DRUG DELIVERY TO BRAIN TUMOR: CHALLENGES AND RECENT DEVELOPMENTS

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ABSTRACT

Drug delivery for brain tumors is a questionable subject which is the major barrier in treatment. Nowadays, a lot of proposals have been developed to increase the amount of intravascular drug reaching the tumor. All drugs have a common disadvantage, only a small amount of delivered drug actually reaches the tumor. The systemic toxicity is the main dose-limiting factor. When we are given directly into the tumor or into the cerebrospinal fluid then 100% of the administered dose is reached to the objective site. So the delivery is connected the spatial distribution and also in the change in drug concentration. The major dose-limiting factor of most local delivery methods will be neurotoxicity. The comparative advantages and disadvantages of the different methods of Drug delivery for brain tumors are presented in this review.

Key words: brain tumor, dose-limiting factor, cerebrospinal fluid, neurotoxicity
INTRODUCTION

In oncology, the treatment of brain cancer is one of the major difficult still now. The brain tumor consists of different types of neoplasm that are primary or metastatic. The tumor that formed from glial cells is referred as primary brain tumor and the cells formed from systemic malignancies and growth in brain parenchyma is referred as metastatic (Davis et al., 2001; Shai et al., 2008). The main classification of brain tumors are oligo-astrocytomas, oligodendrogliomas and astrocytomas (Kleihues et al., 1995). These are again classified and graded based on their history. The malignant astrocytomas comprise of primary tumors in between 50-60% (Friedman et al., 2000). It has a highlight occurrence in the decade. The increase of the brain tumor is a day by day occurrence and it is depends on the genetic and environmental factors. In every year millions of cancer is detected in this world. So some anti-cancer drugs have been discovered that are successful outside to the brain but failed by the clinical trials. Usually the brain tumor treatment includes a surgery, radiotherapy and chemotherapy. A successful treatment for brain tumor includes the delivery of an effective anti-cancer drug to the brain tumor within the blood brain tumor barrier (BTB). But the brain tissue situated near to the tumor is impermeable like blood brain barrier. So, the BTB is still creates stumbling block in the delivery of anticancer drug to the brain tumor (Nagendra).

The capillaries in the cerebrum forms a BBB to defend the brain from toxic particles present in blood. But it also presents an important obstacle to the big and small therapeutic molecule delivery. From the report of Patridge the BBB will prevent approximately 98% CNS drug delivery (Pardridge, 2001; Pardridge et al., 1992). National institute of health having a main goal and it helps in understanding the purpose of BBB and BTB. And also it develops novel drug delivery approaches for molecular targeted therapy. And thus by it developing methods include non-invasive
image response of brain tumor for treatment. Contrasting proposals have been created to avoid the physiological barrier caused by the BBB. The barrier is controlled by a unit called the neurovascular unit. This unit consists of endothelial cells (ECs). The functional protein links the ECs and glia which is interaction with neurons. Normally the cancer therapy consists of some agents like antiangiogenic, bacterial and antisense agents and gene therapy (Pardridge, 2004). Fantastic clinical success for the treatment of cancer is achieved by the above elements. But in these cases also the BBB still poses a difficulty in the treatment of brain barrier. The perfect approach is to segregate the capillaries of brain present in diseased and normal brain and then to examine the proteomic and genomic variations (Nagendra).

THE CHALLENGES OF DRUG DELIVERY TO BRAIN TUMOR

The researches on drug delivery target on different methods like micro particles for carrying the anticancer agents, nanoparticles, monoclonal antibodies (Ferrari, 2005). The research on brain cancer is mainly focused on the endothelial cells present in the neurovascular unit. There are some problems in these cells that are not understood still now (Bazanng et al., 2005). These include the profiling of gene and protein in the diseased brain and normal brain. The major problems can be avoided by recognizing extra targets for increasing the permeability of BBB/BTB. In future the researches will focuses for determining the variation in the level of gene and protein present in the diseased brain and normal brain ECs (Ball et al., 2002).

The main challenges in drug delivery to brain tumor is the permeability in the transportation of the anticancer agents across the BBB and BTB present in the brain tumor. The permeability problem can be improved only by knowing the permeability regulation of BTB in the capillaries. It also includes the primary and metastatic cancer cell interaction with the EC capillaries. From this knowledge it is very easy to improve the delivery of anticancer agents to brain tumors. The BTB
present in the brain tumor capillaries have various functional and structural properties to the normal brain capillaries. The BTB is also responsible to the vascoactive agents. Finally the problem is, almost all anticancer drugs are successive in clinical trials outside the brain but failure in the brain tumors due to the difficulty to cross BBB/BTB. For further studies the prototype of a human brain tumor has been developed with all characteristics of BBB and BTB. It also includes the BBB/BTB mechanism of the brain cell in diseased and normal states (Ruoslhti, 2002).

The active exportation of the drug to the blood from the brain is done by P-glycoprotein. It acts as an efflux transporter at BBB. Apart from this, to expel both large and small drug molecules are used as BBB efflux systems. The efflux transports consist of efflux pumps that may control the transport of drug across the BBB (Ayalasomayajula and Kompella, 2000). In earlier, for understanding the properties, biology and the efflux mechanism of the BBB some developments have been made. By using the pathway of glucose and insulin through the BBB and BTB, the therapeutic agents are delivered to the brain tumor. Other drug delivery process includes developing a drug which can bypass efflux system or present the efflux protein by using inhibitors (Nagendra).

The multi-drug resistance protein controls the accumulation and penetration of the chemotherapeutics in cancer cells. So the drug delivery to the tumor cells is very difficult. The quantity of the drug delivered to the tumor cell is depends upon the permeability of the BBB. When the distance from the tumor increases, the drug concentration decreases. So, the concentration of the drug in the outer most tumors will be very low. But the fact is that this is the region where the tumor cells influence the brain. In this region, the tumor cell proliferation is more since the BBB remains unchanged (Rich and Bigner, 2004).

The transplantation of BTB is changed by the tumor micro environment due to the misalignment of the
The activation of potassium channel has been visualized by using a transmission electron microscope. The potassium channel persuading the transport vesicle formation in capillaries of brain tumor and tumor cell (Ningaraj, 2002). The transportation of vesicles is more responsible for improved drug delivery through BTB. The capillary endothelial vesicles in the brain tumor are increase with the increasing permeability of BTB. The permeability of the BBB is makes several problems in some CNS diseases. It includes HIV, stroke, and vasogenic edema and brain cancer. The breakdown of BBB mechanism is very difficult and it will create astrocytic dysfunction. It is very difficult to make a therapeutic agent to overcome the regulations of BBB and BTB. The influencing nature of tumor cells occupies the normal brain cells which is located near to the tumor, creates a challenge in the delivery of anticancer agents to the tumor cells (Li et al. ., 2001).

**METHODS FOR DRUG DELIVERY TO BRAIN TUMOR**

In earlier a lot of methods have been developed for drug delivery to control the problems caused by BBB. These methods can be categorized in to two types.

I. Increase the rate of drug delivery by controlling the permeability of BBB.

II. Local administration is used to increase the drug delivery (Rintaro Hashizume, 2011).

**Intravascular Drug Delivery**

Recently, some methods are developed to increase the rate of delivered drug to the tumor cell. These methods have their own mechanism to transport across the BBB. To enhance the brain uptake in the case of some therapeutic drugs, thin peptide vectors have been used. These vectors can be used to improve the drug delivery (Yong et al. ., 2009). The method of drug packaging and RNA interfering to liposome can easily cross the BBB, which shows the reduction of tumor. Liposome is drug transport systems; it includes phospholipids membrane shell which is used for the encapsulation of therapeutic molecules that...
allows the increasing solubility (Gabizon et al., 2003). The therapeutic efficiency while minimizing the toxicity will increase when the drug is released from the liposome. The objective antibodies are connected to the liposome to modulate the liposomal drug specificity. It is very needful to develop targeting antibodies which can cross through the BBB in human being (Rintaro Hashizume, 2011).

**Liposomal drug delivery systems**

Liposomes are nature made closed bilayer membranes that are insoluble polar lipids in water which can be used for the encapsulation of drugs and bio-molecules. It is a good biocompatible and its size can be control during its preparation process. It is drug carrier used for the treatment of liposomal diseases. These are used in encapsulated drugs such as antimicrobial compounds, antineoplastic agents, immune modulators, cardiovascular drugs, anti-inflammatory agents etc. Liposomal DOX has been used for treating the brain tumor. Although liposomal drug delivery is promising, it has some disadvantages. They are lack of self stability, low loading efficiency degradation inside the liposome, unsuitability for oral administration routes, and poor control of drug release (Caponigro et al., 2000).

**Intranasal Drug Delivery**

One of the new methods to combine the current improvement in the drug delivery to brain tumor is intranasal delivery. It can eradicate the risk factors during the surgery for direct administration of drug to the brain. Delivered drugs by intranasal method reach the CNS within very few times. For this process the animals under anesthetic condition will positioned in an anesthesia chamber (Dhuria et al., 2010). The solutions of therapeutic agents are delivered, in the rate of 6 µl in each 2 minute by using a small pipette. This process is results in the constant authentication in olfactory epithelium without any side effects in the respiratory system. In the model of a brain tumor a lot of anticancer agents are administered effectively to the tumor cell by using IND (Rintaro Hashizume, 2011).
Table: 1 List of drugs used for brain tumor

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug</th>
<th>Purpose</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEDs: ANTI EPILEPTIC DRUGS</td>
<td>Dilantin, Keppra, Lamictal, Tegretol</td>
<td>Used to decrease the electrical activity of the brain, which can cause to seizures</td>
<td>Varies according to the patient need</td>
<td>Rash, Confusion, Lethargy, Sleepiness, Unsteadiness</td>
</tr>
<tr>
<td>STEROIDS</td>
<td>Dexamethasone</td>
<td>Used to control the swelling of brain.</td>
<td>It should remain constant. Should not stop the usage of this drug without any precaution</td>
<td>Difficulty to sleep, Weakness of muscles, Increase the blood sugar level, Joint pains</td>
</tr>
<tr>
<td>ANTICOAGULANTS</td>
<td>Coumadin</td>
<td>Used to remove the problem in the formation of blood clot</td>
<td>It should take one per day. Don’t try to take double dose at the same time</td>
<td>Severe Headache, Intracranial bleed Unusual staining</td>
</tr>
<tr>
<td>BACTRIM</td>
<td>Sulfamethoxazole/Trimethoprim</td>
<td>Used to treat against infections and to prevent the infection</td>
<td>A double-strength bactrin tablet 3 times in a week</td>
<td>Vomiting Itching Allergy Blood abnormality</td>
</tr>
<tr>
<td>ANTIMETICS</td>
<td>Ondansetron, Granisetron, Dolasetron</td>
<td>Used to reduce the vomiting and nausea.</td>
<td>Depends on the patient condition</td>
<td>Allergy Swelling in hand or face Trouble breathing Diarrhea</td>
</tr>
</tbody>
</table>

DEVELOPMENTS

There are many methods for gene and drug delivery across the BBB. It is done by using carriers like amino acids and glucose, also using receptors like transferring and insulin. The interruption of BBB/BTB causes a wide range of variations in the brain permeability which allows the anti-cancer agents to enter the brain. If the BBB kept open for a few time, it will allows the entry of plasma protein with toxic contents which may cause to chronic neuropathology (Nagendra).

Drug delivery by surgical methods

The current methods can avoid the problem with BBB/BTB during drug delivery, but it needs a placement of catheters to the carotid artery. The delivery of anticancer agents directly to the brain by injection is very costly, and also it have
some disadvantages like, the drug is not reached to all diseased area, and the whole procedure can change some neuropathological functions. In the case of successful delivery of anticancer agents to the tumor cell, drugs are not specified to target only the tumor cells. So it leads to get drugs to the healthy cells of brain also. It may cause some effects to those cells (Reyderman et al., 2004).

Recent studies have developed advanced methods for the drug delivery across BTB, in these methods the drug may infuse via intra-cerebroventricular not across the BBB/BTB. In such cases the drug is infused via the cerebrospinal fluid (CSF) near ventricular system may not preserve by BBB/BTB. The functions of CSF barrier and BBB are entirely different. So the process of drug delivery to the brain via CSF doesn’t mean that the drug is passed through the BBB, it only measures the permeability of blood-CSF barrier. The drug is passed through circumventricular region of brain which is a lack of BBB/BTB (Nagendra).

**Drug Delivery Form Biological Tissue**

Another method to the drug delivery includes the releasing of drug from biological tissues. In this process a tissue is implanted to the brain which can secrete a therapeutic agent naturally. This advance has been more widely applied to Parkinson’s disease treatment. Transplanted tissue frequently did not stay alive due to the innervations of neurovascular system. Currently the enhanced micro vascular permeability and vascularization in neural graft of cell-suspension embryonic cells comparative to solid graft has been established.

An alternative addition of this strategy is to apply gene therapy to expand biological tissue for interstitial drug delivery. Before the implantation the cells can be adapted genetically to combine and discharge targeted therapeutic agents. The beneficial potential of this method in the brain tumor treatment was confirmed. The continued existence of tissue graft may be developed by the advancements in the distinct cell type culturing techniques. The
grafted cells are combined together and which may cause to survive the foreign tissue. Even though this method has a significant therapeutic potential in the CNS treatment, its efficiency has been delayed by some barriers, it includes the permeability problem to cross the BBB that are ineffective host cell transfection and toxic transgene regulation by the host.

CONCLUSION

The BBB is always obstructing the therapeutic agents delivered to the brain. The blood capillaries present in the brain forms BTB, which prevent the delivery of antitumor agents and hydrophilic modules to the brain. In earlier a lot of studies has been done to increase the permeability of BTB and to modulate the rate of anticancer agents delivered to the brain tumor. The delivery of hyper osmotic agents via intra-aortic infusion can increase the BBB permeability but it can also deliver the toxic agents to brain and make some side effects (Pardridge, 2001). Another method has been done by using vectors, which hold modified proteins and monoclonal antibodies that go through transcytosis. This method is very complicated, because it will deliver the therapeutic agents to the normal brain tissues also. Other methods like intracerebral infusion, transport system and CED are clinically successful but cause some side effects. In an attempt to advance on these strategies vasomodulators were used with low dose for the targeted delivery of drug only to selective tumor cells in human. This attempt enhances the permeability of BTB with no side effects to the normal brain cells. It can also deliver small or large sized materials. It is very significant to develop a drug delivery strategy with more positive characteristics by knowing the mechanism of BBB drug transport (Nagendra).
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