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Clinical Investigation

A phase 1/2 study of disulfiram and copper with concurrent radiation therapy and temozolomide for patients with newly diagnosed glioblastoma

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ABSTRACT

Background

This phase 1/2 study evaluates the safety and preliminary efficacy of combining disulfiram and copper (DSF/Cu) with radiation therapy (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM).

Methods

Patients received standard RT and TMZ with DSF (250-375 mg daily) and Cu, followed by adjuvant TMZ plus DSF (500 mg/day) and Cu. Pharmacokinetic analyses determined drug concentrations in plasma and tumors using high-performance liquid chromatography-mass spectrometry.

Results

Thirty-three patients, with a median follow-up of 26.0 months, were treated, including 12 IDH-mutant, 9 NF1-mutant, 3 BRAF-mutant, and 9 other IDH-wildtype cases. In the phase-1 arm, 18 patients were treated; dose-limiting toxicity (DLT) probabilities were 10% (95% CI: 3-29%) at 250 mg/day and 21% (95% CI: 7-42%) at 375 mg/day. The phase 2 arm treated 15 additional patients at 250 mg/day. No significant difference in overall survival or progression-free survival were noted between IDH-mutant and NF1-mutant cohorts compared to institutionally counterparts treated without DSF/Cu. However, extended remission occurred in three BRAF-mutant patients. Diethyl-dithiocarbamate-copper, the proposed active metabolite of DSF/Cu, was detected in plasma but not in tumors.

Conclusions

The maximum tolerated dose of DSF with RT and TMZ is 375 mg/day. DSF/Cu showed limited clinical efficacy for most patients. However, promising efficacy was observed in BRAF-mutant GBM, warranting further investigation.

Section snippets

INTRODUCTION

Glioblastoma (GBM, World Health Organization/WHO grade 4) is the most common malignant and lethal primary brain tumor, affecting over 12,000 adults annually (1). The current standard of care involves maximal safe resection, followed by radiation therapy (RT) and concurrent temozolomide (TMZ), and then adjuvant TMZ with consideration of tumor-treating fields (TTFields) (2,3). Unfortunately, outcomes remain discouraging, with median progression-free survival (PFS) of 6 to 7 months and median…

Study design and Patients

This single-institution, single-arm, open-label, phase 1/2 study aimed to investigate the combination of DSF/Cu with RT and TMZ for newly diagnosed GBM. In the dose-escalation phase 1 arm, the primary objective was to determine the maximum tolerated dose (MTD) of DSF when it is administered concurrently with RT and TMZ. In the dose-expansion phase 2 arm, the primary objective was to evaluate the clinical outcomes of molecular subtypes of GBM treated with the DSF/Cu combination, specifically…

Patient Characteristics

Between November 2016 and June 2022, 41 patients were screened for the study, out of which 6 patients were not eligible: 2 did not meet eligibility criteria, 2 declined participation, and 2 received insurance denials. Additionally, two patients withdrew before initiating the study therapy due to clinical deterioration.

Therefore, a total of 33 patients were treated and evaluated. The CONSORT diagram is provided in **Supplementary Figure S1**. From November 2016 to July 2018, 18 patients were...

DISCUSSION

In the current study, we identified the MTD of DSF/Cu when combined with concurrent RT and TMZ as 375 mg/day, with elevated liver enzymes being the most common DLT. The MTD of DSF when combined with adjuvant TMZ was previously shown to be 500 mg/day (22,23). The reduced MTD of DSF during chemoradiotherapy and slightly higher incidence of elevated liver enzymes may be due to concurrent daily administration of 75 mg/m^2 of TMZ during RT, in contrast to the less frequent schedule in the adjuvant...

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Clinical Trial Registration: ClinicalTrials.gov (NCT02715609).

Data Availability: The data generated in this study are stored in an institutional repository and are not publicly available due to patient privacy and consent, but they are available upon reasonable request from the corresponding author.

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