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Clinical Investigation

Low Dose Fractionated Radiation Therapy As a Chemo-Potentiator of Temozolomide for Recurrent Anaplastic Astrocytoma and Glioblastoma: A Single-Arm Phase I/II Trial

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Abstract

Purpose

Preclinical and clinical studies suggest low-dose fractionated radiotherapy (LDFRT) is a chemopotentiator in several solid tumors. We evaluated chemopotentiation of temozolomide with LDFRT in glioblastoma and brain metastatic lung cancer cell lines, followed by a phase 1/2 trial assessing the safety/efficacy of LDFRT with concurrent/adjuvant temozolomide in patients with recurrent high-grade gliomas (HGG).

Methods and Material

Preclinical - The temozolomide-potentiating effect of LDFRT was tested in glioblastoma and brain metastatic lung cancer cell lines with real-time cell electronic sensing system and flow cytometry. *Clinical* - Patients with recurrent HGG following standard-of-care chemoradiotherapy and adjuvant temozolomide were enrolled. Radiotherapy consisted of 0.5 Gy twice daily fractions with concurrent temozolomide on days 1-5 of a 28-day cycle for 6 cycles, and adjuvant temozolomide for 6 cycles. MRI was performed every 2 months after initiating LDFRT. The Phase

1 primary e`ndpoint was acute hematologic toxicity. The Phase 2 primary endpoint was 1-year overall survival (OS), with a lower bound of 80% CI >28.6% (historical control). Secondary endpoints included pseudoprogression incidence.

Results

Preclinical - LDFRT-mediated temozolomide potentiation appears more effective than 2 Gy-mediated potentiation.

Clinical

- Thirty patients were enrolled from 2013-2021; 80% had recurrent glioblastoma and 90% were ECOG 0-1. Amongst patients with molecular data, 61% were MGMT-methylated and 23% were IDH-mutant. Median RT dose was 30 Gy (range, 28.5-30). Median follow-up was 9.5 months (range, 0.1-66.3). One-year OS was 34.5% (95% CI 20.9-57.0; lower bound of 80% CI=24.8%). 77% experienced pseudoprogression (median dose 10 Gy; range, 6-30), corresponding with improved OS (HR=0.12, 95% CI 0.03-0.40; P<0.01) versus no pseudoprogression.

Conclusions

Preclinical work demonstrates the chemopotentiating effect of LDFRT. In our clinical trial, LDFRT with temozolomide was safe and well-tolerated in patients with recurrent HGG receiving salvage re-irradiation. Although the primary survival endpoint was not achieved, high pseudoprogression rates at low radiation doses support the principle of low-dose radiation hypersensitivity mediated by chemopotentiation and potentially immune-modulation.

Introduction

The management of patients with recurrent high-grade gliomas (HGG) is challenging with poor overall survival. Accepted treatment options include but are not limited to temozolomide or lomustine alone, repeat radiation therapy with or without concurrent temozolomide or concurrent bevacizumab, alternating electric fields, or clinical trials. Unfortunately the response rate to second-line therapies is limited and when effective the durability of response is generally poor.1, 2, 3, 4 Improvements in salvage therapeutic options for HGG are therefore critical.

Numerous studies have shown that the slope of the cell survival curve is greater at very low doses of radiation than at the higher doses of radiation that are conventionally employed in the clinic.5, 6, 7, 8, 9, 10, 11 The mechanism behind this phenomenon known as low dose hyper-radiation sensitivity appears to be two-fold. First, low doses of radiation do not induce cellular repair mechanisms such as ATM and mismatch repair that are typically activated with clinically relevant doses of radiation.[5,12,13] Second, very small fractions of radiation manage to induce pro-apoptotic pathways without inducing pro-survival cascades that are activated with higher doses.[14,15] Studies have shown that hyper-radiation sensitivity persists following multiple fractions of radiation[16] and that the effect is greatest in cells in the G2/M phase.

In spite of these data, low dose fractionated radiation therapy (LDFRT) is not typically employed in the clinic because in order to use it as a primary modality, patients would need to be treated with multiple fractions of radiation per day for many months, and this is not feasible. However, in vitro and in vivo studies have suggested that LDFRT may be used to potentiate full dose chemotherapy, decreasing the development of resistance found with standard doses of radiation and chemotherapy.14, 15, 16, 17

The concept of LDFRT as a chemotherapy-sensitizer has been previously evaluated in humans in the context of early phase clinical trials in other disease sites, with encouraging results.[18,19] Within the context of central nervous system tumors, two additional single-arm phase 2 studies have reported safety and efficacy outcomes with differing low-dose fractionation regimens, with encouraging results compared to historical controls. [20,21]

This study is aimed to investigate the safety and efficacy of LDFRT in enhancing the effects of temozolomide, in patients with recurrent HGG. This investigation aligns with the hypothesis that combining LDFRT with temozolomide and O6-Benzylguanine (a small molecule inhibitor used to increase the sensitivity of cells to alkylating agents), would enhance chemopotentiation and eliminate induced radiation resistance, without increasing toxicity.

Given promising preclinical data in gliomas and other solid tumors as well as clinical data in lung and head and neck malignancies, the purpose of this trial was to examine the safety and efficacy of LDFRT as a chemo-potentiator of temozolomide in patients with recurrent HGG.

Section snippets

Preclinical

CELL LINES AND TREATMENTS: Three different cell lines were utilized for this study: U87 (derived from primary human glioblastoma), H1915 (from human lung cancer cells metastasized in the brain), and DAOY (from primary human medulloblastoma). Twelve treatment groups were designed to study the effects of different treatments such as TMZ, O^6-Benzylguanine (BG), LDFRT (0.5 Gy in 4 fractions, with 8-hour time intervals between each fraction), and a standard 2 Gy radiation dose. In combined …

Eligibility

Patients eligible for study enrollment met the following criteria: (1) histologically confirmed

glioblastoma or anaplastic astrocytoma with recurrence; (2) previously treated with surgical resection and standard of care 59.4-60 Gy in 30-33 fractions of radiation therapy plus concurrent and adjuvant temozolomide; (3) at least 12 months from completion of radiation therapy;[25] (4) at least 2 months from completion of temozolomide; (5) temozolomide re-treatment planned by the treating …

Response kinetics by RT-CES

Figure 1 tracks cell proliferation over time, illustrating that untreated (UT) cells across all cell lines exhibit steady growth. For U87 glioblastoma cells, LDFRT and 2 Gy radiation alone result in only mild reductions in proliferation (Figure 1**A**). However, combinations involving TMZ and BG, especially LDFRT+TMZ+BG, significantly inhibit proliferation, suggesting a synergistic effect that suppresses growth more effectively than single treatments. DAOY medulloblastoma cells show a similar …

Discussion

Experiments in glioma cell lines have suggested that the point of maximum radiation hypersensitivity occurs with fractional doses of approximately 0.5 Gy.[16] Our data in U87 glioblastoma cells demonstrate more substantial decreases in cell proliferation with LDFRT vs 2 Gy radiotherapy alone, providing further evidence in support of this phenomenon. Furthermore, our data suggests that LDFRT may be used to sensitize cells to the effects of temozolomide. Specifically, the preclinical portion of …

Conclusion

We present a unique preclinical model of LDFRT demonstrating its efficacy in temozolomide chemopotentiation relative to 2-Gy fractionated radiotherapy in glioblastoma cells lines. This was followed by a phase I/II study of re-irradiation using LDFRT as a chemo-potentiator of temozolomide in recurrent high grade glioma. These data suggest that the approach is safe and well tolerated. Although the primary survival endpoint was not achieved, the high rates of pseudo-progression observed at very …

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Data Availability Statement for this Work

Research data are not available at this time. …

Conflict of Interest Statement for All Authors

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