RESEARCH ARTICLE CANCER

A window-of-opportunity trial reveals mechanisms of response and resistance to navtemadlin in patients with recurrent glioblastoma

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Editor's summary

Many glioblastomas express wild-type *TP53*, which may make them susceptible to pharmacological inhibition of MDM2 (murine double minute homolog 2), leading to reactivation of p53 signaling and tumor cell death. Here, Rendo and colleagues report the results of a surgical window-of-opportunity trial (NCT03107780) in 21 patients with recurrent glioblastoma, where patients received two doses of the MDM2 inhibitor navtemadlin before resection of their tumors, then continued the drug after resection. Despite the drug showing a pharmacodynamic impact on tumors, progression-free and overall survival were not improved. The authors then used DNA sequencing, transcriptomic and spatial analyses, and glioblastoma neurospheres to explore mechanisms of resistance and suggest that combination with temozolomide may improve results going forward. —Melissa L. Norton

Abstract

Inhibitors of murine double minute homolog 2 (MDM2) represent a promising therapeutic approach for the treatment of *TP53* wild-type glioblastomas (GBMs), reactivating p53 signaling to induce cancer cell death. We conducted a surgical window-of-opportunity trial (NCT03107780) of the MDM2 inhibitor navtemadlin (KRT-232) in 21 patients with *TP53* wild-type recurrent GBM to determine achievable drug concentrations within tumor tissues and biological mechanisms of response and resistance. Participants received navtemadlin at 120 mg (n = 10) or 240 mg (n = 11) for 2 days before surgical resection and after surgery until progression or unacceptable toxicity. Both 120 and 240 mg daily dosing achieved a pharmacodynamic impact, but median progression-free survival was 3.1 months. DNA sequencing of three recurrent tumors revealed an absence of *TP53*-inactivating mutations, indicating alternative mechanisms of resistance. To understand the mechanisms of response and resistance associated with navtemadlin, we conducted functional and spatial analyses of human tissue and patient-derived GBM neurosphere models. Navtemadlin induced partial tumor cell death as monotherapy, and combination with temozolomide enhanced apoptosis in GBM neurospheres while sparing normal bone marrow cells in vitro. We also observed up-regulation of oligodendrocyte differentiation genes with navtemadlin treatment and enrichment of oligodendrocyte transcription factor 2 (OLIG2)–positive cells at relapse, suggesting an unexplored mechanism of navtemadlin tolerance in GBM. Overall, these results indicated that clinically achievable doses of navtemadlin exert pharmacodynamic effects on GBM and suggest that combined treatment with temozolomide may be a route to more durable survival benefits.

Supplementary Materials

The PDF file includes:

Figs. S1 to S7

Table S1

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Other Supplementary Material for this manuscript includes the following:

Data file S1

DOWNLOAD 14.31 KB

MDAR Reproducibility Checklist

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REFERENCES AND NOTES

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