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Keywords

Brain tumour, nanomedicine, nanoparticle, theranostic, glioblastoma, doxorubicin, paclitaxel

Brain metastases and primary CNS tumours

Brain metastases are the most frequently occurring neurologic complications of cancer in adults, with 9 – 17% of all cancers resulting in brain metastasis and brain metastasis occurring in 8 – 14 per 100,000 in the general population [1]. Primary brain tumours, on the other hand, are relatively rare, and comprise about 1.4% of cancers [2]. Brain metastases are associated with a median survival times of about 3 – 25 months [3], and a 5 year survival rate of 1.8% [4]. Treatment modalities employed for brain metastases include: surgical resection, whole brain radiation therapy, radiosurgery and chemotherapy [5]. The choice of treatment would usually be based on several considerations. These include: histopathology of the primary tumour, status of systemic disease, patient’s performance status (general well being and lifestyle activity level), age of the patient, number and sites and precise location of the
brain metastases (such as proximity to sites of vital brain function), co-existing morbidities, and symptoms [2,5].

Glioblastoma multiforme (WHO Classification astrocytoma Grade IV), a metastatic primary brain tumour, accounts for 12 – 15% of all brain tumours [6] and is the most common primary brain tumour in adults [7]. Glioblastoma is an aggressive metastatic astrocytoma with a median survival of 14 months and less than 5% of patients survive for 3 years [8]. This tumour is difficult to diagnose early as the tumour is usually asymptomatic or presents with symptoms which are difficult to associate with GBM, e.g. symptoms associated with a high intracranial pressure (headaches, nausea, vomiting and cognitive impairment) [9]. A major contribution to the poor survival rates is the insufficient transport of therapeutic molecules across the blood brain barrier (BBB) [10]. The current standard of care comprises surgical resection to the maximum possible extent, followed by concurrent radio–chemotherapy and adjuvant chemotherapy with temozolomide [2]. This treatment regimen became the standard of care for newly diagnosed glioblastoma patients after the results of the 2004 European Organisation for Research and Treatment of Cancer 26981-22981/ National Cancer Institute of Canada Clinical Trials Group CE3 randomised phase III trial demonstrated a 20.7% improvement in the median survival as well as 27.2% two-year survival rates in glioblastoma patients, who had received post-surgical concomitant and adjuvant temozolomide (known as the Stupp regimen) compared to 10.9% two-year survival rates with post-surgical radiotherapy alone [11]. For recurrent glioblastoma on the other hand, there is currently no standard treatment regimen [12], and thus patients frequently receive investigational agents in clinical trials [13].

The Blood Brain Barrier (BBB)

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protected by the intact blood brain barrier (BBB), which maintains the brain
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methyltransferase (MGMT), a ubiquitous protein encoded by the MGMT gene [14].

Passive Targeting with Nanoparticles

Nanoparticles have been used to passively target drugs to intracranial tumours, on
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Intravenously administered nanoparticles for delivery of therapeutic agents to brain tumours may theoretically exploit the enhanced permeability and retention (EPR) effect, whereby particles extravasate through a leaky tumour vasculature and achieve closer proximity to the tumour cells [20]. However for the EPR effect to be operational, the BBB must be compromised at the site of the intracranial tumour and while the breakdown of the BBB is diagnostic of a high grade glioma [21] most tumours are associated with an intact BBB [22] and direct evidence of nanoparticle accumulation within intracranial tumour cells is difficult to find. Early activity in this area focused on the delivery of P-gp efflux pump substrates to the brain in an attempt to circumvent the blood tumour-cell barrier. The P-gp substrate [23], doxorubicin, when intravenously injected in poly(butylcyanoacrylate) nanoparticles, resulted in increased tumour tissue accumulation, in a mouse C6 glioma rat model, when compared to healthy tissue and an attendant improvement in tumouricidal activity was observed with these nanoparticles when compared to the drug in solution [24]. Additionally, the formulation was also found to be less cardiotoxic. This provides indirect evidence that nanoparticles are able to take advantage of a variation in the BBB at the tumour site.

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These image competent nanotherapeutics may prove interesting in the treatment of diffuse brain metastasis in multiple brain regions.

Conclusions

Glioblastoma and brain metastasis are still areas of unmet medical need and several nanoparticle formulations are showing promise in glioblastoma rodent models of the disease with a few even transitioning to clinical testing. The leaky vasculature in brain tumours has been exploited to concentrate drug-laden nanoparticles at the tumour site, following intravenous injection. Additionally, various across BBB transport and cell uptake ligands have been employed within a single nanoparticle to enable drug to be concentrated in tumour cells in the presence of an intact BBB, following intravenous injection. These combined systems are known as dual targeting systems. Recent studies have introduced MRI and near infrared imaging to drug loaded nanoparticles, enabling targeting to be imaged with these new theranostics. The transferrin receptor has been widely exploited for across BBB transport, in these experimental studies, and a number of cell uptake ligands employed in the dual targeting approaches. It remains to be seen if the promising rodent data is indeed translatable to the clinical situation and attention will need to be turned to the issue of manufacturability if the ligand targeting systems are to transition into clinical products.

Financial & competing interests disclosure

The authors have no competing interests to declare.
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Imaging agents and drugs transported by a single nanoparticle is another area of innovation that has been applied to the treatment of experimental brain tumours and these are known as theranostics [17,36]. Intravenously administered polymeric nanoparticles loaded with smaller iron oxide nanoparticles (for magnetic resonance imaging – MRI), surface decorated with a tumour vasculature targeting F3 peptide (a 31-amino acid sequence of the NH2-terminal fragment of human high-mobility group protein 2) and encapsulating photofrin for photodynamic therapy (PDT), were accumulated within the intracranial tumour in a 9L glioma rat model, following intravenous administration, as visualised using MRI [37]. This theranostic improved survival rates in this model following PDT when compared to plain nanoparticles in combination with PDT or photofrin alone in combination with PDT. Iron oxide as an MRI imaging agent is the contrast enhancement agent of choice with a number of theranostics. The combination of a tumour homing peptide (CGKRK), which targets the tumour endothelial and tumour cells and specifically their mitochondria with a pro-apoptotic peptide (D[KLAKLAK]2) as the drug, when coupled to elongated iron oxide nanoparticles (nanoworms), as the MRI contrast agent, has been shown to accumulate these targeted nanoworms in the tumour tissue following intravenous injection [38]. The targeted nanoworms were significantly more effective than non-targeted nanoworms in a lentiviral (H-RasV12-shp53) induced mouse brain tumour model.

An alternative method of labelling nanoparticles for imaging in a theranostic platform involves the use of porphyrin for near infrared imaging and as such 30 nm porphyrin-lipid apolipoprotein E3 (apoE3) lipid nanoparticles (pyE-LNs) with intrinsic imaging properties via the porphyrin lipid have been studied [39]. Across BBB delivery and tumour cell uptake properties were achieved using ApoE as ApoE is taken up by the low-density lipoprotein receptor (LDLR) on brain endothelial cells and tumour cells, where in the latter case, the LDLR receptor is upregulated [39]. After intravenous administration to a U87 Green Fluorescent Protein (GFP) mouse model, the particles were found to accumulate within brain tumour tissue.

These image competent nanotherapeutics may prove interesting in the treatment of diffuse brain metastasis in multiple brain regions.
Conclusions

Glioblastoma and brain metastasis are still areas of unmet medical need and several nanoparticle formulations are showing promise in glioblastoma rodent models of the disease with a few even transitioning to clinical testing. The leaky vasculature in brain tumours has been exploited to concentrate drug-laden nanoparticles at the tumour site, following intravenous injection. Additionally, various across BBB transport and cell uptake ligands have been employed within a single nanoparticle to enable drug to be concentrated in tumour cells in the presence of an intact BBB, following intravenous injection. These combined systems are known as dual targeting systems. Recent studies have introduced MRI and near infrared imaging to drug loaded nanoparticles, enabling targeting to be imaged with these new theranostics. The transferrin receptor has been widely exploited for across BBB transport, in these experimental studies, and a number of cell uptake ligands employed in the dual targeting approaches. It remains to be seen if the promising rodent data is indeed translatable to the clinical situation and attention will need to be turned to the issue of manufacturability if the ligand targeting systems are to transition into clinical products.

Financial & competing interests disclosure

The authors have no competing interests to declare.

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