging the cranium or surrounding brain tissue.

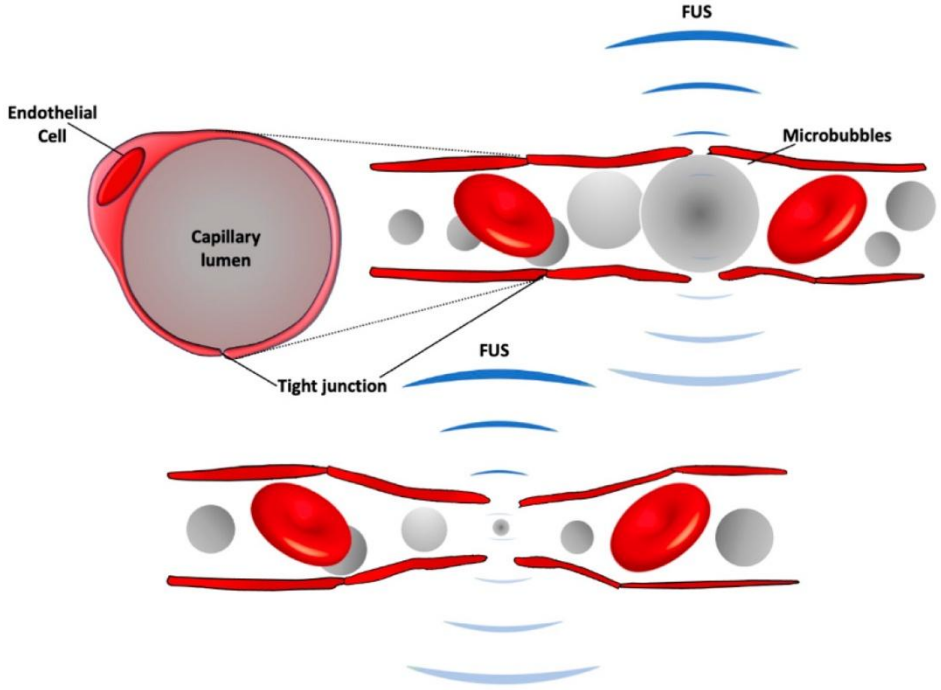

Figure 2. Schematic representation of microbubble cavitation induced by FUS. Cavitation temporally alters permeability across tight junctions in the BBB. FUS delivers high-frequency pulsations of acoustic waves, which act upon intravenously administered microbubbles, to modulate a temporal increase in BBB membrane permeability. This is achieved via the mechanical force generated on BBB endothelial cells by the oscillatory contraction and relaxation of microbubbles. When combined with the delivery of chemotherapeutic agents, FUS-induced microbubble cavitation alters BBB permeability to potentially enhance drug absorption and therapeutic response[86].

6. CONCLUSION

In this review, we discussed current developments regarding endovascular chemotherapy for the treatment of brain cancers. We first briefly described the epidemiology of brain cancers in the US and identified the most common subtypes clinically encountered. We also discussed current chemotherapy options that are utilized and highlighted significant physiological barriers that prevent ideal, or even positive, outcomes following treatment. Particularly relevant to the focus of this discussion is the ongoing challenge of delivering chemotherapeutic agents beyond the blood-brain barrier, a major anatomical structure within the brain that obstructs the entry of pharmaceuticals into the local blood circulation of the brain. Additionally, we underscored how recent developments have made use of endovascular super-selective intra-arterial methods concurrently with focused ultrasound applications to facilitate the delivery of chemotherapeutic drugs by leveraging focused ultrasound's ability to selectively open the blood-brain barrier. Coupled with magnetic resonance imaging, focused ultrasound demonstrates promising solutions for many challenges facing chemotherapeutic drug

delivery, including permeating the blood-brain barrier via microbubble cavitation, P-Glycoprotein suppression, and localized thermal ablation. The potential significance of these novel applications cannot be understated, as they may eventually prove to be invaluable selective treatment options for inoperable brain tumors and have a positive impact on patient post treatment survivability.

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