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Repositioning Antiretroviral Drugs for Glioblastoma

Palima Nexin*

Department of Internal Medicine, University of Texas Health Sciences Center at Houston, Houston, TX 77030, USA

Introduction

Glioblastoma Multiforme (GBM) is the most aggressive and lethal form of primary brain tumor, with a median survival time of approximately 15 months post-diagnosis despite aggressive treatment, which includes surgery, radiation, and chemotherapy. Current treatment options are often insufficient due to the tumor's highly infiltrative nature and resistance to conventional therapies. Therefore, there is a compelling need for novel therapeutic strategies. One promising avenue is the repositioning of existing drugs, including Antiretroviral (ARV) medications originally developed to combat HIV/AIDS, for the treatment of glioblastoma [1].

Description

Drug repositioning, also known as drug repurposing, involves the investigation of existing drugs for new therapeutic purposes. Shortened development time, these drugs have already undergone extensive safety testing, the time required to bring them to clinical use for new indications is significantly reduced. The costs associated with drug development and approval processes are considerably lower. The existing data on pharmacokinetics, pharmacodynamics, and toxicity of these drugs reduce the risk of unforeseen adverse effects. Antiretroviral drugs are primarily classified into several categories based on their mechanism of action against HIV. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) drugs incorporate into the viral DNA and terminate the DNA chain elongation. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) bind to and inhibit the reverse transcriptase enzyme. Protease Inhibitors (PIs) inhibit the HIV protease enzyme, preventing the maturation of viral particles. Integrase inhibitors inhibit the viral integrase enzyme, blocking the integration of viral DNA into the host genome [2,3].

Beyond their antiviral activity, NRTIs and NNRTIs have been observed to induce apoptosis in cancer cells by interfering with mitochondrial DNA synthesis and inducing oxidative stress. Drugs like Zidovudine (AZT) have demonstrated the ability to inhibit DNA polymerases and telomerase, leading to impaired DNA repair and tumor cell death. Protease Inhibitors drugs can disrupt signaling pathways such as PI3K/AKT/mTOR, which are often upregulated in GBM. Protease inhibitors like ritonavir and nelfinavir have shown the ability to inhibit the chaperone function of Heat Shock Proteins (HSPs), leading to the misfolding and degradation of oncoproteins critical for tumor cell survival [4].

The rapid growth of GBM is highly dependent on angiogenesis, the process of new blood vessel formation. Some ARVs, particularly protease inhibitors, have been shown to possess anti-angiogenic properties. For instance, nelfinavir can downregulate the expression of VEGF (Vascular Endothelial Growth Factor), a key molecule in angiogenesis, thus inhibiting tumor vascularization and growth. GBM is known to create an immunosuppressive microenvironment that allows it to evade immune detection. Some ARVs have immunomodulatory effects that could potentially reverse this immunosuppression. For example, certain NNRTIs have been found to enhance the activity of Natural Killer (NK) cells and cytotoxic T Lymphocytes (CTLs), which are crucial for antitumor immunity [5].

Conclusion

While repositioning ARVs for GBM therapy is promising, several challenges need to be addressed. Optimal Dosing and Scheduling determining the most effective dosing regimens for ARVs in the context of GBM is critical. This includes understanding the pharmacokinetics and pharmacodynamics in the Central Nervous System (CNS). Combination therapies Identifying synergistic combinations of ARVs with existing GBM treatments (e.g., temozolomide, radiation) or other novel therapies is essential for maximizing therapeutic efficacy. Biomarkers that predict response to ARV therapy need to be identified to tailor treatments to individual patients' tumor profiles. Repositioning antiretroviral drugs for the treatment of glioblastoma represents a novel and promising strategy that leverages the well-characterized safety profiles and mechanisms of existing medications. Preclinical and early clinical evidence suggests that ARVs, particularly those that target multiple cancer-related pathways, could enhance the effectiveness of current GBM therapies. Future research should focus on optimizing treatment regimens, exploring combination therapies, and identifying predictive biomarkers to maximize the potential of ARVs in combating this devastating disease. By doing so, it is possible to improve outcomes and offer new hope to patients with glioblastoma.

Acknowledgement

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Conflict of Interest

None.

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***Address for Correspondence:** Palima Nexin, Department of Internal Medicine, University of Texas Health Sciences Center at Houston, Houston, TX 77030, USA, E-mail: palima@edu.com*

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