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Innovative approaches to irinotecan-based therapies for glioblastoma: Advancements in drug delivery and combination strategies

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Abstract

Glioblastoma (GBM) remains one of the most lethal human malignancies, characterized by profound heterogeneity, therapeutic resistance, and limited drug penetration across the blood-brain barrier (BBB). Irinotecan (CPT-11), a topoisomerase I inhibitor converted to its active metabolite SN-38, has emerged as a potential chemotherapeutic alternative for GBM due to its distinct mechanism of action and non-cross-resistance with temozolomide (TMZ). However, early clinical trials revealed limited efficacy, largely constrained by subtherapeutic intratumoral exposure, pharmacogenetic variability, and systemic toxicity. Recent advances have redefined the therapeutic landscape of irinotecan through three convergent strategies: biomarker-guided precision, rational combination design, and innovative drug-delivery systems. Biomarker studies have identified predictive indicators such as TIMP-1 expression, TDP1/TOP1 activity ratio, and EGFRvIII-associated replication stress, providing a framework for patient stratification and response prediction. Mechanistic research has expanded irinotecan's therapeutic logic beyond DNA damage, uncovering roles in p21-mediated senescence and metabolic-epigenetic modulation when combined with checkpoint inhibitors or senolytic agents. Parallel innovations in delivery ranging from liposomal and nanoparticle formulations to implantable PLGA devices, peptide-drug conjugates, and MRI-guided convection-enhanced delivery have achieved sustained intraparenchymal SN-38 exposure while minimizing systemic burden. Collectively, these developments mark a translational shift from empirical cytotoxic therapy toward a modular, precision-engineered platform. The integration of biomarker discovery, molecularly rational combinations, and locoregional delivery systems positions irinotecan as a key component of next-generation GBM treatment paradigms, with the potential to overcome historical barriers such as BBB impermeability and therapeutic resistance.

Keywords: Blood-brain barrier (BBB); Combination therapy; Convection-enhanced delivery; Glioblastoma (GBM); Irinotecan (CPT-11); Nanoparticles; Precision medicine; SN-38; Topoisomerase I inhibition.

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