

Intraarterial drug delivery for glioblastoma multiforme

Will the phoenix rise again?

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Abstract Intraarterial (IA) drug delivery is a physiologically appealing strategy as drugs are widely distributed throughout the tumor capillary network and high regional tissue concentrations can be achieved with low total doses. IA treatment of glioblastoma multiforme (GBM) has been attempted since the 1950s but success has been elusive. Although IA treatments have been embraced for the treatment of retinoblastoma and advanced liver cancers, this has not been the case for GBM. The development of IA drug delivery for the treatment of brain cancer over the last several decades reveals a number of critical oversights. For example, very few studies took into consideration the underlying hydrodynamic factors. Therapeutic failures were often blamed on an inability to penetrate the blood brain barrier or on the streaming of drugs. Similarly, there were few methods to investigate the ultra-fast pharmacokinetics of IA drugs. Despite past failures, clinical interest in IA drugs for the treatment of GBM persists. The advent of modern imaging methods along with a better understanding of hydrodynamics factors, better appreciation of the complex morphology of GBM, improved drug selection and formulations, and development of methods to minimize treatment-related neurological injury, promise to considerably advance the application of IA drugs for GBM

treatment. There are several clinical trials with IA treatments in the National Trial Registry that are actively recruiting patients. This review of IA drug delivery for GBM treatment is therefore timely and is intended to assess how this method of drug delivery could be better applied to future treatments.

Keywords Blood–brain barrier · Brain tumor · Chemotherapy · Glioblastoma multiforme · Glioma · Intraarterial

Introduction

Intraarterial (IA) drug delivery to GBM is a physiologically appealing strategy as it enables drug delivery throughout the extensive tumor capillary network and yet the delivery occurs within a limited volume of distribution which can be precisely controlled by careful injection. Tissue drug perfusion in this manner is theoretically very efficient as it follows the path of nutrient diffusion at very high regional concentrations. Notwithstanding, the pharmacokinetics of IA drug delivery is exceedingly complex. For effective IA delivery, drugs must be taken up rapidly and, preferably irreversibly, during their first pass through tissue circulation. In human subjects this occurs on a time scale of approximately 5 s. Full appreciation of IA pharmacokinetics therefore requires an understanding of both physiological and anatomic factors that influence arterial concentrations. These include blood flow hydrodynamic and injection parameters, endothelial-drug interactions, the kinetics of blood brain barrier (BBB) transit, and site-specific pharmacokinetics.

Despite past failures and persistent hurdles to effective GBM treatment, IA drugs are currently being used to treat

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recurrent gliomas and other brain tumors. This review highlights recent pre-clinical studies and ongoing trials utilizing IA drugs for the treatment of GBM. We describe how emerging technologies may offer novel insights into the complex pharmacokinetics of IA drugs, how concurrent reduction of blood flow enhances the regional effectiveness of IA delivery, and how new tumor targeting strategies and nanoparticle delivery could further improve IA delivery to GBM and other brain tumors. Emerging paradigms of IA drug delivery herald more effective and safe chemotherapy than was possible in the past.

Brief history

Modern chemotherapy emerged from toxicological studies with nitrogen mustards that were used during the Second World War [1]. Calvin Klopp at George Washington University used IA chemotherapy for head and neck tumors including GBM in 1950 [2]. In the 1960s, Charles Wilson systematically investigated IA chemotherapy for glioma treatment [3]. In 1972 Stanley Rapport demonstrated hyperosmotic disruption of the BBB [4]. Significant advances were made at the NIH under Oldfield et al. in the 1980s [5]. Robert Dedrick presented some of the key pharmacokinetic concepts at that time [6]. By the 1990s, interest in IA chemotherapy for brain tumor treatment generally started to wane in part due to the neurological complications reported with use of IA carmustine. Despite this trend, a number of individuals have championed the use of IA drugs. Edward Neuwelt, in particular, has kept the subject alive through the Blood Brain Barrier disruption program [7]. Unfortunately, a general loss of interest in IA treatments for brain cancer could not have been more untimely. Modern endovascular technology has rapidly advanced and safer therapeutic compounds are now available. In the last decade, significant advances have also been made in optical imaging and nanoparticle engineering—both of which may have an immense impact on IA drug delivery [8].

The case for IA drug delivery for GBM treatment

Local drug delivery

Effective IA injections rely on drug delivery through capillary networks that in turn are governed by the ability of nutrients to diffuse to the target cells. The diffusion distance for drugs to reach the target site should be short. Furthermore, drug delivery is ideally restricted to the site of pathology. Optimization of these delivery characteristics favorably alters the risk–benefit profile of IA intervention [9].

Success of IA chemotherapy in other cancers

IA chemotherapy has been used in treating many peripheral malignancies such as retinoblastoma [10], head and neck tumors [11], advanced liver [12, 13] and breast cancers [14], pancreatic cancer [15], penile [16] and other urogenital cancers [17]. The success of IA treatments—especially in cases of retinoblastoma and head and neck tumors—indicates that infusing drugs in proximity of the cerebral circulation can be safe. Success in the treatment of liver cancers additionally demonstrates the relevance of high first pass extraction of drugs delivered intraarterially [18].

Dose advantages

The net advantage of IA drug injection over IV injection depends on a number of factors, including the method of injection, the rate of injection, and the duration of infusions. PET measurements in human subjects have revealed a 50-fold increase in tumor tissue concentrations after IA versus IV injections [19].

Unique pharmacokinetics

As a general rule, IA drugs are beneficial when there is high local extraction, low regional blood flow, and high systemic clearance [6]. These parameters can be manipulated to improve IA drug delivery (Fig. 1). One such technique is to transiently reduce blood flow during delivery. Preclinical and clinical studies indicate that this can have a profound effect on IA drug delivery [20–23]. Flow arrest methods have been used to enhance the delivery of chemotherapeutic drugs to treat retinoblastomas, liver cancer, and breast cancer [24, 25].

Emerging real time assessment of tissue drug concentrations

As technology has advanced in recent years, optical methods have emerged that can track tissue tracer concentrations of drugs on a sub-second time scale (Fig. 1). Experimental data tracking of tissue concentrations and blood flow changes are able to generate more accurate pharmacokinetic models that include hydrodynamic factors that are critical to effective and safe IA drug delivery [8, 26, 27].

Systemic rescue

Another advantage of IA drug delivery is the possibility of removing recirculating drugs in order to decrease the systemic side effects. Extracorporeal hemoperfusion has been

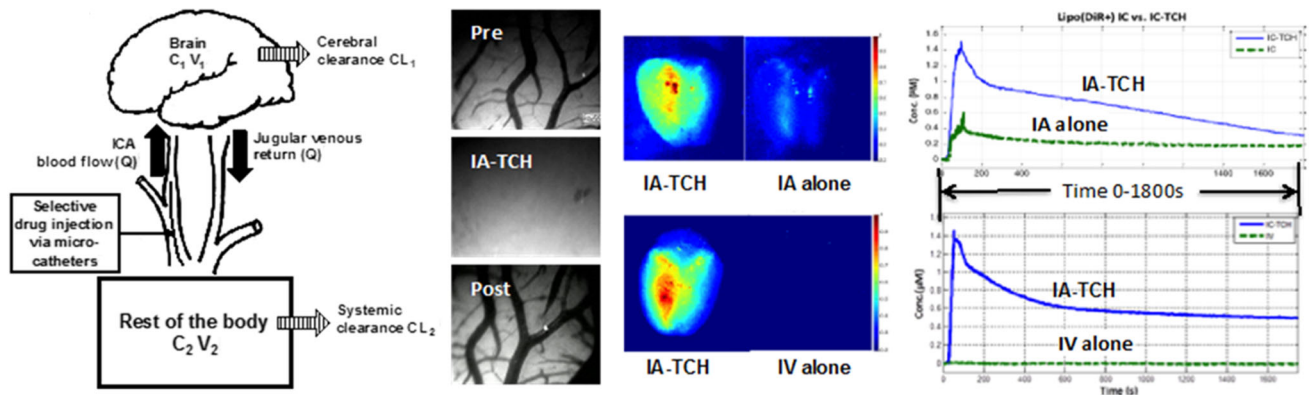


Fig. 1 Pharmacokinetic and hydrodynamic factors involved in IA drug delivery. Dedrick’s mathematical model of intracarotid drug delivery is visually demonstrated (*left panel*). The model shows that IA infusions are useful with reduced Q and rapid regional extraction. However, when IA drugs are injected during transient cerebral hypoperfusion (TCH) the arterial blood concentrations increase approximately 10-fold, the transit time is increased 10 to 50-fold, and contact with blood cells and serum proteins is avoided—as evidenced by the absence of blood in vessels during videomicroscopy of a rabbit brain during IA-TCH injection (*grayscale-center panel*). The Color *center panel* shows the effect of IA-TCH on IA

delivery of cationic liposomes to the brain. These post-mortem, multi-spectral images (MSI) show that cationic liposomal uptake is significantly improved by utilizing intra-arterial delivery with TCH. Corresponding concentration–time curves obtained by diffuse reflectance spectroscopy (DRS, 612 data points each) are shown in the *right panel*. Optical measurements using DRS enable one to track drug and tracer delivery while imaging methods such as MSI can map drug/tracer distributions. Such novel optical technologies have rapidly advanced our understanding of the pharmacokinetics of IA drugs. C concentration, V volume, CL clearance, Q regional blood flow

used in the past for this purpose [5, 28]. Alternately, an antidote that can neutralize recirculating drugs may be effective. For example, ototoxicity is a potential complication of IA carboplatin therapy that can be mitigated with concurrent thiosulfate infusion [29].

The case against IA drugs for GBM treatment

Track record of partial successes

Over 2000 patients have been treated with IA chemotherapy, mostly in Phase I and II trials. Unfortunately, nitrosoureas and cisplatin are the only IA drugs that have been tested in Phase III trials and their failure to significantly improve survival has stymied further clinical research. However, proper case selection, safer drugs, and better drug delivery protocols could improve outcomes [29].

Biological hurdles to IA chemotherapy for GBM

Examination of GBM tissue reveals that certain regions of the tumor are hypo-perfused while others are highly vascular. This vascular heterogeneity within the tumor microenvironment is a major hurdle to effective IA drug delivery. Ongoing research within this arena promises to improve drug delivery protocols and drug selection [30].

Lack of reliable pharmacokinetic models

Many models of IA delivery are overly simplified and ignore background blood flow (Fig. 1) [6]. The relevance of these simplistic models is further challenged by the evolution of nanotechnologies where particles are larger and hydrodynamic forces are considerably greater (Fig. 2). Hydrodynamic models of drug delivery are being developed and they have been tested in computer simulations and in vitro [31].

Inconsistent goals of targeted drug delivery

The primary goal of IA drug delivery is to selectively eradicate neoplastic tissue and, ultimately, to extend life. However, this ideal goal is often difficult to achieve. Without a clear improvement in survival, IA chemotherapy is often evaluated by surrogate end points such as a reduction of tumor size, suppression of tumor metabolism, or safe delivery of drugs. Such differences in therapeutic endpoints make it difficult to compare the results of clinical trials.

Effect of streaming

Streaming results in the mal-distribution of drugs when the infusion rate is less than 20 % of the background blood

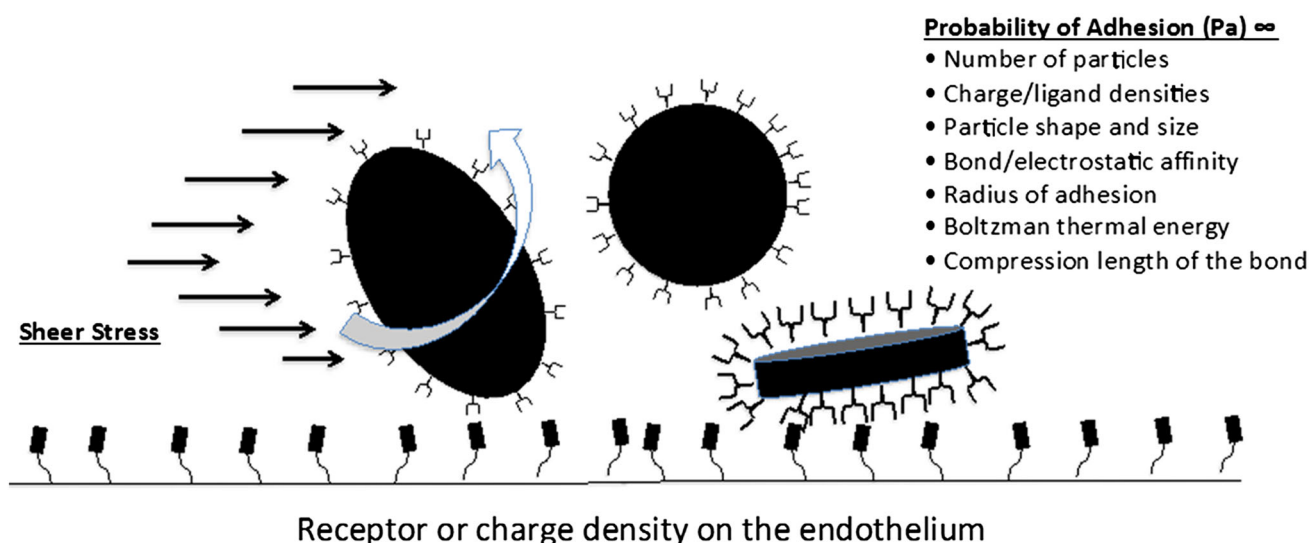


Fig. 2 Nanoparticle-endothelial interaction. The retention of nanoparticles and drugs by vascular endothelium is determined by two forces: (1) the shear stress due to flow and (2) additional forces affecting the probability of adhesion (P_a). Simulation studies show that discoid particle uptake is relatively size-independent. Nano-spheres and nano-rods have a biphasic effect; initially, increasing size

increases the P_a but simultaneous hydrodynamic stress counteracts this. Nano-spheres at higher shear stress demonstrate an axial flow pattern that decreases the P_a while nano-rods that display a tumbling movement have a higher P_a . Such hydrodynamic complexities have a profound effect on IA drug delivery. See [31] and [33] for additional details

flow. It has been invoked to explain both treatment failures and neurotoxicity. Streaming can be decreased by injecting drugs as pulses, at rates exceeding 20 % of the background blood flow rate, injecting drugs during diastole, and by injecting through catheters with side port rather than tip exits. Nonetheless, the role of streaming is controversial and has been disputed [32].

Safety concerns

IA drug delivery carries a number of risks, some of which are unique to this delivery strategy. These may include: (1) complications related to catheter placement and vascular access, (2) local reactions to IA drugs such as, ocular erythema with cis-platin, (3) neurological complications such as seizures or focal deficits, and (4) systemic effects of chemotherapy (infections, marrow suppression etc.).

Methods to investigate the kinetics of IA drugs

Conventional approaches

The conventional methods of determining drug uptake such as brain to plasma partition ratio, in situ perfusion, brain uptake index, and autoradiography usually provide snap shot measurements of tissue uptake. Alternately, microdialysis, PET, and MRI provide real-time data. Micro-

dialysis of lipid soluble compounds is challenging due to the difficulties encountered during extraction of said compounds. Similarly, PET and MR imaging are logistically demanding. In clinical trials, the effectiveness of IA chemotherapy is often judged by concentrations of the drug in the CSF. Incidentally, CSF drug concentration measurements are not reliable as they are both a function of drug uptake by the brain and secretion by the choroid plexus.

Novel optical approaches

In contrast to the conventional approaches for investigating IA delivery kinetics, novel optical tools offer tremendous advantages. Principally, they enable simultaneous measurement of blood flow and optical tracer and drug concentrations in a sub-second time domain [8, 27]. Optical techniques such as diffuse reflectance spectroscopy can provide rapid, site specific and tissue non-destructive tissue concentration measurements for certain drugs. These methods are cost-effective, relatively simple to execute, and do not carry the hazards of radiation and magnetic fields that conventional imaging methods often do. However, optical methods can only be applied to certain drugs. The use of tracers such as dyes and quantum dots that have a narrow light absorption spectrum and high quantum yield, promise to greatly advance pre-clinical research in this field [26].

Complex pharmacokinetics of IA drugs

Basic model of IA drug delivery

The significance of the Dedrick model lies in defining clearly when IA drug delivery really works. As described in Fig. 1, if the advantage of IA regional drug delivery (Rd) is defined as $(C_1/C_2)_{IA}/(C_1/C_2)_{IV}$ then Rd can be represented as follows: $Rd = 1 + CL_{TB}/[Q \times (1 - E)]$. C_1 and C_2 are concentrations in the brain and rest of the body, respectively. CL_{TB} is the total body clearance of the drug, Q is the regional blood flow, and E is the fraction of drug extracted in the first pass through the cerebral circulation.

This basic model reveals that IA drugs work when the regional blood flow (Q) is low, when extraction (E) is high, and when systemic clearance (CL_{TB}) is high. This model has several limitations; it assumes uniform mixing of drug in the arterial blood, it ignores streaming and hydrodynamic factors that affect drug delivery, and it assumes no efflux of drugs [6].

Computational fluid dynamic models of regional drug delivery

New models of drug delivery use human magnetic resonance imaging data to acquire arterial dimensions and flow profiles. Such models assume Newtonian properties of blood. A parabolic wave front presents the nanoparticles to the vascular endothelium. The probability of adhesion of a nanoparticle in this model is determined by several factors as shown in Fig. 2. Such models have been tested in vitro and can predict local deposition of nanoparticles under different flow conditions [31]. Other models reveal how the shape and volume of the particles affect the probability of adhesion [33].

Recent studies on IA GBM treatment

Table 1 summarizes important clinical studies that utilized IA drug delivery for the treatment of GBM and other brain tumors in the last few years [34–43]. The earlier studies have been previously reviewed [44]. Recent studies show noticeable shifts in clinical practice including the use of super-selective drug delivery and the use of less neurotoxic drugs [29, 45]. Interestingly, many investigators continue to use mannitol in an attempt to disrupt the blood brain barrier (BBB), despite reported complications with its use [46] and known variability in the degree of BBB disruption achieved [47]. In experienced hands BBB disruption seems

to be safe [48]. Yet others have avoided routine osmotic disruption while acknowledging its capacity for increasing tumor penetration by chemotherapeutic drugs [37]. Recent studies with IA bevacizumab using concurrent hyperosmotic disruption show that such techniques can be well-tolerated. On the other hand, disruption of the BBB might be more relevant to the delivery of larger therapeutic molecules than to the delivery of smaller (<400 Daltons) ones. Use of modern micro-catheter techniques to focally deliver osmotic agents to disrupt the BBB could improve the safety of the method. Controlled disruption of the blood tumor barrier with focused ultrasound is another strategy that may improve IA delivery of large molecular weight agents.

Also notable is a recent report by Riina et al. that describes the use of balloon occlusion methods to localize bevacizumab to posterior fossa tumors [49]. Such an approach utilizing flow reduction in conjunction with mechanical localization resonates well with pre-clinical efforts to improve IA drug delivery by transient flow arrest [50]. It is also consistent with the clinical observations of Chow et al. who show that tumors with low blood flow respond better to IA chemotherapy [35]. It is clear that reduction of blood flow during IA procedures is technically feasible and that it enhances drug delivery and could augment therapeutic effects. Flow reduction appears to be a reasonable alternative to the strategy of increasing IA drug doses in proportion to arterial flow [38].

Evolutionary advances in IA chemotherapy for GBMs

Catheter technology

Catheter-related complications occur in under 2–3 % of IA procedures [51]. Transient vasospasm and neurological symptoms are often seen but the incidence seems to have declined over the years. Single or double balloon catheters have been designed to facilitate drug delivery by isolating proximal as well as distal arterial irrigations to minimize local complications [25, 49, 52].

Patient selection

As experience increases and new biomarkers emerge, more nuanced patient selection should occur. For example, MGMT gene expression may be used as an indicator for IA temozolamide treatment [53, 54]. Similarly, highly vascular GBMs might be more responsive to bevacizumab than less vascular GBMs.

Table 1 Recent publications describing the use of IA chemotherapy for brain tumors

Author and year	Drug delivery	Patient profile	Response (total and % responders)	Complications
Fortin (2014) [37]	IA Carboplatin and Melphalan infusions	Recurrent GBM (n = 51)	3 complete response, 22 partial response, 14 stable disease, 12 progressions of tumor.	Hematological complications were manageable
Jeon (2012) [42]	SSIA infusion of Bevacizumab after IA mannitol	Recurrent GBM (n = 18)	Stable disease 11/18; partial response 5/18; progression of disease 1/18; and mixed response 1/18	Well-tolerated
Shin (2012) [41]	SSIA infusion of Bevacizumab Temazolamide or Cetuximab after IA mannitol	Recurrent GBM (n = 3)	All three intervention resulted in decrease in tumor size at 1 month.	Well-tolerated
Boockvar (2011) [34]	SSIA infusion of Bevacizumab dose-escalation to 15 mg.kg ⁻¹ (IC and IV) after IA mannitol	Recurrent GBM (n = 30)	Group 1 patients no previous exposure, had 34.7 %; while Group 2 patients with previous IV bevacizumab exposure had a corresponding 15.2 % median volume reduction	IA bevacizumab with concurrent BBB disruption is well-tolerated.
Imbesi (2006) [39]	Nimustine (ACNU) 80-100 mg/m ² every 5-8 weeks for 2–24 cycles	Newly diagnosed GBM, (n = 33) IA versus IV ACNU	Time to progression increased with IA (n = 17) but no improvement in overall survival.	Well-tolerated
Hall (2006) [43]	IA Carboplatin or methotrexate with IV Cytosan and Etoposide	Recurrent pontine GBM (n = 8) different Rx combinations	Survival better compared to historical controls. Multi drugs and radiation Rx and small sample size over 14 years makes evaluation difficult.	Neutropenia; thrombocytopenia; infections; neurological disorientation; hearing loss
Fortin (2005) [36]	IA Carboplatin (or IA Methotrexate for CNS lymphomas) after IA mannitol with IV Cyclophosphamide and Etoposide	20/72 GBM and other tumors	Median survival times from treatment (MST) for GBM was 9.1 months. MST from diagnosis was 32.2 months for GBM.	Seizures in 5 %; orbital myositis 2/72; hematological complications 4/72
Qureshi (2001) [40]	Carboplatin + Cereport	12/24 GBM and other tumors	Reduction of tumor size in 30 %; Increase in tumor size in 30 %	Seizures 7/23; transient neurological complications 5/24; stroke 1/23
Gobin (2001) [38]	Selective when possible. Carboplatin + Cereport	71/113 GBM and other tumors	Fractionation of doses based on vascular territory decreased complication rates.	Seizures in 15 % of procedures; permanent complication.in 3/113
Chow (2000) [35]	Carboplatin + Cereport 2–8 monthly cycles	Recurrent GBM (n = 46)	Tumor volume and hyper-vascularity were adverse predictors of outcome	Not stated

SSIA superselective intraarterial infusions

Drug selection

Due to their high lipid solubility, short biological half-life, and rapid onset of action, nitrogen mustards (BCNU, ACNU, HeCNU) were intensely investigated for the treatment of brain tumors. These compounds were associated with significant neurological complications. Recent studies have therefore focused on drugs that are safer for IA delivery, such as carboplatin and melphalan.

These drugs have reduced local toxicity and their systemic complications seem to be manageable [36]. No significant neurological toxicities have been reported with IA bevacizumab although it has yet proven to be safer than conventional chemotherapy [37]. While bevacizumab and temozolamide are both promising investigational agents for IA treatment of GBM, the potential risks are significant and have yet to be fully appraised in large studies.

Table 2 Ongoing clinical trials with IA drugs for GBM treatment in the National Trial registry

Trail #	Name	Drugs	Tumor type	Location	Status
NCT 01811498	Repeated super-selective IA cerebral infusion of bevacizumab for newly diagnosed GBM	Bevacizumab	GBM	Hofstra-NSLIJ School of Medicine	Active
NCT 01238237	Super-selective IA cerebral infusion of Cetuximab for the Treatment of Recurrent GBM and Anaplastic Astrocytoma	Cetuximab	GBM Anaplastic Astrocytoma	Weill Medical college of Cornell University	Active
NCT 01180816	Super-selective is cerebral infusion of temozolomide (temodar) for treatment of newly diagnosed GBM and AA	Temozolomide	GBM Anaplastic Astrocytoma	Hofstra-NSLIJ School of Medicine	Active
NCT 01269853	Repeated super-selective IA cerebral infusion of bevacizumab for relapsed GBM and AA	Bevacizumab	GBM Anaplastic Astrocytoma	Hofstra-NSLIJ School of Medicine	Active
NCT 00968240	Super-selective IA intracranial infusion of bevacizumab	Bevacizumab	GBM Anaplastic Astrocytoma (AA)	Weill Medical college of Cornell University	Unknown
NCT 00075387	Treating patients with high-grade glioma with IA carboplatin-based chemotherapy, with or without sodium thiosulfate	Carboplatin Cyclophosphamide Etoposide Sodium thiosulfate	Brain and CNS Tumors	OHSU Knight Cancer Institute	Active
NCT 01083966	IA cerebral infusion of avastin for vestibular schwannoma (Acoustic Neuroma)	Bevacizumab (Avastin)	Vestibular Schwannoma	Weill Medical college of Cornell University	Unknown
NCT 00253721	Melphalan with BBBD in treating patients with brain malignancies	Melphalan	Brain and Central Nervous System Tumors Lymphoma Metastatic Cancer	OHSU Knight Cancer Institute	Suspended
NCT 01386710	Repeated super selective IA cerebral infusion of bevacizumab plus carboplatin for treatment of relapsed/refractory GBM and anaplastic astrocytoma	Bevacizumab and Carboplatin	GBM Anaplastic Astrocytoma	Weill Medical college of Cornell University	Active
NCT 00983398	Melphalan, carboplatin, and sodium thiosulfate for patients with central nervous system (CNS) embryonal or germ cell tumors	Melphalan Carboplatin Sodium thiosulfate Filgrastim Pegfilgrastim	Central Nervous System Embryonal Tumor Germ Cell Tumors	OHSU Knight Cancer Institute	Active
NCT 02285959	Super-selective IA intracranial infusion of bevacizumab (Avastin) for GBM	Bevacizumab	GBM	Capital Institute for Neuroscience	Active
NCT 01884740	Phase I/II trial of super-selective IA infusion of erbitux and bevacizumab for treatment of relapsed/refractory intracranial glioma in patients under 22 years of age	SIACI of Erbitux (200 mg/m ²) and Bevacizumab (15 mg/kg)	GBM and other tumors	Weill Medical college of Cornell University	Active

Systemic rescue

The concurrent administration of drugs that can neutralize recirculating chemotherapeutics promises to reduce the systemic toxicity of a number of IA agents [29]. For example, sodium thiosulfate is currently being evaluated as an agent that may decrease the otological toxicity of certain drugs (Table 2).

New paradigms in IA chemotherapy

Relatively non-toxic biological interventions

The development of anti-angiogenic compounds such as the VEGF-A antagonist, bevacizumab, have considerably increased the safety of IA drug delivery, however, there is no evidence that this has impacted survival. As noted in

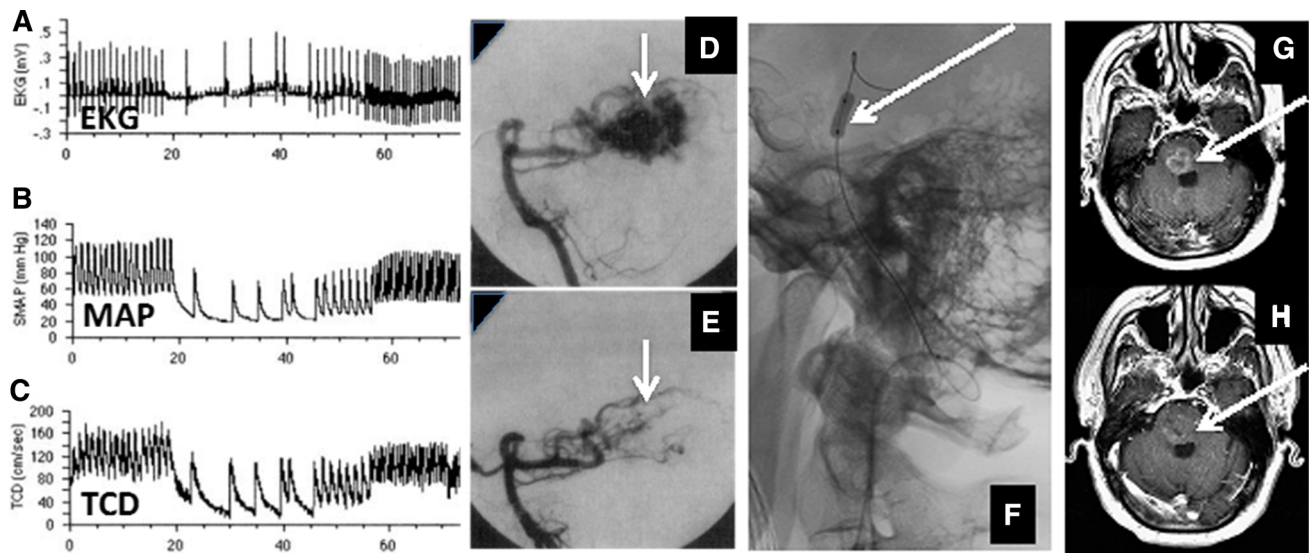


Fig. 3 IA delivery in clinical practice. Translation of IA-TCH assisted delivery to the human brain has been achieved by both temporary cardiac arrest with adenosine and by balloon occlusion during endovascular procedures. The hemodynamic changes in EKG, mean arterial pressure (MAP), and transcranial Doppler (TCD) flow velocity (A–C) indicate that TCH is achieved by administration of

adenosine during embolization of a high flow cerebral arteriovenous malformation (D–E) (see [55]). Similarly, temporary balloon occlusion within the posterior circulation (F) has been used to effect TCH and targeted IA drug delivery to the brainstem glioma seen on axial T1-weighted MRI (G–H) (see [49])

Table 2, clinical trials are underway using blood brain barrier disruption with mannitol and IA bevacizumab to determine its impact on survival. Although tumor phenotype or genotype may predict drug responsiveness, there is still much to be learned. Tumor delivery of genomic drugs for GBM is proving difficult in clinical trials as well. While these drugs are highly tumor specific and generally lack systemic side effects, their use as an alternative to conventional chemotherapy is a matter of future investigation [53].

Flow arrest delivery of drugs

Reduction of blood flow radically alters the pharmacokinetics of IA drugs [20]. Guided by the principle that brain tissue can safely tolerate up to three minutes of ischemia. Flow arrest has been widely used during neurovascular surgery and during neuro-radiological treatments of high flow lesions. Two methods of achieving flow arrest are by systemic arrest (Fig. 3) and by local balloon occlusion [49, 55]. The benefits of transient flow (<1 min) arrest during IA drug delivery include: (1) better targeting of drugs to the tumor site, (2) achieving higher cerebral arterial concentrations, (3) achieving more consistent concentrations in the arterial distribution, (4) increasing transit time, (5) decreasing shear stress on drug molecules and carriers, and (6) avoiding binding with serum proteins and blood cells.

Drug formulations optimized for IA delivery

Due to high resting brain tissue blood flow, the impact of any IA delivery strategy on GBM will be minimal unless rapid extraction during the drug's first pass through the cerebral circulation occurs [56]. A number of strategies have been proposed to improve regional extraction after IA injections. The use of small molecule chemotherapeutics (<400 Daltons) that can diffuse across the BBB, such as Temozolamide, has been effective but treatment response and safety in larger patient samples remains unproven [41]. Increasing drug lipid solubility by adding methyl groups, replacing polar groups, or by adding halogenated alkane chains (ie. tributyl chlorambucil) also enhances brain uptake [57]. Identifying tumor specific receptors and transporters that are overexpressed in GBM allows the development of targeted immuno-conjugated drugs. Anti-transferrin receptor anti-body, OX-26, was shown to be an effective carrier for drug delivery across the BBB. Compounds such as OX26-methotrexate [58] or OX26-daunorubicin were developed but not tested for IA delivery [59]. Likewise, the use of cationic drugs and liposomes, cell penetrating peptides, cationic albumin or other cationic delivery platforms can increase tumor selective drug delivery due to the over-expression of anionic charges on tumor cell membranes [60].

Rationalizing the role of IA drugs for GBM treatment

Given the biological variability and complexity of GBMs, the current “one-size-fits-all” approach is unlikely to be an effective treatment strategy. Transient improvement as evidenced by GBM regression can be readily achieved with current IA treatments. In order to affect the duration of survival, IA drug selection needs to be based on the genotypic and phenotypic characteristics of the tumor. However, given the lack of a single target, even a genomic approach will have to be flexible, requiring several drugs and delivery methods to achieve sustained remission. As the search for greater tumor selective drugs and carriers continues, the unique characteristics of IA delivery will enable it to play a significant role in future GBM treatments.

Conclusions

The history of IA drug delivery to the brain when viewed over several decades reveals several missteps. The complexity of IA delivery with regards to hydrodynamics was not universally appreciated both in preclinical research and during clinical trials. The lessons from these past failures should guide us to new paradigms in IA drug delivery. Given the complexity of GBM, its treatment will require an individualized approach based on patient and tumor profiling. IA drug delivery could play a significant role in delivering novel pharmaceuticals including viral vectors, gene therapy agents, and emerging genomic drugs. These IA treatments may be curative, adjunctive, or palliative as needed. Improved patient and drug selection, advanced drug delivery protocols, and fast, high resolution imaging technology will enable IA therapies to play a significant role in GBM management in the future.

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