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Abstract
The current standard of care in glioblastoma management is surgery followed by chemotherapy and radiotherapy. Temozolomide is an alkylating agent most commonly used with a few other second line options. The efficacy of systemic chemotherapy in brain malignancies is limited due to the nature of the blood-brain barrier. Nanomedicine offers one avenue of improving drug delivery to these tumours in a more focussed and effective way in higher doses than currently possible, while simultaneously reducing systemic toxicity.

Keywords: Glioblastoma multiforme, brain tumour, nanotechnology

Introduction
Glioblastoma (GBM), is a WHO grade IV pathology and has a dismal prognosis.1 Despite advances in treatment, the current therapy based primarily on surgical resection with adjuvant chemotherapy and radiotherapy offers modest temporary disease control.2 The blood-brain barrier (BBB) is a formidable impediment to drug delivery in the brain which limits the promise of effective chemotherapy in vivo. Nanomedicine offers a unique promise of more precise drug delivery with several options currently under investigation.

Review of literature
Nanoparticles (NPs) are natural, incidental or manufactured materials composed of particles ranging between 1 nm and 100 nm in size. NPs are being investigated as an alternative approach in anticancer therapies in order to improve targeted drug delivery, reduce side effects and avoid drug toxicity and resistance.3 The strategy can actively transport small molecular drugs, gene medicines and therapeutic proteins to specific tumours including the commonest primary malignant brain tumour, glioblastoma multiforme (GBM). In order to achieve therapeutic targets, drug delivery systems should exhibit high drug loading capacity, good biocompatibility and biodegradability profiles, effective tumour penetration, enhanced cellular internalization, controlled drug release and the ability to evade mononuclear phagocytic system so as to avoid premature degradation of drugs.4

Accumulation of NPs at tumour site in brain depends upon two factors, a passive deposition due to enhanced angiogenesis, leaky vasculature and restricted lymphatic drainage as compared to normal tissue (Enhanced Permeability and Retention or EPR) and active targeting of moieties that are ligands for BBB or glioma receptors.

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(lactoferrin and folate) since transport of molecules across BBB is receptor mediated. Furthermore, data is present to suggest promising potential in hitchhiking of NPs on blood cells, preferably monocyte and macrophages, thereby exploiting their abilities to circumvent biological membranes.6

Current advances in NPs have generated a wide range of both organic and inorganic NPs that are under investigation for GBM treatment. These include liposomes, polymeric NPs (PNP), lipid nanocarriers (LNC), metal organic framework (MOF), porous silicon (pSi), EnGenIC delivery vehicle (EDV™) and mesoporous silica NPs (MPN) to name a few. Each of these possess, and often share, characteristics that grant certain merits and demerits. Most possess the advantage of penetrating BBB, high drug

Figure: MRI Brain with contrast (T1 weighted post gadolinium) images demonstrating a left frontal deep glioblastoma. Lesions like these are not suitable for gross total resection due to their relationship with important eloquent areas. NPs delivering effective chemotherapy to such lesions would break new grounds in management.
loading capacity, biocompatibility and the ability to convey both hydrophilic and hydrophobic drugs. In particular, liposome drug delivery systems, EDV™ and pSi are simple and suitable for large scale production. Liposomes and PNP exhibit preferential accumulation of drugs in tumour tissue. MOFs have adjustable structure and the potential to act as adjuvant for radio-sensitization. Psi can not only deliver multiple cargos, but also potentially limit GBM invasiveness. High adsorptive properties and organized pore framework of MSN address the issues with NP stability. Moreover, their modifiable particle size, easily functionable surfaces and ability to improve drug pharmacokinetics and stability profile, shows promise to mitigate challenges involved in drug delivery to the brain. PNP improve plasma circulation and half-life of drugs, hence, increase bioavailability. LNCs require less raw material, are stable and have a more sustained drug release.

Most of these approaches are under pre-clinical or early clinical trials for both in-vitro and in-vivo models. There are still significant barriers that limit the utilization of NP based drug delivery systems in treatment of GBM. Most significant among these is the safety profile. Further concerns are stability, regulatory mechanisms, variance of pharmacodynamics among different individuals and need for development of techniques to monitor drug accumulation at target site. In view of constant experiments, it is believed that in-depth knowledge of mechanisms involved in diffusion kinetics of nanoparticles along with cellular and molecular studies focused on understanding GBM microenvironment, will provide crucial information in the quest to design novel GBM specific nanotherapeutics.

**Conclusion**

Despite significant challenges, nanoparticle based drug delivery systems are emerging as a promising field for the treatment of glioblastomas. With numerous formulations being tested, the choice of nanomaterial is an ongoing debate which warrants extensive investigation with regard to their biological and toxicological behaviour. Success might still be a long way, but the application of NPs display optimism to increase long term survival rates and possibly revolutionise the treatment of GBM.

**References**


