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Analysis of Clinical Success and Molecular Mechanisms of Action of Novel Anti-glioblastoma Drugs: A Review

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Abstract

Background: Gliomas and glioblastomas (GBM) are common primary malignant brain tumors, which are highly malignant and have a poor prognosis. The presence of cancer stem cells with unrestricted proliferative capacity and ability to generate glial neoplastic cells, the diffuse nature of GBM, and other specific factors of GBM contribute to poor results of drug therapy in patients with GBM. Despite the worldwide efforts to improve the treatment, many novel anti-GBM drugs are active just in vitro, in silico, and in preclinical trials, and they sometimes demonstrate poor or no activity in clinical trials. In this paper, we have casually selected and analyzed the most promising evidence-based results related to glioblastoma treatment at FDA and Clinical Trials.gov databases. It was observed that the most prospective trend in the development of anti-GBM drugs is combination therapy vs. monotherapy. Our analysis of clinical trials has allowed us to predict that the most promising combination therapy that has shown the best results in patient's surveillance should include drugs that block different growth-promoting signals in glioblastoma cells and that are activated by the V600E BRAF mutation. One drug should inhibit signals from the BRAF protein, whereas the second drug in combination should inhibit signals from the MEK protein Methods: The content of this review is based on information obtained from PubMed, ClinicalTrials. gov, and the U.S. Food and Drug Administration (https://www.fda.gov/). In ClinicalTrials.gov, we retrieved studies published from January 1, 2015. In the data search, "Glioblastoma" was used as the keyword. A study was deleted if it studied remedies for concomitant tumor diseases, as well as if it did not include descriptions of treatment methods and/or if GBM was not mentioned. The analysis of the effectiveness of treatment was carried out according to the increasing overall survival in GBM patients, compared to the gold standard for this cancer.

Results: GBM patients treated with novel immunotherapy agents and drugs acting on epigenetic factors and receptor tyrosine kinase inhibitors have shown encouraging potential for future development in clinic. However, combinations of drugs have led to more significant improvements in the results and an increase in life expectancy of patients. For example, the combination of nivolumab and ipilimumab showed a 72% increase in life expectancy compared to using nivolumab alone (9.8 vs. 16.85).

Conclusion: Combining anti-GBM drugs appears to be a key direction for increasing treatment effectiveness and overall survival. Radiotherapy of GBM can increase the effect of combination drug therapy.

Keywords: Glioblastoma; anti-glioblastoma drugs; drug resistance; epigenetic agents; growth factor receptors; immunotherapy..