

Editorial

Convection-Enhanced Delivery of an Anti-TGFβ RNA Therapeutic as a New Therapeutic Concept for Children with Diffuse Intrinsic Pontine Glioma

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Editorial

Diffuse Intrinsic Pontine Glioma (DIPG), the second most common malignant pediatric brain tumor, has a dismal outcome with available standard treatment modalities [1-4]. No significant therapeutic advances have been accomplished in the treatment of this poor prognosis brain tumor and the average overall survival has remained <1 year with a 2-year survival rate of <10% [1-5].

In solid tumors, the expression level of the Transforming Growth Factor (TGF) Beta (TGFβ) has been identified as a significant contributor to disease progression and poor prognosis as well as resistance to standard therapy and metastasis [6-8]. In particular, TGFβ has been implicated in treatment resistance to targeted therapeutics, chemotherapy as well as immuno-oncology drugs. Importantly, TGFβ restrains anti-tumor immunity by restricting cytotoxic T-cell infiltration, recruiting regulatory T cells and inhibiting the maturation as well as function of Natural Killer (NK) cells [6-8]. Amplified activity of the TGFβ-Smad signaling pathway enhances tumor growth, invasion, as well as angiogenesis and has been implicated in the malignant phenotype and poor prognosis of high-grade gliomas in adults [9-12]. Therefore, TGF-β has emerged as an attractive target for the treatment of high-grade gliomas [9-12].

We recently performed a meta-analysis of TGFβ2 gene expression in primary tumor specimens from 29 pediatric DIPG patients using publicly available archived datasets [13]. Our data provided unprecedented evidence that TGFβ2 is expressed at high levels in pediatric DIPG. Three TGFβ2 probesets exhibited 1.8-fold to 2.5-fold increased levels of expression in DIPG patients [13]. Our meta-analysis provided new evidence that TGFβ2 gene and its interactome

are expressed in pediatric DIPG at significantly higher levels than in normal tissues or low-grade gliomas [13]. Hence, TGFβ2 may serve as a molecular target for immunotherapy of pediatric DIPG.

OT101, a TGFβ2-specific phosphorothioate antisense oligodeoxynucleotide, is a first-in-class RNA therapeutic designed to abrogate the immunosuppressive actions of TGFβ2. OT-101, is intended to reduce the level of TGFβ2 protein in high-grade gliomas, including GBM, and thereby delay the progression of disease. OT101 has orphan drug status for treatment of high-grade gliomas (HGG) and was recently granted the FDA Pediatric Rare Disease Designation for treatment of DIPG. OT101 reduces TGFβ2 production/secretion, inhibits proliferation as well as invasive migration, and increases sensitivity to Lymphokine Activated Killer (LAK) cell-mediated cytotoxicity of TGFβ2-expressing high-grade glioma cells [10]. The preliminary findings of a phase II study (NCT00431561) confirmed its favorable safety profile and showed that OT101 can offer early disease control to R/R high-grade glioma patients at 6 months at a rate comparable to that achieved with the standard alkylating chemotherapy drug temozolomide [14].

We recently reported our post-hoc analysis of the single agent activity of OT101 which showed that OT101 induces durable complete and partial responses in recurrent and refractory adult high-grade glioma patients, including young adults with GBM or AA [15,16]. Notably, OT101 induced durable Complete Response (CR), Partial Response (PR), or Stable Disease (SD) in a subset of radiation-/radiochemotherapy-resistant HGG patients who had experienced a recurrence after surgical resection of their brain tumor and adjuvant radiation therapy with or without concomitant chemotherapy and lead to an overall survival time of >4.5 years. Taken together with the data showing TGFβ2 mRNA, the molecular target of OT101, is expressed at very high levels in both pediatric DIPG patients [13], these results indicate that intratumoral OT101 therapy *via* convection-enhanced delivery has clinical impact potential for pediatric DIPG. OT101 may offer renewed hope for salvage therapy of DIPG patients who have a rare and fatal disease.

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