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Review

A modern approach to glioblastoma using temozolomide and nanoparticles carrier drug: a standard care of combination therapy and treatment

Md Ataur Rahman, Mahesh Kumar Yadab, Meser M. Ali

Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI 48201, USA

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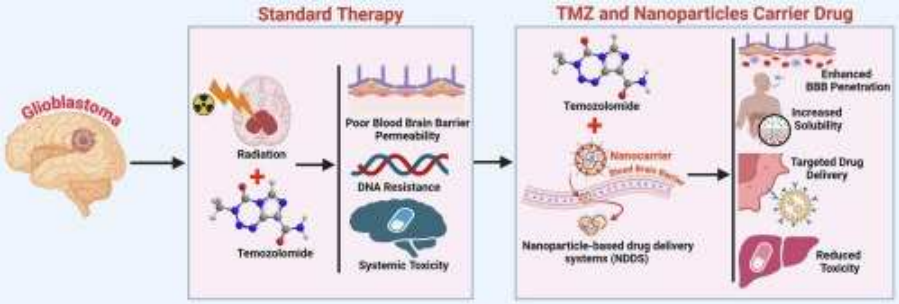
Abstract

Glioblastoma (GBM) is the most fatal primary brain tumor in adults, characterized by fast development, resistance to standard treatments, and a poor prognosis. Although extensive treatments in surgery, radiation, and chemotherapy, resistance to therapy and recurrence persist as unavoidable outcomes. Temozolomide (TMZ), an oral alkylating drug, represents the current standard chemotherapy for GBM. However, its therapeutic effectiveness is severely restricted by its inability to pass through the blood–brain barrier (BBB) properly, its relatively short systemic half-life, and the development of resistance mechanisms, especially those related to O^6-methylguanine-DNA methyltransferase (MGMT) repair activity. Nanoparticles (NPs)-based drug delivery devices represent a significant improvement in GBM therapies, providing a viable

solution to the challenges of conventional TMZ therapy. Nanocarriers enhance medication solubility, facilitate BBB penetration, target tumor-specific receptors, and minimize general toxicity. This review assesses the function of TMZ in the treatment of GBM, the processes underlying drug resistance, and the potential of nanotechnology to enhance the effectiveness of TMZ. Additionally, we would like to discuss the multifunctional and co-delivery systems of TMZ, along with their pre-clinical and clinical successes and the challenges in bringing these medicines into clinical practice. Therefore, the incorporation of TMZ with nanoparticle-mediated delivery systems signifies a transformative advancement in GBM treatment, offering the opportunity for personalized therapy, overcoming resistance, and markedly enhancing patient survival rates.

Graphical abstract



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Introduction

Glioblastoma represents the most aggressive and common variant of malignant glioma, distinguished by significant cellular heterogeneity, rapid proliferation, and a diffusely infiltrative characteristic that complicates surgical resection and leads to inevitable recurrence [1]. GBM is designated as a grade IV astrocytoma by the World Health Organization (WHO) and constitutes roughly 15% of all primary brain tumors [2]. Standard-of-care therapy comprises maximal surgical resection, followed by radiotherapy and both concomitant and adjuvant chemotherapy utilizing TMZ [3]. Despite the implementation of an aggressive multimodal approach, the median survival time for patients with GBM remains low, averaging 12–15 months, and the two-year survival rate is under 30% [4].

Temozolomide is the primary chemotherapeutic agent owing to its capacity to cross the blood–brain barrier, favorable oral bioavailability, and acceptable toxicity profile [5]. However, its clinical efficacy is compromised by several factors, including a short half-life, inadequate tumor-targeting capability, and particularly, resistance mechanisms such as increased MGMT expression and alterations in DNA repair pathways [6]. The identified limitations highlight the need for the advancement of more efficient drug delivery strategies aimed at optimizing the therapeutic index of TMZ while reducing systemic side effects.

Nanotechnology provides a transformative framework in this context. NPs serve to encapsulate chemotherapeutic agents, protecting them from degradation and enabling targeted delivery to tumor cells, thereby preserving healthy tissues [7]. Functionalized nanoparticles can traverse the blood–brain barrier, target tumor-specific markers, and facilitate the controlled release of drug payloads [8]. Nanoparticles, capable of co-delivering multiple agents such as gene therapies and imaging probes, offer a promising solution to the existing challenges in the treatment of GBM [9]. This review examines the integration of TMZ with advanced nanoparticle delivery systems in GBM therapy. It discusses the mechanistic basis of drug resistance, nanoparticle design principles, preclinical successes, and ongoing clinical trials, while addressing existing limitations and future directions.

Section snippets

Molecular pathways in astrocyte-to-glioblastoma transformation

Astrocytes are star-shaped glial cells that facilitate neuronal activity, uphold the blood–brain barrier, regulate neurotransmitter equilibrium, and offer trophic support [10]. In gliomagenesis, these supporting functions are appropriated when certain mutations disturb homeostasis and activate oncogenic signaling [11]. Glioblastoma-associated vascular remodeling and BBB disruption depicts three key stages of glioblastoma vascular interaction: vessel co-option (tumor cells migrate along intact …

Clinical features and challenges of glioblastoma

. The clinical characteristics and treatment of glioblastoma pose considerable difficulties for both healthcare professionals and researchers [34]. Notwithstanding progress in neurosurgery, radiotherapy, and chemotherapy, the typical survival duration for individuals with GBM is roughly 12–15 months post-diagnosis, with a 5-year survival rate below 10% [35]. Despite comprehensive research and advancements in therapeutic approaches, GBM remains a formidable clinical and therapeutic challenge …

Temozolomide: mechanism of action, efficacy, and resistance mechanisms in GBM

Temozolomide is an oral alkylating drug that serves as the foundation of chemotherapeutic therapy for glioblastoma, the most aggressive primary brain tumor in humans [47]. In

accordance with the Stupp protocol, TMZ is provided concurrently with radiation after surgical resection, followed by six cycles of adjuvant TMZ.

The mechanism of action refers to the specific biochemical interaction through which a drug or compound produces its effects in the body. This involves the identification of …

Mechanism of nanoparticle-based drug delivery in glioblastoma

Nanoparticle-based drug delivery systems represent effective therapeutic platforms that address challenges by increasing drug accumulation in tumor tissue, enhancing bioavailability, and facilitating targeted delivery while minimizing off-target toxicity [[62], [63]]. Nanoparticles (NPs), characterized by their adjustable size (generally 10-200nm), surface charge, and potential for functionalization, can be designed to traverse the BBB through mechanisms such as passive diffusion, …

Synergistic potential of TMZ and nanoparticle-based drug delivery in glioblastoma therapy

The combination of TMZ with nanoparticle-based drug delivery methods is a potent synergistic approach in the management of GBM [6]. Although TMZ is fundamental to treatment for GBM, its efficacy is frequently undermined by inherent resistance mechanisms, inadequate tumor penetration, and fast systemic clearance [77]. NPs have emerged as effective carriers to improve the pharmacokinetics of TMZ and simultaneously provide adjuvant therapies that address drug resistance at the molecular level [78 …

Clinical and pre-clinical trial challenges of TMZ and nanoparticle-based drug delivery in glioblastoma therapy

Notwithstanding its prevalent application, TMZ monotherapy is impeded by restricted cerebral absorption, development of resistance, and brief systemic half-life [[96], [97]]. Nanoparticle-based drug delivery methods have emerged as a promising way to boost the efficacy of TMZ and surmount obstacles like the BBB; nevertheless, the translation of these methodologies from laboratory to clinical use is beset with considerable preclinical and clinical problems. …

Future perspectives and limitations of temozolomide and nanoparticle-based drug delivery in glioblastoma therapy

The future of glioblastoma treatment will depend on sophisticated, multifunctional nanoparticle systems that complement conventional therapies such as TMZ. Despite ongoing challenges particularly in delivery, resistance, and clinical translation, the strategic design of next generation nanocarriers presents significant promise for improving therapy results in this severe disease. …

Conclusion

Temozolomide is the primary chemotherapeutic agent in the conventional treatment of glioblastoma, but its clinical effectiveness is significantly constrained by inadequate blood brain barrier penetration, swift systemic degradation, and resistance mechanisms including MGMT overexpression and autophagy activation. Nanoparticle-based drug delivery methods present a viable remedy to these constraints by augmenting TMZ delivery, boosting tumor selectivity, and facilitating the co-delivery of …

CRediT authorship contribution statement

Md Ataur Rahman: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Investigation, Data curation, Conceptualization. **Mahesh Kumar Yadab:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Data curation, Conceptualization. **Meser M. Ali:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. …

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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