Tackling glioblastoma with engineered small molecules

Glioblastoma (GBM) continues to be one of the most aggressive and deadly cancers of the central nervous system. Despite decades of research, the prognosis for patients diagnosed with this disease remains grim, with median survival rarely exceeding 15 months (Poon et al., 2020). A major challenge in treating GBM lies in the tumour's location behind the blood-brain barrier (BBB), a physiological fortress that limits the entry of many potentially effective therapies to the brain. This barrier is a selectively permeable boundary formed by endothelial cells tightly joined together and supported by astrocytic endfeet and pericytes. Its primary function is to protect the brain from harmful substances and pathogens, but this protective role comes at a cost: it significantly limits the delivery of therapeutic agents (Abbott et al., 2010).

The BBB restricts the entry of most macromolecules and over 98% of small molecule drugs (Pardridge, 2012). Active efflux pumps such as P-glycoprotein and breast cancer resistance protein (BCRP) further limit drug accumulation in the brain by actively transporting compounds back into circulation. While glioblastoma can disrupt the BBB in localised regions, this disruption is inconsistent and often insufficient for uniform drug delivery across the entire tumour mass and its infiltrative margins (Arvanitis et al., 2020).

As a result, traditional cancer treatments often fail to deliver therapeutic concentrations to the tumour. Any successful compound must not only be cytotoxic to tumour cells, but must also possess physicochemical properties that allow it to cross the BBB effectively. Recent advances in the design and engineering of biologics, vectors and small molecules offer a promising pathway to surmount this challenge and potentially transform the landscape of GBM treatment.

Some of these approaches, including engineered small molecules developed by our company CNS Pharma, are discussed here.

The anticancer medicine temozolomide remains the most widely used chemotherapeutic for GBM due to its ability to cross the BBB and alkylate DNA, leading to tumour cell death (Stupp et al., 2005). However, resistance develops quickly, often due to MGMT-mediated DNA repair. MGMT (O6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that plays a critical role in protecting cells from DNA damage. Patients with unmethylated MGMT have a poorer response to chemotherapy, as the MGMT gene encodes the enzyme that repairs DNA damage caused by alkylating agents, such as temozolomide.

Newer agents are being developed to overcome these limitations. For example, bispecific antibodies with penetrative abilities to break through the BBB are being developed, and others are taking the approach of optimising molecular vectors to transport drug payloads into the brain.

Small molecules also show a lot of promise as effective therapies to cross the BBB. At CNS Pharma, we're developing anti-cancer therapies derived from well-established, trusted drug classes like taxanes and anthracyclines that are now engineered to cross the BBB. Each of these small molecules inhibits the dynamics of cell division, offering a comprehensive assault on the growth of cancer cells with the aim of becoming a solution for all GBM patients regardless of their MGMT methylation status.

In a recent study, berubicin, CNS Pharma's anthracycline that can cross the BBB, showed non-inferior clinical activity compared to standard of care in patients with recurrent GBM with a favourable safety profile. Although it did not show a statistically significant difference in overall survival, we believe that berubicin still warrants further investigation as a small molecule approach for patients in need of further treatment options. CNS is also advancing our engineered taxane-derivative, TPI 287 as a potential GBM treatment. TPI 287 is lipophilic, unlike traditional taxanes, allowing it to cross the BBB, and it works by stabilising microtubules, disrupting mitosis and promoting cell death. It also shows reduced susceptibility to a variety of efflux pumps that constitute the BBB, which typically cause taxane resistance in tumors.

Glioblastoma remains one of the most formidable challenges in oncology due to its aggressive nature, high recurrence rate, and the protective blood-brain barrier that limits therapeutic options. However, recent advancements in the rational design and engineering of small molecules and other therapeutic modalities offer renewed hope.

By understanding the principles of BBB permeability and applying cutting-edge tools, researchers are now better equipped to develop therapies that not only reach their target but also engage it effectively. While these approaches are still emerging, they represent a critical step toward more effective and personalised treatment strategies for glioblastoma.

With continued interdisciplinary collaboration, the goal of delivering life-extending and ultimately curative therapies for GBM is moving from aspiration to possibility.

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