Glioblastoma Multiforme

Overview of Current Treatment and Future Perspectives

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KEYWORDS

• Glioblastoma multiforme • Glioma • Brain tumor • Chemotherapy • Temozolomide • Bevacizumab

KEY POINTS

- Current first-line treatment regimens combine surgical resection and chemoradiotherapy, providing a slight increase in overall survival.
- Age on its own should not be used as an exclusion criterion for glioblastoma multiforme (GBM) treatment, but performance status should be factored heavily into the decision-making process for treatment planning.
- Despite aggressive initial treatment, most patients develop recurrent disease, which can be treated with reresection, systemic treatment with targeted agents or cytotoxic chemotherapy, reirradiation, or radiosurgery.
- Research into novel therapies is investigating alternative temozolomide regimens, convection-enhanced delivery, immunotherapy, gene therapy, antiangiogenic agents with and without cytotoxic chemotherapy, poly(adenosine diphosphate-ribose) polymerase-1 inhibitors, and targeting of tumor growth-promoting pathways or cancer stem cell signaling pathways.
- Given the aggressive and resilient nature of GBM, continued efforts to better understand GBM pathophysiology are required to discover novel targets for future therapies.

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INTRODUCTION

Nearly 10,000 cases of glioblastoma multiforme (GBM) are diagnosed annually in the United States,[1] making GBM the most common primary malignant tumor of the central nervous system (CNS). Ongoing research has drastically advanced our understanding of GBM pathophysiology; however, meaningful survival improvement has not occurred.

With near-certain relapse, prognostic factors are important in counseling patients and selecting individual patients for specific treatment modalities. Nomograms can be helpful in predicting the prognosis of individual patients, taking into account pertinent molecular and prognostic factors. Age, performance status, extent of surgical resection, temozolomide (TMZ) treatment, O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, and neurologic functioning as expressed by the Mini-Mental State Examination score are important prognostic factors.[2]

Although no treatment has proved curative and overall mortality remains high, continued research promises to lead to novel individualized and localized therapies.

CURRENT TREATMENTS

Current treatment protocols for GBM combine surgery, chemotherapy, and radiation, providing palliation and moderate survival benefit. For newly diagnosed patients with GBM, standard treatment includes maximal surgical resection followed by combined radiotherapy and chemotherapy.

Surgical Resection

The goal of surgery in GBM treatment is to provide maximal tumor resection, with preservation or restoration of neurologic function. Recent studies have shown gross total resection to enhance the overall survival (OS) in GBM. When maximal total resection is not feasible, near-total and subtotal resection provides additional survival benefit. In a study of 451 patients with GBM undergoing primary resection, the median survival after gross-total resection, near-total resection, and subtotal resection was 13, 11, and 8 months, respectively.[3]

Advances in image-guided surgical techniques, including intraoperative magnetic resonance imaging (MRI), cortical mapping, and stereotactic surgery have assisted in the ability to safely increase the extent of tumor resection. These new modalities have had a significant impact on patients with tumors in eloquent cortical areas where resection is frequently abandoned before total removal to avoid neurologic deficits. A phase III trial of 322 patients showed the benefit of fluorescence-guided tumor resections with 5-aminolevulinic acid.[4] When combined with intraoperative monitoring and cortical and subcortical stimulation, fluorescence guidance provides the surgeon with direct visualization of tumor borders and allows for the largest possible resection with minimal neurologic deficits.[5]

Chemotherapy-Impregnated Wafers

Implantation of biodegradable carmustine (1,2-bis[2-chloreoethyl]-1-nitrosourea, BCNU) wafers (CW) is an approved therapeutic option for patients with newly diagnosed and relapsed glioblastoma. These wafers are placed in the surgical resection site at the time of initial operative debulking. The chemotherapeutic agent is released into surrounding brain tissue beginning immediately after tumor resection and lasting for several weeks. Use of CW results in a statistically significant benefit in the OS of patients undergoing initial surgery for malignant gliomas (13.9