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Research Article

Sustained Target Lesion Shrinkage and Favorable Survival Outcome in Radiation and Radio-Chemotherapy Resistant High Grade Glioma Treated by Convection Enhanced Delivery of a TGFβ2-Targeting RNA Therapeutic

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Abstract

Here we report the single agent activity of the TGFβ2-specific synthetic RNA therapeutic OT101 in a select group of 12 patients with high-grade glioma who had experienced their recurrence >90 days after radiation (12 patients; 100%) or radiation + concomitant chemotherapy (8 patients; 67%). OT101 was administered intratumorally for up to 5 months by continuous infusion *via*. a Convection-Enhanced Delivery (CED) platform, CEDOT, designed to maximize the clinical benefit of immuno-oncology drugs for aggressive brain tumors. OT101 resulted in robust size reduction of the target lesions in 10 of the 12 patients. The mean percent reduction for all 12 patients was 71.2 ± 11.9 (Median = 89.7). Four patients achieved 100% reduction in tumor volume over the course of the treatment. The mean $\log_{10}$ reduction was 1.8 ± 05 (Median = 1.1). The mean time for 99% reduction in tumor volumes was 30.4 ± 15.1 (Median = 16.9) months and the mean time for 90% reduction was 15.2 ± 7.6 (Median = 8.5) months. Eight patients (67%) achieved an objective response (CR or PR) and 4 patients achieved stable disease >6 months. The Kaplan-Meier estimates of the median Progression-Free Survival (PFS) and Overall Survival (OS) times were 1281 (95% CI: 1070-NA) days and 1743 (95% CI: 1492-NA) days, respectively. These results demonstrate that CEDOT-administered OT101 can be associated with a favorable survival outcome in aggressive radiation/radio chemotherapy-resistant brain tumor patients who experience a recurrence of their malignancy after radiation therapy with and without concomitant chemotherapy.

Keywords: RNA therapeutic; Glioma; Convection-enhanced delivery; Anaplastic astrocytoma; Immuno-Oncology; Chemotherapy

Introduction

Prognosis of High-Grade Gliomas (HGG) has not significantly improved despite recent advances in neurosurgery, chemotherapy, immuno-oncology, and radiation therapy [1-3]. Most patients experience recurrence or progression of their disease within 12 months after frontline therapy and face a dismal outcome with no effective therapy. Therefore, effective salvage therapies are needed for recurrent/refractory HGG patients who have failed their 1st line standard therapy.

The experimental immuno-oncology drug OT101 (also known as Trabedersen), a TGFβ2-specific Synthetic Antisense Oligodeoxynucleotide (S-ODN), is a first-in-class RNA therapeutic with an FDA orphan drug designation and pediatric rare disease designation, that is designed to abrogate the tumor-promoting and immunosuppressive actions of TGFβ2 in aggressive brain tumors [4]. 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 HGG patients at 6 months at a rate comparable to that achieved with the standard alkylating chemotherapy drug temozolomide [5]. We are now reporting our post-hoc analysis of a select group of 12 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. In an attempt to isolate the single agent activity of OT101 without confounding effects of previous therapy, patients who had less than 3 months since last cancer therapy were excluded from this analysis. In the 12 radiation/radiochemotherapy-resistant HGG patients, OT-101 administered intratumorally *via.* CED exhibited potent single-agent activity, causing a robust shrinkage of the target lesions (10 of 12 patients) and inducing durable Complete Response (CR) (2 of 12 patients), Partial Response (PR) (6 of 12 patients), or Stable Disease (SD) lasting ≥ 6 months (4 of 12 patients). The median Progression-Free Survival (PFS) and Overall Survival (OS) times were 1281 (95% CI: 1070-NA) days and 1743 (95% CI: 1492-NA) days, respectively. These results demonstrate that intratumoral OT101 therapy can result in a favorable survival

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outcome for radiation/radiochemotherapy-resistant HGG patients (AA, WHO grade III and GBM, WHO Grade IV).

Materials and Methods

CED drug delivery platform

OT101 was infused intratumorally using CED, as previously reported [5]. One treatment cycle with OT101 lasted 14 days and involved 7 days continuous infusion of OT101, followed by 7 days continuous infusion of isotonic saline solution. OT101 dissolved in isotonic (0.9%) aqueous sodium chloride solution at a final concentration of either 10 µM or 80 µM was administered at 4 µL/min for 7 days. The total OT101 dose per cycle was 2.5 mg (10 µM group) or 19.8 mg (80 µM group). Patients were to be treated with OT101 for at least 8 weeks corresponding to a minimum of 4 cycles of OT101 and receive a maximum of 11 treatment cycles of OT101.

Patient treatments and ethics statement

The data used in this post-hoc analysis was obtained during the trial registered at ClinicalTrials.gov:NCT00431561. NCT00431561 was a multi-national, multi-center, open-label interventional clinical study in patients with R/R Grade III Anaplastic Astrocytoma (AA) or Grade IV Glioblastoma (GBM). In order to be eligible for the study, patients had to have a brain tumor (either Grade III AA or Grade IV GBM) with supratentorial localization and a measurable lesion with a maximum diameter of 4.5 cm by MRI who had no more than 2 chemotherapy regimens since diagnosis. The diagnosis was confirmed before start of treatments. Patients had to have an expected life expectancy of ≥ 3 months and a baseline KPS score ≥ 70%. Patients with tumour surgery within two weeks prior to study entry were excluded as were patients receiving radiation therapy within eight weeks prior to randomization. Treatment with chemotherapy, hormone therapy, or any other therapies with established or suggested antitumor effects had to be finished 4 weeks to 6 weeks (nitrosoureas only) before randomization. No prior stereotactic radiosurgery or interstitial brachytherapy and no TGF-beta 2 (TGFβ2) targeted therapy or antitumor vaccination were allowed. Patient's participation in another clinical study with investigational medication had to be completed at least 30 days prior to study entry. The study was performed in compliance with the ICH(E6) Good Clinical Practice (GCP) guidelines and with approval from independent ethics committees as well as Institutional Review Boards of the participating institutions. Each patient provided a written informed consent. An independent Data and Safety Monitoring Board participated in the review of the clinical data.

Efficacy measurements

For a standardized response assessment, an independent Central MRI Reading (CMRIR) was performed by a specialized central reading institute (Timaq Medical Imaging Inc, Zurich, Switzerland). Central reading was conducted by two independent neuroradiologists with an additional adjudicator for cases of predefined discrepancies in the reports of the two readers. Best Overall Response (BOR) was defined as the best response documented from randomization until progression of disease (PD). For determining the treatment response of individual patients to OT101, standard Macdonald criteria were used. Overall Survival (OS) was the time from the date of randomization to time of death (censoring at last follow-up for patients alive). Progression-Free Survival (PFS) was the time from randomization to documentation of PD or death. Patients who remained alive without PD were censored at last follow-up. Standard definitions were used for time to progression and duration of objective response.

Statistical analysis

Standard statistical methods were applied for the analysis of data. The distribution of time-to-event survival end points on the OS and PFS curves were estimated by the Kaplan-Meier method. Differences between patient subgroups were evaluated by log-rank statistics. The analyses were performed using JMP software (version 10.02, SAS Institute, Inc, Cary, NC), and R software, version 3.5.2 (R Foundation for Statistical Computing) loaded with statistical packages for survival analysis (survMisc_0.5.5; survival_2.44-1.1 and survminer_0.4.4) with default settings. Survival curves were visualized using the survminer graphing package (Drawing Survival Curves using 'ggplot2'. R package version 0.4.4; https://CRAN.R-project.org/package = survminer). For the patients who had a CR or PR as their BOR, Waterfall plots were used to represent the maximum percentage change in MRI-based tumor volume of the target lesion relative to measurements taken at baseline.

Results and Discussion

Of the 12 patients with recurrent HGG, 4 had GBM (WHO Grade IV) and 8 had AA (WHO Grade III) (Table 1). The 1st line therapy of all patients included surgical resection and radiation therapy (Median dose: 60 Gy, Range: 45-64 Gy) without (4 of 12 patients) or with (8 of 12 patients) concomitant chemotherapy (Table 2). The chemotherapy regimens for the 8 patients who had received radio chemotherapy varied and included

(i) Lomustine (CCNU) + Vincristine (VCR) (2 patients, UPN 524 and UPN 525),

(ii) Nimustine (ACNU) (1 patient, UPN 141),

(iii) ACNU + teniposide (VM26) (1 patient, UPN 102),

(iv)Carboplatin (Paraplatin) (1 patient, UPN 406),

(v) Paclitaxel (Taxol) (2 patients, UPN 417 and UPN 702),

(vi) Procarbazine + CCNU + VCR (PCV) (1 patient, UPN 302) (Table 2).

The time from previous cancer therapy to study entry ranged from 98 days to 475 days (Median: 164 days) (Table 1**).** Patients received 4 cycles to 11 cycles of OT101 (Median: 11 cycles). Seven patients were treated with OT101 at a 2.5 mg/cycle dose level of OT101 and 5 were treated with OT101 at a 19.8 mg/cycle dose level. In 10 of 12 radiation/radio chemotherapy-resistant HGG patients, OT101 administered intratumorally *via.* CED caused a robust shrinkage of the target lesions. The mean percent reduction for all 12 patients was 71.2 ± 11.9 (Median = 89.7). Four patients achieved 100% reduction in tumor volume over the course of the treatment. The mean $\log_{10}$ reduction was 1.8 ± 05 (Median = 1.1). The median time for 90% reduction of the baseline tumor volume was 8.5 months, Range: 4.9 months to 57.7 months (Mean ± SE = 15.2 ± 7.6 months). Waterfall plots depicting the maximum $\log_{10}$ and % reduction values for the tumor volumes of the 12 patients following OT101 treatment are shown in Figure 1**.** OT101 exhibited clinically meaningful single agent activity in each of the 12 patients, inducing durable Complete Response (CR) in 2, Partial Response (PR) in 6, and Stable Disease (SD) lasting ≥ 6 months in 4 patients. Patients with CR had achieved a PR first which deepened to a CR. The median time to onset of PR was 271 days (Range: 185-742) (Figure 2). The median Progression-Free Survival (PFS) and Overall Survival (OS) times were 963 days and 1592 days (Figure 2), respectively. These results provide clinical proof of concept

that CEDOT-administered OT101 can be associated with a favorable survival outcome in HGG patients who experience recurrence after radiation therapy with and without concomitant chemotherapy.

TGFβ has been shown to curb the anti-tumor function of TME by both limiting T-cell infiltration and suppressing the function of the immune system elements [6,7]. TGFβ is being explored as a therapeutic target for the treatment of HGGs, due to the compelling evidence that the amplified activity of the TGFβ-SMAD signaling pathway contributes to the malignant phenotype and poor prognosis of GBM in adult patients by enhancing tumor growth, invasion, and angiogenesis as well as compromised immune surveillance [8-14]. The presented data provides the proof of concept that targeting TGFβ2 with intratumoral OT101 therapy can result in a favorable survival outcome for radiation/radiochemotherapy-resistant HGG patients (AA, WHO grade III and GBM, WHO Grade IV).

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Declaration of Interests

Drs. Uckun, Trieu, and Hwang are employees and shareholders of Oncotelic/Mateon Therapeutics, the sponsor for clinical development

Table 1: Patient Information (N = 12).

Diagnosis # (%)	
AA (WHO grade III)	8 (66.7)
GBM (WHO grade IV)	4 (33.3)
Age (Years)	
Median (Range)	42.5 (26-65)
Mean ± SE	44.4 ± 3.3
Sex	
Male	9 (75.0)
Female	3 (25.0)
Race	
Asian	5 (41.7)
Caucasian	7 (58.3)
Black	0 (0.0)
KPS Score at Baseline	
Median (Range)	90 (70-90)
Mean ± SE	87 ± 2
Size of Largest Target Tumor Lesion	
2-D in cm^2 – Median (Mean ± SE)	9.0 (9.2 ± 1.0)
3-D in cm^3 – Median (Mean ± SE)	24.8 (24.8 ± 3.3)
OT101 Dose Cohort - # (%)	
Low (2.5 mg/cycle)	9 (75.0)
High (19.8 mg/cycle)	3 (25.0)
Number of OT101 Cycles	
Median (Range)	11 (4-11)
Mean ± SE	9.7 ± 0.6
Total OT101 Dose (mg/m^2)	
Median (Range)	15.9 (9.6-136.9)
Mean ± SE	32.9 ± 11.5
Time from last cancer therapy	
Median (Mean ± SE)	164 (206 ± 38)
Time from Diagnosis	
Median (Mean ± SE)	322 (345 ± 53)

Table 2: History of Previous Therapies.

Patient ID	Diagnosis	Previous Therapy	Time (Days) from Previous Therapy
309538	GBM	Resection, RAD(64Gy)	106
301525	GBM	Resection, RAD(60Gy), Chemo (VCR+CCNU ×3)	227
404702	AA	Resection, RAD(60Gy), Chemo (Paclitaxel ×6)	100
405402	AA	Resection, RAD(45 Gy)	257
203302	AA	Resection, RAD (60 Gy), Chemo (PCV ×5)	475
404417	AA	Resection, RAD(60Gy), Chemo (Paclitaxel ×6)	103
407409	AA	Resection, RAD(55Gy)	208
502201	AA	Resection, RAD(60 Gy)	118
107102	AA	RAD (60Gy), Chemo (ACNU/VM26 ×4)	225
301524	GBM	Resection, RAD (60Gy), Chemo (CCNU+VCR ×2)	435
102141	GBM	Resection, RAD, Chemo (ACNU ×4)	98
404406	AA	Resection, RAD (60Gy), Chemo (Carbo ×6)	120

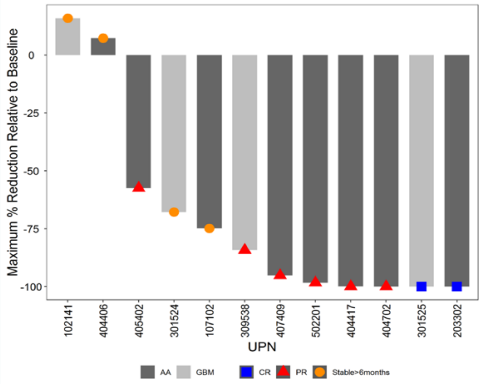

Figure 1: Waterfall plot of OT101-Induced Maximum Tumor Reductions of Radiation-/Radiochemotherapy-Resistant High-Grade Glioma Patients (N = 12). A waterfall plot is depicted to show the maximum tumor reduction relative to baseline (% reduction of the 3-D volume of the target lesion) in each of the 12 patients. Vertical bars on these plots measured maximum reduction in tumor volumes of the treated target lesions following OT101 treatment. The BOR for each patient are indicated with specific symbols.

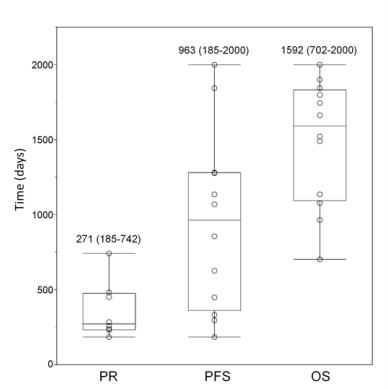

Figure 2: Treatment Outcome of Radiation-/Radiochemotherapy-Resistant High-Grade Glioma Patients Treated with OT101. Depicted are the Box and Whisker plots of the time to PR, PFS and OS for 12 radiation-/radiochemotherapy-resistant HGG Patients treated with OT101. All 12 patients achieved a PR at a median of 271 days. The median PFS was 963 days and the median OS was 1592 days based on the actual data from the individual patients. The Kaplan-Meier estimates of the median PFS and OS times on the PFS and OS curves were 1281 (95% CI: 1070-NA) days and 1743 (95% CI: 1492-NA) days, respectively.

of OT101. Drs. Trieu and Hwang are listed as inventors on patents and patent applications related to OT101. Dr. Qazi received compensation from Oncotelic as a consultant. No other disclosures were reported.

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