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Perspective

Translating Laboratory Discoveries into Clinical Approaches for High-Grade Gliomas

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DESCRIPTION

High-grade gliomas remain one of the most difficult types of brain tumors to manage in both clinical and research settings. Characterized by rapid progression, infiltration into healthy brain tissue, and resistance to conventional therapies, these tumors often lead to poor outcomes despite surgery, radiation, and chemotherapy. The last two decades have seen a shift in how researchers and clinicians approach these tumors, with increasing attention paid to the molecular and cellular features that influence behaviour and treatment response.

Temozolomide, a DNA-alkylating agent, continues to be used in the management of glioblastoma, the most aggressive form of high-grade glioma. Its use, in combination with radiotherapy, has modestly improved survival rates, particularly in patients whose tumors show methylation of the *MGMT* gene promoter. This epigenetic marker is associated with a better response to temozolomide due to reduced DNA repair capability in tumor cells. However, even with this combination, recurrence is common, and overall survival remains limited.

Surgical resection remains the initial step for most patients. Maximizing the removal of tumor tissue while preserving surrounding brain function is a delicate process. Intraoperative technologies such as fluorescence-guided surgery and MRI-based neuro navigation have been adopted to assist in identifying tumor margins more clearly during the procedure. Although complete removal is rarely possible due to the infiltrative nature of these tumors, reducing the bulk of the mass has been linked with improved response to adjuvant therapies.

In recent years, attention has turned toward the genetic profile of gliomas to identify potential therapeutic targets. Mutations in IDH1 and IDH2, found more frequently in certain glioma subtypes, have both diagnostic and therapeutic significance. These mutations alter cellular metabolism and are associated with better outcomes compared to IDH-wild type tumors. Several compounds are under development that directly inhibit the metabolic products of these mutated enzymes, though many remain under clinical evaluation.

EGFR amplification and mutation, particularly the EGFRvIII variant, are common in glioblastoma and have been studied for potential treatment options. While initial efforts to target EGFR with small molecule inhibitors or monoclonal antibodies yielded limited clinical results, more recent studies are exploring vaccine-based and cellular therapies that focus on tumor-specific variants. These strategies aim to generate an immune response against tumor cells while sparing normal brain tissue.

Another focus has been the tumor microenvironment, especially the presence of immunosuppressive elements that allow glioma cells to persist. Unlike other cancers where immunotherapies have made significant progress, the brain presents unique challenges. The presence of the blood-brain barrier, a tightly regulated cellular structure that limits the passage of substances from blood to brain tissue, restricts the effectiveness of many systemic therapies. Furthermore, gliomas often manipulate local immune cells such as microglia and tumor-associated macrophages, turning them into supporters of tumor growth rather than defenders against it.

Tumor Treating Fields (TTFs), an approach involving the use of low-intensity alternating electric fields, has been approved in several countries as an adjunct to chemotherapy. By interfering with mitotic spindle formation, these fields aim to slow tumor cell division. Clinical studies have shown improved progression-free and overall survival in some patients using this method alongside standard therapy, although acceptance varies depending on access and practicality.

Recurrent tumors present a particular challenge. At recurrence, the tumor often exhibits different molecular traits compared to its original form. Re-biopsy and advanced imaging play a role in guiding further treatment decisions. In some cases, re-irradiation or re-resection is considered, but options become more limited as the disease progresses.

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The development of personalized medicine approaches, involving comprehensive genomic and epigenomic profiling, continues to shape clinical research. By analyzing the specific alterations present in each tumor, clinicians aim to identify relevant pathways and align treatment more closely with tumor biology. While many of these efforts are still part of clinical trials, early results suggest that a more detailed molecular understanding of gliomas may inform future treatment strategies.

Efforts to translate laboratory findings into clinical use for high-grade gliomas remain active and multifaceted. Despite persistent challenges, the increased collaboration between basic science and clinical disciplines is gradually influencing how this complex disease is approached. Continued investigation and refinement of these methods are expected to influence future decisions in both diagnosis and treatment, with the goal of improving quality of life and extending survival for affected individuals.