

Editorial

Monotherapy of High-Grade Gliomas with a TGFβ₂-Targeting RNA Therapeutic

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Editorial

High-grade gliomas (HGG), including Anaplastic Astrocytoma (AA; WHO grade III) and Glioblastoma Multiforme (GBM; WHO grade IV), represent about 60% of all primary malignant brain tumors. GBM is the most common malignant brain tumor and carries an extremely poor prognosis. Prognosis of high-grade gliomas has only marginally improved despite technical advances in neurosurgery and radiotherapy and the approval of novel anticancer agents. The median overall survival of patients with glioblastoma in population-based studies is only 10 months to 12 months [1]. Even when aggressively treated with surgery, radiation and chemotherapy, the median survival remains <2 years. The standard of care for 1st line treatment of high-grade gliomas involves a multi-modality treatment strategy that includes surgical resection, adjuvant postoperative radiation therapy, and adjuvant chemotherapy. In GBM, adjuvant chemotherapy with the alkylating agent Temozolomide (TMZ) administered concomitantly with radiation as well as post-radiation in 1st line setting has resulted in improved survival when compared to radiation alone [2]. A portable medical device that delivers low-intensity alternating electric fields (TT Fields) in the adjuvant setting has also been shown to contribute to improved survival when used in combination with maintenance TMZ therapy [3]. Furthermore, a recent study provided early evidence that dual therapy with lomustine plus TMZ might further improve survival compared with TMZ standard therapy in patients with newly diagnosed GBM with methylated MGMT promoter [4]. However, recurrent or progressive disease in GBM still occurs in the vast majority of patients within the first year after initiation of 1st line therapy and it is characterized by a dismal prognosis with no effective therapy. Therefore, there is an urgent and unmet medical need to identify and develop effective salvage therapies for recurrent/refractory (R/R) HGG patients who have failed their 1st line standard therapy [5].

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The immunoregulatory pleotropic cytokine Transforming Growth Factor (TGF) beta has 3 isoforms, TGFβ₁, TGFβ₂, and TGFβ₃. TGFβ binds to its serine/threonine kinase receptor TGFβR2 and activates a Smad-dependent intracellular signal transduction pathway. TGFβ can also stimulate Smad-independent signaling *via* activation of the phosphatidylinositol 3-kinase (PI3K)-AKT signal transduction pathway. In oncology, TGFβ has been implicated in (i) treatment resistance to targeted therapeutics, chemotherapy as well as immune checkpoint inhibitors, (ii) metastasis, (iii) disease progression, and (iv) poor survival [6,7]. TGFβ has emerged as an attractive target for the treatment of HGG, including GBM [8,9]. It is noteworthy that a selective knock-down of TGFβ expression significantly enhances tumor-cell immunogenicity and 3 to 4 fold amplified lymph node effector cell anti-glioma cytotoxic activity in the rat 9 glioma model of HGG [10]. Notably, TGFβ induces the self-renewal capacity of GBM-initiating cells that have been implicated in the initiation and recurrence of GBM [11]. Several studies have documented amplified TGFβ₂ mRNA and protein expression in recurrent/refractory (R/R) HGG, including GBM. Compared to normal brain tissue, TGFβ₂ expression is increased by >3 fold and >20 fold in newly diagnosed and recurrent tumors, respectively [9]. TGFβ₂ protein levels were reported to be 2 to 3 fold (200% to 300%) higher than the protein levels of the other TGFβ isoforms [8]. Notably, GBM is characterized by a T-cell exhaustion signature and pronounced T-cell hyporesponsiveness of the tumor microenvironment (TME) and TGFβ₂ has been implicated as a key contributor to the immunosuppressive landscape of the TME in high-grade gliomas, especially during the later stages of disease progression.

OT101, a TGFβ₂-specific synthetic phosphorothioate antisense oligodeoxynucleotide (S-ODN) with a complementary sequence to a segment of the mRNA of the human TGFβ₂ gene, is designed to abrogate the tumor-promoting and immunosuppressive actions of TGFβ₂ [11]. OT101 was granted both the FDA Orphan Drug Designation and FDA Pediatric Rare disease Designation. At low micromolar concentrations, OT101 has been shown to inhibit the proliferation, invasive migration as well as TGFβ₂ secretion of primary malignant glioma cells [12]. In the presence of OT101, IL2-stimulated Lymphokine Activated Killer (LAK) cells derived from the peripheral blood samples of HGG patients exhibited markedly augmented cytolytic activity against autologous glioma cells [13]. Intracerebral infusion of OT101 was well tolerated in preclinical studies and resulted in rapid distribution of OT101 from the infusion site to other parts of the brain, including remaining cerebrum, cerebellum, pineal body, and spinal cord [14]. The feasibility of intratumoral application of OT101 for treatment of recurrent/refractory (R/R) HGG patients was established in phase I clinical trials that also provided early

activity signals, including 2 sustained Partial Responses (PR) patients. The preliminary findings of a randomized phase II study further confirmed the feasibility of intratumoral application of OT101 *via* Convection Enhanced Delivery (CED) for up to 5 months and showed that it results in early disease control at 5 months [15]. We recently performed a post-hoc analysis of the clinical data from the phase II study (ClinicalTrials.gov, NCT00431561), in R/R supratentorial HGG patients with prolonged follow-up regarding the safety and efficacy of OT101 along with a multivariate analysis of predictive parameters for favorable overall responses and survival outcome. OT101 was administered to 89 R/R High-Grade Glioma (HGG) (Anaplastic Astrocytoma/AA:27; Glioblastoma multiforme/GBM:62) patients with an intratumoral catheter 77 patients (Efficacy population; GBM:51; AA:26) received at least the intended minimum number of 4 OT101 treatment cycles. Nineteen patients had a Complete Response (CR) or Partial Response (PR) following a slow but robust size reduction of their target lesions. In addition, 7 patients had Stable Disease (SD) lasting \geq 6 months [16,17]. Hence, OT101 administered intratumorally exhibits clinically meaningful single-agent activity and induces durable CR/PR/SD in R/R HGG patients.

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