

# Noscapine – a Novel Anticancer Drug for the Treatment of Primary/Secondary Brain Tumor

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## Abstract

Glioblastoma multiforme and anaplastic astrocytomas are the most common type of primary brain tumors in adults. Tumor recurrence (96% cases), adjacent to resection margin after surgical resection, is seen calling out for adjuvant therapy. Due to the presence of blood–brain barrier, the current chemotherapeutics are unable to reach the brain tumor. Noscapine, an antitussive pediatric preparation, at higher concentration induces apoptosis and metaphase arrest in dividing cells with minimal or less toxicity in primary and secondary brain tumor. Nanoparticulate-based drug delivery systems have opened new avenues for the treatment of gliomas and other types of brain tumors. Due to small size, nanometric material causes better permeability of therapeutic agents into cells compared to conventional therapy. Nanoparticulate drug delivery systems that are currently under investigation for treatment and diagnosis of primary brain tumor include liposomes, polymeric nanoparticles, quantum dots, and polymeric micelles. Nanoparticles may offer an improvement to nose-to-brain drug delivery since they are able to protect the encapsulated drug from biological and/or chemical degradation and extracellular transport by P-gp efflux proteins. This would increase central nervous system availability of the drug. To achieve the ultimate clinical translation of noscapine nanoparticles delivery system, a great deal of effort through interdisciplinary collaborations will be required to optimize dose, the design of nanocarrier, to improve the bioavailability at target site with minimal toxicity, *in vivo* pharmacokinetics, and targeting efficacy through intranasal route.

**Key words:** Blood brain barrier, brain tumor, cytotoxic, glioblastoma, noscapine

## INTRODUCTION – CANCER

Cancer is a common cause of death in the world; about 10 million new cases occur each year. Moreover, cancer is responsible for 12% of deaths worldwide, making it the third leading cause of death.<sup>[1]</sup> Glioblastoma multiforme and anaplastic astrocytomas are the most common type of primary brain tumors in adults. The incidence rate of all primary malignant brain tumors is 78%.<sup>[2]</sup> Median survival rate of brain tumor patients is approximately 1 year. Low survival rate of the patients suffering from brain tumor depicts the failure of effectiveness of the prescribed chemotherapy.

### Current treatment approaches and associated problems

Treatment of brain tumors requires a multidisciplinary approach that includes a combination of surgery, radiation, or

chemotherapy.<sup>[3]</sup> Tumor recurrence (96% cases), adjacent to resection margin after surgical resection, is seen calling out for adjuvant therapy. Post-resection, radiation therapy and chemotherapy are used for the treatment of glioma patients. This review is limited to chemotherapeutic agents used in primary and secondary brain tumors.

### Chemotherapeutic agents

Temozolomide (TMZ) is the first-generation agent used for the treatment of brain tumors and is given orally. Few other agents that can be used include irinotecan, carmustine,

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cisplatin, and lomustine. Many of the drugs have proved effective in the treatment of brain tumors in laboratories when used against cell lines. However, clinical failure was observed with such drugs due to insufficient barrier passage. The major fraction of such expensive molecules of the drugs is thus lost with the expression of side effects. These drawbacks are observed either due to hydrophilic nature of the molecules or due to large molecular weight.<sup>[2]</sup>

Currently employed chemotherapeutic agents for the treatment of gliomas with few of the relevant are provided in Table 1.

### Chemotherapy fails - A major reason

This is due to deep invasion of the brain parenchyma, cells being naturally resistant to most cytotoxic drugs and radiotherapy. The major hindrance to prognosis of brain tumor is the autoprotective nature of the brain (blood–brain barrier [BBB] and alignment of brain cells), genomic alterations occurring in tumor cells, efflux transporters on the barrier, and properties of chemical agents used for the treatment of brain tumors.<sup>[4]</sup>

### BBB and brain–tumor barrier (BTB)

The presence of BBB is the major obstacle to passage of chemotherapeutic agents. The BBB is composed of the three barriers:

1. The BBB formed by the cerebrovascular endothelial cells between blood and brain interstitial fluid
2. The choroid plexus epithelium between blood and ventricular CSF
3. The arachnoid epithelium between blood and subarachnoid CSF.

The three barrier layers regulate and limit the molecular exchange at the interface between the blood and the neural tissue or its fluid spaces.<sup>[5]</sup>

### Chemotherapeutic agents and associated side effects

Brain allows passage of some of endogenous materials, a few hydrophobic agents and particles with molecular weight of <500 Da. Lipophilicity of the drug is one of the important factors that should be considered while designing

**Table 1: Physicochemical properties of chemotherapeutics used in brain tumor**

Name of the drug	Mechanism of action	Permeability coefficient	Type of brain tumor to be treated	Molecular mass (g/mol)	Half-life	Log P	BBB passage
Carmustine	Alkylating agent	$0.92 \times 10^{-4} \text{ cm.s}^{-1}$	Glioblastoma multiforme	214.049	15–30 min	1.5	Yes
Lomustine	Alkylating agent	$3.16 \times 10^{-4} \text{ cm.s}^{-1}$	Oligodendrogliomas	233.695	94 min	3	-
Temozolomide	Alkylating agent	-	Glioblastoma multiforme, astrocytomas, oligodendrogliomas	194.151	1.8 h	-0.99	Yes
Cyclophosphamide	Alkylating agents	-	Glioblastoma multiforme	261.086	3–12 h	0.8	No
Methotrexate	Inhibition of DHFR	$1.77 \times 10^{-7} \text{ cm.s}^{-1}$	CNS lymphomas	454.44	3–15 h	-0.91	-
Imatinib mesylate	Inhibition of tyrosine kinase enzyme	-	Glioblastoma multiforme, CNS lymphomas	493.603	18 h, metabolite- 40 h	1.198	-
Vincristine	Inhibition of mitosis at metaphase through its interaction with tubulin	$1.58 \times 10^{-7} \text{ cm.s}^{-1}$	Oligodendrogliomas	923.04	19–155 h	2.8	No
Procarbazine	Breaking of DNA strands	$3.01 \times 10^{-5} \text{ cm.s}^{-1}$	Glioblastoma multiforme, astrocytomas, oligodendrogliomas	221.229	10 min	0.06	Yes
Cisplatin	Crosslinking of DNA	-	Glioblastoma multiforme	300.05	40–45 min	-	-
Everolimus	mTOR inhibitors, selective immunosuppressants	-	Glioblastoma multiforme, astrocytomas, oligodendrogliomas	958.224	~30 h	5.01	No

BBB: Blood–brain barrier, CNS: Central nervous system

new entities for treatment of tumors. Improvement in passage of drug across the BBB is possible with increased lipophilicity, but this may be associated with increased drug uptake by other tissues, causing an increased tissue burden. This non-selectivity in delivery of drugs to non-targeted site is detrimental, especially when cytotoxic agents are used, because drug toxicity would be higher at non-target sites.

### **Noscapine – An unexplored anticancer drug**

Noscapine is a phthalide isoquinoline alkaloid obtained from opium latex. Unlike other opium alkaloids, noscapine is non-sedative and has been used as antitussive drug in the pediatric preparation in various countries. In higher concentrations than those used for suppressing cough, noscapine induces apoptosis and metaphase arrest in dividing cells.<sup>[6]</sup> Many other anti-mitotic compounds such as paclitaxel and vinblastine are also being used clinically in the treatment of different cancers, but all are associated with side effects and have multiple drug resistance. Many studies have been conducted highlighting its effectiveness as an antineoplastic remedy for a wide range of cancers, and noscapine is currently in phase I/II clinical trials. The significant *in vivo* antitumor activity coupled with its minimal toxicity is probably derived from the weak interaction between noscapine and tubulin.

#### ***Mechanism of noscapine as anticancer drug***

The mechanism by which noscapine kills the cancer cells is a result of this kinetic stabilization of the microtubules and not the action of the drug on the assembly and disassembly of the polymer. Noscapine has been shown to have negligible toxicity and does not suppress humoral- or cell-mediated immunity. This is the unique combination of properties that makes noscapine so special. Therefore, noscapine and its analogs have great potential as novel anticancer agents.<sup>[7]</sup>

#### ***Noscapine in primary/secondary brain tumor***

Glioblastoma is challenging cancer to find therapeutic agents that can cross BBB without being cytotoxic to the rest of the brain tissue. The current chemotherapeutics poorly penetrate this barrier. Patients with glioblastoma live on average only another 9–12 months because astrocytic tumor growth is so infiltrative that complete surgical resection is difficult. Often, 90% of the tumors recur within 2 cm of the original tumor. Importantly, noscapine can cross the BBB and inhibit glioblastoma cell proliferation. The downside would be the short plasma half-life and rapid elimination, requiring frequent injections for a successive chemotherapeutic approach.

Noscapine significantly inhibits proliferation of C6 glioma cells. When noscapine administered orally to mice that were implanted with rat C6 glioblastoma tumor cells, tumor volume was reduced significantly.

Microtubule-targeting agents can cause peripheral neuropathy such as tubulovesicular accumulations and axonal degeneration. There is no evidence of any peripheral neuropathy with noscapine. The glioblastoma-ridden mice experienced no toxicity in the duodenum, spleen, liver, or hematopoietic cells.

TMZ is the current standard of care, but its efficacy has been challenged. Glioblastoma typically recurs and then are resistant to the TMZ treatment, further dwindling the survival rate. Noscapine showed its strength as an anticancer drug by inhibiting the growth of TMZ-resistant glioma cells by causing G2/M arrest.

When given in combination with the current chemotherapeutics, noscapine increases the anti-proliferation effects of TMZ, BCNU, and CIS in U87MG human glioblastoma cells *in vitro*.

However, even at the highest experimental dose, noscapine had little effect on the survival and proliferation of normal and glioma-associated brain endothelial cells. Noscapine improves radiation sensitivity of gliomas, causing a significant growth delay and a decrease in tumor vessel density and tubule formation; hence, this drug may prove especially useful in glioblastoma patients who are candidates for radiation therapy.<sup>[8]</sup>

#### **Current treatment modalities used for primary/secondary brain tumors**

In light of these findings, it is evident that in certain pathological conditions, opening of the BBB occurs. An advantage of this knowledge is taken to deliver drugs across the BBB. The approach involves deliberate opening of the tight junctions of the BBB or delivery of drugs “through” or “behind” BBB by manipulating the physicochemical properties of the drug.

- BBB opening method involves use of hyperosmolar agent (1.4 M mannitol) administered through intracarotid infusion followed by delivery of active agent
- Chemical modification of BBB can also be brought about by administration of vasoactive compounds including bradykinin, interleukin, and leukotrienes; intrathecal or intraventricular administration of drug or site administration (e.g., intra-tumor injection, gliadel wafer placed at the tumoral region) can also be performed for effective delivery.
- Convection-enhanced delivery is another method for delivery of agents to the brain.

However, above-mentioned methods have major drawbacks including irreversible opening of BBB that potentially allows entry of exogenous materials such as viruses and bacteria and allows limited spatial distribution of the drug.<sup>[9]</sup>

#### ***Nanoparticles particles in the treatment of primary and secondary tumors***

Nanoparticulate-based drug delivery systems have opened new avenues for the treatment of gliomas and other types of

brain tumors. Due to small size, nanometric material causes better permeability of therapeutic agents into cells compared to conventional therapy. Particles less than 200 nm can easily pass the BTB due to leaky vasculature and around 100 nm size surface-modified particles can circumvent the barrier. Nanoparticles due to small size and modifiability warrant their selective uptake by tumor cells. They can be formulated out of variety of substances and can carry multiple loads of drugs directing the substance toward the tumor cells. Due to the feature of modifiability possessed by the nanoparticles, they reduce the peripheral side effects and increase the relative amounts of drug reaching the brain by crossing the barrier.<sup>[10]</sup> Thus, in comparison to conventional therapies, nanoparticles reduce the side effects. This concept of nanoparticulate-based drug delivery systems for the treatment of brain tumors is discussed below.

### ***Predominant nanoparticulate drug delivery systems used for the treatment of primary/secondary brain tumor***

Nanoparticulate drug delivery systems that are currently under investigation for the treatment and diagnosis of primary brain tumor include liposome, polymeric nanoparticles, quantum dots, and polymeric micelles.

#### ***Liposomes***

Surface-engineered liposomes designed by attaching ligands, carriers, and other entities make them act as a cargo system for drug delivery within the brain.<sup>[11]</sup> These are suitable systems to deliver the drug across the barrier because of the compositional similarity of liposome and endothelial cells of the barrier. Endothelial cells of the barrier and astrocytes of the brain are composed of phosphatidylinositol, phosphatidylserine, phosphatidylcholines, and phosphatidylethanolamines. First attempts to use liposomes for active brain targeting were made by conjugating murine 0X26, the monoclonal antibody to pegylated liposomes for targeting the rat transferrin receptor.

#### ***Polymeric nanoparticles***

Polymeric nanoparticles are submicron-sized colloidal particles (100–500 nm) with a therapeutic agent of interest

encapsulated within their polymeric matrix adsorbed or conjugated onto the surface. They are promising drug delivery systems due to their capacity to release the loaded drug, relatively high intracellular uptake, biodegradable nature, and improvement in stability of the drug.<sup>[12]</sup> The luminal and abluminal protein composition of the capillary endothelial cells of the BBB is different, indicating protein requirement of the cells. Nanoparticles of these protein structures loaded with the drug can be prepared and administered. These protein nanoparticles might be mistaken for endogenous proteins and thus can cross the BBB. Further anchoring of these particles with endogenous nutrients such as glucose, choline, amino acids and monocarboxylic acids promotes passage through the barriers with increased concentrations on the other side of the barrier [Table 2].

### **Nose-to-brain transport of nanoparticles**

Nanoparticles may offer an improvement to nose-to-brain drug delivery since they are able to protect the encapsulated drug from biological and/or chemical degradation and extracellular transport by P-gp efflux proteins. This would increase central nervous system (CNS) availability of the drug. A high relative surface area means that these nanoparticles will release drug faster than larger equivalents. Their small diameter potentially allows nanoparticles to be transported transcellularly through olfactory neurons to the brain via the various endocytic pathways of sustentacular or neuronal cells in the olfactory membrane. Surface modification of the nanoparticles could achieve targeted CNS delivery of a number of different drugs using the same “platform” delivery system which has known and well-characterized biophysical properties and mechanism(s) of transit into the CNS.<sup>[23]</sup>

## **CONCLUSION**

Both brain metastasis and primary glioblastoma are devastating brain cancer. Despite aggressive therapeutic

**Table 2:** List of nanoparticles used in primary/secondary brain tumor

Formulation	Size (nm)	Materials	Loaded molecules	Applications on brain tumors	Refs
Liposomes	60–500	Soy phosphocholine, DSPC	Doxorubicin, cisplatin,	Brain metastasis	[13]
Micelles	10–60	mPEG-b-PCBLLys	siRNA, Platinum, Paclitaxel	Glioblastoma	[14]
Dendrimer	5–250	PAMAM, PPI, PEG, PCL, PLLA	Paclitaxel, Gadolinium, Cy5.5, 5-fluorouracil	Glioblastoma	[15-17]
Polymer	10–60	PLGA, poly(beta-amino ester), poly(trimethylene carbonate), PLA-PEG-PLL	miR-7, DNA, siRNA, paclitaxel	Brain metastasis	[18,19]
Suprapara magnetic iron oxide	5–30	Iron oxide oleic acid amphiphilic polymer	Doxorubicin TMZ	Brain tumor theranostics	[20-22]

TMZ: Temozolomide

interventions, the prognosis of these brain cancer patients remains extremely poor. The emerging of nanotechnology and tumor biology opens up great possibilities for effective delivery of the novel molecules to facilitate brain tumor treatment.

To achieve the ultimate clinical translation of noscapine nanoparticles delivery system, a great deal of effort through interdisciplinary collaborations will be required to optimize dose, the design of nanocarrier, to improve the bioavailability at target site with minimal toxicity, *in vivo* pharmacokinetics, and targeting efficacy through intranasal route.

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