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What are the prospects for combination therapy for glioblastoma?

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Combination therapy, consisting of maximal safe surgical resection followed by combined chemoradiotherapy and adjuvant temozolomide, currently represents the standard of care for patients with newly diagnosed glioblastoma (GBM). This regimen was established after publication of the landmark study by Stupp et al., which demonstrated a modest survival benefit with the addition of temozolomide chemotherapy to standard radiotherapy [1]. Unfortunately, 12 years later, this standard remains largely unchanged, and there has been little improvement in the dismal prognosis for patients with GBM, who face a median overall survival of 14.6 months [1] with essentially no therapies proven effective in the recurrent setting. Increasingly, it has been recognized that IDH wild-type GBM is a different biological entity from IDH-mutated GBM, and many clinical trials now limit enrollment according to IDH mutation status. Here, we will focus on developments in the treatment of IDH wild-type GBM, which is associated with overall resistance to therapy and shorter survival.

The past decade has seen the identification of a multitude of novel targeted agents, all of which have shown promise in the preclinical and early clinical settings, but ultimately proved disappointing in Phase II and III trials. These agents have included inhibitors of the epidermal growth factor receptor (EGFR), which is amplified in approximately 40% of GBM [2] and which has proven a valuable target in other solid malignancies, particularly non-small-cell lung cancer [2]. These agents have included small-molecule tyrosine kinase inhibitors: erlotinib, gefitinib, and afatinib, as well as the monoclonal antibodies cetuximab and nimotuzumab [2,3]. Despite promising results in Phase II studies, rindopepimut, a peptide vaccine targeting the EGFRvIII mutation, failed to show benefit when administered in the first-line setting in a randomized Phase III trial (ACT IV) [4]. The fact that EGFRvIII expression was lost in patients on progression after treatment with rindopepimut [5] underscores the increasing evidence that targeting isolated, heterogeneously expressed markers is unlikely to provide long-term control in GBM.

Antiangiogenic therapies have also been extensively investigated in both the first-line and the recurrent settings, with agents including multikinase inhibitors such as sorafenib and vandetanib, the integrin inhibitor cilengitide [3], and direct anti-vascular endothelial growth factor monoclonal antibodies including bevacizumab [6]. Of these, only bevacizumab has been approved for use in recurrent GBM, based on a Phase II study showing improved PFS compared to historical controls [7]. Two Phase III clinical trials, AVAglio [8] and RTOG-0825 [9], attempted to demonstrate a benefit of bevacizumab in the first-line setting, in combination with concurrent chemoradiotherapy. However, neither trial met its primary end point, and use of bevacizumab remains limited to the recurrent setting.

Recent discoveries in the molecular biology of GBM have contributed to a growing appreciation of both inter- and intratumoral heterogeneity which may partially underlie the overall failure of molecularly targeted therapy in GBM [3]. Through genome sequencing of tumor tissue from 500 patients with GBM, The Cancer Genome Atlas Network has identified four separate subtypes of GBM, each characterized by unique patterns of somatic mutations and DNA copy number [10].

Furthermore, there is evidence that there exists significant intratumoral heterogeneity with clonal populations with different phenotypic profiles and mosaic amplification of associated receptor tyrosine kinases including EGFR, MET, and PDGFRA [11]. Thus, targeted therapy against a single mutation will result in selection for the resistant cell population, leading to eventual treatment resistance and recurrence. This is supported by studies showing both spatial and temporal heterogeneity in mutation profile, as well as a shift towards a treatment-resistant, mesenchymal phenotype in tumors sampled at recurrence after primary therapy [12]. These findings suggest that, while selection of patients for clinical trials by molecular subtype may help identify patients likely to benefit, effective personalized therapy of GBM will likely require detailed genetic sequencing and individualization of therapy as well as rational combination of targeted agents with those less dependent on aberrant receptor expression.

A potential new tool in the first-line treatment of GBM may be the use of tumor-treating fields (TTF). Recent preclinical and clinical trial evidence suggests that exposure of proliferating cells to low-intensity, alternating electric fields in the intermediate-frequency range (100 kHz to 1 MHz) may have an antiproliferative effect on cells undergoing mitosis through disruption of mitotic spindle formation and dielectrophoretic movement of charged particles and organelles, with selective effects on tumor cells due to their increased mitotic rate
relative to normal tissue [13]. TTF treatment was approved by US FDA for first-line treatment of GBM base on the results of EF-14 [14], a randomized, Phase III study comparing standard chemoradiotherapy with temozolomide followed by adjuvant temozolomide in combination with use of TTF for a minimum of 18 h/day vs. standard-of-care treatment. Alternating electrical fields were generated using the Optune device (Optune, NovoCure Ltd, Haifa, Israel) which consists of a ceramic transducer array affixed to the patient’s shaved scalp, which is connected to a battery-operated power source carried as a backpack. This trial demonstrated a 3.1-month survival benefit when used in the first-line setting, while recent results released in abstract form suggest that this benefit may be as much as 4.9 months [15]. While these results are promising, experts have questioned several aspects of this trial, such as the lack of a sham device in the control arm. In addition, as randomization occurred after completion of chemoradiotherapy, patients with very early disease progression were excluded, leading to a population that was relatively enriched for better outcome [16]. Significant questions remain regarding the future use of TTF in clinical practice. The current price of Optune at $20,000 USD/month places it far outside the widely accepted limit of approximately $50,000 per year of life gained [17]. This makes it unlikely that use of TTF will be widely approved outside the United States unless the cost of treatment decreases dramatically [18]. It remains to be seen how this modality will fit within the global standard of care.

The advent of cancer immunotherapy, marked by the rapidly expanding use of immune checkpoint inhibitors, represents a paradigm shift in clinical oncology. These agents have shown evidence of durable response and survival benefit in a wide variety of solid and hematological malignancies. Despite the long-standing dogma of immune privilege of the CNS, early trials suggest that these agents are active in primary brain tumors as well as brain metastases [19]. The challenge in adapting immunotherapy for use in CNS malignancies lies in overcoming the innate immunosuppressive milieu of the brain parenchyma and the mechanisms by which these tumors avoid immune surveillance. Techniques currently under development include the use of vaccines against tumor-associated antigens. Vaccine therapy is associated with a favorable side-effect profile due to the specificity of the target antigen, but as suggested by the loss of EGFRvIII expression in recurrent GBM after treatment with rindopepimut, efficacy may be impaired by immunological tolerance and escape [5,20]. Combination vaccine therapy trials, including the use of autologous dendritic-cell vaccines and addition of immune sensitizers including checkpoint inhibitors, are underway [20]. Immune checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1/PD-L1 pathway inhibitors are also being tested in the recurrent setting as well as in combination with first-line chemoradiotherapy. Preliminary results of a cohort of Checkmate 143 comparing nivolumab (a monoclonal antibody targeting PD-1) with bevacizumab in recurrent GBM have recently been reported and showed no OS benefit of nivolumab over bevacizumab [21], while studies in newly diagnosed patients are still ongoing. Other novel modalities being investigated include ABT-414, an antibody–drug conjugate targeting EGFR-overexpressing tumor cells [22], as well as numerous trials using oncolytic viruses in newly diagnosed or recurrent GBM.

Recent discoveries in the field of malignant gliomas have been, in a sense, contradictory, with great increases in our understanding of the molecular biology and pathogenesis of GBM, accompanied by many promising, but ultimately unsuccessful attempts at treatment of this devastating condition. Molecularly targeted therapy which relies on the expression of specific mutated or amplified markers, despite widespread success in other solid and hematological cancers, seems unlikely to be the answer in GBM, as intratumoral heterogeneity of receptor expression leads to rapid development of treatment resistance. Increasingly, it seems clear that a single, targeted, ‘one-size-fits all’ approach is unlikely to be effective. Recent advances in the fields of immune-oncology have led to attempts to adapt these treatments to the unique immunologic milieu of the central nervous system, and clinical trials are ongoing. As we come to appreciate both the molecular heterogeneity of GBM and the mechanisms of immunosuppression and evasion of immune surveillance, neuro-oncologists are faced with potential new targets and mechanisms for treatment, but also a deepening understanding of the challenges posed by this disease.

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Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.

   • Study which established standard-of-care chemoradiotherapy with temozolomide for glioblastoma.
   • A concise review of targeted agents in glioblastoma and the challenges of molecularly targeted therapy.