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Advances in Brain Cancer Therapy: Exploration of Small Molecules and Nanomedicine

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Abstract:

Brain cancer remains one of the most challenging malignancies of the central nervous system, with high recurrence rates and poor prognosis posing a serious threat to patient survival. Current therapeutic approaches, including surgery, radiotherapy, and chemotherapy, have improved survival to some extent but remain limited by the blood–brain barrier (BBB), tumor heterogeneity, and drug resistance. In recent years, small-molecule drugs and nanomedicine-based delivery systems have shown great potential in overcoming these barriers. Small molecules such as temozolomide (TMZ) and targeted agents play important roles in combination therapies, yet issues of BBB penetration and resistance persist. Nanomedicine platforms—including liposomes, polymeric nanoparticles, micelles, and exosomes—enable enhanced drug accumulation at tumor sites and controlled release, offering new strategies to break through the limitations of conventional therapies. However, clinical translation faces challenges related to safety, regulatory approval, and high costs. Looking ahead, emerging technologies such as artificial intelligence–driven drug discovery, CRISPR-based gene editing, liquid biopsy for early detection, and theranostics (therapy combined with diagnostics) hold promise for more precise and personalized treatment of brain cancer. This review summarizes the current therapeutic strategies and limitations of brain cancer, highlights advances in small-molecule and nanomedicine approaches, and discusses challenges and future perspectives for their clinical translation.

Keywords: Brain cancer; Small molecules; Nanomedicine; Blood–brain barrier (BBB); Targeted therapy; Drug delivery

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1. Introduction

Brain cancer is among the most aggressive and life-threatening malignancies of the central nervous system. Glioblastoma multiforme (GBM), oligodendroglioma, and ependymoma are the most common subtypes, with GBM being the most prevalent and lethal (Chang *et al.*, 2025). Despite advances in neurosurgery, radiotherapy, and chemotherapy, the prognosis of brain cancer patients remains poor, with median survival for GBM typically less than two years. The highly invasive nature of brain tumors, combined with their location in functionally critical regions of the brain, makes complete surgical removal difficult and recurrence almost inevitable (Jani *et al.*, 2025).

A major obstacle in brain cancer therapy is the blood–brain barrier (BBB), a highly selective physiological barrier that protects the central nervous system from harmful substances but simultaneously prevents most therapeutic agents from reaching tumor sites. Conventional chemotherapies such as temozolomide (TMZ) have limited efficacy due to poor BBB penetration and the emergence of drug resistance (Kang and Ko, 2023). Similarly, radiotherapy and targeted therapies often provide only modest benefits, as tumor heterogeneity and adaptive resistance reduce their effectiveness. These challenges underscore the urgent need for novel therapeutic strategies that can bypass or overcome the BBB and improve treatment outcomes (Shalgunov *et al.*, 2023).

Recent years have witnessed rapid progress in molecularly targeted drugs and nanomedicine-based delivery systems. Small molecules with favorable physicochemical properties can achieve better brain penetration, while nanocarriers such as liposomes, polymeric nanoparticles, micelles, and exosomes provide innovative platforms for controlled and targeted delivery of anticancer agents. At the same time, emerging technologies—including artificial intelligence–driven drug discovery, CRISPR-based gene editing, and liquid biopsy for early detection—are reshaping the landscape of brain cancer research. Against this backdrop, this review aims to summarize current therapeutic approaches and their limitations, highlight advances in small molecules and nanomedicine, and explore the opportunities and challenges for their clinical translation (Wu *et al.*, 2022).

2. Current Treatments and Limitations

2.1 Surgery

Surgical resection remains the cornerstone of brain cancer treatment, with the primary goal of removing as much of the tumor mass as possible while preserving neurological function. Craniotomy is the most common approach and is often followed by radiotherapy and/or chemotherapy to reduce recurrence. However, complete surgical removal is rarely feasible due to the infiltrative nature of brain tumors and their frequent proximity to critical brain regions. As a result, residual tumor cells often remain, leading to recurrence. Moreover, surgical procedures carry significant risks, including neurological deficits, infection, and postoperative complications.

2.2 Radiotherapy

Radiotherapy is an essential adjunct to surgery, designed to eliminate residual tumor cells. Techniques include external beam radiation therapy, stereotactic radiosurgery (e.g., Gamma Knife, CyberKnife), and fractionated radiotherapy, which aims to protect surrounding healthy tissue. While radiotherapy can prolong survival and reduce tumor burden, it is not curative. Side effects such as fatigue, hair loss, and cognitive decline remain common. Additionally, the radioresistance of some tumor cells and damage to healthy neural tissue limit its long-term efficacy.

2.3 Chemotherapy

Chemotherapy plays a pivotal role in the management of brain tumors, with temozolomide (TMZ) being the most widely used oral alkylating agent. TMZ demonstrates synergistic effects when combined with radiotherapy, making it a standard part of treatment regimens. Nevertheless, its clinical efficacy is constrained by limited BBB penetration and the frequent development of drug resistance. Other chemotherapeutic agents, including lomustine (CCNU) and carmustine (BCNU), have also been used but are associated with significant systemic toxicity. Despite decades of use, chemotherapy has not significantly improved overall survival for patients with high-grade brain tumors (Doolittle *et al.*, 2007).

2.4 Targeted Therapy

Targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors (e.g., erlotinib, gefitinib) and vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab), have been developed to block specific signaling pathways critical to tumor growth and angiogenesis. Although promising in preclinical studies, their effectiveness in clinical brain cancer treatment has been limited. The reasons include insufficient BBB penetration, intratumoral heterogeneity, and the ability of tumors to activate compensatory pathways that circumvent targeted inhibition. Consequently, targeted therapies alone rarely produce durable responses in brain cancer patients (Del Grosso *et al.*, 2019).

Despite the integration of surgery, radiotherapy, chemotherapy, and targeted therapy into current treatment regimens, brain cancer remains largely incurable. The blood–brain barrier significantly restricts drug delivery, tumor heterogeneity contributes to variable treatment responses, and recurrence is nearly universal. Even with aggressive multimodal treatment, survival improvements are limited, highlighting the pressing need for novel therapeutic strategies that can overcome these barriers and improve long-term outcomes for patients.

3. Small Molecules for Brain Cancer

Small-molecule drugs have long been a mainstay in the treatment of brain tumors due to their relatively simple structures and potential to cross the blood–brain barrier (BBB). Several agents have been approved for clinical use, and ongoing research continues to refine their efficacy and delivery strategies.

3.1 Approved Small Molecules

Temozolomide (TMZ) is the most widely used oral alkylating agent for glioblastoma treatment. Its mechanism of action involves the methylation of DNA at the O6 position of guanine, leading to apoptosis of rapidly dividing tumor cells. Although TMZ significantly prolongs survival when combined with radiotherapy, resistance mechanisms, such as overexpression of the DNA repair enzyme MGMT (O6-methylguanine-DNA methyltransferase), reduce its long-term efficacy. Lomustine (CCNU), another alkylating agent, and carmustine (BCNU), which can also be administered via biodegradable wafers implanted directly into the tumor cavity, have been employed as alternative or adjunct therapies. However, both agents are associated with significant systemic toxicity and limited overall benefit (Choi *et al.*, 2018).

3.2 Targeted Small Molecules

Targeted therapies focus on inhibiting molecular pathways crucial to tumor proliferation and angiogenesis. Epidermal growth factor receptor (EGFR) inhibitors, including erlotinib and gefitinib, were developed to block aberrant EGFR signaling, a common alteration in glioblastoma. Vascular endothelial growth factor (VEGF) inhibitors, such as bevacizumab, aim to suppress tumor angiogenesis. While these agents demonstrate promise in theory, their effectiveness in brain tumors has been modest, largely due to the adaptive resistance of tumor cells and insufficient BBB penetration.

3.3 Strategies for BBB Penetration

The limited ability of small molecules to cross the blood–brain barrier (BBB) has led to the development of several innovative delivery strategies. One approach is lipophilic drug design, in which increasing the lipophilicity of compounds facilitates passive diffusion across the BBB. Another method involves carrier-mediated transport, which takes advantage of endogenous systems such as glucose or amino acid transporters to enhance drug uptake. Similarly, receptor-mediated transcytosis enables drug conjugation to ligands that bind to BBB receptors, such as transferrin or insulin, allowing transcellular passage into the brain. In addition, BBB disruption techniques, including focused ultrasound, can transiently increase barrier permeability, thereby improving drug delivery to tumor sites. Together, these strategies aim to overcome one of the most formidable obstacles in brain cancer therapy and expand the therapeutic potential of small molecules.

4 Nanomedicine in Brain Cancer

Nanomedicine has emerged as a promising strategy to overcome the limitations of conventional small-molecule therapies. By leveraging nanoscale carriers for drug delivery, researchers aim to improve blood–brain barrier (BBB) penetration, prolong circulation time, and achieve targeted release of therapeutic agents at tumor sites. Several classes of nanocarriers have been developed and tested in preclinical and early clinical studies (Ali *et al.*, 2025).

4.1 Types of Nanocarriers

Several classes of nanocarriers have been developed for brain cancer therapy, each offering unique advantages. Liposomes are biocompatible vesicles composed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs, thereby enhancing solubility, reducing systemic toxicity, and allowing surface modifications for tumor-specific targeting. Polymeric nanoparticles, made from biodegradable polymers, provide controlled and sustained drug release; their tunable size and surface chemistry also permit functionalization with ligands to facilitate receptor-mediated delivery across the blood–brain barrier. Micelles, formed through the self-assembly of amphiphilic molecules, are particularly effective at carrying hydrophobic drugs, improving solubility, and enhancing circulation stability. Finally, exosomes, which are naturally secreted extracellular vesicles, offer excellent biocompatibility and inherent targeting potential. Their demonstrated ability to cross the BBB has made them one of the most promising platforms for brain cancer nanomedicine (Brighi *et al.*, 2020; Amulya *et al.*, 2023).

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4.2 Advantages of Nanomedicine

Nanocarrier-based delivery systems provide multiple benefits compared to conventional formulations. They can improve pharmacokinetics by prolonging drug half-life, enhance selective accumulation in tumor tissue via the enhanced permeability and retention (EPR) effect, and reduce systemic toxicity. Furthermore, by incorporating targeting ligands, nanomedicines can preferentially bind to receptors overexpressed on tumor cells, improving therapeutic specificity.

4.3 Challenges in Clinical Translation

Despite encouraging preclinical results, nanomedicine faces several hurdles before widespread clinical adoption. Regulatory approval requires comprehensive evaluation of safety, long-term toxicity, and biodistribution. Manufacturing under Good Manufacturing Practice (GMP) standards adds complexity and cost, while patient recruitment for clinical trials remains slow. Moreover, differences between animal models and human brain tumors often limit the predictive value of preclinical studies, delaying translation to clinical application.

Nanomedicine therefore represents both a promising opportunity and a considerable challenge in brain cancer therapy. Continued innovation, combined with global collaboration and regulatory support, will be essential to bring nanomedicine-based treatments into clinical reality (Duan *et al.*, 2024).

5. Future Directions

The ongoing evolution of brain cancer therapy is closely tied to technological innovation and interdisciplinary collaboration. While current approaches provide incremental benefits, several emerging strategies hold the potential to revolutionize treatment paradigms and improve patient outcomes.

5.1 Artificial Intelligence–Driven Drug Discovery

Artificial intelligence (AI) and machine learning are increasingly being applied to accelerate drug discovery and optimize treatment regimens. By analyzing vast datasets of genomic, proteomic, and clinical information, AI can identify novel drug candidates, predict drug–target interactions, and design personalized treatment strategies. In brain cancer, AI has the potential to uncover small molecules with improved blood–brain barrier (BBB) penetration and to optimize nanocarrier formulations for enhanced delivery.

5.2 CRISPR-Based Gene Editing

The development of CRISPR–Cas9 gene editing technology offers new opportunities for precision therapy. CRISPR allows for targeted modification of oncogenes and tumor suppressor genes implicated in brain tumor progression. Potential applications include correcting genetic mutations, silencing resistance-associated pathways, and engineering immune cells for more effective immunotherapy. However, challenges such as off-target effects, delivery efficiency, and ethical considerations must be addressed before CRISPR-based therapies can be widely implemented.

5.3 Liquid Biopsy and Early Detection

Early and accurate diagnosis remains critical for improving brain cancer prognosis. Liquid biopsy technologies, which detect circulating tumor DNA, RNA, or extracellular vesicles in blood or cerebrospinal fluid, provide a non-invasive means of monitoring tumor progression and treatment response. For brain cancer patients, liquid biopsy could facilitate earlier intervention, guide therapy selection, and enable real-time assessment of resistance mechanisms.

5.4 Theranostics

The concept of theranostics—integrating therapeutic and diagnostic functions into a single platform—offers a promising avenue for personalized medicine. Nanoparticles can be engineered to deliver drugs while simultaneously providing imaging contrast, enabling clinicians to track treatment distribution and monitor efficacy in real time. This dual functionality enhances treatment precision and reduces the risk of overtreatment or ineffective therapy.

5.5 Collaborative and Regulatory Perspectives

The successful translation of these emerging technologies into clinical practice will require global collaboration among researchers, clinicians, regulators, and industry partners. Regulatory agencies such as the FDA and EMA must balance innovation with patient safety, ensuring robust evaluation of novel therapies. At the same time, international cooperation can help overcome challenges in clinical trial design, patient recruitment, and cost barriers, accelerating the path from laboratory discovery to clinical application.

6. Conclusion

Brain cancer remains a major therapeutic challenge, with conventional approaches such as surgery, radiotherapy,

chemotherapy, and targeted therapy offering only limited survival benefits due to issues like incomplete tumor removal, drug resistance, and the blood–brain barrier (BBB). Advances in small molecules and nanomedicine provide promising opportunities to improve treatment efficacy, particularly through enhanced drug delivery and tumor targeting, yet clinical translation is still constrained by safety, cost, and regulatory hurdles. Looking forward, emerging technologies—including artificial intelligence, CRISPR-based gene editing, liquid biopsy, and theranostics—hold the potential to transform brain cancer therapy into a more precise, personalized, and effective discipline, provided that global collaboration and multidisciplinary efforts continue to drive innovation from laboratory research to clinical practice.

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