Losartan and Immune Checkpoint Inhibitors in Glioblastoma: An Appropriate Substitute for Steroids

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Introduction

Glioblastoma (GBM) is a type of primary brain tumor that is believed to develop from stem cells or their precursors in the subventricular zone of the central nervous system (CNS). In recent times, there has been a change in the way gliomas are diagnosed and prognosticated, with greater emphasis on molecular information. This trend is reflected in the latest World Health Organization (WHO) classification of CNS tumors.[1] There is now a more defined differentiation between IDH-mutant and wildtype gliomas, and the term "secondary" or IDH-mutant GBM has been replaced with "diffuse IDH-mutant astrocytoma, WHO grade 4." Additionally, diffuse gliomas that have molecular features of GBM and are IDH-wildtype can now be categorized as GBM, even if they do not exhibit high-grade histological features.[1,2] Its destructive biological nature and reluctance to be treated make it a challenging disease to manage. GBM has a global incidence rate of 0.59–3.69/100,000 population, with an average onset age of 63.0 years.[3,4]

The management of GBM typically follows the National Comprehensive Cancer Network (NCCN) guidelines, which include tumor resection, radiotherapy with concomitant temozolomide (TMZ), and adjuvant TMZ chemotherapy. The combination of radiotherapy and these treatments has been shown to increase 5-year survivorship from 1.9% to 9.8%, compared to radiotherapy alone. Despite these treatments, the average life expectancy of GBM patients is only 12−15 months following its detection.[5,6]

Main Text

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment by targeting negative regulatory pathways that inhibit T-cell activation.[7–9] By blocking surface receptors called immune checkpoints, ICIs can promote a T-cell immune response against tumors. The use of programmed cell death ligand 1 (PD-L1) checkpoint inhibitor has significantly impacted the treatment of various cancers,[10,11] leading to investigations of ICIs in GBM. PD-L1 is highly expressed in glioblastoma cells, and combinatory ICIs have demonstrated success in preclinical GBM mouse models.[12,13] However, ICIs have not shown favorable results in phase III GBM clinical trials due to a unique problem of cerebral edema that is exacerbated by anti-PD1/PD-L1 antibodies.[14] Steroids are used to control cerebral edema, but they are highly immunosuppressive and can oppose the advantages of ICIs. To address this issue, researchers have investigated alternative medications that can safely manage edema without suppressing the immune system. Recent studies suggest that the blood pressure medication Losartan may prevent edema induced by immunotherapy.[15]

Losartan is an FDA-approved drug that is used to treat various conditions, including hypertension and diabetic nephropathy.[16] It has the ability to cross the blood-brain barrier (BBB) and has been found to be associated with a decreased incidence of brain edema and decreased steroid regimens among GBM patients undergoing chemoradiation therapy.[17] Researchers conducted a study utilizing different factors such as mouse prototypes of cancer, single-cell RNA sequencing, immune cell blocking investigations, and inspection of patient imaging scans. The results showed that edema induced from immunotherapy is caused by an

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inflammatory response that disturbs the BBB, which is already altered due to brain cancer. This phenomenon is associated with the enzymes matrix metalloproteinases 14 and 15, which are present in cells lining tumor-correlated blood vessels and can lead to blood vessel outflow resulting in edema. The study found that losartan can stop immunotherapy-related edema by reducing the expression of the aforementioned enzymes. In addition, Losartan demonstrated multiple valuable conclusions in the tumor environment that boosted the body's anti-tumor immune response. When combined with an ICI, Losartan significantly increased the life expectancy of mouse prototypes with glioblastoma, healing 20% of mice when used with conventional care consisting of chemoradiation followed by surgery.[15]

Conclusion

The research findings provide a basis for subsequent clinical investigations assessing the use of Losartan with ICIs in glioblastoma patients. The combination of Losartan and ICIs could be a potentially groundbreaking discovery as steroids and other immunotherapy regimens leave the patients susceptible to infections and other potential risk factors. Losartan, being cheap and readily available with few drawbacks in comparison to steroids, provides a new dimension in GBM therapy that can finally break free from the use of steroids and increase ICI efficacy in the process. Currently, the treatment options for GBM are limited, and this increase in the efficacy of ICIs will be a major plus point. It is imperative that more trials should take place to investigate this deeply so that further routes to control this devastating ailment can be discovered. The findings of this study pave the way for a potentially groundbreaking approach to GBM therapy and offer hope for patients suffering from this devastating disease. Further investigation and clinical trials are necessary to fully understand the potential of Losartan and ICIs in treating GBM, and the results of these trials could have a significant impact on the future of GBM therapy.

Authors' Contributions

The conceptualization was done by BSR and MAS. The literature and drafting of the manuscript were conducted by BSR, AS, MSM, HSR, and HF. The editing and supervision were performed by MAS. All authors have read and agreed to the final version of the manuscript.

Declaration of Conflicting Interests

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