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Isaac Yang and Seunggu J. Han

**Immunotherapy for Glioma: Promises and Challenges** **357**

Seunggu J. Han, Corinna Zygourakis, Michael Lim, and Andrew T. Parsa

Novel immunotherapeutic modalities are being pursed in the treatment of high-grade gliomas. This article explains how tumors suppress immune function in the brain. It specifically describes the ways in which tumors limit effective communication with immune cells, secrete immune-inhibitory cytokines and molecules, and express molecules that induce apoptosis of immune cells. It also defines 3 different immunotherapeutic approaches to counteract this tumor-associated immunosuppression: cytokine therapy, passive immunotherapy (either serotherapy or adoptive immunotherapy), and active immunotherapy. Although immunotherapeutic approaches have met with mixed success so far, immunotherapy continues to be actively pursued because of its potential to attack infiltrating high-grade gliomas.

**Glioblastoma Multiforme Treatment with Clinical Trials for Surgical Resection (Aminolevulinic Acid)** **371**

David W. Roberts, Pablo A. Valdés, Brent T. Harris, Alexander Hartov, Xiaoyao Fan, Songbai Ji, Frederic Leblond, Tor D. Tosteson, Brian C. Wilson, and Keith D. Paulsen

5-Aminolevulinic acid (5-ALA)-induced tumor fluorescence can be used to identify tissue for resection using an adapted operating microscope. A multi-institutional clinical trial comparing fluorescence-guided versus white light tumor resection reported significant improvement in completeness of resection and 6-month progression-free survival. The degree of 5-ALA-induced fluorescence correlates with histopathologic grade of tumor, degree of tumor cell infiltration, and proliferation indices. Quantitative methodologies for assessment of tissue fluorescence have significantly improved the ability to detect tumor tissue and intraoperative diagnostic performance. These developments extend the applicability of this technology to additional tumor histologies and provide the rationale for further instrumentation development.

**Potential Role for STAT3 Inhibitors in Glioblastoma** **379**

Christopher Jackson, Jacob Ruzevick, Anubhav G. Amin, and Michael Lim

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. Signal transducers and activators of transcription 3 (STAT3) is a transcription factor that translocates to the nucleus to modulate the expression of a variety of genes associated with cell survival, differentiation, proliferation, angiogenesis, and immune function. Several cancers induce constitutive STAT3 activation. Most studies have reported that STAT3 inhibition has antineoplastic activity; however, emerging evidence suggests that the role of STAT3 activity in GBM may be more nuanced than initially appreciated. The authors review the roles of STAT3 in GBM and discuss potential strategies for targeting STAT3.

**CD133 as a Marker for Regulation and Potential for Targeted Therapies in Glioblastoma Multiforme** 391

Winward Choy, Daniel T. Nagasawa, Andy Trang, Kimberly Thill, Marko Spasic, and Isaac Yang

The CD133 epitope has been identified as a tumor marker for the purification of a subpopulation of glioblastoma multiforme (GBM) cells demonstrating cancer stem cell phenotypes. Isolated tumorsphere-forming $CD133^+$ GBM cells demonstrated heightened in vitro proliferation, self-renewal, and invasive capacity. Orthotopic transplantation of $CD133^+$ cells led to the formation of heterogeneous tumors that were phenocopies of the original patient tumor. In this article, the authors discuss the complex regulation of CD133 expression in gliomas, its role in tumorigenesis, and its potential as a marker for targeted and personalized therapeutic intervention.

**Clinical Trials of Small Molecule Inhibitors in High-Grade Glioma** 407

Samuel E. Day and Allen Waziri

High-grade gliomas are rapidly progressing and generally fatal neoplasms of the brain. Chemotherapy has continued to provide only limited benefit for patients harboring these tumors. The recurrence of common mutations, combined with the similarities of many of the acquired capabilities and characteristics of solid tumors, suggest many common therapeutic targets. During the past few decades, an increased understanding of many of the cellular regulatory mechanisms associated with carcinogenesis has provided an opportunity for the development of pathway-specific small molecule targeted inhibitors (SMIs). This article reviews the use of SMIs in the treatment of high-grade glioma.

**Molecular Characteristics and Pathways of Avastin for the Treatment of Glioblastoma Multiforme** 417

Marko Spasic, Frances Chow, Claire Tu, Daniel T. Nagasawa, and Isaac Yang

This article provides historical background and current research involving the use of bevacizumab for the treatment of recurrent glioblastoma. Although bevacizumab, approved by the Food and Drug Administration, prolongs glioblastoma progression free survivial, decreases tumor vascularization, and reduces permeability of vessels, it does not seem to prolong overall survival. Despite slowed primary tumor progression, bevacizumab treatment may facilitate transformation to a more invasive phenotype. Adaptive responses, which make glioblastoma particularly resistant to various treatment modalities have been described. Conferred benefits, adverse effects, mechanisms of resistance, and potential areas for future research are discussed.

**Potential Usefulness of Radiosensitizers in Glioblastoma** 429

Yasuaki Harasaki and Allen Waziri

High-grade glioma continues to impart poor prognosis in spite of maximal treatment. Attempted gross total surgical resection followed by concurrent temozolomide and radiation therapy has become standard of care for glioblastoma. Ongoing clinical efforts have been directed at the further development of radiosensitizing agents that exploit tumor biology to maximize effects of concurrently administered radiation. The current article outlines the scientific rationale for the use of radiosensitizing agents and preliminary results from clinical trials using a variety of these approaches.

**Nanotechnology Applications for Glioblastoma** 439

Edjah K. Nduom, Alexandros Bouras, Milota Kaluzova, and Costas G. Hadjipanayis

Glioblastoma remains one of the most difficult cancers to treat and represents the most common primary malignancy of the brain. Although conventional treatments have found modest success in reducing the initial tumor burden, infiltrating cancer cells beyond the main mass are responsible for tumor recurrence and ultimate patient demise. Targeting residual infiltrating cancer cells requires the development of new treatment strategies. The emerging field of cancer nanotechnology holds promise in the use of multifunctional nanoparticles for imaging and targeted therapy of glioblastoma. This article examines the current state of nanotechnology in the treatment of glioblastoma and directions of further study.

**Endogenous Vaults and Bioengineered Vault Nanoparticles for Treatment of Glioblastomas: Implications for Future Targeted Therapies** 451

Jian Yang, Daniel T. Nagasawa, Marko Spasic, Misha Amolis, Winward Choy, Heather M. Garcia, Robert M. Prins, Linda M. Liau, and Isaac Yang

Endogenous vaults are ribonucleoproteins expressed throughout various cell types and across numerous species. Several central nervous system (CNS) tumors have been reported to exhibit high levels of major vault protein (MVP). The vault has been hypothesized to play a role in cellular transport. Although further studies are needed to elucidate the mechanisms of endogenous vault function, these advances may enable the development of targeted therapies to prevent cancer cells from acquiring MVP-related drug resistance. In addition, they seem suited for use as nanocapsules for delivering various therapeutic agents and immunogenic proteins, representing a promising prospect for CNS tumor immunotherapy.

**Clinical Trials with Immunotherapy for High-Grade Glioma** 459

Jacob Ruzevick, Christopher Jackson, Jillian Phallen, and Michael Lim

Immunotherapy is a potential new therapeutic option in patients with high-grade gliomas (HGGs). Phase I/II trials have assessed the efficacy of increasing immune activity using vaccines made from lymphokine-activated killer cells, cytotoxic T cells, autologous tumor cells, or dendritic cells. Studies to decrease tumor immunoresistance have focused on cytokine modulation of known immunosuppressive factors in the tumor microenvironment. Several early studies have reported a survival benefit using different forms of immunotherapy. This article discusses past clinical trials using immunotherapy in HGGs, their efficacy, limits, and biologic and clinical design challenges that must be overcome to advance immunotherapy for patients with HGGs.

**IDH Mutations in Human Glioma** 471

Won Kim and Linda M. Liau

A novel mutation of isocitrate dehydrogenase-1 (IDH1) was recently found in a large percentage of secondary human gliomas. Unlike previously discovered prognostic molecular characteristics, IDH1 mutations were found across gliomas of many different grades and histologies. Further studies have illuminated its utility as a prognostic marker in low-grade and high-grade gliomas and its ability to aid the differentiation and diagnosis of various tumors with histologic ambiguity. As a metabolic enzyme, its inhibitory actions and neomorphic activity present a unique avenue in the understanding of these tumors and potentially a novel mechanism through which they may be treated.

**Passive Immunotherapeutic Strategies for the Treatment of Malignant Gliomas** **481**

Daniel T. Nagasawa, Christina Fong, Andrew Yew, Marko Spasic, Heather M. Garcia, Carol A. Kruse, and Isaac Yang

This review provides historical and recent perspectives related to passive immunotherapy for high-grade gliomas. The authors discuss approaches that use lymphokine-activated killer cells, cytotoxic T lymphocytes, and monoclonal antibodies.

**Use of Language Mapping to Aid in Resection of Gliomas in Eloquent Brain Regions** **497**

Matthew C. Garrett, Nader Pouratian, and Linda M. Liau

Studies looking at resection in high-grade gliomas have had mixed results. The authors briefly review the literature regarding the value of the extent of resection. They proceed to the preoperative and intraoperative tools available to the neurosurgeon to distinguish eloquent from noneloquent language cortex and fibers, including the emerging roles of functional magnetic resonance imaging diffusion tensor imaging tractography and direct cortical/subcortical stimulation in the surgical management of tumors in eloquent areas. Finally, the authors evaluate the postoperative course of these patients and the effect of language deficits on their quality of life.

**Quality of Life and Outcomes in Glioblastoma Management** **507**

Chaim B. Colen and Elizabeth Allcut

This article explores the effects of modern treatment on the health-related quality of life in patients who suffer from glioblastoma multiforme.

**High-Grade Gliomas in Children** **515**

Tene A. Cage, Sabine Mueller, Daphne Haas-Kogan, and Nalin Gupta

High-grade gliomas (HGGs) are malignant tumors and typically include glioblastoma multiforme and anaplastic astrocytoma subtypes. Brainstem gliomas and ependymomas are separate entities with respect to clinical presentation, treatment, prognosis, and outcome in comparison with supratentorial HGGs. In children, these tumors account for 3% to 7% of newly diagnosed brain tumors and 20% of all diagnoses of pediatric supratentorial brain tumors. These neoplasms are highly proliferative and mitotically active and of glial origin. This article reviews clinical, diagnostic, and pathologic features of HGG and current treatments and potential future therapies specific to pediatric patients with HGGs.

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