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Review article

Intranasal delivery in glioblastoma treatment: prospective molecular treatment modalities

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ABSTRACT

Glioblastoma multiforme (GBM) is rare and fatal glioma with limited treatment options. Treatments provide minimal improvement in prognosis and only 6.8% of GBM patients have a life expectancy greater than five years. Surgical resection of this malignant glioma is difficult due to its highly invasive nature and follow-up radiotherapy with concomitant temozolomide, the currently approved standard of care, and will only extend the life of patients by a few months. It has been nearly two decades since the approval of temozolomide and there have been no clinically relevant major breakthroughs since, painting a dismal picture for patients with GBM. Although the future of GBM management seems bleak, there are many new treatment options on the horizon that propose methods of delivery to circumvent current limitations in the standard of care, i.e., the blood brain barrier and treatment resistance mechanisms. The nose is a highly accessible non-invasive route of delivery that has been incorporated into many investigational studies within the past five years and potentially paves the path to a brighter future for the management of GBM. Intranasal administration has its limitations however, as drugs can be degraded and/or fail to reach the site of action. This has prompted many studies for implementation of nano-particle systems to overcome these limitations and to accurately deliver drugs to the site of action. This review highlights the advances in intranasal therapy delivery and impact of nanotechnology in the management of GBM and discusses potential treatment modalities that show promise for further investigation.

1. Introduction

1.1. Glioblastoma: epidemiology, diagnosis and treatment

Glioblastoma multiforme (GBM) is a devastating and fatal malignant brain tumor that occurs in roughly 3.22 in every 100,000 adults as reported by the Central Brain Tumor Registry of the United States (CBTRUS) with a mean age of diagnosis of 65 [1]. The World Health Organization (WHO) classifies GBM as a grade IV tumor which encompasses malignancies that have an evolutionary pattern that is rapidly changing throughout the course of the disease resulting in an unfavorable prognosis in many, if not all, patients [2]. GBM in comparison to other malignant CNS tumors occurs the most frequently, encompassing 48.3% of CNS tumors classified as malignant [1].

GBM diagnosis begins with presence of symptomology (e.g. cognitive decline, headaches, vomiting) that warrants further investigation by means of magnetic resonance imaging (MRI) as a means to identify the suspected tumor and begin the currently accepted treatment protocol involving surgical resection followed by radiotherapy and temozolomide (TMZ)

chemotherapy [3, 4, 5]. Patients battling GBM receiving current SOC have an overall life expectancy of around 15 months and only 6.8% of patients diagnosed with GBM have a life expectancy greater than five years following their initial diagnosis [1, 2, 3]. In the past few decades, several treatment avenues have been explored but their efficacy in improving patient prognosis while preventing morbidity and mortality has been minimal [6].

The issue with GBM management is a lack of treatment methods that can bypass the blood brain barrier (BBB), reach the site of action, and initiate tumor cell apoptosis without added cytotoxicity to normal brain cells [6]. Several avenues have been studied, but each contains its own set of complications, e.g., off-target accumulation, extensive side effect profile, and toxic drug concentrations. Bypassing the BBB via the intranasal (IN) route seems to be the most plausible method in delivering therapy at a reasonable dose and reaching the correct target [7]. This ensures accurate drug accumulation and additionally a means of circumventing the previously mentioned limitations. The purpose of this review article is to highlight the current and prospective treatment approaches in the management of GBM with a focus on IN route of administration and the role of nanoparticles (NP) as an IN-delivery platform.

Figure 1 highlights the nose to brain drug delivery in overcoming the challenges in the treatment of GBM.

2. Methods

To compile relevant studies discussing the use of IN delivery of nanotechnology in GBM, PubMed and Google Scholar were utilized, and search criteria were restricted to articles published in the past decade. To ensure specificity, key words such as "intranasal", "nanoparticles", "nanotechnology", "glioblastoma", and "GBM" were used. A search using the phrase "intranasal delivery of nanoparticles in GBM" populated 18 articles that were analyzed and included based on their relevancy. Articles that highlighted the effectiveness and safety of NP delivery in the management of GBM were chosen to compose this review. The different IN NP strategies are discussed in depth and a speculatory evaluation is proposed on the future of IN nanomedicine in GBM.

3. TMZ in GBM management

TMZ was FDA approved for the management of GBM in 2005, which provided a ray of hope for the bleak picture that is GBM by improving patient survival by 2.5 months. It has been nearly two decades since the approval of TMZ, and it remains the standard of care for GBM management, but survival rates have unfortunately remained stagnant. TMZ remains a mainstay treatment.

3.1. Existing TMZ modalities

In the hallmark study performed by Stupp et al., the efficacy of radiotherapy as monotherapy vs combination therapy (radiotherapy plus TMZ) was compared. The study reported a 2.5 month increase in survival rate with combination therapy when compared to radiotherapy alone which only had a mean survival rate of 12.1 months. It was determined upon completion of this study that combination therapy is beneficial and results in a 17% increase in overall survival of patients diagnosed with GBM [3]. Since this study, a variety of agents such as bevacizumab, curcumin, nivolumab and leveteracetam have been tested in combination with TMZ with limited success and need to be evaluated further to determine their place in GBM management [8, 9, 10, 11]. This list of agents is not exhaustive and improving the efficacy of TMZ is still an area of interest in GBM management.

a. Prospective Modalities with Concomitant TMZ

More recently, the use of tumor treatment fields (TTF) as a noninvasive strategy to target the GBM tumor microenvironment is being explored and its efficacy in combination with TMZ shows promise in improving overall patient survival [12]. Minea et al. experimented with attaching TMZ to perillyl alcohol (POH) to form the novel compound NEO212 to overcome radiosensitization limitations that occur with radiotherapy and concomitant TMZ. The result of *in vivo* administration of the novel compound resulted in targeted delivery and efficient BBB penetration that exceeded that of TMZ [13].

Puente et al. experimented with TMZ hydrogel and radioactive isotope ^{131}I to be locally administered to the tumor as an implant. The study reported a 10-fold increase in TMZ accumulation in the tumor region and tumor suppression was reported in both treatment groups compared to the control group and warrants further investigation [14]. Khan et al. also experimented with incorporating TMZ in a novel chitosan hydrogel to be delivered IN and established its safety and efficacy as a targeted drug delivery system to the brain, but follow-up studies have not been performed to establish its role as an approved non-invasive platform for GBM management [15].

The use of the IN route to deliver immunostimulant compounds prior to initiation of TMZ therapy is also an area of interest. Yin et al. and Sukumar et al. explored the use of nanotechnology to IN deliver double
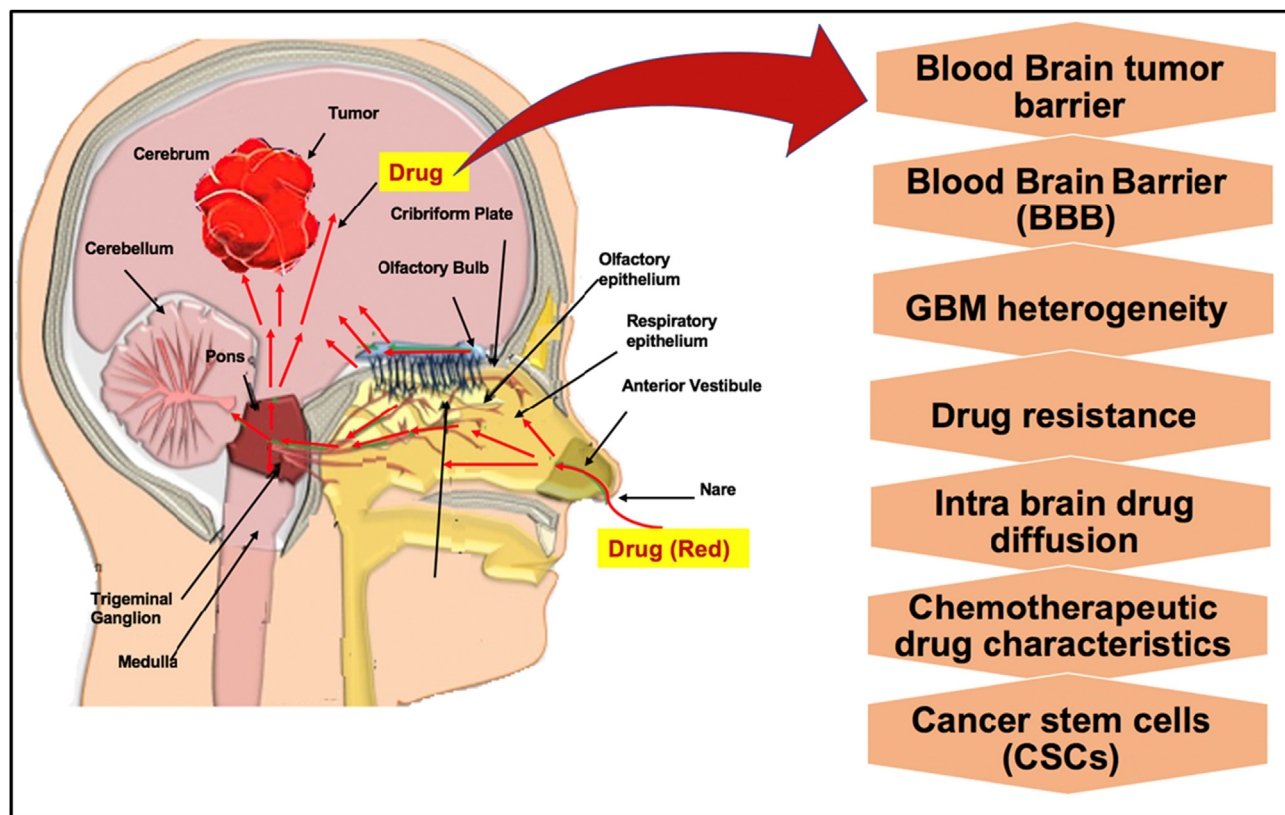

Figure 1. Illustrates challenges and opportunities in the nose to brain drug delivery approaches for the treatment of GBM. The olfactory and trigeminal nerve pathways play a key role in circumventing the traditional barriers of brain targeting.

stranded RNA (dsRNA) and microRNA (miRNA), respectively, the results of which will be discussed in this review [16, 17]. These studies highlight the future of non-invasive and invasive approaches that can be implemented in conjunction with TMZ therapy.

4. Issues in GBM management (Figure 1)

a. The BBB

The complexity of this glioma is a function of multiple factors such as the protective gateway of the brain known as the BBB, the development of treatment-resistant tumor cells, lack of targeted delivery to the tumor, and off-target drug accumulation in the periphery [6, 18]. The BBB consists of endothelial cells, a basement membrane, astrocytes, and immune cells [6, 19]. In an effort to maintain brain homeostasis and any type of interaction with the brain parenchyma, the BBB is also equipped with tight junctions to prevent pathogens, toxins, and in most cases, drug therapy from infiltrating the brain [19].

b. Treatment Resistance

The DNA alkylating oral agent TMZ has been proven to be effective in penetrating the BBB and improving patient survival in GBM, but resistance occurs. Mechanisms such as expression of O^6-methylguanine methyltransferase (MGMT) rendered the treatment ineffective in LN-18, T98G, and U138 GBM cell lines [20]. The combination of MGMT expression and other resistance mechanisms results in 50% of GBM patients becoming ineligible for TMZ therapy [21]. Methods of overcoming this resistance involving the use of levetiracetam and interferon alpha (IFNα) to inhibit MGMT expression in MGMT positive cell lines such as U138, GSC-1, U118, and T98 G are currently being studied [22]. Resistance mechanisms and physiological barriers continue to hinder the development of effective treatment options in GBM and alternative treatment methods are desperately needed.

5. Potential impact of in delivery and nanotechnology

a. The IN Route

The IN route has been studied for many years as a means to deliver drugs locally and systemically for a multitude of conditions, and in the past decade this concept has been explored to deliver drugs directly to the brain in an effort to circumvent the BBB and treat many disorders of the CNS [23]. The nose has many appealing aspects regarding drug delivery. It is easily accessible, highly vascularized, and allows for lower doses of medications due to minimal first pass metabolism [7, 24]. This route is ideal when a particular therapy has been deemed effective in treating a condition but cannot be delivered orally or intravenously [24]. IN delivery is applicable in GBM because it is non-invasive, has potential to decrease the side effect profile of current therapies, and allows for targeted treatment delivery to the tumor region via the olfactory and trigeminal nerves [25]. The IN route does have some complications however, such as irritation of the nasal cavity, mucociliary clearance, and IN metabolism mediated by a variety of enzymes [26, 27]. These IN complications become less of an issue when therapy is delivered via nanocarriers, which are biocompatible formulations that are readily absorbed by the nasal mucosa [28, 29].

b. Nanoparticles (NPs) and the IN Route

IN using nano delivery systems might overcome and optimize efficient drug delivery across the BBB and BTB. In that regard, some factors like hydrophilicity/lipophilicity of a drug, rapid nasal clearance, enzymatic degradation could hinder the bioavailability via nasal route. Therefore, using nano delivery system for prolonged nasal residence time could improve the pharmacokinetics/biodistribution for adequate pharmacodynamic response along with efficient BBB and BTB delivery (Table 1).

NPs are a well-established delivery platform with several formulations that vary in composition (lipid-based, polymer-based, metal-based), size (1–100 nm), biocompatibility, release profile and targeting ability depending on their surface moiety [30, 31]. In the past decade numerous studies have been conducted exploring the application of NPs to carry chemotherapeutic agents while simultaneously decreasing side effects, prolonging drug release, and reaching physiological targets efficiently [32, 33, 34, 35]. IN delivery of NPs is of particular interest more recently as strategies are regularly being developed to overcome and improve upon therapies that have been documented as efficacious but present with limitations as a result of the BBB [36].

c. Examples of IN Delivery Application

i. IN Delivery of Bevacizumab Polymeric-NPs

As discussed previously, treatment resistance to TMZ occurs in roughly 50% of GBM patients and in an effort to bypass this limitation, the anti-angiogenic agent bevacizumab (BVZ), an intravenous monoclonal antibody, was developed to cut off tumors' access to vascular endothelial growth factor (VEGF) and ultimately halt further tumor growth. The agent was determined to be unviable in GBM however, because of low BBB penetration efficiency and peripheral toxicity, which is the long-standing issue in the treatment of GBM [36, 37, 38].

Sousa et al. sought to determine the viability of BVZ when delivered IN via poly (lactic-co-glycolic) acid (PLGA) NPs to increase BBB penetration and decrease the systemic toxicity issues associated with IV administration. The BVZ-PLGA-NPs and

Table 1. Summary of Prospective Treatment Strategies for the Management of GBM Based on in vivo preclinical Studies.

Drug Carrier	Agent	Mechanism of Action	Route of Administration	Preclinical Results	References
Polymeric NPs (PLGA)	Bevacizumab	Anti-VEGF monoclonal antibody	Intranasal	Decrease in tumor size and VEGF	[36]
	Paclitaxel	Mitotic Inhibitor	Intranasal	Inhibition of tumor cell growth	[41]
	Doxorubicin	Topoisomerase II Inhibitor	Intranasal	Inhibition of tumor cell growth	[42]
Polyfunctional Gold–Iron Oxide NPs (polyGIONs)	antimiR-21	Inhibition of p53	Intranasal	Tumor suppression and enhanced TMZ efficacy	[17]
	miR-100 + TMZ	Inhibition of PLK1			
Gold NPs	Polycytidylic acid + TMZ	Induction of Type 1 Interferon + DNA Methylator	Intranasal	Tumor suppression	[16]
Heavy Chain Ferritin Nanocage	Paclitaxel	Mitotic Inhibitor	Intravenous	Inhibition of tumor cell growth	[49]
PLA Polymeric Micelle	Paclitaxel	Mitotic Inhibitor	Intravenous	Inhibition of tumor cell growth	[51]
sHDL Mimicking Nanodiscs	Docetaxel	Inhibition of Microtubular Depolymerization	Intracranial	Tumor regression	[57]

TMZ = Temozolomide, PLGA = Poly Lactic Glycolic Acid, VEGF = Vascular Endothelial Growth Factor, PLA = Poly Lactic Acid, sHDL = Synthetic High-Density Lipoprotein, PLK1 = Polo-kinase 1.

free-BVZ were delivered IN in healthy mice models and both agents accumulated in the brain (5400 ± 2313 ng/g of brain tissue and 1346 ± 391 ng/g of brain tissue, respectively), but unlike free-BVZ, the BVZ-PLGA-NPs maintained residence within the brain for >7 days with no off-site accumulation. Mice were then implanted with a human (U87 MG) GBM xenograft and IN administered free-BVZ and BVZ-PLGA-NPs to determine GBM treatment efficacy. The two-week post treatment analysis displayed free-BVZ accumulation in the lung and liver and none in the brain. Conversely, the BVZ-PLGA-NP group was remarkable for BVZ accumulation only in the brain, resulting in a decrease in VEGF and tumor size. The use of novel BVZ-PLGA-NP should be transitioned to the clinical setting to establish its role as a potential mono- or adjunct therapy in the management of GBM [36].

ii. IN Delivery of Novel RGD-NP-PTX

In a study performed by Ullah et al., IN delivery of NPs composed of PLGA loaded with paclitaxel (PTX) conjugated to a cancer targeting moiety, arginyl-glycyl-aspartic tripeptide (RGD), was evaluated for therapeutic efficacy and viability in mice implanted with human U87 MG GBM cells. PTX is a mitotic inhibitor known to specifically target malignant cells with a low risk in harming normal cells [39]. The RGD targeting moiety binds with high affinity to the integrin $\alpha_v\beta_3$, which is highly expressed by tumor cells [40]. It was determined that IN delivery of the RGD coated PLGA NPs loaded with PTX (RGD-NP-PTX) resulted in successful delivery of the nanoformulation to the GBM tumor microenvironment with a prolonged residence time of 48 h. Also, tumor cell death occurred in ~80 ± 5% of the U87 MG cells when assayed, and there was a tumor volume reduction of 26 ± 14 mm^3 in the U87 MG implanted mice models. It was concluded that PTX is a viable and efficacious treatment option in mice when loaded in the novel RDG-PLGA nanocarrier and delivered via the IN route. This preclinical discovery warrants further investigation in the realm of IN delivery of nanocarriers loaded with chemotherapeutic agents in the clinical setting [41].

iii. IN Delivery of Novel RGD-NP-DOX

An additional study was performed by Ullah et al. evaluating the use of doxorubicin (DOX) loaded PLGA-NPs with an RGD surface moiety (RGD-NP-DOX) for targeted delivery to the GBM tumor microenvironment [42]. The agent DOX is a topoisomerase II inhibitor already approved for the treatment of other malignancies and CNS disorders, but this study highlights its relevance as a viable treatment option when used IN in the management of GBM at the preclinical level [43]. Rats were intracranially implanted with GBM C6 cell lines and subsequently treated IN with RGD-NP-DOX and a 48-hour residence time, primarily in the tumor region, was observed. Also, IN delivery of RGD-NP-DOX resulted in 76 ± 3.91% tumor growth inhibition, and 15 ± 3.95 mm^3 reduction in tumor burden compared to control and other formulations of free-DOX and NP-DOX without RGD [42]. These results are indicative of targeted delivery to the tumor region via nanocarrier-mediated IN administration with promising inhibition of GBM cell growth. Thus Ullah et al. confirmed on the preclinical level the relevance of nose-to-brain delivery of DOX via a PLGA nanoformulation with promising results that should be transitioned to clinical trials.

iv. IN Delivery of T7-polyGIONs-miRNA with Concomitant TMZ

Sukumar et al. used the IN route not only to deliver NPs loaded with microRNA therapy to enhance TMZ therapy in GBM, but also to subsequently obtain a roadmap of the nasal cavity and its associated nerve pathways during drug delivery. In this study, miRNA therapies (antimiR-21 and miR-100) were loaded into novel theranostic polyfunctional gold-iron oxide NPs (polyGIONs) with a β-cyclodextrin-chitosan (CD-CS) hybrid polymer coated with PEG-T7 (targeting molecule) peptide and delivered IN in conjunction with TMZ therapy for *in vivo* analysis of tumor targeting efficiency and enhanced therapeutic efficacy. The T7-CD–CS–polyGIONs-miRNA was IN delivered into mice implanted with a U87 MG xenograft. Nanocarrier delivery was tracked using dye tagged to the miRNA molecules, which allowed accurate tracking from the nasal mucosa to associated nerve pathways and ultimately the brain. The NP containing miRNA accumulated in the appropriate region of the brain and resided there for ~8 days. In terms of tumor regression and overall survival, the T7-CD–CS–polyGIONs-miRNAs provided a ~42% reduction in tumor size, accumulation exclusively in the brain region, and survival >44 days with the control group surviving <16 days. The T7-coated NP group was compared to mice receiving the non-T7 coated NP, which yielded only a ~7.8% reduction in tumor size with diminishing accumulation in the brain and eventual peripheral organ off-loading [17]. This experiment demonstrated once again the viability of the IN route for targeted delivery to the GBM tumor microenvironment. It was shown that CD–CS–poly-GIONs loaded with miRNA followed by TMZ therapy is a suitable method to enhance an already approved GBM treatment option [17].

v. IN Delivery of Immunostimulant-NPs with Concomitant TMZ

Yin et al. utilized the IN route to deliver gold NPs (AuNP) combined with polyinosinic-polycytidylic acid (poly(I:C)), a synthetic dsRNA, to form novel compound Au@PP/poly(I:C). This novel NP is being used to initiate immunogenic cell death (ICD) by inducing the production of type I interferon (IFN–I) to enhance TMZ chemotherapy. ICD is not induced when TMZ is used alone, as this agent does not initiate the production of IFN-I, which warranted the investigation of supplementing TMZ with an immunostimulant [16, 44, 45]. Mice were intracranially implanted with GL261 glioma cells and treated with TMZ monotherapy, Au@PP/poly(I:C) monotherapy, TMZ in combination with Au@PP/poly(I:C), or not treated at all to compare tumor size and overall survival after five days of treatment. A significant decrease (p < 0.05) in tumor size was observed between the untreated group and all the other groups with the most notable difference observed between the untreated group and the combination therapy group, 16.80 ± 1.625 mm^2 vs. 3.800 ± 1.562 mm^2, respectively. Furthermore, the TMZ group had less decrease in tumor volume when compared to the combination therapy group, 5.200 ± 2.131 mm^2 vs. 3.800 ± 1.562 mm^2, respectively, and this difference was also significant (p < 0.05), indicating greater tumor regression in the combination therapy group. In terms of overall survival, mice in the combination therapy group had a median survival time (MST) of 36 days compared to the TMZ alone group and control groups with MSTs of 31 and 21 days, respectively [16]. This study highlighted the potential of IN delivery of AuNPs combined with immunostimulants. Clinical application of this method in GBM management is hard to determine based on the results of this study because treatment was only administered for five days and tumor volume increased 17 days post treatment. Prolonged combination therapy administered >5 days should be assessed to determine efficacy and viability of this treatment approach.

6. Emerging novel mechanisms in GBM

Literature on novel mechanisms for the management of GBM has appeared in the past decade and there are several promising treatment mechanisms and mechanistic targets on the horizon for the management of GBM.

a. Ferritin Nanocage Delivery of Paclitaxel

The chemotherapeutic agent PTX has been evaluated for over two decades for its role in treating gliomas. Its utilization is hindered due to

toxicity issues and suboptimal CNS penetration [46, 47]. PTX and its role in GBM has not been counted out however, as it is currently being used in emerging delivery strategies that overcome its side effect profile and lack of BBB penetration.

To exploit the transferrin receptor (TfR1) present in normal brain cells and highly expressed in malignant glioma cells, Liu et al. used heavy chain ferritin nanocages loaded with PTX (HFn-PTX) to test its ability to cross the BBB and deliver PTX to the tumor site [48, 49]. The *in vivo* experiment involved three groups of glioma-implanted mice that were injected with either saline, PTX, or HFn-PTX for 10 days. Groups receiving saline or PTX had MSTs of 13 and 14 days, respectively. The group receiving HFn-PTX had an MST of 30 days with minimal PTX-related toxicity. These results provide evidence that this novel nanocage could potentially be used to overcome CNS permeability issues and toxicity associated with PTX, as well as provide an advantageous delivery platform in GBM management [49].

b. Transferrin Targeted Delivery of Paclitaxel Loaded Polymeric Micelles

Sun et al. also sought to exploit the TfR because of its high level of expression in GBM cells compared to normal brain cells, but in this case the nanocarrier of choice was a polymeric micelle loaded with PTX (PTX-PM) [50, 51]. The PM was composed of polylactic acid (PLA), polyethylene glycol (PEG), and a T12-peptide (TfR targeting moiety) that was coated on the surface of the PM to allow passage through the BBB as a result of receptor-mediated transcytosis (RMT) that occurs through the TfR [52]. The theory that this study sought to confirm was that following BBB entry via RMT, the T12 coated PTX-PM (T12-PTX-PM) can reach the tumor and gain entry via receptor mediated endocytosis. Mice implanted with U87 MG glioma cells were injected with free PTX, PTX-PM, and T12-PTX-PM to evaluate drug distribution to the tumor and peripheral regions. In the PTX group there was necrosis of the lung and liver, and in the PTX-PM group there was heart tissue damage, indicating drug distribution outside of the tumor region. In the T12-PTX-PM group there was no notable organ damage and no treatment-associated weight loss, indicating targeted delivery and limited PTX related toxicity. The MST for the PTX-PM and T12-PTX-PM groups was 46 days and 63 days, respectively, both indicating tumor suppression. Further evaluation of this delivery method could confirm its applicability in GBM management because it shows promise in targeting the tumor and inducing GBM cell apoptosis [51].

c. Perillyl Alcohol and the Ketogenic Diet

The role of POH, a monoterpene, and its effectiveness in inducing cell death in human GBM cell lines was established in 2005 [3], which led to a clinical trial involving 37 patients receiving IN delivery of POH for the management of recurrent GBM. It was determined that IN POH diminished the side effect profile compared to POH delivered orally and resulted in a decrease in tumor mass. Progression free survival (PFS) was ~3–8 months, similar to of the PFS with TMZ (~2–7 months), thus warranting further investigation of this potential GBM therapy [53, 54]. A four-year follow-up study was conducted on patients in this study and remission was maintained in 19% of patients continuing daily IN POH [55].

Further studies have since been released discussing the implementation of the ketogenic diet (KD) in conjunction with IN POH as a method to prevent further disease progression and potentially decrease tumor size. Patients with recurrent GBM (n = 32) were administered four divided doses of IN POH (220 mg POH total) daily for three months while on a standard diet (n = 15) or on KD (n = 17). Of the surviving patients in the KD group (n = 9), 7 had decreased LDL-C and triglyceride levels and MRI imaging consistent with tumor regression. Although the patient group was small, these results indicate a potential alternative treatment for the management of recurrent GBM [56].

There is currently a phase 2a clinical trial involving NEO100 (a synthetic POH with >99% purity) and its place in GBM therapy. The agent will be delivered IN four times daily for 6 months to determine the appropriate maximum dose, treatment efficacy, and PFS of patients with progressing or recurrent GBM. Preliminary results of this trial may further establish the potential for IN POH to become a mainstay of GBM treatment and transition this model to phase 3 trials (ClinicalTrials.gov Identifier: NCT02704858).

d. HDL Nanodiscs

In the realm of nanotechnology, the role of synthetic high-density lipoprotein (sHDL) mimicking nanodiscs that encompass apolipoprotein A-1 mimetic peptide, phospholipids, and oligodeoxynucleotides (CpG) in intracranial delivery of chemotherapeutic agents to the GBM tumor microenvironment is being studied. Intracranial inoculation of GL26-wt mice with docetaxel (DTX) loaded sHDL mimicking nanodiscs conjugated with CpG (DTX-sHDL-CpG) was evaluated [57]. Intracranial delivery of DTX-sHDL-CpG had the highest MST of 55 days post implantation (~2-fold increase (p < 0.001)) compared to the other groups. Also, 40% of the mice treated with DTX-sHDL-CpG maintained tumor regression with no recurrence >90 days post inoculation even after inoculation with the same GL26-wt tumor 60 days post inoculation. Kadiyala et al. determined that sHDL-mimicking nanodiscs have a place in GBM therapy because their nanoformulation increased bioavailability and tumor penetration efficacy. It was concluded that DTX-sHDL-CpG is effective in initiating tumor cell apoptosis, eliciting immunologic immunity, prolonging MST, and diminishing GBM recurrence [57].

7. Conclusion

GBM continues to be one of the most devasting malignant brain tumors due to complexity in surgical resection and limited benefits of available treatment modalities that only partially improve patient prognosis. The management of GBM improves only slightly when TMZ is administered to patients with newly developed and recurrent GBM. Many studies have been conducted to find alternatives to the current standard of care but have been unsuccessful in improving the overall lifespan of patients. The lack of advancements in treatment for GBM is in part due to the protective barriers of the brain and a lack of delivery methods that can circumvent these barriers.

The utilization of the IN route as a means to bypass the BBB shows promise and seems to be the most plausible method to deliver novel therapies and therapies deemed inefficient in penetrating the BBB. Utilizing nanotechnology to deliver these therapies not only ensures targeted delivery to the tumor region, but also prevents drug degradation and nasal irritation by encapsulating the drug within the NP. The studies discussed in this review provide novel carriers and delivery methods that may provide a way forward in the management of GBM. Most studies discussed are preclinical in nature, but these approaches could, and should, be transitioned to the clinical because they show promise in promoting GBM tumor cell apoptosis and ultimately GBM tumor regression.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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