Medical Management of High-Grade Astrocytoma: Current and Emerging Therapies

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High-grade astrocytomas are aggressive and incurable primary brain tumors. Radiation therapy with concurrent and adjuvant temozolomide chemotherapy is the standard-of-care treatment for newly diagnosed glioblastoma, while the role of chemotherapy in the initial treatment of anaplastic astrocytoma is evolving. Currently available medical options at tumor progression include further cytotoxic therapy and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab. Investigational treatments including numerous molecularly targeted agents and immunotherapeutic approaches are currently being evaluated. Significant future progress will require better understanding and exploitation of the molecular heterogeneity within high-grade astrocytoma, as well as innovative trial designs to evaluate efficiently targeted therapies in the subsets of patients in which they are most likely to be effective.
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High-grade astrocytoma, the collective term for glioblastoma (World Health Organization [WHO] grade IV astrocytoma) and anaplastic astrocytoma (WHO grade III astrocytoma), is the most common and most aggressive category of primary brain tumor. Median survival after diagnosis of glioblastoma is approximately 14–16 months, and only 5% of patients survive to 5 years after diagnosis.[1] Anaplastic astrocytoma is less aggressive but still uniformly fatal, with a median survival time of 3–5 years. New standard-of-care therapies have emerged for both newly diagnosed and progressive glioblastoma over the course of the past decade, and optimal treatment of anaplastic astrocytoma is an area of active investigation. Despite these advances, improvements in survival have been modest, and fundamental changes in the way in which high-grade astrocytoma is categorized and treated will likely be necessary before significant progress can be realized.

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STANDARD-OF-CARE THERAPY

Glioblastoma

Newly Diagnosed Glioblastoma

The current standard of care for newly diagnosed glioblastoma is radiation therapy with concurrent and adjuvant temozolomide chemotherapy. Temozolomide is an oral chemotherapeutic agent that induces methylation of O^6-guanine to O^6-methylguanine, which in turn triggers a futile cycle of DNA mismatch repair. Radiation therapy, usually dosed as 60 Gy in 30 fractions, has been the cornerstone of glioblastoma therapy for decades.[2] No advantage of radiation dose increase up to 90 Gy has been demonstrated using a variety of radiation techniques such as stereotactic radiosurgery, brachytherapy, or intensity-modulated radiation therapy.[3,4] The European Organization for Research and Treatment of Cancer (EORTC) 26981/22981 and National Cancer Institute of Canada Trials Group (NCIC) CE3 phase III trial of radiation alone versus radiation with temozolomide in 2005 provided for the first time evidence that addition of a chemotherapy agent can improve overall survival in the setting of newly diagnosed glioblastoma.[5] Prior to this time, numerous other chemotherapeutic agents had been evaluated without obvious benefit, though meta-analysis of randomized trials had suggested a modest improvement in survival associated with the addition of chemotherapy to radiation.[6]

In the pivotal trial that proved the efficacy of temozolomide, the drug was given concurrently

with a 6-week course of radiation at the dose of 75 mg/m^2 daily. After a 4- to 6-week rest period, temozolomide was resumed with an additional six adjuvant cycles being administered: starting dose was 150 mg/m^2 on days 1–5 every 28 days in the first cycle, with escalation to 200 mg/m^2 on days 1–5 in subsequent cycles if the first cycle was well-tolerated. In this trial, median survival was 12.1 months in the radiation-only arm versus 14.6 months in the temozolomide-containing arm, a statistically significant improvement. More importantly, chemoradiotherapy increased the proportion of relatively long-term survivors from 10.9% to 27.2% at 2 years and from 1.9% to 9.8% at 5 years.[1] The enzyme O^6-methylguanine DNA methyltransferase (MGMT) repairs the methylation of O^6-guanine, one of the changes induced by temozolomide. A subgroup analysis based on 206/572 patients of the EORTC/NCIC study showed that patients in whom expression of this enzyme is low due to promoter methylation have longer median survival regardless of treatment.[7] The addition of temozolomide to radiation appears to benefit both patients with methylated tumors and those with unmethylated tumors, though the magnitude of benefit is greater in patients with methylated tumors.[1]

The clinical trial that led to the approval of temozolomide used six adjuvant cycles of chemotherapy after the end of concurrent chemoradiotherapy, but there is significant variation in clinical practice with regard to treatment duration. In Europe, the six-cycle schedule is the most prevalent. In the United States, however, there is more divergence in practice, with six-cycle, 12-cycle, and even 24-cycle schedules all finding advocates.[8] Radiation Therapy Oncology Group (RTOG) 0525, a large randomized phase III trial, was conducted to determine whether a "dose-dense" schedule of adjuvant temozolomide for 21 of 28 days was superior to the standard 5 of 28 days adjuvant temozolomide schedule.[9] Protocol treatment included six adjuvant temozolomide cycles in each arm with the potential to extend to 12 cycles at the discretion of the treating oncologist if treatment was well tolerated and there was evidence of continuing benefit. This study demonstrated no statistically significant difference in survival between the two temozolomide schedules, and comparable toxicity between the two arms with the exceptions of fatigue and lymphopenia, which were somewhat more frequent in the dose-dense arm. Among patients who remained in the trial and had not experienced tumor progression following the completion of six adjuvant temozolomide cycles, only 22 patients (8%) stopped adjuvant temozolomide treatment at that time, while 239 (92%) received additional cycles. The median overall survivals for those 22 and 239 patients were 24.9 months (95% confidence interval [CI], 19.2–36.2 months) and 30.2 months (95% CI, 25.5–35.4 months). This study prospectively validated the prognostic importance of MGMT promoter methylation status: although prognostic, MGMT promoter methylation status was not predictive of response to standard versus dose-dense temozolomide.

Temozolomide chemotherapy is generally well tolerated. Leukopenia is common and usually asymptomatic, whereas thrombocytopenia, neutropenia, and anemia are less frequent but potentially life-threatening. In the EORTC study, which proved the efficacy of temozolomide in newly diagnosed glioblastoma, 7% of patients developed grade 3 or 4 hematologic toxicity during the concomitant phase and 14% of patients developed grade 3 or 4 toxicity during the adjuvant phase.[5] The most significant nonhematologic toxicity of temozolomide is fatigue, with moderate-to-severe fatigue occurring in 33% of patients treated with chemoradiotherapy and only 26% of patients treated with radiation alone. Nausea and constipation are also common in patients receiving temozolomide. Routine use of supportive medications helps to limit toxicity of treatment. All patients receiving temozolomide should receive prophylactic anti-emetic therapy, usually employing serotonin 5-HT3 receptor antagonists such as granisetron or ondansetron. Temozolomide-induced lymphopenia puts patients at risk for *Pneumocystis jirovecii* pneumonia (PCP), and routine use of PCP prophylaxis is recommended.[10] Trimethoprim/sulfamethoxazole is the agent in greatest use for PCP prophylaxis, often at a dose of one single-strength tablet daily or one double-strength tablet three times per week. In patients that cannot tolerate treatment with trimethoprim/sulfamethoxazole due to allergy or other reasons, alternatives include dapsone, atovaquone, and inhaled pentamidine.

Bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor A, is approved by the US Food and Drug Administration (FDA) as treatment for recurrent glioblastoma. Two large international phase III trials of radiation therapy and temozolomide plus bevacizumab versus placebo, RTOG 0825 and AVAglio, were conducted to evaluate the efficacy of bevacizumab in the setting of newly diagnosed glioblastoma.[11,12] Neither of these trials demonstrated an improvement in overall survival in bevacizumab-treated patients, though both trials showed improvements in progression-free survival in the bevacizumab arm: 10.7 months versus 7.3 months ($P = .007$) in RTOG 0825 and 10.6 months versus 6.2 months ($P < .001$) in AVAglio. Further, in RTOG 0825 molecularly defined subgroups based on a nine-gene signature could not predict outcome, though ongoing bioinformatic analyses may ultimately identify molecularly defined