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Review Article

Elacridar as Adjuvant with Anticancer Drugs for Brain Tumors - Delivery, Safety, Efficacy and Toxicity

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Abstract

Elacridar (N-(4-(2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl)phenyl)-9,10-dihydro-5-methoxy- 9-oxo-4-acridine carboxamide) is a potent inhibitor of P-glycoprotein (PgP) and breast cancer resistance protein (BCRP). It has been investigated as modulator of efflux transporters, which are shown to be very active in various cancers. The PgP is over expressed on tumor cells and plays a key role cancer resistance to anti-cancer drugs, specifically chemotherapeutics that are thrown out of the tumor cells making them ineffective over time. Researchers are investigating whether inhibiting the PgP may shut down efflux pumps, particularly on cancer cells, thus facilitating entry of drug in cancer cells leading to selective damage to cancer cells rather than normal cells. Elacridar, one such PgP pump inhibitor holds promise as an adjuvant in cancer therapy since clinical trials are underway to test its safety and efficacy in humans. This short review will address very specifically the prospect of using elacridar as adjuvant with anticancer drugs to brain tumors. Since Blood Brain Barrier (BBB) and Brain Tumor Barrier (BTB) pose hurdles to anticancer drug delivery and their reverse transport possibly due to efflux transport proteins on BTB. This review elucidates ongoing research on elacridar delivery across BBB/BTB, and the drug's safety, efficacy and toxicity. We further seek to present evidence that PgP modulators along with BTB permeabilizing agents such as potassium channel activators can be clinically developed as adjuvants with anticancer drugs.

Keywords: *Elacridar; Blood-Brain Barrier (BBB); Blood-Tumor Barrier (BTB); Calcium-Dependent Potassium Channels (BKCa); BTB Permeability; Anticancer Drugs; PgP Efflux Pump*

Abbreviations

BBB: Blood-Brain Barrier; BTB: Blood-Tumor Barrier; BBKCa: Large Conductance Calcium Activated Potassium Channels; PgP: P-glycoprotein, MRI: Magnetic Resonance Imaging

Introduction

The Central Brain Tumor Registry (USA) has estimated global incidence of primary brain tumors to be about 256,213 in 2012, which increased to 26,070 in 2017. Furthermore, the incidence of secondary (metastatic) brain tumors will be nearly 10-fold higher than the primary brain tumors. Majority of brain tumor patients have very short life expectancy (1 year) even after receiving brain radiation and/or surgical resection [1]. Glioma, specifically glioblastoma multiforme (GBM) is a deadly form of brain tumor and its management is extremely difficult because of heterogeneity, chemo resistance followed by inadequate delivery of anticancer drugs due to P-glycoprotein (PgP) transport pumps expression on tumor cells as well as in blood brain tumor barrier (BTB). BBB is a physical and biological barrier consisting of endothelial cells (ECs), tight junction proteins (TJp) connecting the ECs, glial, pericytes, and astrocytic foot processes allows essential nutrients, such as glucose and amino acids through receptor mediated endocytosis to maintain vital brain functions. The nutrients and most anticancer drugs (except lipohilic drug entities) that are generally water soluble (hydrophilic) require carrier-mediated transport, receptor-mediated transcytosis and absorptive-mediated transcytosis to enter the brain cells (Figure 1). Studies have shown that BBB obstructs delivery of over 98% of CNS drugs [2]. Hence, various methods are employed to get around the physiological barrier posed by the blood-brain tumor barrier (BTB), including inhibiting PgP proteins.

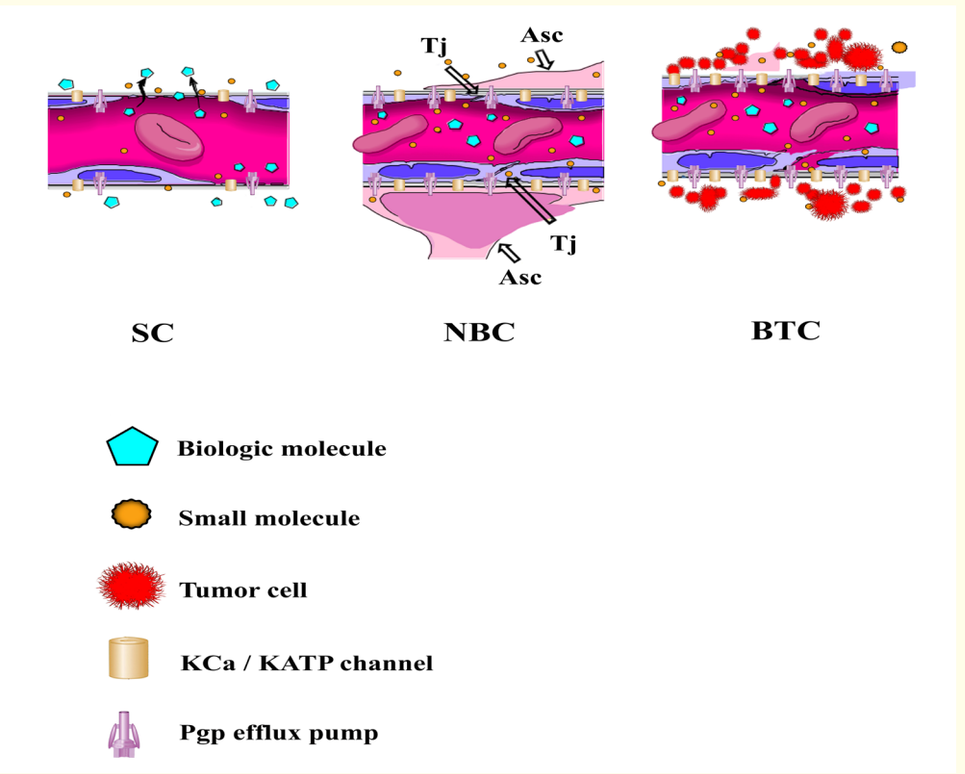

Figure 1: *Cross sections of major constituents of normal brain capillary (NBC) and brain tumor capillary (BTC) compared with systemic blood capillary (SC).*

BBB/BTB and Drug Delivery

Most anti-cancer drugs generally fail to cross the BTB in sufficient quantities. The invading glioma cells in the tumor edges are ideal targets for anti-cancer agents due to the presence of unique gene/protein expression pattern [3]. Several promising anticancer drugs are effective against cancers outside the brain but fail against brain tumors in clinical trials, in part due to poor BTB penetration. For instance, Gleevec (Novartis, USA) is ineffective against brain tumors since it hardly crosses BTB, but has demonstrated efficacy in patients with chronic myelogenous leukemia and gastrointestinal stromal tumor [4]. Similarly, invading edges of brain tumor are not clearly detected by imaging agents as the agents do not penetrate intact BTB easily [5,6]. In order to develop methods for increasing delivery of new wave of targeted drug entities referred as nanomedicines to brain tumor, we need to have precise understanding of the basics of BBB and BTB biology and their permeability and efflux regulation.

Glioma treatment

Conventional diagnosis and treatment are not successful in reducing glioma patient mortality. Further, low penetration of anticancer drugs across BTB makes the treatment very difficult. Complete excision of diffused gliomas is nearly impossible partly due to low detection by CT and MRI as the imaging agents do not fully penetrate the intact BBB at the tumor edges. In order to address this issue, we biochemically modulated BTB to increase permeability to drug and imaging agents, selectively to brain tumors in experimental glioma models [5].

Elacridar- Research and Development

Elacridar development as a clinical drug candidate has been well reviewed elsewhere [7], which documents drug transporter families, including PgP and BCAR. There is extensive discussion on ADME, PK-PD and translational aspect in drug discovery and development of these classes of PgP inhibitors.

Many studies have shown that elacridar is a potent inhibitor of PgP and breast cancer resistance proteins (BCRP) [8,9] and have described elacridar as a multidrug resistance-reversal drug that restored sensitivity of multidrug-resistant tumors to doxorubicin. A recent animal study reported brain distribution and bioavailability of elacridar after different routes of administration [10]. It was shown with different routes of elacridar administration that the brain-to-plasma partition coefficient of elacridar increased as plasma exposure

increased, suggesting saturation of efflux transporters at BBB. The role of P-gP and BCRP in limiting the distribution of substrate drugs across BBB has been examined using elacridar as a dual inhibitor of both P-gP and BCRP. Drugs such as morphine and amprenavir were shown to be at higher levels in brain after coadministration with Elacridar [11,12]. Furthermore, elacridar increased brain distribution of several tyrosine kinase inhibitors (TKIs) including imatinib, dasatinib, gefitinib, sorafenib, and sunitinib [13-19]. Studies in mice have shown that P-gP and BCRP at the BBB limits brain penetration of sunitinib and its active metabolite, however, oral administration of elacridar improved brain penetration of sunitinib [19,20].

Furthermore, preclinical studies have shown that paclitaxel penetration was improved by coadministration of elacridar or tariquidar in brain tumor [21]. These studies further advances the claim that elacridar can be clinically useful in delivering and retention of anticancer drugs across BTB for better control of brain tumors.

Chronic administration of elacridar poses many hurdles, including formulation due to its unfavorable physicochemical properties. Elacridar is extremely lipophilic making it insoluble in water and poorly soluble in most other aqueous solvents [22]. Preclinical studies have shown the variability in plasma and tissue concentrations. Even clinical trials found inter-subject variability after oral dosing [23]. With respect to brain tumors, its availability in brain tumors and its ability to shut down PgP is the key to its development as adjuvant with anticancer drugs. In this regard, elacridar brain penetration in mice was dose-dependent and affected by the P-gP and BCRP at the BBB as shown by positron emission tomographic imaging [24,25]. Therefore, its versatile clinical candidacy as adjuvant in brain tumor treatment is hampered by its unpredictable adsorption and elimination as shown in both preclinical models and clinical applications. Furthermore, careful elucidation of elacridar BTB penetration mechanism and its distribution in brain tumors when coadministered with anticancer drugs, including monoclonal antibodies (MAbs) and nanomedicines is critical.

In addition, co-administration of elacridar with anticancer drugs that are substrates for P-gP and BCRP might improve its BTB penetration for better efficacy. As the brain tumor is heterogeneous with uneven BTB permeability [26] across the tumor spread (metastatic brain tumors), it may throw an uncertain pharmacokinetic challenge with uneven spread of target tumor cells. Nevertheless, safe and efficacious elacridar is what we need at the moment if we need to control brain tumor growth by targeting tumor cells that express BCRP and PgP. Major concern in glioma therapy is tumor resistance to chemotherapy, partly due to their insufficient delivery and lack of retention in tumor cells [27]. Major interest with this strategy will be the efficient use of targeted therapies such as Herceptin, TRKIs and emerging nanomedicines that have shown promise in peripheral cancers while failing in controlling brain tumors due to reasons discussed above. Added advantage of improved delivery and longer retention of anticancer therapies is the potential use of low doses and milder neuro/peripheral toxicity.

Hence, drug delivery strategies must involve understanding of these BBB/BTB constituents and their interaction with tumor cells, as well. The BTB around the tumor allow very little while mostly throwing out anticancer drugs by efflux mechanism, including small molecules and therapeutic monoclonal antibodies (MAbs) back to the circulation. Researchers are working on variety of carriers such as nanomedicines and nanospheres that might penetrate BTB. Such nanomedicines armed with targeted drugs are expected to supplement conventional chemotherapy and radiotherapy. Development of nanomedicines for treatment of cancer is defined by their penetration across BTB vasculature that surrounds the tumor. Further nanomedicines' retention in tumor cells without being expelled by multi drug resistant P-glycoprotein (PgP) efflux system (Figure 2) determines their efficacy. Recent success in controlling cancer by targeting tumor and tumor blood vessel-specific marker(s) has renewed interest in development of more precise and less toxic anticancer drugs [28]. More research is required to investigate how to increase tumor-specific drug delivery, improve bioavailability of cytotoxic agents to neoplasms, and at the same time minimize toxicity to normal tissues. Due to advances in personalized therapy, more targeted drugs like cetuximab (Erbitux®), and therapeutic MAbs like Herceptin, ABX-EGF, EMD 720000 and h-R3 are shown to be effective in treating cancers outside of brain. However, they fail to control brain tumors because they fail to cross BTB in adequate quantity. These targeted anticancer drugs are ineffective to block epidermal growth factor receptors (EGFR), which are often amplified and mutated in human gliomas. Despite evidence of 'leaky' tumor centre, the capillaries surrounding the proliferating glioma as well as the brain tissue surrounding the tumor are nearly as impermeable as the BBB [29]. It is incorrect to assume that the disrupted BBB facilitates drug delivery to gliomas because diffuse tumor-cell invasion is a hallmark of even low-grade gliomas. Hence, understanding the biochemical regulation of the BBB in its normal and abnormal state (BTB) is of great importance as efforts continue to deliver therapeutic compounds to brain tumors.

PgP efflux inhibition -Opportunity and Scientific Knowledge Gap

Drug delivery research has focused on several innovative methods (Figure 2), including nanoparticles [30], microparticles as carriers of anticancer agents, PEG technology, encapsulating anticancer drugs in liposomes, and MAbs for the delivery of anticancer payloads [31]. One area of research has focused on brain microvascular endothelial cells (BMVEC) and pericytes, which are major components of the neurovascular unit. However, many issues that are related to BMVEC are still not well understood, including gene and transporter protein profiling in normal brain and brain tumor capillary endothelial cells [32]. Research in this field is hampered due to the complexities that are involved in isolating pure BMVEC devoid of pericytes, neurons and tumor cell populations, as well as due to differences between and within brain tumors. For instance, significant differences were found between normal human brain and brain tumor capillaries, including differential expression of large conductance calcium activated potassium (BBKCa) channels [33,34] and ATP-sensitive potassium (KATP) channels [35]. Recent progress in the molecular targeting of tumor-specific antigens with specific agents, however, can be exploited by identifying additional novel targets for modulating BTB permeability. Studies in our laboratory are investigating whether there are any significant differences in the expression levels of certain genes and proteins between normal and brain tumor capillary endothelial cells.

The challenge posed by metastatic brain tumors is more complex. The BTB capillaries surrounding "tiny islets" of metastatic tumors have intact BBB to prevent adequate delivery of most anticancer drugs. Recent advances in biologics as targeted and safer anticancer drugs has added urgency to solve the drug delivery problem to metastatic breast cancer that typically arise due to inefficient treatment

of systemic breast cancers [36,37]. For e.g. Herceptin targeting epidermal growth factor receptor -2 (EGFR-2/ Her-2 neu) in brain tumors are mostly water soluble and big, hampering their delivery to brain tumors. Her-2 -positive breast cancer cells are sensitive to Herceptin while metastatic cancer cells in brain are usually non-responsive to the drug. Most studies indicate that this ineffectiveness of Herceptin to target cancer cells in the brain is due to inadequate delivery across the BTB. In this regard, our work showed that delivery of Herceptin across the BTB in rat glioma models is increased by activating BKCa and KATP channels. We biochemically opened the BTB with BKCa and KATP channel agonists, NS1619 and Minoxidil sulfate, respectively to deliver Herceptin to metastatic breast cancer in brain [33-35].

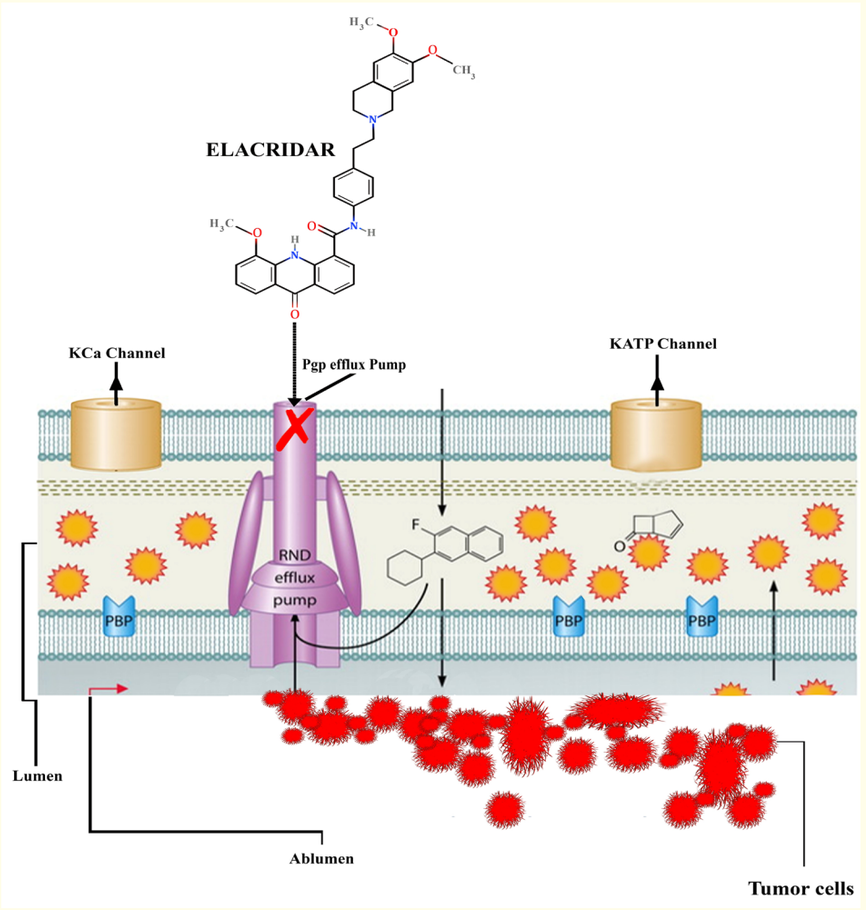

Figure 2: *Ways to by-pass the BBB/ BTB to deliver anticancer drugs to tumor cells.*

Functional potassium channels on BTB

Several researchers including us have shown the importance of ion channels on BTB permeability regulation and their role in anti-cancer drug delivery [33-36,38]. We recently reviewed the role of BTB- associated ion channels in increasing the BTB permeability for delivering therapeutic, prophylactic and diagnostic agents to brain tumors [39]. We showed that BTB can be modulated to increase delivery of combination of drugs: trastuzumab with temozolomide in glioma models [35]. The underlying mechanism is not completely understood, but it involves formation of brain vascular endothelial transcytotic vesicles to facilitate transport of the drugs as demonstrated by us earlier. Recently, we described the role of BKCa and KATP channels in brain tumor cell growth. We also showed that modulators of BKCa and KATP channels may be utilized to enhance the delivery of anti-neoplastic drugs and imaging agents to glioma cells in brain tumor models [39].

The KATP channels couple intracellular metabolic changes to the electrical activity of the plasma membrane to regulate cerebral vascular tone and to control relaxation of cerebral vessels in response to diverse stimuli, including vasomodulators, in both normal and disease state. These channels, are composed of pore forming (inward-rectifying Kir 6.1 or 6.2) and sulfonylurea receptor subunits [40]. These channels are widely distributed in a variety of tissues and cell types including human aorta and brain microvascular endothelial cells. Activation of these channels produces hyperpolarization, relaxation and dilatation of cerebral arteries in humans. Sulfonylurea analogs, minoxidil sulfate, pinacidil, cromakalim, and diazoxide, stimulate KATP channels. These channels are over-expressed on both glioma cells and tumor microvessels. In human gliomas, we showed differential expression of KATP channels at both post-transcriptional (mRNA) and post-translational (protein) levels. We also showed the co-localization of KATP channels in normal and tumor brain microcapillary endothelium (using endothelial cell-specific von Willebrand Factor antibody) and tumor cells. These observations are crucial in that over-expressed KATP channels in the tumor, capillary endothelium and/or tumor cells could be potential targets for opening BTB with known and novel KATP channel agonists. We showed that MS-mediated biochemical modulation significantly increases BTB permeability of temozolomide (TMZ), selectively to brain tumor and brain tissue surrounding tumor, which represents proliferating edge of tumor where the BTB may be intact [35]. KATP channel modulation does not require any modifications to the drug being delivered and

can deliver multiple drugs selectively to tumor, an important consideration as most glioma patients are treated with multiple drug combinations. The duration of opening of BTB can be tightly controlled and the effect can be achieved with a simple i.v. infusion or "Trojan horse" approaches [41] or employing PgP inhibitors [42]. Increasing evidence suggests that brain tumor vascular endothelial cells overexpress PgP transport proteins and ion channels, which play an important role in modulating endothelial cell functions including in BTB permeability regulation (Figure 2).

Drug Delivery to Gliomas and its microsatellites

In smaller aggregates of glioma cells, the disruption of BTB is less significant. Therefore, a smaller amount of drug reaches these "so-called" microsatellites allowing them to develop resistance, grow, develop neovasculature structures, and ultimately reach a clinically significant size. A number of studies investigated levels of chemotherapy agents in brain tissues including etoposide, cisplatin, vinorelbine, and mitoxantrone, and found higher levels at sites of larger tumors than in neighboring tissues [42]. Previous studies have achieved some success in drug delivery, but the toxicities are significant and insufficient drug retention due to rapid efflux of drugs via PgP complex. PgP is expressed in high levels both in cultured brain capillary ECs and in intact brain capillaries [43]. It is localized at the luminal surface of the endothelium, and therefore is in the right location to restrict permeation of a variety of drugs into the brain [38,40]. Taxol (paclitaxel) and its derivatives are active against various cancers [44] but the therapeutic benefit of paclitaxel has been variable and low in brain tumors. This could be attributed to their limited entry into the brain and higher efflux by PgP [45]. The agents tested clinically to inhibit PgP include quinidine, cyclosporine, PSC-833 (valspodar) and GF120918 (elacridar) [46].

The activation of KATP channels by MS may selectively increase paclitaxel and cetuximab delivery while PgP inhibitor elacridar helps to retain paclitaxel longer in gliomas and induce tumor cell death. Preclinical translational studies are warranted to determine whether enhanced and selective delivery of anticancer drugs and prolonged retention in glioma cells due to PgP inhibition can be achieved. Paclitaxel and cetuximab that are effective against cancers outside the brain may be co-administered with MS and elacridar in human glioma mouse models. Such studies are pivotal in the design of future clinical studies aimed at promoting increased drug delivery and retention in human gliomas, and controlling tumor growth.

Challenges of Efflux Mechanism to Drug Delivery

Active efflux transporters at the BTB, such as multi drug resistant P-glycoprotein (PgP), which actively exports the drug from the brain to the blood, play a major role in restricting drug transport across the BTB. Drug delivery to gliomas presents a formidable clinical challenge because PgP limits the penetration and accumulation of chemotherapeutics in cancer cells (Figure 2). There is ample evidence for the presence and critical role of PgP in clinical resistance to chemotherapy in primary brain tumors [43]. Although taxol and many anticancer agents are highly lipophilic, they barely cross the BTB, largely due to active efflux by PgP [44,45]. The amount of drug that reaches at the tumor site depends on BTB permeability, which varies considerably among brain tumor patients [47]. Drug concentrations in brain tissue usually drop with increasing distance from tumor core, and thus the drug concentration is fairly low in the peripheral parts of the tumor where tumor cells infiltrate normal brain. In these areas, where tumor proliferation is most rapid, BTB is relatively intact. Novel approaches for effective delivery anticancer agents as nanomedicines should circumvent PgP mediated efflux to bypass BTB. Such nanomedicines provide neuro-oncologists precision anticancer agents for effective treatment of gliomas thereby increasing patient survival rates.

Glioma and Elacridar: Impact on Brain tumor patients

Generally, chemotherapy that does not pass intact BTB is of little value in treatment of gliomas. The significance of research investigating site-specific drug delivery to gliomas by biochemical modulation of BTB will be huge. The strategy to increase drug delivery and retention of drug in glioma by inhibiting PgP mediated efflux is also key in controlling tumor growth. Not only does this improve the bioavailability of drugs selectively in tumor cells thus reducing drug dosing but also would minimize toxicity in normal tissues. The increased delivery and retention of paclitaxel and cetuximab in the gliomas may affect several signaling molecules. Besides the known protein targets for these drugs, there may be additional biomolecules affected by such targeted therapies, which can be identified by MALDI-MS/TOF protein profiling studies. We hope such data will be useful in identifying sets of protein biomarkers that are predictive of early tumor response to targeted anticancer therapy.

Overall, chemotherapy has traditionally played only a salvage role for glioma when all other treatments have failed [48]. In contrast, research that specifically focuses on systemic options such as administration of paclitaxel and cetuximab with PgP inhibitor (elacridar) to block efflux pathways specific to brain and also on novel BTB modulation technique to increase drug delivery, will increase treatment options for glioma patients.

Gliomas strike children as well as adults; however, older individuals are at higher risk of developing brain tumors. It does not discriminate among genders and severely affects quality-of-life with debilitating neurological symptoms. Gliomas have been one of the most devastating cancers because they are highly difficult to treat. Furthermore, glioma patients die within 1 - 2 years of initial diagnosis costing human lives. Unlike systemic cancers, gliomas grow in the limited intracranial space by invading and destroying the normal brain cells. A glioma tumor is particularly damaging because it tends to quickly sprout and spread within the brain and develop in to a high grade glioblastoma multiforme (GBM), which has the worst prognosis.

Present status of Elacridar: Due to toxicity and differences in PgP expression and function in various cancers, the clinical trials to develop PgP inhibitor for reversing resistance to chemotherapy appear to have been stalled due to persisting toxicity profiles of anticancer drugs. However, PgP function and expression are also associated with physiological and pathophysiological conditions of Alzheimer's disease. It could become a new therapeutic target for treatment of Alzheimer's disease.

Nanotechnology combined with prolonged drug retention in Brain tumors

The application of nanotechnology using nanoparticles for increasing drug delivery across BBB has been recently reviewed by Zhang and coworkers [49]. Figure 2 summarizes the innovative ideas being studied in laboratories across the world to deliver nanomedicines and nanoparticles that carry payloads of nanoimaging molecules or targeted therapies for better BBB penetration in order efficiently detect and treat tumors. Nanoparticles have been developed that are able to carry therapeutics across the BBB [48]. Nanoparticle-tagged drugs have some advantages. They may be administered intracerebrally to release drugs in a sustained manner and prevent degradation when administered systemically. To improve drug targeting, some researchers have encapsulated doxorubicin in nanoparticles, which are readily taken up by the BBB/BTB endothelium. Such encapsulation may also prevent drug being effluxed by the endothelial efflux system. EL Amrawy and coworkers [30] have extensively reviewed on noninvasive treatment of glioblastoma and other brain tumors using several technologies and patent applications from 2010-15. Malatestat and coworkers [50] showed that chitosan nanoparticles can deliver a hypometabolizing synthetic opioid, D-Ala2- D-Leu5-enkephalin across BBB and release drugs in the brain. They concluded that intensive research efforts are necessary to develop novel CNS delivery systems that can be used in clinics. Few laboratories have developed nanomedicine techniques employing liposomal and polymeric nanoparticles to deliver drugs to brain tumors [51,52]. Biodegradable polymer-based nanoparticles and gold nanoparticles have shown greater promise for carrying drugs across the BTB to treat glioma [53]. Specifically, gold nanoparticles permeate BBB through endothelial cells [48]. Similarly, Jensen and coworkers [54] showed BBB penetration of RNA interference-based gold nanoparticles following systemic injection. These findings suggest that the nanoparticle-based delivery systems hold great promise in improving specific and efficient intracerebral delivery of anti-cancer drugs for the treatment of glioma [52,53,55]. Interestingly, nano particles are often integrated with techniques such as hyperthermia or a molecular "Trojan horse", discussed to improve delivery of anticancer drugs [52]. Nanospheres ranging in size from 1 - 100 nm, have shown better binding capacity for specific molecules, allowing varied surface modification and multivalent binding of targets. Hence, they have new applications in molecular imaging and nanomedicines [53,55-59]. A greater emphasis is given to build nanospheres with their payload- therapeutics or imaging agents or combination of both that can penetrate BTB and retained in tumor tissue without being ejected by efflux pumps [45]. Nanostructures of 100 nm diameter whose surface charge and flexibility may be modified to allow increased nanostructure biodistribution [59,60] could be developed for the above purpose. Such flexible nanospheres may be labeled with a radionuclide to develop molecular imaging probes using PET or SPECT. The two major strategies for labeling nuclides onto nanostructures depend on whether or not chelating agents are used. Few studies have shown the chelation free labeling methods by combining nanoparticles such as gold nanoparticles, carbon-based nanomaterials, and quantum dots [53,55-60], through a chelating agent, such as DOTA and NOTA. DOTA now has the FDA approval for human application. Recent article has reviewed chelating agent-mediated nanostructures such as gold nanostructures (colloidal gold nanoparticles (AuNPs) with biomolecules (e.g. DNA and peptides) and 64Cu-chelated AuNS that showed better penetration and accumulation in squamous cell carcinoma region.

Moreover, molecular targeting with anticancer drugs by themselves or tagged/encapsulated with nanostructures/nanospheres might allow good BTB penetration to reach tumor tissue (Figure 2). Several translational studies have shown that nanospheres tagged with anticancer drugs have overcome BTB problem but more clinical studies are needed to develop this strategy as a clinical tool.

Conclusion

Brain tumors, specifically gliomas are mutagenic cancers [61] requiring varied strategies to develop targeted drugs and how to deliver them specifically to cancer cells in the brain. Recent works on BBB and BTB permeability regulation have increased our understanding of molecular events and mechanisms that regulate permeability to various agents including therapeutic and imaging molecules. We are seeing an essential shift in brain tumor treatment. Brain tumor genomics and advent of personalized medicine have also contributed to an improved brain tumor treatment strategies. Despite ground breaking research on gliomas, mortality rate of GBM is still stubbornly high. Timely therapeutic intervention with highly targeted drug delivery by enhancing and retaining anticancer drugs might improve brain tumor patients' survival rate. These novel technologies might block brain tumor growth and its spread. Without doubt, discovery of nanomedicines, nanospheres that carry a payload of anticancer drugs combined with radio therapies are expected to improve the diagnoses and prognoses of brain tumors in the present decade. Once we know how BBB/BTB function, researchers will have a better tool to manipulate their permeability to gain control over tumor growth and dispersion in brain. Towards this goal, we have employed certain vasomodulators, such as potassium channel antagonists for targeted and enhanced delivery of chemotherapeutics selectively to brain tumor in rodents and Bradykinin (BK) or its analog, RMP-7 in humans [1]. BTB modulation should help deliver small- to large-sized substances, including contrast-enhancing agents, nanomedicines, antitumor compounds, therapeutic proteins and viral vectors, all of which can be encapsulated with newer delivery vehicles including nanospheres. Further, the non-invasive biochemical approach to enhance BTB permeability (Figure 2) along with coadministration of PgP inhibitor such as Elacridar has an advantage because the therapeutic drugs are delivered directly to brain tumors and retained longer to kill cancer cells without affecting normal brain.

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Conflict of Interest

The authors have no potential conflict of interest.

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