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New Therapeutic Strategies for the Treatment of Brain Tumor

Rintaro Hashizume
Department of Neurological Surgery
University of California San Francisco, San Francisco
USA

1. Introduction

Despite significant advances in tumor imaging, neurosurgery, and radiotherapy, the prognosis for patients with malignant gliomas is extremely poor. The five-year survival rate for patients with glioblastoma (GBM), the most aggressive form of malignant glioma, is less than 5% after initial diagnosis (CBTRUS statistical report, 2010). Factors that contribute to the dismal prognosis associated with GBM include its infiltrative nature throughout the brain, which precludes total surgical resection and impair radiotherapy targeting, and resistance to most types of conventional cancer therapeutics. Many clinical studies using potent chemotherapeutic drugs conducted in the past decade have not demonstrated significant improvement in survival. A fundamental limitation in the treatment of brain tumors is that many systemically administered therapeutic agents do not cross the blood-brain barrier (BBB) (Abbott et al., 2010; Brightman, 1977; Huynh et al., 2006; Schlosshauer, 1993). While some small and lipophilic molecules, peptides, and protein-based agents delivered by systemic routes can reach the brain parenchyma by crossing the BBB, high doses are usually needed to achieve therapeutic levels, which can lead to substantial toxicity.

In this chapter, the application of intranasal delivery (IND), in comparison with systemic (intravascular) and/or direct invasive (intraparechymal) drug delivery, for the treatment of brain tumors is discussed.

2. The BBB: An obstacle for drug delivery to brain tumor

The brain parenchyma has both physiological and biological safeguards to prevent the entry of toxins from the bloodstream, which are collectively known as the BBB. The endothelial cells that comprise the cerebral micro-vessels are linked by tight junctions and surrounded by astrocytic processes and adjacent pericytes and a characteristic composition of the extracellular matrix. This structural arrangement prohibits most drugs from entering the brain through pericellular diffusion. Drugs that are able to diffuse through the barrier must be small (<400 Da) and lipophilic. In addition to this physiological barrier, drugs are rapidly cleared by efflux pumps such as P-glycoprotein, and a rapid turnover rate of extracellular fluid in the brain. In combination, these factors have limited the number of successful pharmacologic treatments for diseases of the brain and necessitate a closer examination of

both traditional and novel methods of drug delivery (Choi et al., 2008; Eyal et al., 2009; Saunders et al., 2008).

In brain tumors such as GBM, the BBB is progressively disrupted with tumor growth by inducing large gaps between endothelial cells (Coomber et al., 1985). However, the extent of BBB disruption among individual patients, and/or among various regions within a single tumor, appears to be highly variable. BBB is most likely disrupted in the necrotic center, not at the infiltrative edge of the tumor (Gerstner & Fine, 2007). Recently, the artificially disruption of the BBB using hyper osmotic solutions has demonstrated by intra-arterial infusion of the VEGF specific antibody bevacizumab in patients with recurrent malignant glioma (Boockvar et al., 2010). However, disruption of the BBB could potentially lead to other serious complications, such as brain edema. Therefore, development of strategies to deliver targeted agents across the BBB is a critical priority.

3. Strategies for drug delivery to the brain

In the past decade a number of drug delivery strategies have been developed to overcome challenges presented by BBB. These strategies can be divided into two categories: (a) attempt to increase drug delivery of intravascularly administered drugs by manipulating either the drugs or capillary permeability, and (b) attempt to increase drug delivery by local administration.

3.1 Intravascular delivery

Several strategies have recently developed to increase the fraction of intravascular drug reaching the tumor. These include i) intra-arterial administration, ii) packaging drugs such as microcapsules and liposomes, iii) use of biologically active agents (such as bradykinin and histamine) (Greenwood, 1992), iv) use of replication-competent retroviruses to deliver oncolytic therapies (Tai & Kasahara, 2008), v) use of mesenchymal (Yong et al., 2009) or neural stem cells to deliver small molecules, antibodies, or toxic payloads (Aboody et al., 2000; Frank et al., 2009). There are also several specific transport mechanisms that have been exploited, involving the activity of several independent transporters that mediate the flux of substances important for brain function, such as carrier-mediated transporters, including the glucose and amino acid transporters (Rapoport, 1996; Tamai & Tsuji, 1996; Deeken & Loscher, 2007; Saunders et al., 2008), active efflux transporters, including P-glycoprotein and the other ATP-binding cassette (ABC) gene family members, and receptor-mediated transporters, of which transferrin receptor (TfR), insulin receptor, and low-density lipoprotein receptor (Pardridge, 2007). A further strategy has been to conjugate the therapeutic drug with a protein or a monoclonal antibody that gains access to the brain by receptor-mediated transcytosis (Pardridge, 1999). Small peptide vectors have been used to enhance brain uptake of several therapeutic drugs (Rousselle et al., 2000). These peptide-vectors cross cellular membranes safely and efficiently and have been used successfully to enhance penetration of several drugs.

The strategy of a packaging drugs and/or interfering RNAs into liposomes that more readily cross the BBB and show tumor reduction and increase in survival in mice. Liposomes are a drug carrier system consisting of a phospholipid membrane shell surrounding a hollow core used to stably encapsulate therapeutic molecules allowing increased solubility and half-life resulting in increased bioavailability. Gradual release of the drug from the liposome increases therapeutic efficacy while reducing toxicity (Gabizon,

2003). Liposomal anticancer agents have been widely used in humans and are currently approved for ovarian cancer (Tanguay, 2009) and multiple myeloma (Moreau, 2009), but remain investigational in their use for brain tumors. To increase the specificity of liposomal drugs, targeting antibodies can be attached to the surface of the liposome (Elbayoumi & Torchilin, 2009; Mamot et al., 2005). Antibody-conjugated liposomes increase the rate of liposome internalization, which increase intracellular drug concentration, thereby achieving heightened anti-tumor activity (Mamot et al., 2005). EGFR, a tyrosine kinase receptor that is over-expressed in 30-40% of high grade gliomas (Ekstrand et al., 1991). Attempts to target GBM by delivering EGFR-targeted immunoliposomes encapsulated anti-cancer agents or EGFR-specific shRNA in PEGylated liposomes bearing insulin receptor– and TfR-specific antibodies in an in vivo model has shown some promise (Mamot et al., 2005; Zhang et al., 2004). However, these antibody-based approaches have yet to translate into the clinic. Developing the right targeting antibodies to facilitate crossing of the BBB in humans, and uncovering the molecular mechanism by which the process works, remain significant impediments to clinical application.

3.2 Convection-enhanced delivery

Technology to improve direct drug delivery into the central nervous system (CNS) are currently part of intensive research, and include intraventricular or intraparenchymal injections [e.g. convection-enhanced delivery (CED)]. In particular, CED has shown promising results in both animal models and clinical trials (Huynh et al., 2006; Kawakami et al., 2004; MacKay et al., 2005; Mamot et al., 2004; Ozawa et al., 2002; Saito et al., 2006). CED is a continuous infusion that uses a convective (versus diffusive) flow to drive the therapeutic agent throughout a larger region of tissue. CED uses a slow drug infusion rate by micro infusion pump coupled with a specially designed catheter which is a 1-mm stepped design with a fused silica tubing into 24 gage needle. These optimal CED devices increase drug distribution and reduce reflux (Serwer et al., 2010) (Figure 1,2).

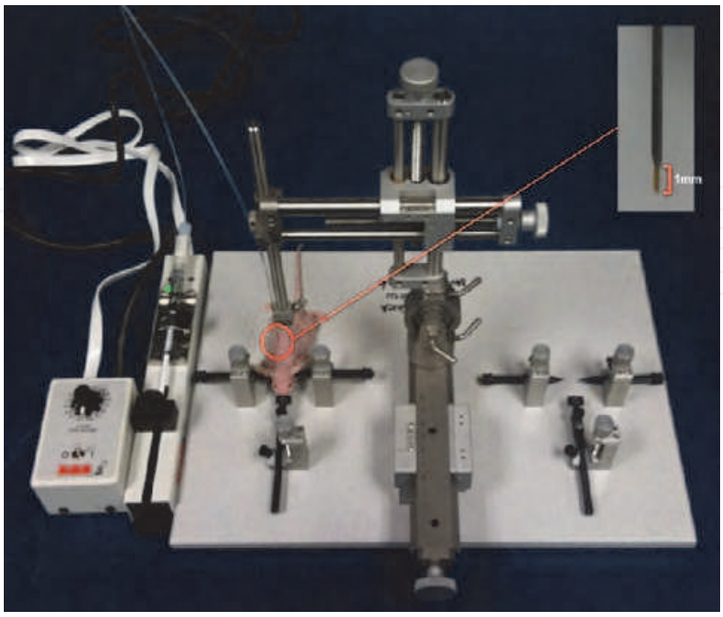


Fig. 1. CED cannula and surgical set-up.

CED is well suited for the delivery of liposomes and particulate drug carriers which have the potential to provide a sustained level of drug and to reach cellular targets with improved specificity (Murad et al., 2006; Saito et al., 2004). CED of liposomal anti-cancer agents have shown greater brain and tumor retention, and effective anti-tumor activity in GBM xenografted animals, as compared to free drugs delivery (Bidros & Vogelbaum, 2009; Noble et al., 2006; Yamashita et al., 2007). Importantly, prolonged exposure to liposomal anti-cancer agents resulted in no measurable CNS toxicity, whereas free drugs induced severe CNS toxicity.

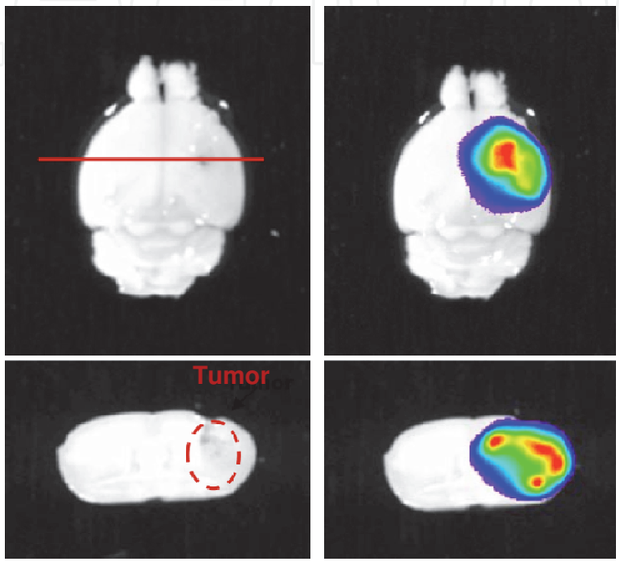


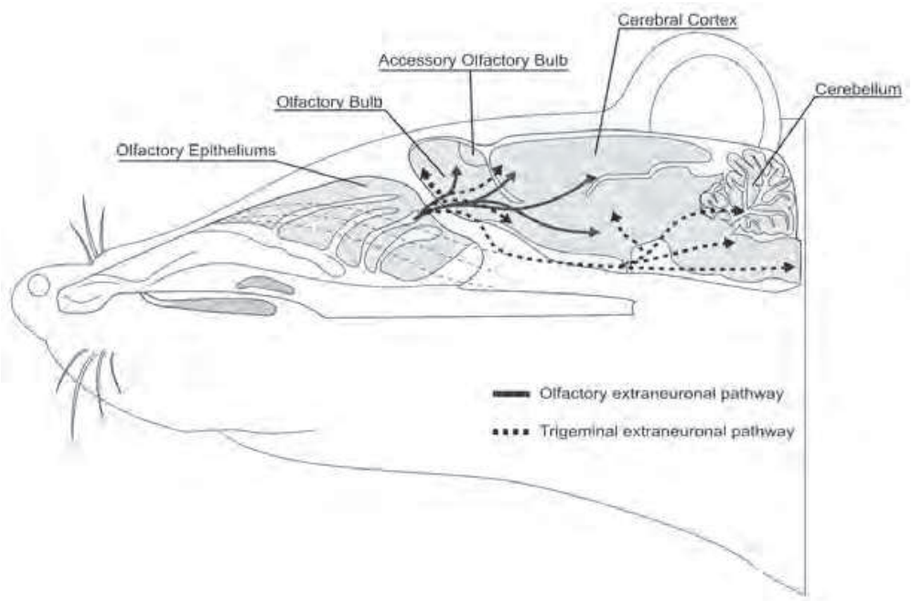
Fig. 2. Representative image of successful CED into the mice brain tumor.

CED has also been used to deliver larger particles, including purified virus and proteins. Currently, CED is being evaluated in 17 clinical trials for the delivery of small molecules, antisense oligonucleotides, and proteins (United States National Institutes of Health, 2011). However, this technique requires the use of potentially risky surgical procedures to position the catheter into the patient's brain parenchyma, and is expensive techniques. Additional limitations of these methods are inadequate CNS distribution due to reflux and leakage along with the needle tracts from the injection site and rapid turnover of the cerebrospinal fluid (CSF). The reflux and leakage through the implanted catheter leads to a measurable and significant inflammation and local edema, because drug solution infuse continuously beyond the tumor boundary into adjacent normal brain tissues (Kawakami et al., 2004; Marmot et al., 2004; Ozawa et al., 2004; Sandberg et al., 2002). Finally, CED infusions can be variable by investigators, in one study the rate of successful infusion was reported as 19% (Sampson et al., 2008).

3.3 Intranasal delivery

One technique under current investigations is to integrate a recent innovation in drug delivery to the brain, intranasal delivery (IND). IND is a practical and noninvasive method of bypassing the BBB and eliminating the surgical risk associated with direct drug administration into the brain parenchyma. It is an alternative to systemic (intravascular) and/or direct invasive (intraparechymal) drug delivery. IND relies upon the unique anatomic connections of

the olfactory and trigeminal nerves from the nasal mucosa to the CNS (Dhuria et al., 2010; Thorne et al., 2004). These nerves arise in the brainstem and innervate the nasal mucosa, allowing detection of odors and other sensory stimuli (Dhanda et al., 2006; Thorne et al., 2004). Intranasally administered drugs reach the CNS and/or CSF within minutes of administration by using an extracellular route through perineural and perivascular channels, without binding to any receptor or relying upon axonal transport (Dhuria et al., 2010; Thorne et al., 2004) (Figure 3a). To administer the drugs through the nasal cavity, animals were anesthetized with 2–2.5% isoflurane and placed in an anesthesia chamber. Six µl drops of soluble form of therapeutic agents were administered with a small pipette every 2 min into alternate sides of the nasal cavity for a total of 22 min (a total volume of 66 µl). This method of administration results in consistent deposition in the olfactory epithelium without respiratory distress. Following IND, the animals remained in a supine position for 15 min in order for absorption to occur through the nasal mucosa (Figure 3b).



(a) Anatomical pathways of IND



(b) IND in athymic rats

Fig. 3. (a) Anatomic and extraneuronal pathways of the olfactory and trigeminal nerves following IND (b) Demonstration of IND in an anesthetized athymic rat.

In addition to bypassing the BBB, advantages of IND are the avoidance of hepatic first-pass elimination, thereby reducing systemic side effects, and convenient self-administration for patients, a feature that would clearly aid in clinical applications, particularly in the treatment of brain tumors where repeated dosing is necessary (Dhuria et al., 2010).

Many therapeutic agents, including small molecules, growth factors, proteins, peptides, viral vectors, liposomes, nanoparticles and vaccines, have been delivered into the CNS in both animals and humans using IND for a variety of CNS disorders. Thorne *et al* reported that IGF-1 can be rapidly transported into the rat brain and upper spinal cord via the olfactory and trigeminal pathways (Thorne et al., 2004) and, IFNβ-1b can be delivered into the CNS in monkeys (Thorne et al., 2008). Furthermore, rat mesenchymal stem cells and human glioma cells have been delivered to the brain through the nasal pathway (Danielyan et al, 2009). In humans, IND with insulin improves memory in healthy adults (Banks et al., 2004; Benedict et al., 2004) and in patients with early-stage Alzheimer's disease (Reger et al., 2008) without changing the blood levels of glucose or insulin. Also, IND with the neuropeptide oxytocin has been reported to improve trust (Baumgartner et al., 2008; Kosfeld et al, 2005), social behavior (Domes et al., 2007a, 2007b; Guastella et al., 2009), and social memory (Rimmele et al., 2009), and decreased fear and anxiety (Kirsch et al., 2005; Parker et al., 2005).

In brain tumor model, many anti-cancer agents such as methotrexate (Shingaki et al., 1999; Shingaki et al., 2010), 5-fluorouracil (Sakane et al., 1999) and raltitrexed (Wang et al., 2005) have been delivered successfully to the brain using IND. Shingaki *et al* reported that intranasally delivered methotrexate reached the CSF and reduced tumor weight in rodent glioma allografts (Shingaki et al., 1999). Drug targeting of the chemotherapeutic agent raltitrexed to the brain was significantly higher following IND compared with that of intravenous administration (Wang et al., 2005). However, these chemotherapeutic agents do not discriminate between tumor and normal tissues. Thus, the application of drugs at concentrations required to kill tumor cells can also lead to toxicity in normal neural tissues. To achieve therapeutic efficacy without toxicity, the drugs need to preferentially target brain tumors while sparing normal tissue from damage.

3.3.1 Intranasal delivery of a telomerase inhibitor

Given that telomerase is expressed in essentially all cancer cells, but not in normal somatic cells (Kim et al., 1994; Phatak & Burger, 2007), the inhibition of this enzyme is an attractive therapeutic strategy for selectively targeting brain tumors while sparing normal brain tissue. The human telomerase enzyme is a specialized ribonucleoprotein reverse transcriptase containing essential RNA (hTR) and protein (hTERT) subunits. Telomerase elongates telomeres by adding the (TTAGGG)n telomeric repeats to the ends of chromosomes, protecting the chromosome ends from fusion and DNA damage recognition (Feng et al., 1995; Greider & Blackburn, 1985). During cell division in cancer cells, DNA is continuously extended or maintained by telomerase to compensate for the lost telomeric repeats resulting from the 'end-replication' problem of DNA polymerase (Levy et al., 1992; Röth et al., 2003). In the absence of telomerase activity, chromosome ends shorten with each cell division, eventually resulting in growth arrest or cell death, termed replicative senescence or crisis (Allsopp et al., 1992; Shay & Wright, 2006). Although cancer cells express telomerase, these cells typically have relatively short but stable telomere length, whereas normal cells do not express telomerase and have long, slowly shortening telomeres. These differences between cancer and normal cells make cancer cells more sensitive to telomerase inhibitors, and may

allow for a substantial therapeutic window for telomerase inhibition-based treatments (Asai et al., 2003).

GRN-163, a telomerase enzyme antagonist, is a 13-mer oligonucleotide N3'→P5' thiophosphoramidate, that exhibits high RNA binding affinity for the targeted template region of hTR in a sequence-specific manner (Gryaznov et al., 2001; Herbert et al., 2002). GRN-163 has demonstrated potent inhibitory activity against human telomerase in several biochemical assays, with IC_{50} values of < 1 nM (Gryaznov et al., 2001; Herbert et al., 2002). *In vitro*, telomerase inhibition by GRN-163 induced cellular senescence and apoptosis in various human cancer cell lines (Ozawa et al., 2004; Asai et al., 2003; Herbert, 2002; Akiyama et al., 2003; Gryaznov et al., 2003; Wang et al., 2004). Although a potential limitation of oligonucleotide therapies is the bioavailability in tumor tissues (Corey, 2002), GRN-163 inhibited tumor growth in prostate cancer, multiple myeloma, lymphoma, hepatoma and glioblastoma xenografts in rodents (Ozawa et al., 2004; Asai et al., 2003; Wang et al., 2004; Hashizume et al., 2008; Djojosubroto et al., 2005). GRN-163 has been delivered successfully into the brain using IND and shown impressive oncolytic activity without harming normal brain tissue (Hashizume et al., 2008). Intranasally delivered GRN-163 exhibited favorable tumor uptake, inhibited tumor growth in human glioblastoma xenografts in rats and increased the survival of tumor-bearing animals. Following the IND of the highest possible dose of GRN-163 (0.65 µmol/µl, based on the solubility of the compound in saline solution), the compound could be detected in the cerebral hemispheres, brainstem and intracranial sections of the trigeminal nerve in naïve rats within 10 min of administration. In tumor-bearing rats, GRN-163 was detected at the edge of the tumor after 30 min, and throughout the tumor between 4 and 24 h after administration (Figure 4).

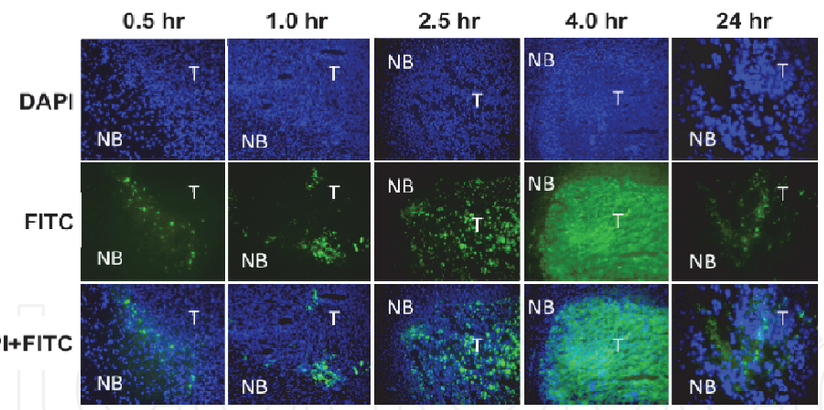


Fig. 4. Distribution of fluorescein-labeled GRN163 by IND into intracerebral tumors in athymic rats. Abbreviations: T, tumor; NB, normal brain.

Importantly, very little or no GRN-163 was found in healthy brain cells adjacent to the tumor or in any other part of the brain. This apparent selectivity may be a result of the specific binding affinity that GRN-163 exhibits for tumor cell telomerase (Herbert et al., 2002). The specificity achieved with IND appears to be superior to the results obtained using CED, which reportedly delivers drugs beyond the tumor boundary into adjacent healthy brain tissue, leading to damage to healthy sections of the brain (Kawakami et al., 2004; Mamot et al., 2004, Ozawa et al., 2004). In addition, intranasally delivered GRN-163 inhibited telomerase activity in intracranial glioblastoma xenografts in rats in a dose-dependent manner (Figure 5).

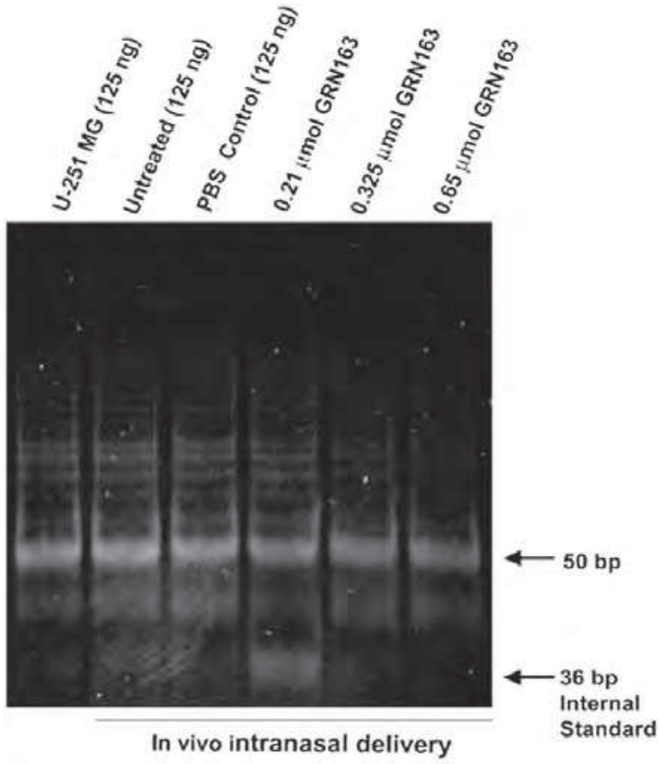


Fig. 5. Inhibition of telomerase activity by GRN163 in intracerebral GBM xenografts.

Moreover, GRN-163 (qd for 12 days) delivered intranasally at the highest solubility dose significantly prolonged the median survival from 35 days in the control group to 75.5 days in the GRN163-treated group. None of the rats that were treated with GRN-163 exhibited signs of toxicity or behavioral abnormalities during the 12-day treatment period (Figure 6).

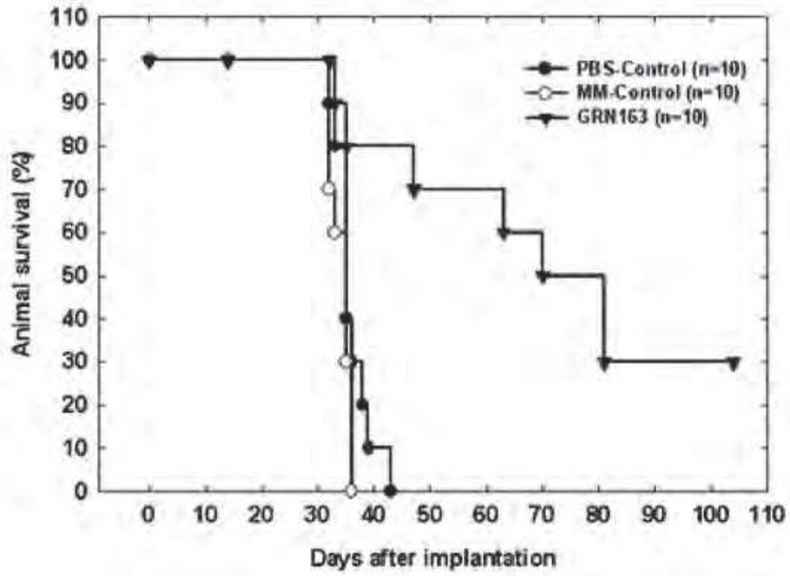


Fig. 6. Survival of rats treated with intranasal GRN163.

Because the mechanism of action of oligonucleotide-based telomerase antagonists such as GRN-163 is through the competitive inhibition of the telomerase enzyme (Gryaznov et al., 2001; Herbert et al., 2002), treated tumor cells can regain baseline telomerase activity following termination of treatment with the telomerase inhibitor. Thus, it is possible that telomerase inhibitor agents will need to be administered for an extended period of time to achieve efficacy. Hypothetically, repeated intranasal treatment is possible, and may be practical as a convenient self-administered treatment.

The lipid-modified N3'→P5' thiophosphoramidate oligonucleotide imetelstat represents the most advanced anti-telomerase therapeutic, and is a more potent derivative of GRN-163 (Herbert et al., 2005). Because of increased lipophilicity, imetelstat exhibits increased bioavailability and cellular uptake in tumors compared with nonlipidated compounds, and it is more acid-resistant than other telomerase-targeted phosphoramidate oligonucleotides (Herbert et al., 2005). Imetelstat also inhibits telomerase activity in various tumor cell lines with IC_{50} values between 3 and 300 nM in the absence of any cellular uptake enhancers (Graznov et al., 2007). In cell-based studies with GRN-163, there was generally a phenotypic lag of at least a few weeks between the onset of exposure and growth inhibition (Akiyama et al., 2003); however, with imetelstat, the addition of a 5' lipid (palmitate) moiety increased potency and resulted in a more rapid loss of telomeres (population doubling [population doubling (PD) ~ 8 for GRN-163L-treated cells and PD ~ 13 for GRN-163-treated cells] and inhibition of cell growth (Herbert et al., 2005). *In vivo* inhibition of tumor growth by imetelstat has been reported in multiple animal models (Djojosubroto et al., 2005; Dikmen et al., 2005; Hochreiter et al., 2006; Marian et al., 2009) and Phase I/II clinical trials with imetelstat have been initiated in patients with chronic lymphocytic leukemia, refractory or relapsed solid tumors, NSCLC, multiple myeloma and breast cancer (Geron Corp., 2009).

3.3.2 Limitations and future prospects of telomerase inhibition by IND as a therapy for GBM

Although the inhibition of telomerase offers exciting therapeutic possibilities for the treatment of GBM patients, there are some potential limitations of this approach, such as the engagement of an alternative telomere-lengthening mechanism that can lead to anti-telomerase treatment (Bollmann et al., 2007). In addition, anti-telomerase therapy may be associated with a delay in efficacy because of the lag period between the initiation of anti-telomerase therapy (telomerase shortening) and the onset of therapeutically beneficial effects (cell death) (Bechter et al., 2004). The combination of IND of telomerase inhibitors with chemotherapy or radiotherapy may produce more rapid effects, and may provide an approach for minimizing the lag phase, potentially preventing or delaying tumor recurrences (Shay & Wright, 2006). The combination of imetelstat with existing chemotherapeutic agents has been demonstrated to enhance chemosensitivity in various human cancer cells (Djojosubroto et al., 2005; Godblatt et al., 2009a, 2009b). More specifically, imetelstat increased doxorubicin sensitivity of Hep3B human hepatoma cells (Djojosubroto et al., 2005), sensitized human breast cancer cells to paclitaxel and trastuzumab (Godblatt et al., 2009a, 2009b), and also enhanced hyperthermia-mediated radiosensitization in human 293 cell lines (Gomez-Millan et al., 2007). Recently, imetelstat in combination with radiation and temozolomide had a statistically significant effect on cell survival and activated the DNA damage response pathway in GBM tumor-initiating cells (Marian et al., 2010).

Further potential limitations of oligonucleotide-based therapies using IND are the low bioavailability and absorption in the nasal mucosa and tumor tissues because of low permeability and solubility (Kausch & Böhle, 2003; Dias & Stein, 2002). The poor absorption of drugs across the nasal membrane is due to low permeability of the nasal membrane, mucociliary clearance, enzymatic degradation, and efflux mechanisms, such as P-glycoprotein and ABC transporters (Dhuria et al., 2010).

3.3.3 Intranasal delivery of liposomal therapeutic agents

Liposomes can be used as biocompatible carriers to improve delivery properties across the nasal mucosa perhaps by increasing residence time of the formulation in the nasal cavity, resulting in higher concentration of encapsulated drugs in the brain. A study of IND with rivastigmine, an acetyl cholinesterase inhibitor, showed that the liposome drug formulation had a longer half-life compared to the free drug due to sustained release of rivastigmine from the liposomes (Arumugam et al., 2008). Migliore *et al* also reported that IND of the liposomal preparation resulted in a higher net delivery and longer retention of ovalbumin in the brain than the nonliposomal preparation (Migliore et al., 2010). Increased tissue retention may be a consequence of the protein's association with cationic lipids, rendering it more likely to undergo cellular binding and adsorptive endocytosis and impeding its diffusion and clearance from the brain (Kumagai et al., 1987). IND with liposomal therapeutic agents is conceptually attractive, and its appeal as a minimally invasive therapeutic strategy would facilitate its translation into clinical trials for the treatment of brain tumor patients.

4. Conclusion

IND of therapeutic agents is an innovative therapeutic strategy capable of targeting drug delivery to the brain for the treatment of brain tumors and could provide an alternative to systemic (intravascular) and/or direct (intraparechymal) drug administrations. IND is a practical and noninvasive method of bypassing the BBB, and is amenable to self-administration by patients. This technique has demonstrated promising results in the treatment of human CNS neurological disorders and rodent brain tumor without obvious toxicity. IND with GRN-163, an oligonucleotide-based telomerase inhibitor, has exhibited impressive oncolytic activity without inducing toxicity to healthy tissue (Hashizume et al., 2008). Data support further development of intranasal GRN-163 as a potential therapy for patients with brain tumors and perhaps as a means for treating multifocal brain tumors, such as metastatic brain tumors and/or pediatric brainstem tumors, which are less amenable to surgical procedures. A telomerase inhibitor, imetelstat, has reached clinical trials, and may therefore become a part of the available cancer therapeutic armamentarium in the future. IND can be further optimized by the use of liposomal drug carriers which provide stable encapsulation for various anticancer agents.

Given the promising results from current animal studies, intranasal therapeutic agents would seem to be prime candidates for clinical trials in patients with brain tumors. Initial trials of intranasal perillyl alcohol have begun in patients with recurrent malignant gliomas, and a reduction in the size of the brain tumors has been reported (Da Fonseca et al., 2006a, 2006b, 2008).

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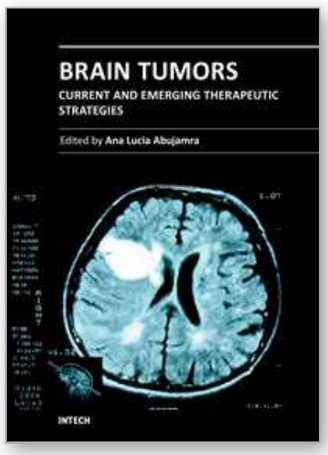
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Brain Tumors - Current and Emerging Therapeutic Strategies
Edited by Dr. Ana Lucia Abujamra

ISBN 978-953-307-588-4
Hard cover, 422 pages
Publisher InTech
Published online 23, August, 2011
Published in print edition August, 2011

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Phone: +86-21-62489820
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