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Glioblastoma

First-in-Human Phase I Clinical Trial of Pharmacologic Ascorbate Combined with Radiation and Temozolomide for Newly Diagnosed Glioblastoma.

Allen BG, Bodeker KL, Smith MC, Monga V, Sandhu S, Hohl R, Carlisle T, Brown H, Hollenbeck N, Vollstedt S, Greenlee JD, Howard MA, Mapuskar KA, Seyedin SN, Caster JM, Jones KA, Cullen JJ, Berg D, Wagner BA, Buettner GR, TenNapel MJ, Smith BJ, Spitz DR, Buatti JM.

Clin Cancer Res. 2019 Aug 19. doi: 10.1158/1078-0432.CCR-19-0594. [Epub ahead of print]

PURPOSE

Standard treatment for glioblastoma (GBM) includes surgery, radiation therapy (RT), and temozolomide (TMZ), yielding a median overall survival (OS) of approximately 14 months. Preclinical models suggest that pharmacologic ascorbate (P-AscH-) enhances RT/TMZ antitumour effect in GBM. We evaluated the safety of adding P-AscH- to standard RT/TMZ therapy.

PATIENTS AND METHODS

This first-in-human trial was divided into an RT phase (concurrent RT/TMZ/P-AscH-) and an adjuvant (ADJ) phase (post RT/TMZ/P-AscH- phase). Eight P-AscH- dose cohorts were evaluated in the RT phase until targeted plasma ascorbate levels were achieved (≥20 mmol/L). In the ADJ phase, P-AscH- doses were escalated in each subject at each cycle until plasma concentrations were ≥20 mmol/L. P-AscH- was infused three times weekly during the RT phase and two times weekly during the ADJ phase, continuing for six cycles or until disease progression. Adverse events were quantified by common terminology criteria for adverse events (CTCAE) (v4.03).

RESULTS

Eleven subjects were evaluable. No dose-limiting toxicities occurred. Observed toxicities were consistent with historical controls. Adverse events related to the study drug were dry mouth and chills. Targeted ascorbate plasma levels of 20 mmol/L were achieved in the 87.5 g cohort; diminishing returns were realised in higher dose cohorts. Median progression-free survival (PFS) was 9.4 months and median OS was 18 months. In subjects with undetectable methylguanine-DNA methyltransferase (MGMT) promoter methylation (n = 8), median PFS was 10 months and median OS was 23 months.

CONCLUSIONS

P-AscH-/RT/TMZ is safe with promising clinical outcomes warranting further investigation.